infusion of 5-FU. To our knowledge, however, combination therapy with docetaxel, cisplatin, and S-1 (TPS) in the treatment of HNC has not been investigated.

Here, we conducted a phase I study of a combination therapy with TPS in patients with locally advanced or recurrent/metastatic HNC.

patients and methods

eligibility criteria

All patients had a histologically or cytologically confirmed diagnosis of HNC with recurrent/metastatic or unresectable locally advanced disease. Eligibility also required an Eastern Cooperative Oncology Group performance status of zero or one, age 20–75 years, and adequate organ function. Written informed consent was required from all patients before the start of study therapy.

Patients were excluded for any of the following conditions: history of prior chemotherapy; concurrent active malignancy except excised intramucosal gastric or esophageal cancer, which could be removed by endoscopic mucosal resection; pharyngeal fistula; active bleeding from the GI tract; active infection; serious medical problem that might interfere with the achievement of study objectives; pregnancy or lactation; or expected survival of <3 months.

The study was approved by the Institutional Review Board at the National Cancer Center.

study design

The study was conducted as an open-label, single arm, phase I, single-institution dose-escalation study aimed at testing the safety of combination therapy with TPS in patients with locally advanced or recurrent/metastatic HNC. A total of six dose combinations were planned (Table 1).

Toxic effects were evaluated according to National Cancer Institute—Common Toxicity Criteria for Adverse Events version 2.0. A minimum of three assessable patients was treated at each dose level. If one of the three patients at a given dose level experienced a dose-limiting toxicity (DLT), three additional patients were accrued at the same dose level. The maximum tolerated dose (MTD) was defined as the dose at which two or more patients of six experienced a DLT. After the MTD was determined, three more patients were treated at the next lower dose level. If no or only one of the six patients experienced a DLT, an additional six patients were accrued at the same dose level to determine the recommended dose (RD). No intra-patient dose escalation was allowed.

DLT was defined as any of the following adverse events occurring within 30 days after completion of the first cycle of TPS: (i) febrile neutropenia lasting >4 days; (ii) grade 4 thrombocytopenia (<10 000/mm^3); (iii) grade 4 vomiting; (iv) grade 3 or 4 nonhematological toxic effects except grade 3 anorexia, nausea, vomiting, stomatitis, esophagitis, and infection due to stomatitis; (v) cessation of treatment due to an adverse event; or (vi) treatment-related death.

treatment

Chemotherapy consisted of a 1-h infusion of docetaxel at escalating doses of 50, 60, and 70 mg/m^2; a 2-h infusion of cisplatin at 70 mg·m^2/day on day 1; and S-1 twice daily on days 1–14 at escalating doses of 40, 60, and 80 mg·m^2/day. This regimen was repeated every 3 or 4 weeks. Prophylactic use of granulocyte colony-stimulating factor was not allowed but ciprofloxacin was administered on days 5 through 15.

The dose escalation schema is depicted in Table 1. At dose levels 1–4, treatment was repeated every 4 weeks, with a maximum of six cycles allowed until unacceptable toxicity, patient refusal or disease progression was observed. At dose levels 5 and 6, the subject had to have locally advanced HNC and to have received TPS every 3 weeks with a maximum of three cycles allowed. Patients with locally advanced HNC who recorded a response after completion of three cycles of TPS were able to receive definitive treatment, including concurrent chemoradiotherapy.

treatment evaluation and dose modifications

Baseline evaluation consisted of history, physical examination, radiographic imaging, routine laboratory studies, and electrocardiogram. Safety assessments were repeated weekly after the start of chemotherapy.

Doses were modified in case of severe hematological or nonhematological toxic effects. Since patients received three chemotherapeutic agents, dose adjustment was carried out for each individual agent based on its estimated causal relationship to the toxicity; if multiple agents were felt to be causing the toxicity, dose reduction was carried for multiple agents according to the RD reduction schedule below. If multiple toxic effects occurred during a treatment cycle, the toxicity with the highest grade was used as the parameter for dose adjustment.

Grade 4 hematological toxic effects or grade 3 infection required a dose reduction of all three drugs. Grade 3 diarrhea, mucositis, or skin reaction required a reduction in S-1 dose. Grade 2 neurotoxicity required a reduction in cisplatin dose. Grade 3 neurotoxicity required the discontinuation of cisplatin. Creatinine clearance (CCr) was calculated at the beginning of each cycle according to the Cockcroft–Gault formula. CCr values >60 ml/min required no dose modification; those from 50 to <60 ml/min required a reduction in both S-1 and cisplatin by one dose level; those from 40 to <50 ml/min required a reduction of both S-1 and cisplatin by two dose levels; and those <40 ml/min required the cessation of both S-1 and cisplatin. Patients were removed from treatment if more than two dose reductions were required or if there was a treatment delay of >21 days due to toxicity.

Tumors responses were evaluated according to RECIST.

Table 1. Dose escalation schema and DLTs

Dose level	Docetaxel (mg/m^2)	Cisplatin (mg/m^2)	S-1 (mg·m^2/day)	Cycle (weeks)	Subject	DLT frequency	DLT
1	50	70	40	4	R/M and LA	0/4	
2	60	70	40	4	R/M and LA	0/3	
3	60	70	60	4	R/M and LA	0/3	
4	60	70	80	4	R/M and LA	1/12	Grade 3 infection
5	70	70	80	3	LA	2/6	Grade 3 infection, grade 3 hyperbilirubinemia
6	70	70	60	3	LA	2/12	Grade 3 diarrhea, grade 3 ALT/AST↑

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; LA, locally advanced disease; R/M, recurrent/metastatic disease.

end points and statistical methods

The primary end point in this study was the MTD and RD of this regimen. Secondary end points included the safety and tolerability of this combination and relative dose intensity and efficacy, including response rate, progression-free survival (PFS), and overall survival (OS).

Relative dose intensity was calculated as the ratio of the actual to planned dose intensity in milligrams per square meter per week. The survival curve was estimated using the Kaplan–Meier method. Safety and efficacy analyses were both conducted on an intention-to-treat (ITT) population, defined as all patients enrolled in the study who received at least one dose of chemotherapy. A subject's PFS was defined as the time from the date of the first administration of chemotherapy to the first documentation of disease progression, subsequent therapy, or death. OS was determined from the date of the first administration of chemotherapy to the date of death or the last confirmation of survival. Statistical data were obtained using the SPSS software package (SPSS 11.0 Inc., Chicago, IL).

results

patient and disease characteristics

From November 2004 to September 2008, a total of 40 patients were enrolled, consisting of 33 males and 7 females with a median age of 50 years (range 22–74 years). Patient characteristics in the ITT population are listed in Table 2.

Table 2. Patient characteristics

Characteristic	No. of patients (n = 40)
Age, years	
Median	50
Range	22–74
Sex	
Male	33
Female	7
Eastern Cooperative Oncology Group performance score	
0	35
1	5
Site of primary tumor	
Hypopharynx	9
Oral cavity	1
Oropharynx	10
Salivary gland	3
Nasopharynx	13
Nasal cavity	3
Histology	
Squamous cell carcinoma	23
Adenoid cystic carcinoma	3
Undifferentiated carcinoma	9
Others	5
Disease status	
Recurrent/metastatic disease	11
Locally advanced disease	29
Prior treatment	
None	31
Surgery alone	4
Surgery with adjuvant radiotherapy	1
Radiotherapy alone	4

Twenty-nine cases were locally advanced cancer and 11 were recurrent/metastatic cancer.

treatment administration

A total of 116 cycles was administered (median = 3, range 1–6) over six dose levels. Twenty cycles required dose reduction, while six required a delay of >7 days due to toxicity. Six patients discontinued treatment due to disease progression and two due to treatment-related toxicity, while two other patients refused further treatment due to fatigue. Three of 11 patients with recurrent/metastatic disease completed six cycles of TPS as a palliative chemotherapy, whereas 27 of 29 patients with locally advanced disease completed three cycles of TPS as induction chemotherapy. Twenty-four patients received subsequent chemoradiotherapy concurrently with cisplatin (cisplatin 20 mg/m^2, i.v., days 1–4, days 22–25, days 43–46) after completion of TPS. One patient received chemoradiotherapy with 5-FU plus cisplatin (5-FU 400 mg/m^2, i.v., days 1–5, days 29–33, cisplatin 20 mg/m^2, i.v., days 1–4, days 29–32). Four patients received proton beam therapy concurrently with cisplatin at the same schedule as chemoradiotherapy. One patient for whom no response was documented after two cycles of TPS received palliative chemoradiotherapy. Median total dose of photon therapy and proton beam therapy was 70 Gy (range 66–70) and 70 Gy (range 65–70), respectively.

dose escalation and DLT

DLTs are listed in Table 1. No DLTs were observed until dose level 3. At dose level 4, one patient experienced grade 3 infection, leading cohort expansion, but no further DLTs were observed at this dose level. Although MTD was not reached by this level, further escalation was not initially planned. An additional six patients were accrued at this level to determine the RD. Since MTD was not reached by dose level 4 and the dose intensities of docetaxel and cisplatin at this level (docetaxel 15 mg·m^2/week, cisplatin 17.5 mg·m^2/week) were markedly lower than that of previous studies of induction TPF for locally advanced HNC (docetaxel 25 mg·m^2/week, cisplatin 25 mg·m^2/week), we amended the protocol to include a dose escalation of docetaxel and shortening of treatment cycle and limited the subjects to patients with locally advanced disease. In other words, MTD was evaluated at dose level 5 or 6 to determine the RD of TPS as induction chemotherapy for locally advanced HNC.

At dose level 5, two DLTs were observed, namely one grade 3 infection and one grade 3 hyperbilirubinemia, establishing this as the MTD. The relative dose intensity at this dose level was 0.67 (range 0.40–0.85). In the 12 patients at dose level 6, two DLTs were observed, namely one grade 3 elevation of alanine aminotransferase/aspartate aminotransferase and one grade 3 diarrhea. The relative dose intensity at this dose level was 0.92 (range 0.41–1.0). Based on the results, the RD of this combination was determined as docetaxel 70 mg/m^2, cisplatin 70 mg/m^2, and S-1 60 mg/m^2 for 14 days, every 3 weeks.

toxicity

Overall toxic effects during TPS administration are listed in Table 3. Grade 3 or 4 hematological toxic effects are listed by

dose level in Table 4. At dose level 5, all patients experienced grade 4 neutropenia. Grade 2 or 3 nonhematological toxic effects are listed by dose level in Table 5. No grade 4 nonhematological toxic effects were observed during any course.

Major common grade 3 or 4 toxic effects in patients with locally advanced disease during chemoradiotherapy or proton beam therapy were mucositis (48%), dysphagia (34%), leucopenia (28%), anemia (17%), dermatitis (17%), and neutropenia (14%). Toxicity was as expected and manageable.

Table 3. Overall toxicity during TPS administration (n = 40)

Toxicity	No. of patients				%
	Grade				Grade
	1	2	3	4	3–4
Hematological toxicity					
Leucopenia	6	20	12	0	30
Neutropenia	6	9	12	12	60
Febrile neutropenia	0	0	5	0	13
Anemia	22	14	3	0	8
Thrombocytopenia	15	2	0	0	0
Nonhematological toxicity					
Nausea	16	14	1	0	3
Vomiting	12	3	0	0	0
Anorexia	15	14	6	0	15
Fatigue	13	7	0	0	0
Mucositis	5	3	1	0	3
Diarrhea	6	3	1	0	3
Elevated bilirubin	5	12	1	0	3
Elevated AST	14	3	1	0	3
Elevated ALT	10	6	1	0	3
Elevated creatinine	6	1	1	0	0

ALT, alanine aminotransferase, AST, aspartate aminotransferase.

treatment outcomes

Efficacy data are listed in Table 6. All patients enrolled in this study were assessable for response to TPS. There were 6 complete and 22 partial responses, giving an overall response rate of 70% [95% confidence interval (CI) 59.1–80.8], broken down as 4 complete and 18 partial responses in the 29 patients with locally advanced disease, and 2 complete and 4 partial responses in the 11 with recurrent/metastatic disease. One of these latter two complete responders, who had residual disease after completion of radiotherapy for poorly differentiated squamous cell carcinoma of the nasopharynx, achieved a complete response after receiving three cycles of TPS without further treatment and remains alive without evidence of recurrence as of ~5 years later. Another patient, who had previous radiotherapy for undifferentiated carcinoma of the nasopharynx and multiple mediastinal lymph node metastases 4 months after receiving lobectomy for lung metastasis, achieved a complete response after completion of six cycles of TPS followed by S-1 alone for 2 years and is alive without evidence of disease progression as of >4 years after treatment. Although no objective response was observed in patients with adenoid cystic carcinoma, eight of nine patients with undifferentiated carcinoma achieved an objective response.

Of the 29 patients with locally advanced disease, 23 (79%; 95% CI, 64% to 93%) experienced complete remission after completion of definitive chemoradiotherapy or proton beam

Table 4. Grade 3 or 4 hematological toxicity during TPS administration by dose level

Toxicity	Grade 3 or 4 hematological toxicity											
	No. of patients											
	Dose level 1 (n = 4)		Dose level 2 (n = 3)		Dose level 3 (n = 3)		Dose level 4 (n = 12)		Dose level 5 (n = 6)		Dose level 6 (n = 12)	
	Grade		Grade		Grade		Grade		Grade		Grade	
	3	4	3	4	3	4	3	4	3	4	3	4
Leucopenia	1	0	0	0	0	0	3	0	5	0	1	0
Neutropenia	0	1	0	0	0	0	5	0	0	6	5	4
Febrile neutropenia	0	0	0	0	0	0	0	0	1	0	4	0
Anemia	0	0	0	0	0	0	0	0	0	0	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0	0	0	0	0

Table 5. Grade 2 or 3 nonhematological toxicity during TPS administration by dose level

Toxicity	Grade 2 or 3 nonhematological toxicity											
	No. of patients											
	Dose level 1 (n = 4)		Dose level 2 (n = 3)		Dose level 3 (n = 3)		Dose level 4 (n = 12)		Dose level 5 (n = 6)		Dose level 6 (n = 12)	
	Grade		Grade		Grade		Grade		Grade		Grade	
	2	3	2	3	2	3	2	3	2	3	2	3
Anorexia	0	0	2	0	0	1	6	2	3	0	3	3
Nausea	1	0	0	0	1	0	5	1	2	0	4	0
Mucositis	0	0	0	0	2	0	1	1	0	0	0	0
Diarrhea	0	0	0	0	0	0	1	0	2	0	0	1
Infection	0	2	0	0	0	0	0	1	0	1	0	3

Table 6. Efficacy ($n = 40$)

Subject	No. of patients					%	
	CR	PR	SD	PD	NE	RR	95% CI
All ($n = 40$)	6	22	10	1	1	70	59.1–80.8
Disease status							
LA ($n = 29$)	4	18	6	1	0	76	62.2–89.8
R/M ($n = 11$)	2	4	4	0	1	55	38.7–71.2
Histology							
SCC ($n = 23$)	3	15	4	1	0	78	56.3–92.5
ACC ($n = 3$)	0	0	3	0	0	0	0–70.8
Undiff ($n = 9$)	2	6	1	0	0	89	51.8–99.7
Others ($n = 5$)	1	1	2	0	1	40	5.3–85.3

ACC, adenoid cystic carcinoma; CI, confidence interval; CR, complete response; LA, locally advanced disease; NE, not evaluated; PD, progressive disease; PR, partial response; RR, response rate; R/M, recurrent/metastatic disease; SCC, squamous cell carcinoma; SD, stable disease; Undiff, undifferentiated carcinoma.

therapy. Three patients achieved a partial response and the remaining three patients showed progressive disease, including bone metastasis ($n = 2$). With a median follow-up time of 19 months (range 6–52 months), locoregional recurrence and distant metastasis were observed in nine and four patients, respectively. A total of six patients died due to disease progression. Although the patient population was heterogeneous, the estimated 1-year PFS and OS in all patients were 64% and 85%, respectively. The estimated 1-year PFS in patients with recurrent/metastatic and locally advanced disease were 33% and 74%, respectively.

discussion

The past 5–10 years has seen an increasing trend for the substitution of conventional 5-FU with oral prodrugs of 5-FU, including S-1 and capecitabine, in chemotherapy regimens. Two randomized trials for advanced gastric cancer evaluated the safety and efficacy of S-1 compared with that of 5-FU: in one trial, S-1 showed statistically significant noninferiority to 5-FU ($P < 0.001$) [12], while in another trial [13], S-1 plus cisplatin was statistically noninferior to 5-FU plus cisplatin and had a significantly superior safety profile. These randomized trials have identified S-1 as a valuable substitute for bolus or infusional 5-FU in the treatment of gastric cancer.

Three trials of TPS in the treatment of advanced gastric cancer have been reported [14–16]. Given recognition in Japan that S-1 is a key drug in the treatment of gastric cancer, S-1 dose was fixed (S-1 80 mg·m^2/day on days 1–14) in all three trials, whereas dose intensities of docetaxel and cisplatin were markedly lower (docetaxel 10 or 20 mg·m^2/week, cisplatin 17.5 or 20 mg·m^2/week) than those of the standard TPF regimen (docetaxel 25 mg·m^2/week, cisplatin 25 mg·m^2/week) for SCCHN [2, 3]. Given the outcomes of the TAX 323 and TAX324 studies [2, 3], which demonstrated that, in addition to cisplatin, docetaxel is a key drug in the treatment of SCCHN, these TPS regimens would therefore not be appropriate substitutes for TPF in the treatment of SCCHN.

In contrast to the situation for gastric cancer, no randomized trial has compared S-1 with 5-FU for HNC and no previous studies have investigated TPS in the treatment of HNC. The present study is thus the first trial of TPS in the treatment of HNC. Results showed that the incidence of hematological toxic effects was comparable to that in TAX 323 and TAX324, whereas no grade 4 nonhematological toxic effects or treatment-related deaths were seen. At dose level 5 (docetaxel 70 mg/m^2, cisplatin 70 mg/m^2, and S-1 80 mg/m^2, every 3 weeks), two DLTs were observed, establishing this as the MTD. All patients at this level experienced grade 4 neutropenia and the relative dose intensity was 0.67, suggesting that this dose would not be feasible. At dose level 6 (docetaxel 70 mg/m^2, cisplatin 70 mg/m^2, and S-1 60 mg/m^2, every 3 weeks), 2 of 12 patients developed DLTs and the relative dose intensity at this dose level was 0.92, suggesting the feasibility of this dose as the RD of a phase II trial.

The rate of treatment-related death with the most widely accepted standard TPF regimen is 2.3% [2]. This is of concern, given that the goal of treatment for patients with locally advanced SCCHN is cure. Although the docetaxel and cisplatin doses at dose level 6 (docetaxel 70 mg/m^2, cisplatin 70 mg/m^2, and S-1 60 mg/m^2, every 3 weeks) were slightly lower than those with standard TPF, the incidence of febrile neutropenia (33%) was higher than that with standard TPF (5.2%), suggesting that further dose escalation may increase the risk of the treatment-related death. Hence, no further dose escalation was undertaken.

Many patients with locally advanced HNC experience dysphagia due to the primary tumor, and difficulty in swallowing capsules containing S-1 may be problematic. Nutritional support via feeding tube replacement in these patients is indispensable. Our previous pharmacokinetic findings showed that administration of S-1 as a suspension via a feeding tube was interchangeable with oral administration of whole capsules [17]. S-1 can therefore be administered to all HNC patients regardless of difficulty in swallowing capsules.

Although efficacy was not a primary end point of this study, antitumor activity (overall response rate 70%) was highly promising. Moreover, both patients with recurrent/metastatic nasopharyngeal cancer achieved a complete response after treatment, and remain alive and without recurrence at >4 years post-treatment. Although the number of patients was small and nasopharyngeal cancer is more sensitive to chemotherapy than other primary sites of HNC, antitumor activity was noteworthy. Furthermore, toxic effects during definitive therapy were relatively mild compared with those in previous studies of concurrent chemoradiotherapy for locally advanced SCCHN, suggesting that three cycles of TPS would not compromise the delivery of subsequent chemoradiotherapy.

During dose levels 1–4, this study included patients with recurrent/metastatic disease. If TPS had shown feasible and promising efficacy in these patients, this would have been encouraged further investigation to establish a new standard of care in the treatment of recurrent/metastatic SCCHN. Of 11 patients with recurrent/metastatic disease, however, 2 refused further treatment due to fatigue, even though they had achieved a clinical response and experienced no severe toxic effects, and almost all had limited treatment options if they had proved refractory to this combination. We therefore excluded patients with recurrent/metastatic disease from receiving dose levels 5

and 6. Recently, the addition of cetuximab to platinum-based chemotherapy was shown to significantly prolong OS without exacerbating chemotherapy-associated toxicity or quality of life in patients with recurrent/metastatic SCCHN [18]. The addition of molecular-targeted drugs such as cetuximab to platinum-based chemotherapy would therefore be more feasible and appropriate than that of docetaxel to platinum-based chemotherapy in the treatment of recurrent/metastatic SCCHN.

Concern has been expressed over the considerable ethnic differences in the tolerated doses of S-1. These relate to the varying efficiency rates of conversion of tegafur to 5-FU by CYP2A6 of the CYP450 enzyme system, now identified as the principal enzyme responsible for this conversion process [19–22]. A phase I study of S-1 plus cisplatin in Western patients with advanced gastric carcinoma showed that the S-1 dose tolerated by Western patients is lower than that by Japanese patients but that the area under the curve of 5-FU appears higher in white than Japanese patients in a comparable dose range of S-1 [23]. This is mostly attributed to different polymorphisms in the *CYP2A6* gene among Asians and whites. The RD of the present study is likely unsuitable for Western patients, and further study to determine the RD of TPS for these patients is required. Moreover, further study of the present TPS should be done in Asian patients to clarify whether TPS is superior to TPF.

In conclusion, we found that treatment with TPS was well tolerated and feasible in patients with locally advanced HNC. This regimen demonstrated sufficient activity to warrant phase II testing and may be an optimal substitute for TPF in the treatment of locally advanced SCCHN. A randomized trial comparing TPS with TPF in patients with locally advanced SCCHN is warranted.

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disclosure

None of the authors declare conflicts of interest.

references

1. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer 1999; 80: 827–841.
2. Vermorken JB, Remenar E, van Herpen C et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007; 357: 1695–1704.
3. Posner MR, Hershock DM, Blajman CR et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007; 357: 1705–1715.
4. Shirasaka T, Shimamato Y, Ohshimo H et al. Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs 1996; 7: 548–557.
5. Shirasaka T, Shimamoto Y, Fukushima M. Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. Cancer Res 1993; 53: 4004–4009.
6. Inuyama Y, Kida A, Tsukuda M et al. [Late phase II study of S-1 in patients with advanced head and neck cancer]. Gan To Kagaku Ryoho 2001; 28: 1381–1390.
7. Fujii M. [Combination therapy with S-1 and CDDP for head and neck cancer]. Gan To Kagaku Ryoho 2006; 33 (Suppl 1): 150–154.
8. Yoshida K, Ninomiya M, Takakura N et al. Phase II study of docetaxel and S-1 combination therapy for advanced or recurrent gastric cancer. Clin Cancer Res 2006; 12: 3402–3407.
9. Tsutani Y, Ohara M, Suzuki T et al. Docetaxel and S-1 as a first-line treatment in patients with advanced or recurrent gastric cancer. Anticancer Res 2009; 29: 2775–2779.
10. Atagi S, Kawahara M, Kusunoki Y et al. Phase I/II study of docetaxel and S-1 in patients with previously treated non-small cell lung cancer. J Thorac Oncol 2008; 3: 1012–1017.
11. Ozaki T, Tamura K, Satoh T et al. Phase I study of combination therapy with S-1 and weekly docetaxel for advanced gastric cancer. Anticancer Res 2007; 27: 2657–2665.
12. Boku N, Yamamoto S, Fukuda H et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol 2009; 10: 1063–1069.
13. Ajani JA, Rodriguez W, Bodoky G et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol 2010; 28: 1547–1553.
14. Nakayama N, Koizumi W, Sasaki T et al. A multicenter, phase I dose-escalating study of docetaxel, cisplatin and S-1 for advanced gastric cancer (KDOG0601). Oncology 2008; 75: 1–7.
15. Takayama T, Sato Y, Sagawa T et al. Phase I study of S-1, docetaxel and cisplatin combination chemotherapy in patients with unresectable metastatic gastric cancer. Br J Cancer 2007; 97: 851–856.
16. Fushida S, Fujimura T, Oyama K et al. Feasibility and efficacy of preoperative chemotherapy with docetaxel, cisplatin and S-1 in gastric cancer patients with para-aortic lymph node metastases. Anticancer Drugs 2009; 20: 752–756.
17. Tahara M, Minami H, Kawada K et al. Phase I trial of concurrent chemoradiotherapy with S-1 and CDDP in patients with unresectable locally advanced squamous cell carcinoma of the head and neck(SCCHN). In 3rd International Conference on Cancer Therapeutics, Edition (Abstr 105). Tokyo, Japan 2006.
18. Herrero FR, Hitt R, Kawecki A et al. Cetuximab plus platinum-based therapy first line in patients with recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): a quality of life (QOL) analysis of the EXTREME trial. In 33rd ESMO Congress, Edition: Annals of Oncology; 219 (Abstr 693PD). Stockholm, Sweden 2008.
19. van der Weide J, Steijns LS. Cytochrome P450 enzyme system: genetic polymorphisms and impact on clinical pharmacology. Ann Clin Biochem 1999; 36 (Pt 6): 722–729.
20. Yoshida R, Nakajima M, Nishimura K et al. Effects of polymorphism in promoter region of human CYP2A6 gene (CYP2A6*9) on expression level of messenger ribonucleic acid and enzymatic activity in vivo and in vitro. Clin Pharmacol Ther 2003; 74: 69–76.
21. Daigo S, Takahashi Y, Fujieda M et al. A novel mutant allele of the CYP2A6 gene (CYP2A6*11) found in a cancer patient who showed poor metabolic phenotype towards tegafur. Pharmacogenetics 2002; 12: 299–306.
22. Ikeda K, Yoshisue K, Matsushima E et al. Bioactivation of tegafur to 5-fluorouracil is catalyzed by cytochrome P-450 2A6 in human liver microsomes in vitro. Clin Cancer Res 2000; 6: 4409–4415.
23. Ajani JA, Faust J, Ikeda K et al. Phase I pharmacokinetic study of S-1 plus cisplatin in patients with advanced gastric carcinoma. J Clin Oncol 2005; 23: 6957–6965.

Long-term outcome of transoral organ-preserving pharyngeal endoscopic resection for superficial pharyngeal cancer

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Background: Early detection of pharyngeal cancer has been difficult. We reported that narrow-band imaging (NBI) endoscopy can detect superficial pharyngeal cancer, and these lesions can be treated endoscopically.

Objective: To assess the safety and long-term efficacy of transoral organ-preserving pharyngeal endoscopic resection (TOPER) for superficial pharyngeal cancer.

Design and Setting: Retrospective 2-center cohort study.

Patients: The study included 104 consecutive patients with superficial pharyngeal cancer.

Intervention: TOPER with the patients under general anesthesia.

Main Outcome Measurements: Safety of the procedure, long-term survival, clinical outcome.

Results: A total of 148 consecutive lesions were resected in 104 patients. There was no severe adverse event. Temporary tracheostomy was required in 17 patients (16%) to prevent airway obstruction. The median fasting period and hospital stay after TOPER were 2 days (range 1-20 days) and 8 days (range 3-58 days), respectively. Ninety-six patients (92%) had no local recurrence or distant metastases. Local recurrence at the primary site developed in 6 patients, but all were resolved by repeat TOPER. With a median follow-up period of 43 months (range 3-96 months), the overall survival rate at 5 years was 71% (95% CI, 59-82). Cause-specific survival rate at 5 years was 97% (95% CI, 93-100). The cumulative development rate of multiple cancers in pharyngeal mucosal sites at 5 years was 22% (95% CI, 12-33). The pharynx was preserved in all patients, and they experienced no loss of function.

Limitation: Retrospective design.

Conclusions: Peroral endoscopic resection of superficial pharyngeal cancer is a feasible and effective treatment with curative intent. (Gastrointest Endosc 2011;74:477-84.)

Pharyngeal cancer other than nasopharyngeal cancer (130,000 new cases and 83,000 deaths worldwide in 2002) is predominantly a cancer of men.[1] Smoking and alcoholic beverages are the class I carcinogens for these cancers.[2] Furthermore, acetaldehyde-associated alcoholic beverages were reclassified as a class I carcinogen in 2009 by the International Agency for Research on Cancer.[2]

Abbreviations: EMR-C, EMR with a cap; ESD, endoscopic submucosal dissection; NBI, narrow-band imaging; TOPER, transoral organ-preserving pharyngeal endoscopic resection.

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Although the definite risk factors are well known, it has been quite difficult to detect pharyngeal cancer at an early stage. Thus, most of the cases are diagnosed at an advanced stage and have a poor prognosis. In addition, the standard treatments of surgical resection and/or chemoradiotherapy worsen the patients' quality of life, resulting in speech defects, swallowing disorders, salivary disorders, and cosmetic deformities of the neck.

We previously reported that a new image-enhanced endoscopic technology,[3] narrow-band imaging (NBI), was very useful for detecting these cancers at an early stage and that these superficial cancers could be treated with peroral endoscopic resection with minimal invasiveness.[4-6] Shimizu et al[7] and Iizuka et al[8] also reported the usefulness of endoscopic resection for oropharyngeal and hypopharyngeal cancer. However, these reports included small numbers of patients, and their long-term outcome has not been reported. In addition, it seems to be premature to conduct a prospective study of peroral endoscopic resection for superficial pharyngeal cancer because its feasibility and safety have not been fully evaluated. In this study, we assess a large number of patients with a longer follow-up time to address the feasibility and usefulness of peroral organ-preserving endoscopic resection for superficial pharyngeal cancers.

Take-home Message

- Peroral endoscopic laryngopharyngeal mucosal resection is a feasible and effective method for superficial pharyngeal cancer. This minimally invasive procedure can preserve the organ itself and is expected to improve the patient's quality of life and survival.

PATIENTS AND METHODS

During the period from June 2002 to April 2008, 148 consecutive superficial oropharyngeal and hypopharyngeal cancers in 104 patients were treated by transoral organ-preserving pharyngeal endoscopic resection (TOPER) while under general anesthesia at National Cancer Center Hospital East and Kyoto University Hospital. Written informed consent for the treatment was obtained from all patients, and this study was approved by the local ethics committee.

Histological diagnosis of the lesions was made according to the World Health Organization classification of the tumor (head and neck tumors).[9] Evaluation of the invasion of the tumor was also made according to the general rules for clinical studies of head and neck cancer by the Japanese Society for Head and Neck Cancer and the Japanese classification of esophageal cancer by Japan Esophageal Society.[10] According to these guidelines, carcinoma in situ and subepithelial cancers are defined as a superficial cancer regardless of lymph node or distant organ metastasis. To date, there is no generally accepted definition of superficial cancer in this field. Thus, a cancer limited to the subepithelial layer of the pharynx is defined as superficial cancer in this study.

If the lesion was evaluated as carcinoma in situ or carcinoma with invasion to the subepithelial layer (not to the muscular layer), TOPER was indicated as a minimally invasive treatment (Fig. 1). Patients who received radiotherapy to the head and neck region previously were not indicated. All patients refused radical surgical resection or chemotherapy or chemoradiotherapy. All lesions were detected by NBI with a magnifying endoscope and histologically confirmed by biopsy specimen as severe dysplasia/carcinoma in situ or squamous cell carcinoma.

TOPER was based on the methods of EMR using a cap (EMR-C)[11] or endoscopic submucosal dissection (ESD),[12] and the procedures were performed as previously reported[11,12] by using a high-definition endoscope (Q240Z, Q260J, or H260Z; Olympus Medical Systems, Tokyo, Japan). For EMR-C, a soft food attachment (D-206-06; Olympus Medical Systems) to the tip of the endoscope was used. For ESD, an insulated-tip electrosurgical knife (IT knife; Olympus Medical Systems) was used. In both methods, the lesion was removed after inserting a needle beside the lesion and injecting an adequate volume of saline solution or glycerol containing diluted epinephrine (0.02 mg/mL) beneath the epithelium to lift it above the surrounding mucosa. We used a rigid laryngoscope (Nagashima, Tokyo, Japan) to obtain a sufficient working space by lifting the larynx. Iodine staining was used both to delineate the exact margin of the cancer lesion before resection and to detect residual lesion after resection. If a small residual lesion was endoscopically identified after EMR or ESD, argon plasma coagulation was done to prevent local recurrence. To check whether the larynx was swollen after resection, an endoscopic examination was performed on the day after resection with the patient under conscious sedation by periodic intravenous administration of pethidine hydrochloride (in total 0.5 mg/body weight). If the movement of the pharynx and larynx was unimpaired, the patient was encouraged to start eating semisolid food. If the larynx was swollen, the patient continued fasting until the swelling disappeared.

All resected specimens were cut into longitudinal slices measuring 2 mm in width. The slices were embedded in paraffin and stained with hematoxylin-eosin. All specimens were microscopically evaluated by 3 pathologists (S.F., A.Y., A. Ochiai) according to the World Health Organization classification.[9]

Follow-up endoscopy was performed after 1 to 3 months to check the healing of the mucosal defect and local residue after TOPER, and thereafter every 6 months to detect metachronous superficial cancer in

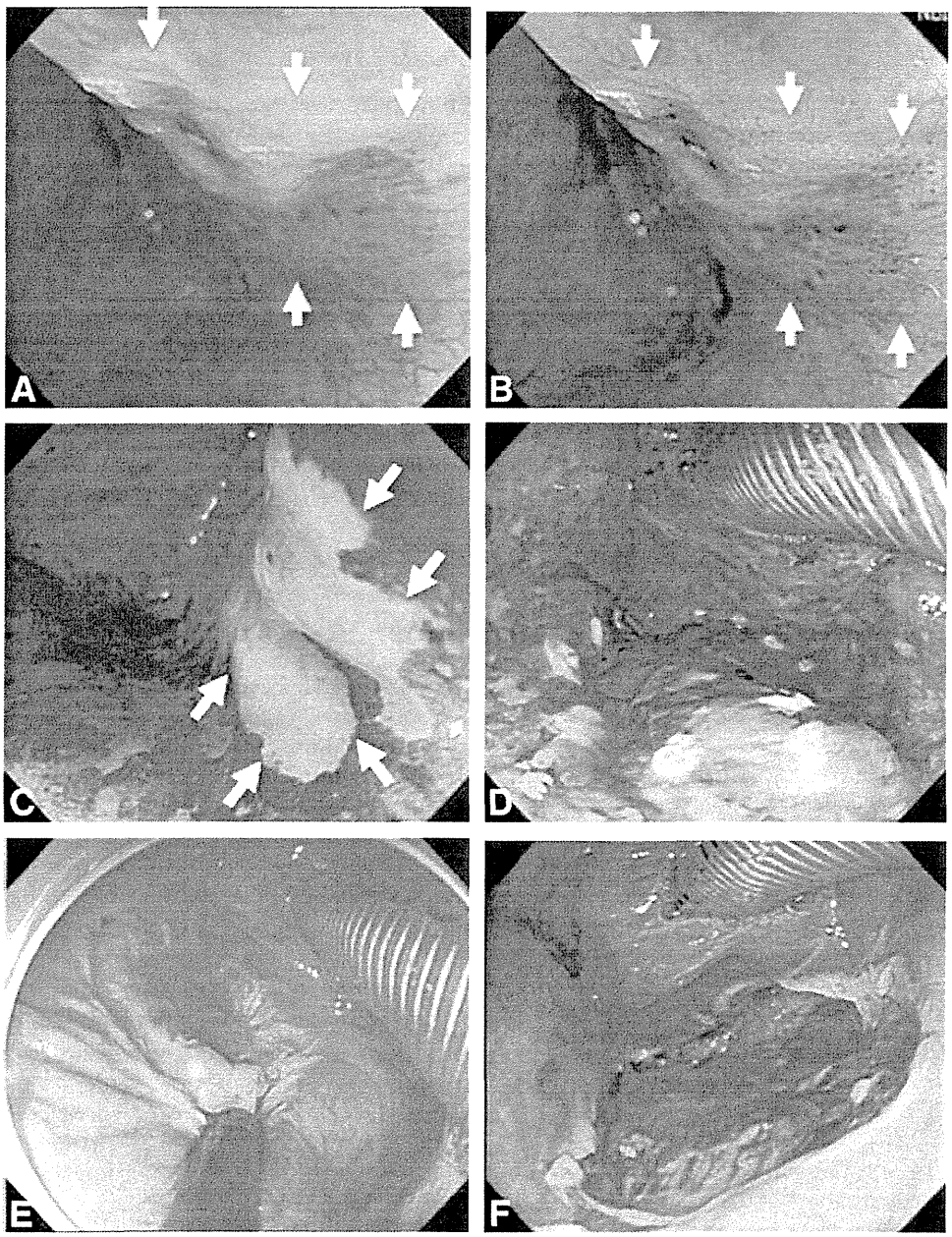

Figure 1. TOPER for superficial pharyngeal cancer. **A,** Endoscopic photograph showing the right piriform sinus with superficial pharyngeal cancer. The slight reddish-color mucosa is the neoplastic lesion (*arrows*). **B,** Narrow-band imaging corresponding with **A** showing well-demarcated brownish area (*arrows*). In the brownish area, tiny brown dots can be seen, which are irregular morphological changes in superficial microvessels in the neoplastic lesion. **C,** Iodine chromoendoscopy showing well-demarcated iodine voiding lesion (*arrows*). **D,** Marking around the lesion with a needle-knife with coagulation mode. **E,** Mucosal incision outside the marking after submucosal injection. **F,** The mucosal defect immediately after resection. **G,** Resected specimen with the neoplastic lesion in en bloc fashion. **H,** Histologically, this lesion was diagnosed as carcinoma in situ.

these regions. Local recurrence was defined as when the cancer was detected at the site of the TOPER scar. Patients underwent a CT scan of the neck, chest, and abdomen annually to detect lymph node and distant metastases.

StatView version 5.0 (SAS Institute Inc, Cary, NC) was used for statistical analysis. The results are expressed as median (range). The Fisher exact test was used to analyze categorical data to compare proportions. Cause-specific and overall survival rates were estimated by using the Kaplan–Meier method.

RESULTS

Patient characteristics are shown in Table 1. They were predominantly male (97%), and the median age was 63

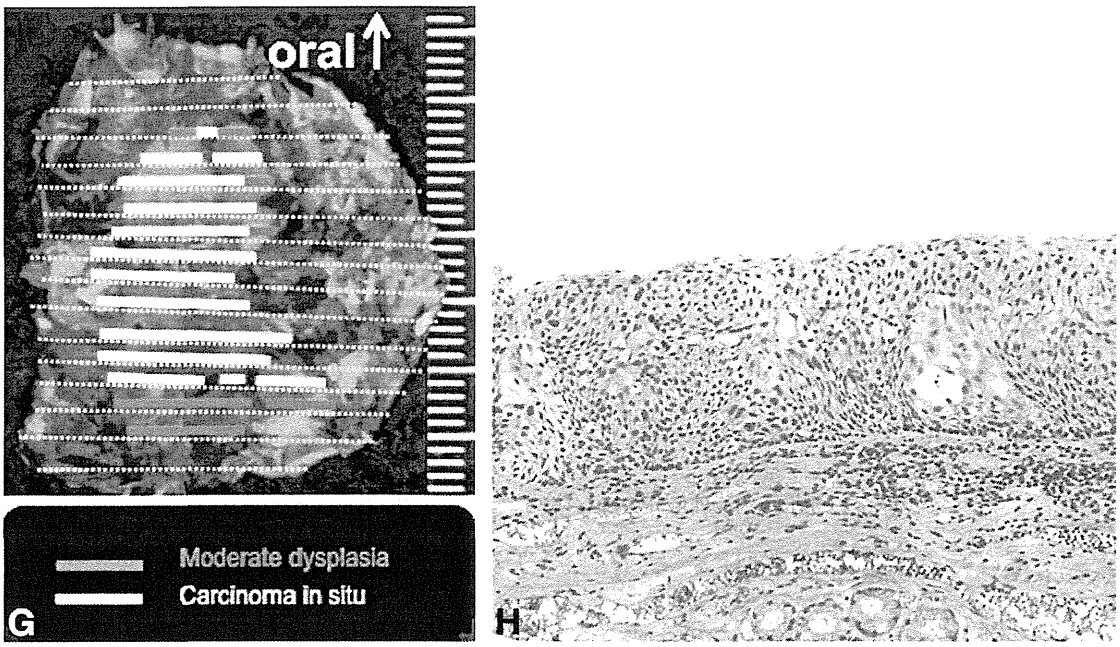

Figure 1. (*continued*)

years old (range 42-88 years). Of the 104 patients, 89 (86%) and 25 (24%), respectively, had esophageal cancer and/or head and neck cancer synchronously or previously. All of the cancers in the esophagus and the head and neck region were primarily treated with methods such as endoscopic resection, (chemo)radiotherapy, and surgery with curative intent. Most of the patients were identified as having cancer by follow-up examination for esophageal cancer or head and neck cancer. Of the 104 patients, 6 initially had unknown primary lymph node metastasis. Among them, the superficial lesion in the pharynx was finally found after radical dissection of the lymph node, and it was then treated by TOPER as a minimally invasive treatment.

Among the 104 patients, EMR-C method was indicated for 85 cases and the remaining 19 cases were indicated for ESD method. The selection was depended on the skill of the investigator. Before March 2006, all procedures of TOPER were performed by EMR-C method. After that, we turned to the treatment used by the ESD method for TOPER.

Lesion characteristics are shown in Table 2. Multifocal superficial cancer was found in 26 patients (25%). Nine lesions (6%) were finally diagnosed as severe dysplasia. Ninety-seven lesions (66%) were histologically confirmed to be carcinoma in situ, and the remaining 42 lesions (28%) showed slight invasion beneath the epithelium. The piriform sinus was the most frequent primary region (71%, 105/148).

The overall complication rate was 4.8% (5/104). Although subcutaneous emphysema developed in 2 patients immediately after the procedure, they improved with conservative medical management within 1 week. Aspiration pneumonia developed after 1 patient started eating. This patient improved after intravenous administration of antibiotics. Delayed bleeding developed the day after resection in 2 patients. These patients were treated with endoscopic hemostasis. Temporary tracheostomy was indicated for 17 patients because their larynx was swollen and they were considered at risk of airway obstruction after extubation. All of the tracheostomies were closed within 2 weeks. No procedure-related deaths occurred.

The median fasting period after TOPER was 2 days (range 1-20 days). The median hospital stay after TOPER was 8 days (range 3-58 days).

The median follow-up period was 43 months (range 3-96 months). The overall survival rates at 3 and 5 years were 84% (95% CI, 77-92) and 71% (95% CI, 59-82), respectively (Fig. 1). Cause-specific survival rates at 3 and 5 years were 99% (95% CI, 97-100) and 97% (95% CI, 93-100), respectively (Fig. 2). Cumulative development of multiple cancers in the pharyngeal mucosal site at 3 and 5 years were 20% (95% CI, 10-29) and 22% (95% CI, 12-33), respectively (Fig. 3).

Patterns of recurrence and the clinical course are summarized in Figure 4. Of 104 patients, 96 (92%) had no recurrence in either the primary site or lymph node or distant metastasis. Although local recurrence developed in 6 patients at the primary site, 5 of them were cured by repeat TOPER. Although the remaining patient died of the disease, this patient had a history of surgical resection of large oropharyngeal cancer 3 months earlier. We then considered the cause of death of this patient as previous

TABLE 1. Patient characteristics (N = 104)

Sex, no.	
Male	101
Female	3
Age, y (range)	63 (42-88)
History of EC, no.	89
Treatment for EC, no.	
EMR including endoscopic treatment	39
CRT/RT	37
Surgery	13
History of HNC, no.	25
Treatment for HNC, no.	
RT	4
Surgery	21
Initial reason for detection, no.	
Discomfort of pharynx	6
Pretreatment detailed examination for EC	12
Follow-up after surgery for EC	10
Follow-up after CRT/RT for EC	27
Follow-up after EMR for EC	16
Follow-up after surgery for HNC	21
Follow-up after RT for HNC	4
Unknown primary lymph node metastasis	6
Screening for upper GI endoscopy	2
Method	
EMR-C	85
ESD	19

EC, Esophageal cancer; *CRT*, chemo/radiotherapy; *RT*, radiotherapy; *HNC*, head and neck cancer; *EMR-C*, EMR with a cap; *ESD*, endoscopic submucosal dissection.

TABLE 2. Lesion characteristics (N = 148)

No. (%) of lesions per patient	
1	78 (75)
2	16 (15.4)
>3	10 (9.6)
Location of the lesions, no. (%)	
Oropharynx	20 (13.5)
Soft palate	1 (0.7)
Uvula	2 (1.4)
Posterior wall	10 (6.3)
Lateral wall	5 (3.4)
Vallecula	2 (1.4)
Hypopharynx	128 (86.5)
Left pyriform sinus	50 (33.8)
Right pyriform sinus	56 (37.8)
Postcricoid area	9 (6.1)
Posterior wall	13 (8.8)
Histological depth of the lesions, no. (%)	
Severe dysplasia	9 (6.1)
Carcinoma in situ	97 (65.5)
Carcinoma with subepithelial invasion	42 (28.3)

oropharyngeal cancer. There was no difference in the local recurrence rate between EMR-C and ESD methods. Although lymph node metastasis in the neck developed in 2 patients, their superficial cancers were initially found during surveillance of the primary site of a lymph node metastasis of an unknown primary tumor. Thus, the possibility that the lymph node metastasis already existed before TOPER could not be excluded. Ninety patients (86.5%) had survived without disease at the time of this analysis. Although it was difficult to determine the direct cause of death in those who died, 10 patients were considered to have died of previous head and neck cancer or esophageal cancer rather than superficial pharyngeal cancer because the previous cancers were far advanced. Four patients died of other diseases.

DISCUSSION

This study demonstrates that peroral organ-preserving endoscopic resection for superficial pharyngeal cancer is a feasible treatment option with no severe adverse events and an extremely good prognosis. To our knowledge, this is the largest series of the patients to show the long-term effectiveness of endoscopic resection for superficial pharyngeal cancer. A recent report by Suzuki et al[15] with 37 superficial pharyngeal cancers in 31 patients also showed the safety and effectiveness of endoscopic resection for these lesions. Until now, many patients with pharyngeal cancer were diagnosed at an advanced stage and thus required invasive surgery including the resection of the pharynx and larynx, resulting in speech defects and swallowing disorders, a major challenge from the aspect of the patients' quality of life. Our results demonstrating a new strategy of early detection and a minimally-invasive treatment for pharyngeal cancer are expected to be of great significance to these patients.

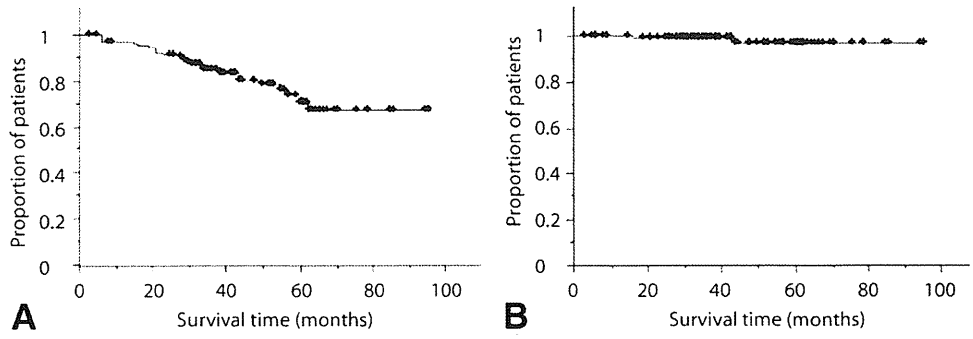

Figure 2. Overall survival (**A**) and cause-specific survival (**B**) after TOPER for superficial pharyngeal cancer.

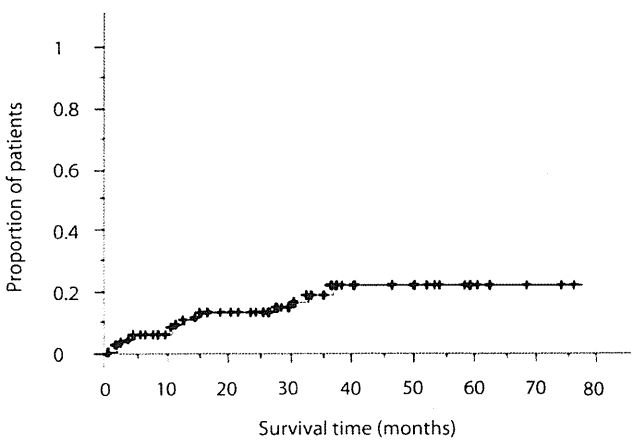

Figure 3. Metachronous development of superficial pharyngeal cancer after TOPER.

In the field of GI tract diseases, advances in the technology of endoscopic diagnosis have accelerated the detection of early cancer, leading to improvements in the technology of minimally-invasive endoscopic treatment such as EMR and ESD.[14-16] Thus, EMR and ESD are now widely accepted as standard treatments for early cancer in the GI tract. In contrast, in the region of the oropharynx and hypopharynx, a reflection occurs at the time of endoscope insertion, causing pain and discomfort for patients. Therefore, this area has not been fully examined by routine endoscopic examination, even in the field of GI endoscopy. Furthermore, the resolution of the otolaryngeal endoscope was insufficient to identify a subtle change in the structure of the mucosal surface and microvasculature, which are important characteristics of superficial pharyngeal cancer. Thus, it has been almost impossible to detect early cancer in this region.

However, we previously reported that NBI combined with a magnifying endoscope enables early detection of pharyngeal cancer.[4-6] Although this was a breakthrough in the diagnosis of cancer in the pharyngeal region, the treatment of superficial cancer has become a major issue because the standard treatment for pharyngeal cancer is surgery or chemoradiotherapy, which appears to be overtreatment for these superficial cancers. Similar to the case for early cancer in the GI tract, endoscopic resection is the optimal treatment for superficial pharyngeal cancer because it is minimally invasive and curative. However, endoscopic resection for these lesions is not established as the first choice of treatment because it is not clear whether this treatment is feasible or improves the prognosis. Our results suggest that endoscopic resection could be the first choice of treatment for superficial pharyngeal cancer.

In carcinoma in situ, there is theoretically no risk of lymph node metastasis, but in pharyngeal cancers with subepithelial invasion, there is a risk of lymph node metastasis. However, we could not estimate the risk because we saw no cases of superficial cancer before NBI was developed. In our current analysis, lymph node metastases developed in 2 patients after TOPER. However, these patients had lymph node metastasis from an unknown primary tumor before endoscopic resection. Thus, the possibility could not be excluded that the lymph node metastasis existed before TOPER was recommended for them. Except for these patients with unknown primary lymph node metastasis, no lymph node metastasis developed in any patient in our series after TOPER. This result indicates that the risk of lymph node metastasis is quite low and thus prophylactic irradiation for cancers with subepithelial invasion appears unnecessary at this time, considering its disadvantages, including salivary disorders and mucosal inflammation.

In this study, multiple metachronous cancers at a pharyngeal mucosal site (22% at 5 years) developed in many patients. Suzuki et al[13] reported that metachronous superficial pharyngeal cancer developed in 16% (5/31) of the patients. This possibly results from the "field cancerization" phenomenon.[17] All patients included in this study were screened for the presence of multiple cancers by iodine staining of the entire pharynx when they underwent TOPER under general anesthesia. The fact that metachronous cancer frequently develops despite this screening suggests that the mucosa itself in this area has a high potential for cancer development. Therefore, close surveillance may be required after less invasive therapy that

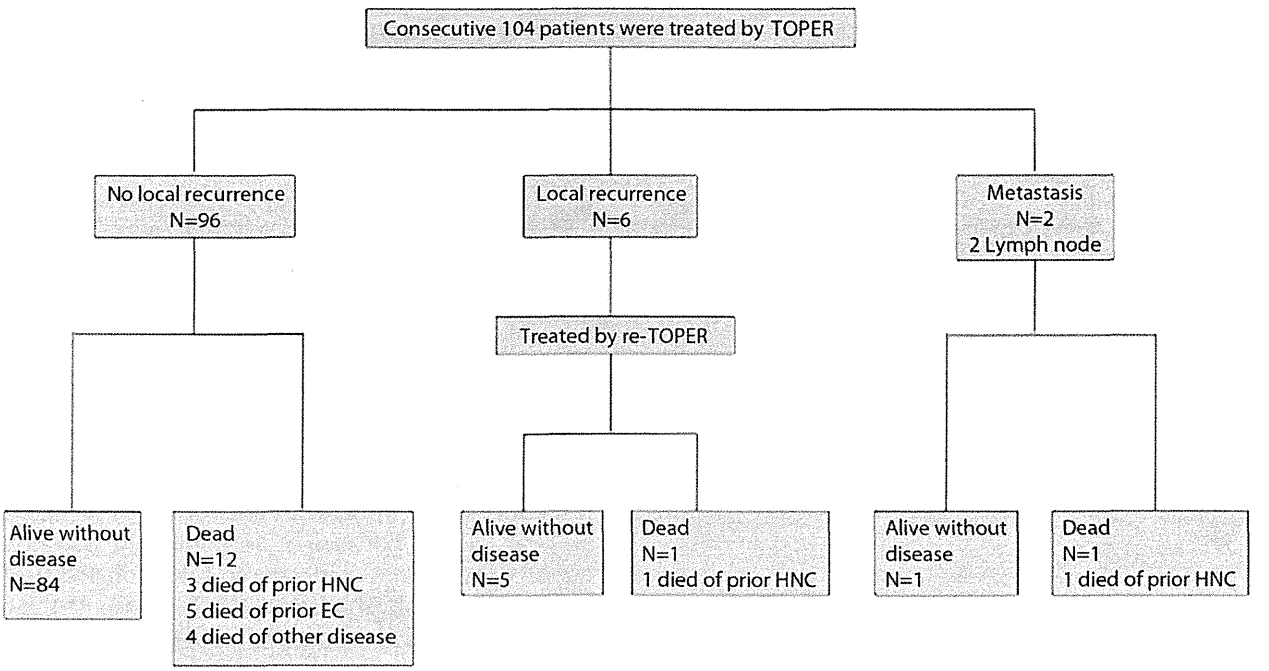

Figure 4. Clinical outcomes after TOPER for superficial pharyngeal cancer.

preserves the mucosa. Alternatively, if an effective prophylaxis were discovered, development of metachronous multiple cancers could be inhibited.

According to the TNM (tumor-node-metastasis) classification[18] of pharyngeal cancer, the depth of tumor is unrelated to the staging, and the T number increases as the tumor size increases in cases of widespread superficial cancer. However, there is no risk of metastasis in intraepithelial cancer compared with invasive cancer of the same size, and, theoretically, the rate of lymph node metastasis is anticipated to be low, even in the case of microinvasive cancer. Thus, as many more superficial cancers are detected, a discrepancy becomes apparent between the current TNM classification system and actual clinical practice. In the future, the relationship between the depth of superficial cancer in the head and neck and the risk of lymph node metastasis, as well as its prognosis after endoscopic therapy, needs to be determined.

Generally, the survival of patients with multiple cancers is reported to be poor.[19] However, the overall and cause-specific survival of the patients in this study could be regarded as acceptable because 93% (97/104) of the patients had a history of esophageal cancer or head and neck cancer and then would have poor prognosis. This result in part means that if the primary treatment succeeds with its curative intent, a second primary cancer should be detected at an earlier stage to obtain better survival. To date, there is no guideline for the optimal surveillance interval and the indication of TOPER. In addition, we have to determine the effective surveillance schedule and the limitations and indications for the TOPER method.

In conclusion, TOPER for superficial pharyngeal cancer is a feasible and effective treatment with curative intent. The strategies of evaluation of definitive risk (alcohol and smoking), identifying the superficial cancer by image-enhanced endoscopy, and minimally-invasive treatment by TOPER can provide a chance of organ preservation and survival for pharyngeal cancer patients.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics 2002. CA Cancer J Clin 2005;55:74-108.
2. Beatrice S, Kunt S, Robert B, et al. A review of human carcinogens-part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol 2009;10:1033-4.
3. Kaltenbach T, Sano Y, Friedland S, et al. American Gastroenterological Association (AGA) Institute technology assessment on image-enhanced endoscopy. Gastroenterology 2009;134:327-40.
4. Muto M, Katada C, Sano Y, et al. Narrowband imaging: A new diagnostic approach to visualize angiogenesis in the superficial neoplasm. Clin Gastroenterol Hepatol 2005;3:S16-20.
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. Muto M, Minashi K, Yano T, et al. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. J Clin Oncol 2010;28:1566-72.
7. Shimizu Y, Yamamoto J, Kato M, et al. Endoscopic submucosal dissection for treatment of early stage hypopharyngeal carcinoma. Gastrointest Endosc 2006;64:255-9.
8. Iizuka T, Kikuchi D, Hoteya S, et al. Endoscopic submucosal dissection for treatment of mesopharyngeal and hypopharyngeal carcinomas. Endoscopy 2009;41:113-7.

9. World Health Organization Classification of tumors. Pathology and genetics, head and neck tumors. Barnes D, Eveson JW, Reichart P, et al, editors. Lyon (France): IARC Press; 2005. p. 118-21.
10. Japanese classification of esophageal cancer, 10th ed. Tokyo (Japan): Kenehara, 2008.
11. Inoue H, Endo M. A new simplified technique of endoscopic esophageal mucosal resection using a cap-fitted panendoscope. Surg Endosc 1992;6:264-5.
12. Fujishiro M, Yahagi N, Kakushima N, et al. Endoscopic submucosal dissection of esophageal squamous cell neoplasms. Clin Gastroenterol Hepatol 2006;4:688-94.
13. Suzuki H, Saito Y, Oda I, et al. Feasibility of endoscopic mucosal resection for superficial pharyngeal cancer: a minimally invasive treatment. Endoscopy 2010;42:1-7.
14. Makuuchi H. Endoscopic mucosal resection for early esophageal cancer: indication and techniques. Dig Endosc 1996;8:175-9.
15. Ono H, Kondo H, Gotoda T, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001;48:225-9.
16. Saito Y, Fukuzawa M, Matsuda T, et al. Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. Surg Endosc 2010;24:343-52.
17. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium: clinical implications of multicentric origin. Cancer 1953;6:963-8.
18. TNM classification of malignant tumors (UICC), 7th ed. Sobin LH, Gaspodarwicz MK, Wittekind C, editors. Hoboken (NJ): Wiley-Blackwell, 2009.
19. Erkal HS, Mendenhall WM, Amdur RJ, et al. Synchronous and metachronous squamous cell carcinomas of the head and neck mucosal sites. J Clin Oncol 2001;19:1358-62.

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Early Detection of Superficial Squamous Cell Carcinoma in the Head and Neck Region and Esophagus by Narrow Band Imaging: A Multicenter Randomized Controlled Trial

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ABSTRACT

Purpose
Most of the esophageal squamous cell carcinomas (ESCCs) and cancers of the head and neck (H&N) region are diagnosed at later stages. To achieve better survival, early detection is necessary. We compared the real-time diagnostic yield of superficial cancer in these regions between conventional white light imaging (WLI) and narrow band imaging (NBI) in high-risk patients.

Patients and Methods
In a multicenter, prospective, randomized controlled trial, 320 patients with ESCC were randomly assigned to primary WLI followed by NBI (n = 162) or primary NBI followed by WLI (n = 158) in a back-to-back fashion. The primary aim was to compare the real-time detection rates of superficial cancer in the H&N region and the esophagus between WLI and NBI. The secondary aim was to evaluate the diagnostic accuracy of these techniques.

Results
NBI detected superficial cancer more frequently than did WLI in both the H&N region and the esophagus (100% *v* 8%, $P < .001$; 97% *v* 55%, $P < .001$, respectively). The sensitivity of NBI for diagnosis of superficial cancer was 100% and 97.2% in the H&N region and the esophagus, respectively. The accuracy of NBI for diagnosis of superficial cancer was 86.7% and 88.9% in these regions, respectively. The sensitivity and accuracy were significantly higher using NBI than WLI in both regions ($P < .001$ and $P = .02$ for the H&N region; $P < .001$ for both measures for the esophagus, respectively).

Conclusion
NBI could be the standard examination for the early detection of superficial cancer in the H&N region and the esophagus.

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INTRODUCTION

Esophageal cancer is the eighth most common cancer worldwide, accounting for 462,000 new cases in 2002, and is the sixth most common cause of cancer-related death (386,000 deaths).[1] Squamous cell carcinoma (SCC) is the most common histologic type worldwide.[1] Head and neck (H&N) cancer accounted for 607,000 new cases and 261,000 deaths in 2002.[1] The most common histologic type of H&N cancer is also SCC.

The early detection of cancer offers the best prognosis. Currently, however, esophageal SCC (ESCC) and H&N SCC (HNSCC) are detected at a late stage and then have poor prognoses.[1] Early detection of these cancers is difficult by conventional endoscopic white light imaging (WLI). Lugol chromoendoscopy can be used to detect superficial ESCC, but it causes unpleasant adverse effects such as severe chest pain and chest discomfort,[2-4] and it cannot be used for HNSCC screening because of the risk of aspiration.

The narrow band imaging (NBI) system is an innovative optical image-enhanced technology that uses narrow bandwidth NBI filters.[5,6] The central wavelengths of the NBI filters are 415 and 540 nm and each has a bandwidth of 30 nm. This system is easily activated by pushing a button on the endoscope. NBI combined with magnifying endoscopy can clearly visualize the microvascular structure of the organ surface,[6,7] because the 415-nm light is well absorbed by hemoglobin. Surface microvascular irregularities provide useful landmarks for identifying an early neoplasm in the H&N region, bronchus,

and the GI tract.[7-15] We previously reported that NBI was useful for identifying HNSCC at an early stage.[8] Watanabe et al[16,17] also reported the usefulness of NBI rhinolaryngovideoscopy for the diagnosis of HNSCC. Yoshida et al[18] reported that NBI improves the accuracy of magnifying WLI in the assessment of ESCC.

However, the diagnostic yield of NBI in the early detection of superficial SCC has not been investigated. We conducted a prospective randomized study to directly compare WLI and NBI in the early diagnosis of SCC in the H&N region and the esophagus among high-risk patients.

PATIENTS AND METHODS

Study Rationale

Because ESCC patients frequently develop multiple intraesophageal SCC and second primary HNSCC synchronously and metachronously,[4,19-22] they provide a good cancer screening model. Whereas massively invasive SCC is easy to detect by endoscope, superficial cancer has been difficult. Furthermore, detection of high-grade intraepithelial neoplasia (HGIN) is clinically important because HGINs have the potential to become malignant invasive cancers.[23,24] Therefore, in this study, we targeted only macroscopic superficial cancer including HGIN that appeared as slightly elevated lesions lower than 5 mm, flat lesions, and lesions with a shallow depression. Lesions with an apparent elevation greater than 5 mm or those with apparent deeper ulceration were not evaluated.

The primary analysis of this study was a comparison of the detection rates of superficial cancer (HGIN, carcinoma in situ, and microinvasive SCC) using WLI and NBI. The secondary analysis was a comparison of the diagnostic accuracy (sensitivity and specificity) of the two imaging methods, size of the lesion detected, and the examination time. To evaluate diagnostic accuracy, we used the histologic diagnosis from a biopsy specimen as the gold standard diagnosis.

Study Populations

The protocol and consent form for this study were approved by the institutional review board at each participating institution, and written informed consent was obtained from all patients. The inclusion criteria were histologically confirmed present or previous ESCC and an age of 20 years or older. Although this study included patients with advanced ESCC, we evaluated only concomitant superficial cancer but not primary advanced cancer. Patients who had been previously treated for ESCC by endoscopic mucosal resection were included, because their esophagus was preserved with minimal damage. Patients with prior chemotherapy, radiotherapy, chemoradiotherapy, or surgical resection for ESCC or HNSCC were excluded, because their esophagus or pharynx was removed or too damaged to evaluate. Patients referred from another hospital with newly diagnosed ESCC were also included because they required more detailed examination (Fig 1) . The endoscopists were blinded to the endoscopic information. Patients with esophageal stricture, esophageal varices, or allergy to lugol dye solution were excluded.

Study Design

Patients were randomly assigned to receive primary WLI or primary NBI. To investigate whether a lesion detected by primary imaging could be identified subsequently by the other type of imaging, or whether a lesion missed by primary imaging could be identified subsequently by the other type of imaging, we performed both imaging methods in a back-to-back fashion so that primary WLI was followed by NBI and primary NBI was followed by WLI. To avoid affecting the first imaging results, the report of the first examination was completed before the second imaging was started.

To improve the quality of the reporting in the diagnostic accuracy study, we complied with the Standards for Reporting of Diagnostic Accuracy (STARD) initiative.[25] We set WLI as reference standard and NBI as index test.

Random assignment was performed in each case by an investigator using a computer-aided system on Medical Research Support Web site (Kyoto, Japan). This Web site was available only to the study participants. Using a minimization algorithm, the selection of the primary examination was balanced with respect to five stratification variables: institution, age (< 60 and ≥ 60 years), sex, alcohol consumption, and smoking habit.

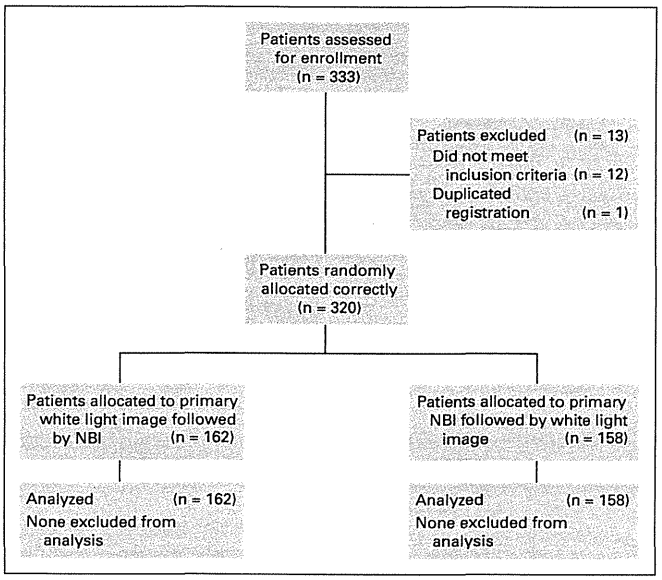

Fig 1. CONSORT diagram; overview of the study design. NBI, narrow band imaging.

Calculation of the Sample Size

For the purposes of this study, we set the probability for error (α) to .05 with a power of 0.80 (reflecting a β error of .2). Because there are no published comparative studies of NBI in ESCC patients, we estimated that the NBI system would increase the detection yield for superficial cancer by at least threefold compared with conventional WLI. This resulted in a calculated sample size of 250 patients (125 per group). Finally, we recruited an additional 50 patients in anticipation of instances of ineligibility or withdrawal during the examination because of discomfort (25 per group).

Endoscopic Examination

We used the same magnifying endoscope, with the capability for 80 times optical magnification (GIF-Q240Z, Olympus Medical Systems, Tokyo, Japan) for both WLI and NBI. The two imaging methods can be performed in a same video-endoscopy system (EVIS LUCERA system, Olympus Medical Systems, Tokyo, Japan). The details of the NBI system have been published elsewhere.[1,2,26,27] To maintain the quality of the endoscopic images, we used the same liquid-crystal color display for both imaging methods. Before the study started, all the participating endoscopists were trained using a central review of demonstrable NBI images of superficial squamous lesions (13 neoplasias and seven non-neoplastic lesions).

All endoscopic observations were made according to the protocol. During the first imaging, all parts of the oropharynx and hypopharynx were evaluated. The nasopharynx was not included the examination. After the first imaging was completed, an assistant physician immediately recorded the results on the case record form (CRF). After completion of the first imaging CRF, the second imaging of the oropharynx and hypopharynx was performed and the results were recorded on the CRF.

Next, all parts of the esophagus were evaluated using the same imaging as used for the H&N region. The endoscope was inserted to gain a view from the cervical esophagus to the esophagogastric junction, and the results were recorded on the CRF. The second imaging was performed on withdrawal of the endoscope, and the results were recorded on the CRF. During the procedure, we measured the examination time from start to finish of each imaging at each site. These procedure times included the evaluation of the lesion but not the biopsy procedure. The findings obtained by lugol chromoendoscopy are not included in this study.

Endoscopic Evaluation of Superficial Cancers

In this study, the real-time on-site diagnosis was evaluated because making an accurate diagnosis during an examination is clinically more important than a retrospective evaluation using a stored database. On WLI, if the lesion showed both a reddish color with uneven surface and disappearance of the vascular network pattern (Fig 2A), we diagnosed it as endoscopically suspected "superficial cancer." On NBI, if the lesion exhibited a well-demarcated brownish area as well as irregular microvascular patterns (Fig 2B), we diagnosed it as endoscopically suspected "superficial cancer." Details of these findings have been described previously.[7,8] If the lesion did not show these characteristics, the lesion was diagnosed as "non-cancer." Mucosal abnormalities were recorded with regard to endoscopic diagnosis, location, and size of the lesion.

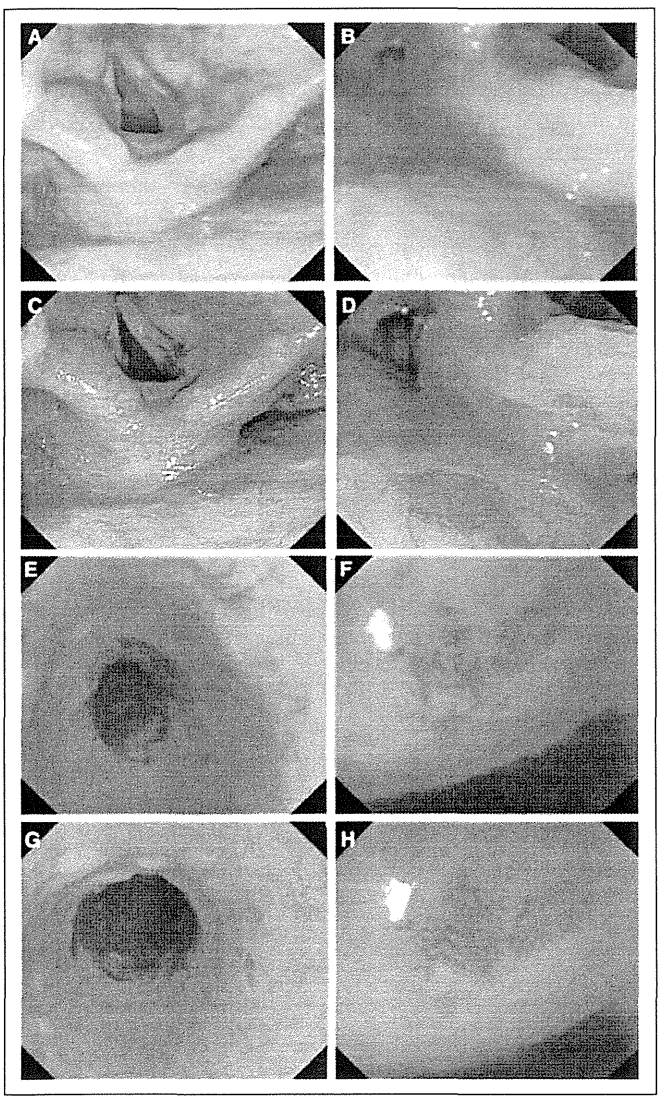

Fig 2. Superficial cancer in the head and neck region and esophagus. (A) White light imaging (WLI) shows a small reddish area (arrows) in the posterior wall of the hypopharynx. (B) Magnifying WLI shows a slightly reddish area with tiny microdots. (C) Narrow band imaging (NBI) shows a well-demarcated brownish area (arrows) in the posterior wall of the hypopharynx. (D) Magnifying NBI shows many tiny dots in the brownish area. This lesion was diagnosed histologically as squamous cell carcinoma in situ. (E) WLI shows a slightly reddish and depressed lesion (arrows) in the esophagus, although it is difficult to detect by WLI alone. (F) Magnifying WLI shows a slightly reddish area with an irregular microvascular pattern. (G) NBI shows a well-demarcated brownish area (arrows). (H) Magnifying NBI shows many tiny dots in the brownish area. This lesion was diagnosed histologically as high-grade intraepithelial cancer.

Pathologic Evaluation

Biopsy specimens were taken from each lesion after the completion of both types of imaging. Histologic evaluation was performed by central review by four experienced pathologists (H.S., A.O., T.S., and H.W.) who were blinded to the recorded endoscopic assessment. Histologic diagnoses were made according to WHO criteria[23] and were classified into two groups. One group included superficial cancers and the other group included non-cancers such as parakeratosis and inflammation. Microinvasion was estimated by the subepithelial invasion. The final pathologic diagnosis was made by the agreement of three of the four pathologists.

Statistical Analysis

The absolute and relative frequencies for qualitative variables were calculated for each group. Statistical analysis was performed using SPSS version

Table 1. Characteristics of Patients

Characteristic	Primary WLI (n = 162) No.	%	Primary NBI (n = 158) No.	%	P
Age, years					
Median	64		64		
Range	39-84		46-84		.99
Male sex	143	88	141	89	.86
Alcohol habit					
Drinking duration, years	157	97	148	94	.19
Median	41		40		.17
Range	10-63		5-60		
Favorite beverage					
Beer	61	38	59	37	1.00
Shochu	66	41	55	35	.30
Sake	43	27	48	30	.71
Whisky	22	14	24	15	.75
Wine	8	5	7	4	1.00
Others	1	0.6	0	0	1.00
Hot flashes					
Formerly had hot flashes	117	72	109	69	.62
Currently has hot flashes	75	46	70	44	.91
Smoking habit					
No. of smokers	145	90	142	90	1.00
Smoking duration, years					
Median	37		40		
Range	1-61		5-61		.41
No. of packs per day					
Median	1		1		
Range	0.05-4		0.125-4		.64
No. of packs per year					
Median	41		42		
Range	0.5-180		1.3-160		.89
Esophageal cancer					
No. of patients newly diagnosed	110	68	115	73	.39
Previously treated EMR	52	32	43	27	.39
Duration from previous EMR, years					
> 1	17	10	20	13	.60
1	45	28	33	21	.16
Depth of invasion					
Tis-T1a	74	46	67	42	.57
T1b	25	15	20	13	.27
T2	12	7	22	14	.07
T3	49	30	46	29	.90
T4	2	1	3	2	.68

Abbreviations: WLI, white light imaging; NBI, narrow band imaging; EMR, endoscopic mucosal resection.

17 software (SPSS, Chicago, IL). The continuous variables are expressed as medians and ranges. Continuous data were compared using the Mann-Whitney U test. Pearson's χ^2 test or Fisher's exact test was used to analyze categoric data to compare proportions. All P values were two-tailed, and a P value of $< .05$ was considered significant.

RESULTS

Between March 2005 and December 2005, 333 patients were enrolled onto this study (Fig 1). Twelve patients did not meet the inclusion criteria, and one was registered twice, so the remaining 320 patients were randomly assigned correctly into two groups: (1) 162 patients who underwent primary WLI followed by NBI, and (2) 158 patients who were examined by primary NBI followed by WLI.

The characteristics of the two groups are listed in Table 1. The two groups did not differ significantly in age, sex, alcohol consumption, smoking habits, or history of esophageal cancer treatment. In both groups, approximately 70% of the patients had newly diagnosed ESCC. Sixty-three (39%) patients in the primary WLI group and 71 (45%) patients in the primary NBI group had advanced ESCC deeper than the submucosal layer.

Table 2 provides the distribution of histologically confirmed superficial cancers. The total numbers of superficial cancer in the H&N region and the esophagus were 28 and 212, respectively. Total numbers of histologically confirmed non-cancer were 36 and 38 in each region. In all patients, superficial cancers were detected in 8% (26 of 320) in the H&N region and in 38% (121 of 320) in the esophagus. Multiple cancers were found in 0.6% of the patients in the H&N region and in 12% in the esophagus. The number of patients with superficial cancer, total number of superficial cancers, and their sizes and distribution did not differ between the two groups.

The diagnostic yields for superficial cancer using primary WLI and primary NBI detection are summarized in Table 3. The total numbers of superficial cancers detected by primary imaging differed between the two groups. In the H&N region, primary NBI detected all (100%; 15 of 15) of the superficial cancers, but primary WLI detected only one lesion (8%; 1 of 13). In the esophagus, only 58 (55%) lesions were detected by primary WLI, whereas 104 (97%) lesions were detected by primary NBI. All these differences were statistically significant ($P < .001$). The detection rate was significantly higher with primary NBI than with primary WLI, even for small lesions (< 10 mm in diameter) in both the H&N region ($P < .001$) and the esophagus ($P = .03$).

In the back-to-back analysis, secondary NBI after primary WLI significantly increased the detection rate in both the H&N region (8% *v* 77%; $P < .001$) and esophagus (55% *v* 95%; $P < .001$; Appendix Table A1, online only). In contrast, secondary WLI after NBI significantly decreased the detection rate (Appendix Table A1). Moreover, 16 (57%) superficial cancers in the H&N region and 48 (23%) superficial cancers in the esophagus were detected only by NBI (Appendix Table A2, online only). In contrast, no lesion was detected only

Table 2. Distribution of Histologically Confirmed Superficial Cancer According to Lesion in the Head and Neck Region and the Esophagus

Variable	Primary WLI (n = 162)			Primary NBI (n = 158)			P
	No.	%	95% CI	No.	%	95% CI	
Head and neck region							
No. of patients	12	7	3.3 to 11.4	14	9	4.4 to 13.3	.66
No. of lesions per patient							
1	12	7	3.3 to 11.4	14	9	4.4 to 13.3	> .999
≥ 2	1	0.6	−0.6 to 1.8	1	0.6	−0.5 to 1.9	
Total No. of superficial neoplasias	13			15			
Size threshold, mm							
< 10	7			10			.50
11-20	5			5			
≥ 21	1			0			
Histologic diagnosis							
High-grade intraepithelial neoplasia or carcinoma in situ	10			15			.09
Microinvasive cancer	3			0			
Esophagus							
No. of patients	58	36	28.4 to 43.2	63	40	32.2 to 47.6	.49
No. of lesions per patient							
1	39	24	17.4 to 30.7	43	27	20.3 to 34.2	> .999
≥ 2	19	12	6.7 to 16.7	20	13	7.4 to 17.9	
Total No. of superficial cancers	105			107			
Size threshold, mm							
< 10	18			18			.91
11-20	21			19			
≥ 21	66			70			
Histologic diagnosis							
High-grade intraepithelial neoplasia or carcinoma in situ	73			84			.16
Microinvasive cancer	32			23			

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

Table 3. Diagnostic Yield of Primary WLI and Primary NBI for Detection of Superficial Cancer in the Head and Neck Region and the Esophagus

Variable	Primary WLI (n = 162)			Primary NBI (n = 158)			P
	No.	%	95% CI	No.	%	95% CI	
Head and neck region							
No. of superficial cancers	1/13	8	0.2 to 36.0	15/15	100	78.2 to 100	< .001
Size of superficial cancer, mm							
< 10	0/7	0	0 to 41.0	10/10	100	69.2 to 100	< .001
11-20	1/5	20	0.5 to 71.6	5/5	100	48.7 to 100	.12
≥ 21	0/1	0	0.0 to 0.0	to			—
Esophagus							
No. of superficial cancers	58/105	55	45.2 to 65.0	104/107	97	92.0 to 99.4	< .001
Size of superficial cancer, mm							
< 10	7/18	39	17.3 to 64.3	17/18	94	72.7 to 99.9	.03
11-20	7/21	33	14.6 to 57.0	18/19	95	74.0 to 99.9	.02
≥ 21	44/66	67	54.0 to 77.8	69/70	99	92.3 to 100	< .005

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

by WLI, except one lesion of > 20 mm in the esophagus. No lesions were undetected by both WLI and NBI in either region.

Table 4 summarizes the diagnostic performance of primary WLI and primary NBI for detecting superficial cancer. The sensitivity of primary NBI was significantly higher than that of primary WLI in both the H&N region (100% *v* 7.7%; $P < .001$) and the esophagus (97.2% *v* 55.2%; $P < .001$). Accuracy was also significantly higher for primary NBI than for primary WLI in both regions (85.7% *v* 62.9%, $P = .02$ and 88.9% *v* 56.5%, $P < .001$, respectively). Specificity was not significantly different in the two regions ($P = .28$ and $P = .33$, respectively). The positive predictive value did not differ between the two imaging techniques, but the negative predictive value was significantly higher for primary NBI than for primary WLI in both the H&N region ($P = .02$) and the esophagus ($P < .002$).

The median procedure times of primary WLI and primary NBI for the H&N region were 120 seconds (range, 34 to 275 seconds) and 162 seconds (range, 30 to 525 seconds), respectively. Those for the esophagus were 95 seconds (range, 30 to 360 seconds) and 135 seconds (range, 30 to 616 seconds), respectively. These differences were statistically significant ($P < .001$). The procedure times in the secondary imaging in the back-to-back experiments also differed significantly between WLI and NBI in both regions (Appendix Table A3, online only). There were no serious adverse events related to examination with either procedure. All patients tolerated both procedures well.

DISCUSSION

This study clearly demonstrates that NBI is a more sensitive method for detecting and diagnosing superficial SCC in the H&N region and the esophagus. According to the concept of "field cancerization,"[28] patients with ESCC or HNSCC are at high risk for the development of multiple SCCs. In the clinical context, the early detection strategy for superficial SCC is the same between patients at high risk and those at risk because of heavy drinking, smoking, or aldehyde dehydrogenase 2 deficiency.[20-35] In addition, detection technique should not only be sensitive but should also be easily applicable. From this perspective, NBI is easily applied with a modicum of experience and will have a rapid learning curve compared with WLI. Thus, NBI is the ideal method for effectively detecting superficial SCC.

Table 4. Diagnostic Performance of Primary WLI and Primary NBI Observation for Detection of Superficial Cancer in the Head and Neck Region and the Esophagus

Variable	Primary WLI			Primary NBI			P
	No.	%	95% CI	No.	%	95% CI	
Head and neck							
Sensitivity	1/13	7.7	0.2 to 36.0	15/15	100	100	< .001
Specificity	21/22	95.5	77.2 to 99.9	11/14	78.6	54.6 to 98.1	.28
Accuracy	22/35	62.9	47.6 to 76.4	26/29	86.7	72.6 to 97.8	.02
PPV	1/2	50	1.3 to 98.7	15/18	83.3	58.6 to 96.4	.37
NPV	21/33	63.6	54.1 to 79.6	11/11	100	100	.02
Esophagus							
Sensitivity	58/105	55.2	45.2 to 65.0	104/107	97.2	92.0 to 99.4	< .001
Specificity	12/19	63.2	38.4 to 83.7	8/19	42.1	20.3 to 66.5	.33
Accuracy	70/124	56.5	47.3 to 65.3	112/126	88.9	82.1 to 93.8	< .001
PPV	58/65	89.2	79.1 to 95.6	104/115	90.4	85.3 to 95.1	.80
NPV	12/59	20.3	11.0 to 32.8	8/11	72.8	39 to 94	< .002

Abbreviations: WLI, white light imaging; NBI, narrow band imaging; PPV, positive predictive value; NPV, negative predictive value.

Detecting cancer at an early stage is an optimal strategy for preventing the development of advanced cancer and improving survival. Furthermore, early detection uses a minimally invasive treatment (eg, endoscopic resection) with curative intent.[8,36-38] In fact, in our study, 75% (21 of 28) of the superficial HNSCCs were completely removed by endoscopic resection or biopsy alone, while early detection of HNSCC had been quite difficult. These results provide us with new diagnostic and treatment strategies for ESCC patients, because the risk of development of HNSCC after esophagectomy is quite high.[21]

As the criteria for diagnosing superficial SCC by NBI, we used two endoscopic findings: a well-demarcated brownish area and an irregular microvascular pattern.[7-9] Using only these two findings, the sensitivity of primary NBI for the diagnosis of superficial SCC was 100% in the H&N region and 97.2% in the esophagus. The diagnostic accuracy was nearly 90%. These results indicate that these NBI findings are quite useful for the accurate diagnosis of superficial SCC.

Lugol chromoendoscopy is useful for the detection of superficial ESCC.[2-3] However, the administration of lugol solution is time-consuming, and accurate diagnosis by lugol chromoendoscopy is difficult[4] because the staining pattern shows wide variations.[2] This increases the incidence of false-positive lesions and leads to unnecessary biopsies. In contrast, NBI is easily manipulated and shows high sensitivity. Thus, NBI could reduce the number of unnecessary biopsies and shorten examination time. Furthermore, lugol chromoendoscopy is more invasive than both WLI and NBI, and WLI is still the gold standard for cancer screening. Therefore, we did not compare the diagnostic yield of NBI and lugol chromoendoscopy, and we used WLI as the standard reference to compared the diagnostic yield of WLI and NBI.

NBI required a significantly longer examination time than WLI. This might be related to the high detection rate and more frequent time spent in magnification during NBI, because if the lesions were not seen by WLI, no magnification was performed. The actual time difference between NBI and WLI was only 20 to 42 seconds. This is clinically acceptable, because the important time issue is not that NBI takes slightly longer than WLI, but rather that endoscopists spend more time in the careful observation of high-risk patients.

In this study, ESCC patients referred from another hospital were included. Even if the biopsies were previously done, the earlier biopsy sites were healed by the time of this study and were not generally detectable by either imaging method. Therefore, we thought that it was not a confounding factor.

The same endoscopists performed both imaging procedures in this study, whereas the endoscopists ideally should be separated and blinded to each imaging procedure. However, it was clinically impossible to change and blind the endoscopists during this series of examinations. Furthermore, the result produced with NBI first followed by WLI might underestimate the benefit of NBI because NBI is more sensitive than WLI. However, the detection and diagnosis of superficial SCC by NBI was significantly better than that using WLI in both the H&N region and the esophagus, regardless of whether NBI was primary or secondary. These results indicate that NBI should be the standard examination.

Significant detection results seen in this study were all achieved without the newest generation high-definition endoscope. If we use the newest high-definition endoscope with NBI, the rates of detection might increase compared with those found in this study. Furthermore, the endoscopy system used in this study and in most Asian countries was different from those used in North America and Europe.[26,27] However, we previously reported that even the nonmagnifying laryngoscope based on same system as that used in North America and Europe could dramatically improve the visualization of both the brownish area and irregular microvascular patterns.[39] Therefore, we believe that differences in the system are no longer as important as careful observation by NBI.

In conclusion, NBI combined with magnifying endoscopy significantly improved the detection rates for SCC with quite high sensitivity, and this new image-enhanced technology can be applied easily in clinical practice. Furthermore, early detection facilitates the potential of minimally invasive treatment, such as endoscopic resection or partial surgical resection.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al: Global cancer statistics, 2002. CA Cancer J Clin 55:74-108, 2005
2. Mori M, Adachi Y, Matsushima T, et al: Lugol staining pattern and histology of esophageal lesions. Am J Gastroenterol 88:701-705, 1993
3. Inoue H, Rey JF, Lightdale C: Lugol chromoendoscopy for esophageal squamous cell cancer. Endoscopy 33:75-79, 2001
4. 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 56:517-521, 2002
5. Gono K, Yamazaki K, Doguchi N, et al: Endoscopic observation of tissue by narrow band illumination. Opt Rev 10:211-215, 2003
6. Gono K, Obi T, Yamaguchi M, et al: Appearance of enhanced tissue feature in narrow-band endoscopic imaging. J Biomed Opt 9:568-577, 2004
7. Muto M, Katada C, Sano Y, et al: Narrow band imaging: A new diagnostic approach to visualize angiogenesis in the superficial neoplasia. Clin Gastroenterol Hepatol 3:S16-S20, 2005 (suppl 1)
8. Muto M, Nakane M, Katada C, et al: Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites. Cancer 101:1375-1381, 2004
9. Muto M, Ugumori T, Sano Y, et al: Narrow-band imaging combined with magnified endoscopy for the cancer at the head and neck region. Dig Endoscopy 17:S23-S24, 2005

10. Shibuya K, Hoshino H, Chiyo M, et al: High magnification bronchovideoscopy combined with narrow band imaging could detect capillary loops of angiogenic squamous dysplasia in heavy smokers at high risk for lung cancer. Thorax 58:989-995, 2003

11. Hamamoto Y, Endo T, Nosho K, et al: Usefulness of narrow-band imaging endoscopy for diagnosis of Barrett's esophagus. J Gastroenterol 39:14-20, 2004

12. Sharma P, Bansal A, Mathur S, et al: The utility of a novel narrow band imaging endoscopy system in patients with Barrett's esophagus. Gastrointest Endosc 64:167-175, 2006

13. Nakayoshi T, Tajiri H, Matsuda K, et al: Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: Correlation of vascular pattern with histopathology. Endoscopy 36:1080-1084, 2004

14. Sumiyama K, Kaise M, Nakayoshi T, et al: Combined use of a magnifying endoscope with a narrow band imaging system and a multibending endoscope for en bloc EMR of early stage gastric cancer. Gastrointest Endosc 60:79-84, 2004

15. Machida H, Sano Y, Hamamoto Y, et al: Narrow-band imaging in the diagnosis of colorectal lesions: A pilot study. Endoscopy 36:1094-1098, 2004

16. Watanabe A, Tsujie H, Taniguchi M, et al: Laryngoscopic detection of pharyngeal carcinoma in situ with narrowband imaging. Laryngoscope 116: 650-654, 2006

17. Watanabe A, Taniguchi M, Tsujie H, et al: The value of narrow band imaging endoscope for early head and neck cancers. Otolaryngol Head Neck Surg 138:446-451, 2008

18. Yoshida T, Inoue H, Usui S, et al: Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. Gastrointest Endosc 59:288-295, 2004

19. Shimizu Y, Tukagoshi H, Fujita M, et al: Metachronous squamous cell carcinoma of the esophagus arising after endoscopic mucosal resection. Gastrointest Endosc 54:190-194, 2001

20. Shimizu Y, Tsukagoshi H, Fujita M, et al: Head and neck cancer arising after endoscopic mucosal resection for squamous cell carcinoma of the esophagus. Endoscopy 35:322-326, 2003

21. Matsubara T, Yamada K, Kakegawa A: Risk of second primary malignancy after esophagectomy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 21:4336-4341, 2003

22. Kumagai Y, Kawano T, Nakajima Y, et al: Multiple primary cancers associated with esophageal carcinoma. Surg Today 31:872-876, 2001

23. Tumors of the esophagus, in Hamilton R, Aaltonen LA, eds. WHO Classification of Tumors of the Digestive System. Lyon, France, IARC Press, 2000, pp 11-19

24. Schlemper RJ, Dawsey SM, Itabashi M, et al: Differences in diagnostic criteria for esophageal squamous cell carcinoma between Japanese and Western pathologists. Cancer 88:996-1006, 2000

25. Moher D, Schulz KF, Altman D: The CONSORT statement: Revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 285:1987-1991, 2001

26. Muto M, Horimatsu T, Ezoe Y, et al: Narrow-band imaging of the gastrointestinal tract. J Gastroenterol 44:13-25, 2009

27. Muto M, Horimastu T, Ezoe Y, et al: Improving visualization techniques by narrow band imaging and magnification endoscopy. J Gastroenterol Hepatol 24:1333-1346, 2009

28. Slaughter DP, Southwick HW, Smejkal W: Field cancerization in oral stratified squamous epithelium: Clinical implications of multicentric origin. Cancer 6:963-968, 1953

29. Bossuyt PM, Reitsma JB, Bruns DE, et al: Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD Initiative. Ann Intern Med 138:40-44, 2003

30. Franco EL, Kowalski LP, Kanda JL: Risk factors for second cancers of the upper respiratory and digestive systems: A case-control study. J Clin Epidemiol 44:615-625, 1991

31. Hsairi M, Luce D, Point D, et al: Risk factors for simultaneous carcinoma of the head and neck. Head Neck 11:426-430, 1989

32. Morita M, Kuwano H, Ohno S, et al: Multiple occurrence of carcinoma in the upper aerodigestive tract associated with esophageal cancer: Reference to smoking, drinking, and family history. Int J Cancer 58:207-210, 1994

33. Yokoyama A, Kato H, Yokoyama T, et al: Genetic polymorphisms of alcohol and aldehyde dehydrogenases and glutathione S-transferase M1 and drinking, smoking, and diet in Japanese men with esophageal squamous cell carcinoma. Carcinogenesis 23:1851-1859, 2002

34. Yokoyama A, Watanabe H, Fukuda H, et al: Multiple cancers associated with esophageal and oropharyngolaryngeal squamous cell carcinoma and the aldehyde dehydrogenase-2 genotype in male Japanese drinkers. Cancer Epidemiol Biomarkers Prev 11:895-900, 2002

35. Muto M, Takahashi M, Ohtsu A, et al: Risk of multiple squamous cell carcinomas both in the esophagus and the head and neck region. Carcinogenesis 26:1008-1012, 2005

36. Katada C, Muto M, Momma K, et al: Clinical outcome after endoscopic mucosal resection for esophageal squamous cell carcinoma invading the muscularis mucosae—a multicenter retrospective cohort study. Endoscopy 39:779-783, 2007

37. Katada C, Muto M, Manabe T, et al: Local recurrence of squamous-cell carcinoma of the esophagus after EMR. Gastrointest Endosc 61:219-225, 2005

38. Shimizu Y, Yamamoto J, Kato M, et al: Endoscopic submucosal dissection for treatment of early stage hypopharyngeal carcinoma. Gastrointest Endosc 64:255-259, 2006

39. Ugumori T, Muto M, Hayashi R, et al: Prospective study of early detection of pharyngeal superficial carcinoma with the narrowband imaging laryngoscope. Head Neck 31:189-194, 2009

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Appendix

Results

Among the 28 superficial head and neck squamous cell carcinomas (HNSCCs) detected, 16 lesions were treated with endoscopic resection, five lesions disappeared after only biopsy, and one lesion was treated with radiotherapy. The remaining six lesions were not treated, because the concomitant esophageal cancers had distant metastasis. Among 16 lesions removed by endoscopic resection, seven lesions were carcinoma in situ and the remaining nine lesions were microinvasive SCC. With a median follow-up of 33 months (range, 6 to 59 months), no patients developed lymph node metastasis from HNSCC.

Among the 212 superficial esophageal squamous cell carcinomas, those with accompanying advanced cancers and those with submucosal invasive cancers were treated with surgery or chemotherapy with or without radiotherapy. The remaining superficial cancers within the mucosal layer were removed by endoscopic resection.

Discussion

Most research on the endoscopic detection and diagnosis of GI disease has been performed by retrospectively reviewing static images in a database and selecting only the best of the stored images (Singh R: Endoscopy 40:457-463, 2008; Sharma P: Gastroenterology 133:454-464, 2007; Chiu HM: Gut 56:373-379, 2007). Evaluating selected stored images by retrospective review does not exclude the