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ORIGINAL ARTICLE

Retrospective Study

Clinical impact of surveillance for head and neck cancer in patients with esophageal squamous cell carcinoma

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Abstract

AIM

To evaluate the clinical impact of surveillance for head and neck (HN) region with narrow band imaging (NBI) in patients with esophageal squamous cell carcinoma (ESCC).

METHODS

Since 2006, we introduced the surveillance for HN region using NBI for all patients with ESCC before

treatment, and each follow-up. The patients with newly diagnosed stage Ⅰ to Ⅲ ESCC were enrolled and classified into two groups as follows: Group A (no surveillance for HN region); between 1992 and 2000), and Group B (surveillance for HN region with NBI; between 2006 and 2008). We comparatively evaluated the detection rate of superficial head and neck squamous cell carcinoma (HNSCC), and the serious events due to metachronous advanced HNSCC during the follow-up.

RESULTS

A total 561 patients (group A: 254, group B: 307) were enrolled. Synchronous superficial HNSCC was detected in 1 patient (0.3%) in group A, and in 12 (3.9%) in group B (P = 0.008). During the follow up period, metachronous HNSCC were detected in 10 patients (3.9%) in group A and in 30 patients (9.8%) in group B (P = 0.008). All metachronous lesions in group B were early stage, and 26 patients underwent local resection, however, 6 of 10 patients (60%) in group A lost their laryngeal function and died with metachronous HNSCC.

CONCLUSION

Surveillance for the HN region by using NBI endoscopy increase the detection rate of early HNSCC in patients with ESCC, and led to decrease serious events related to advanced metachronous HNSCC.

Key words: Esophageal squamous cell carcinoma; Head and neck squamous cell carcinoma; Narrow band imaging; Endoscopic resection; Surveillance; Metachronous cancer

Core tip: This is a retrospective study to evaluate the clinical impact of intensive surveillance for head and neck (HN) region by using narrow band imaging (NBI) endoscopy in patients with esophageal squamous cell carcinoma. The detection rate of superficial head and neck squamous cell carcinoma (HNSCC) which could be easily treated with endoscopic resection was dramatically increased after introduction of surveillance for HN region with NBI, and the serious events (loss of laryngeal function, death) due to metachronous advanced HNSCC were led to decrease when comparing with historical control. Surveillance for HN region with NBI might have a clinical impact at the point of reduction of head and neck cancer death in esophageal cancer survivor.

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INTRODUCTION

Most of patients with esophageal squamous cell carcinoma (ESCC) have a high prevalence of second primary head and neck squamous cell carcinoma (HNSCC)[1]. Matsubara *et al*[2] reported an assessment of the risk of a second primary cancer in patients with ESCC undergoing esophagectomy. In that report, HNSCC was the highest risk after esophagectomy and the prognosis after the detection of HNSCC was significantly unfavorable compared to that of other malignancies because of the difficulty in the early detection of HNSCC. An image-enhanced endoscopic technology system, narrow-band imaging (NBI), was reported to be useful for the detection of superficial HNSCC[3-6]. These superficial lesions are depicted clearly as well-demarcated brownish areas without magnification, and increased intraepithelial papillary capillary loops (IPCL) with irregularity are visible as the endoscopic features of superficial HNSCC with magnification[3]. Muto *et al*[3] reported that both detection rate and diagnostic accuracy of HNSCC were higher in NBI than in white light imaging. Furthermore, several studies have also reported that minimally invasive treatment, such as peroral endoscopic resection (ER) of superficial pharyngeal cancer, was a feasible and effective treatment with curative intent[7-9].

At the beginning of 2006, we introduced intensive surveillance program for the head and neck (HN) region, including the oropharynx, hypopharynx, and larynx, using NBI for all ESCC patients before treatment and at every follow up visit. If early HNSCCs were detected, these lesions were mainly treated with ER after the confirmation of cured esophageal cancer. However, it has not been yet clarified whether prompt detection and intervention for early HNSCC in patients with ESCC would decrease the death rate or the loss of laryngeal function related to metachronous advanced HNSCC. In this study, we compared the detection rate of early HNSCC, and the number of serious adverse events related to metachronous advanced HNSCC, in periods before and after the commencement of NBI surveillance for the head and neck region.

MATERIALS AND METHODS

Patients

Patients were recruited from our database of patients who have received definitive treatments, such as ER, surgery and chemoradiotherapy (CRT), for ESCC in the National Cancer Center Hospital East. Selection criteria of this study were as follows: (1) initial treatment histologically confirmed ESCC; (2) clinical stage Ⅰ to Ⅲ; (3) no prior HNSCC; (4) absence of synchronous advanced cancer containing HNSCC; (5) no recurrence or metastasis of ESCC detected within 6 mo after initial ER or surgery for ESCC; (6) complete response (CR) was achieved and a recurrence after achieving

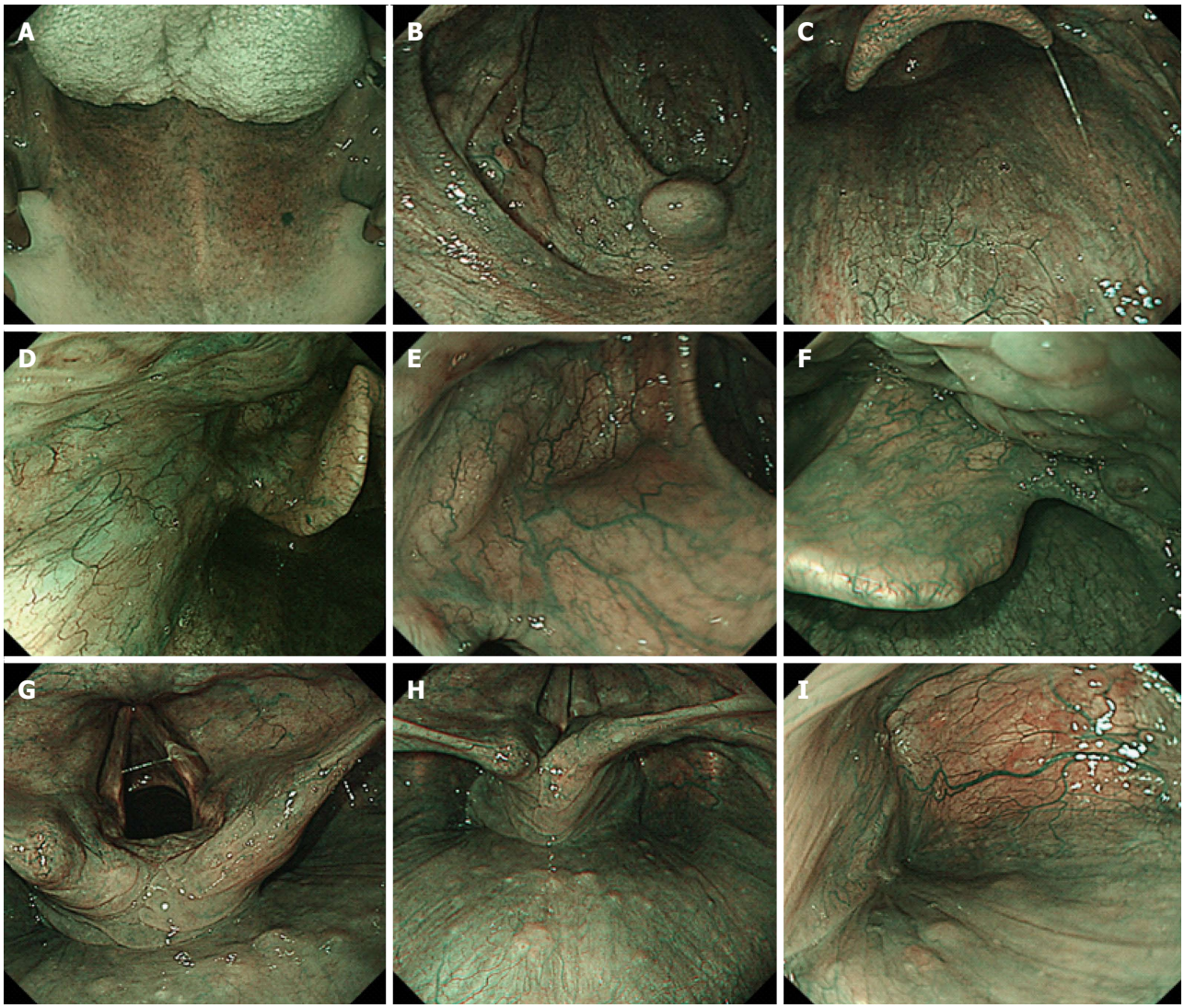

Figure 1 Narrow Band Imaging observations in individual regions from the oropharynx to the pharynx. A : The view seen from the entrance of the oral cavity: dorsal side of tongue, hard palate and soft palate; B: Uvula, palatoglossal arch and lateral walls of oropharynx; C: Posterior wall of oropharynx; D: The lateral wall of oropharynx; E: Vallecula of epiglottis, median glossoepiglottic fold; F: The right side of epiglottis, base of tongue; G: Vocal cord, arytenoids and aryepiglottic fold; H: Post-cricoid area and posterior wall of hypopharynx; I: The lateral wall and apex of right piriform sinus.

CR or metastasis was not detected within 6 mo of CRT; (7) an observation period longer than a year after treatment for ESCC; and (8) provided written informed consent before all endoscopic evaluation and treatment.

Two groups were classified between the periods before and after commencement of surveillance for the HN region. ESCC patients who were treated between October 1992 and December 2000, with a follow-up until December 2004 were defined as a control group (group A). During this period, the HN region was not intensively observed to detect superficial lesion with endoscopy before treatment or during follow up periods. Group B was defined patients who were treated between January 2006 and December 2008 and followed until December 2014. These patients in group B routinely received intensive surveillance using magnified NBI endoscopy in the HN region.

Endoscopic examination and follow-up schedule

Since the patients in group A underwent conventional endoscopy with white light illumination, intensive surveillance to detect superficial HNSCC was not performed actively. In contrast, the HN regions including the oropharynx, hypopharynx and larynx, were observed using endoscope equipped with a NBI system (Olympus Medical Science, Tokyo, Japan) in group B. The endoscopic observation order in the HN region using NBI endoscopy in our hospital is shown in Figure 1[10].

The follow-up schedule of endoscopic observation after the treatment for esophageal cancer was as follows. Patients who received CRT were evaluated every 6 mo after achieving CR. The initial examination was performed at 3 mo in patients after ER, and every 6 mo thereafter, and an annual examination was performed in patients after esophagectomy.

Table 1 Characteristics of patients with esophageal squamous cell carcinoma *n* (%)

	Group A (*n* = 254)	Group B (*n* = 307)	*P* value
Sex			
Male	214 (84)	260 (85)	0.907
Female	40 (16)	47 (15)	
Age (yr), median (range)	64 (39-81)	66 (41-86)	< 0.001
Baseline clinical TNM-stage			
Ⅰ	119 (47)	155 (50)	0.39
Ⅱ	66 (26)	88 (29)	0.50
Ⅲ	69 (27)	64 (21)	0.09
Treatment for primary ESCC			
Surgery	84 (33)	124 (40)	0.079
Endoscopic resection	77 (30)	113 (37)	0.010
Chemoradiotherapy	93 (37)	70 (23)	0.001
Follow-up period			
Median months (range)	60 (13-145)	67 (12-107)	0.150

ESCC: Esophageal squamous cell carcinoma.

Pathological evaluation of HNSCC

The histologic diagnosis was made according to criteria proposed by World Health Organization[11]. Clinical staging was determined according to the Japan Society for Head and Neck Cancer, same as the TNM classification 7th edition. Superficial cancers without lymph node or distant metastasis were defined as early cancer and cancers invading muscularis propria and deeper layers were defined as advanced cancer.

Treatment strategy and details of treatment for HNSCCs

Treatment for early HNSCC was provided after initial treatment for ESCC was completed. However, second primary HNSCC was not treated if the ESCC was not cured, because there was few possibility that the treatment for HNSCC affected the prognosis.

Endoscopic resection for HNSCC under general anesthesia was introduced in our hospital at the beginning of 2003. Subsequently, early HNSCC was mainly treated with ER after the confirmation of cured ESCC. When a lesion was small (approximately 10 mm in diameter or less), endoscopic mucosal resection with the cap technique was performed[8,12-14], and endoscopic submucosal dissection (ESD) was performed for larger lesions (over 10 mm in diameter)[7,9]. The procedure of ESD was as follows. A videoendoscope with a water jet system (JIFQ-260J, Olympus, Tokyo, Japan) was used for the entire procedure. And then 7 mL to 10 mL of 2.0% glycerin-free Lugol iodine solution, consisting of 2.0 g potassium iodine and 4.0 g iodine in 100 mL distilled water was sprayed to delineate the margins of the lesion. Markings were placed outside the margin of the lesion with a dual knife (Olympus KD-650L) and an electrosurgical current generator (ICC200, Erbe, Tübingen, Germany) set at 25 W for forced coagulation mode. A saline solution with epinephrine and indigo carmine dye was injected into the subepithelial layer. A circumferential incision around the lesion was performed and then the subepithelial tissue was dissected by the dual knife with 50 W current for forced coagulation mode. After the lesion was resected, a temporary tracheostomy was performed by a head and neck surgeon if laryngeal edema was severe.

Analysis and statistics

The detection rate of superficial HNSCC was evaluated for each group. The incidence rate of metachronous HNSCC and serious events related to metachronous HNSCC, such as death or loss of laryngeal function, were also evaluated.

All information was collected from the medical records or was provided by the patients' physicians. This retrospective study was approved by the institutional review board of the National Cancer Center in accordance with the Declaration of Helsinki.

SPSS Statistics 22 was used for statistical analysis. The results were expressed as medians. The Fisher's exact test was used to analyze categorical data to compare proportions. Risks of metachronous HNSCC were estimated by using the Kaplan-Meier method. *P* value of < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 470 patients with stage Ⅰ to Ⅲ ESCC were initially treated with definitive treatments (ER: 125, surgery: 119, CRT: 173) between October 1992 and December 2000 as group A, whereas 443 patients with stage Ⅰ to Ⅲ ESCC were initially treated (ER: 159, surgery: 161, CRT: 123) between January 2006 and December 2008 as group B. Patients consisting of 254 in group A and 307 in group B were recruited in this study according to the eligibility criteria. The characteristics of these patients are shown in Table 1. The male-to-female ratio, clinical stage of ESCC, and the follow up period were not significantly different between group A and group B, however, median age was significantly higher in patients of group B than in patients of group A. There was a significant difference in a treatment for ESCC in both groups (P = 0.025): the frequency of CRT were higher in group A (group A: 37%, group B: 23%).

Synchronous HNSCC

Synchronous superficial HNSCC was detected in only 1 patient (0.3%) in group A. In contrast, the synchronous superficial HNSCC was found in 12 (3.9%) patients in group B (P = 0.008) (Table 2). Among these all 13 patients, 9 patients (69%) were cured of ESCC and 7 of the 9 patients with synchronous HNSCC were treated after the treatment for ESCC. In these 7 patients who were treated for HNSCC, 5 patients underwent organ preserved local resection (ER or surgery). One patient with hypopharyngeal cancer in

Table 2 Synchronous superficial head and neck squamous cell carcinoma lesions *n* (%)

	Group A (*n* = 254)	Group B (*n* = 307)	*P* value
Synchronous HNSCC			
No. of patients	1 (0.3)	12 (3.9)	0.008
No. of lesions	1	14	0.010
Location of cancer			
Oropharynx	0	5	
Hypopharynx	1	8	
Larynx	0	1	
Treatment for synchronous HNSCC			
ER or surgical local resection	0	7 (58)	
TPLE	0	1 (8)	
Radiation and/or chemotherapy	1 (100)	0	
No treatment	0	4 (33)	
Death due to synchronous HNSCC	0	0	

ER: Endoscopic resection; TPLE: Total pharyngo-laryngo-esophagectomy; HNSCC: Head and neck squamous cell carcinoma.

Table 3 Characteristics of metachronous head and neck squamous cell carcinoma *n* (%)

	Group A (*n* = 254)	Group B (*n* = 307)	*P* value
Metachronous HNSCC			
No. of patients	10 (3.9)	30 (9.8)	0.008
No. of lesions per patients			0.404
1	9	22	
⩾ 2	1	8	
Total number of cancers	11	53	0.007
Location of cancer			
Oropharynx	3	13	
Hypopharynx	7	34	
Larynx	1	6	
Clinical stage			< 0.001
Ⅰ / Ⅱ	4 (36)	53 (100)	
Ⅲ / Ⅳ	7 (64)	0	
Interval between ESCC and HNSCC			
Median months (range)	56 (7-80)	31 (7-107)	0.130

HNSCC: Head and neck squamous cell carcinoma.

group A underwent radiotherapy and 1 patient with hypopharyngeal cancer in group B underwent total pharyngo-laryngo-esophagectomy (TPLE) because the tumor was located in a position where treatment to preserve laryngeal function was impossible. The remaining 4 patients did not receive any treatment for synchronous HNSCC because their ESCC was not cured. Most of the patients who were cured of ESCC and received treatment for superficial HNSCC had preserved laryngeal function. No patient died due to synchronous HNSCC in both groups.

Metachronous HNSCC

Metachronous HNSCC lesions were detected in 10 patients (3.9%) in group A and in 30 patients (9.8%) in group B (P = 0.008; Table 3). The cumulative risk of metachronous HNSCC after treatment of ESCC is shown in Figure 2. The 5-year cumulative risk of developing metachronous HNSCC after treatment for ESCC was only 2.5% in group A, whereas it was 8.7% in group B (P < 0.001).

The characteristics of metachronous HNSCCs are shown in Table 3. Eleven metachronous HNSCC lesions were detected in 10 patients in group A, and 53 lesions in 30 patients in group B (P = 0.008). In the clinical stages of metachronous HNSCC, only 4 (36%) lesions were superficial type and stage Ⅰ / Ⅱ in group A, however, all 53 lesions were superficial lesions in group B (P < 0.001), and these lesions were stage Ⅰ / Ⅱ.

Table 4 Clinical course of patients with metachronous head and neck squamous cell carcinoma *n* (%)

	Group A, patients (*n* = 10)	Group B, patients (*n* = 30)	*P* value
Metachronous HNSCC	11 lesions	53 lesions	< 0.001
Ⅰ / Ⅱ	4 (36)	53 (100)	
Ⅲ / Ⅳ	7 (64)	0 (0)	
Treatment			
Local resection	2 (18)	49 (92)	< 0.001
Endoscopic resection	0	44	
Surgical local resection	2	5	
TPLE	3 (27)	0 (0)	0.001
Radiotherapy alone and/or chemotherapy	4 (36)	2 (4)	0.006
No treatment	2 (18)	2 (4)	0.133
Laryngeal function			< 0.001
Maintained	4 (40)	30 (100)	
Lost	6 (60)	0	
Outcome			0.001
Alive	3 (30)	26 (87)	
Death	7 (70)	4 (13)	
Death with metachronous HNSCC	6 (60)	0 (0)	< 0.001

HNSCC: Head and neck squamous cell carcinoma; TPLE: Total pharyngo-laryngo-esophagectomy.

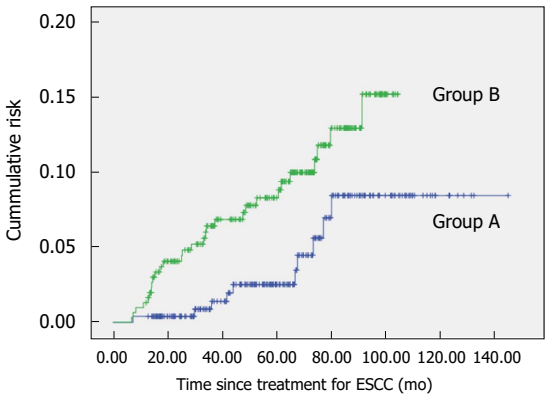

Figure 2 Cumulative risk of metachronous head and neck squamous cell carcinoma after treatment of esophageal squamous cell carcinoma. ESCC: Esophageal squamous cell carcinoma.

Clinical course of patients with metachronous HNSCC

The clinical course of patients with metachronous HNSCC is shown in Table 4. There were no patients in group A who underwent ER as an initial therapy. Of 10 patients in group A, 7 (70%) who were detected

Table 5 Clinical outcome of all patients with esophageal squamous cell carcinoma *n* (%)

	Group A (*n* = 254)	Group B (*n* = 307)	*P* value
Occurrence of advanced metachronous HNSCC	7 (2.8)	0	0.003
Loss of laryngeal function	6 (2.4)	0	0.008
Outcome			< 0.001
Alive	172 (68)	254 (83)	
Dead	82 (32)	53 (17)	
ESCC	43 (17)	41 (13)	0.284
HNSCC	6 (2.4)	0	0.018
Other cancer	6 (2.4)	4 (1.3)	0.360
Gastric cancer	3 (1.2)	0	0.092
Lung cancer	0	2 (0.7)	0.0503
Lymphoma	1 (0.4)	1 (0.3)	> 0.999
HCC	1 (0.4)	1 (0.3)	> 0.999
Prostate cancer	1 (0.4)	0	0.452
Other/unknown	27 (11)	8 (2.6)	< 0.0001
Radiation pneumonia	8 (8.1)	1 (0.3)	0.013
Heart failure	6 (2.4)	1 (0.3)	0.050

HNSCC: Head and neck squamous cell carcinoma; ESCC: Esophageal squamous cell carcinoma; HCC: Hepatocellular carcinoma.

metachronous HNSCC had stage Ⅲ/Ⅳ HNSCC at diagnosis. In these 7 patients, only one patient who received radiotherapy achieved a cure for HNSCC.

In contrast, metachronous HNSCC was found in 30 patients with 53 lesions in group B (Table 4). Furthermore, all the 53 lesions were superficial cancer alone. ER was performed in 44 of the 53 lesions and only 2 of 44 lesions had local recurrence. One of the 2 patients had re-ER and was cured, and another patient has not receive any active treatments for the superficial cancer. There were no patients who developed lymph node or distant metastasis within the observation period. In addition, 2 patients were received RT alone, and the remaining 2 were not treated for HNSCC because their ESCC recurred after the initial treatment for ESCC.

As serious events, the 7 of 10 patients in group A died due to cancer, and 6 of the 7 patients died due to metachronous HNSCC (group A: 60%, group B: 0%. $P < 0.001$; Table 4). Furthermore, 6 of the 10 patients (60%) in group A who were detected in metachronous HNSCC lost laryngeal function due to intensive treatment, otherwise none of the 30 patients with the 53 lesions in group B lost laryngeal function ($P < 0.001$).

Clinical outcome of all patients with ESCC

Clinical outcome is shown in Table 5. A total of 82 (32%) patients in group A and 53 (17%) patients in group B died during the follow up periods. While there was no significant difference in the frequency of deaths due to the progression of ESCC between both groups [group A *vs* B: 43 (17%) *vs* 41 (13%), $P = 0.28$], the deaths related to metachronous HNSCC were more frequent in group A (group A *vs* B: 6 (2.4%) *vs* 0 (0%), $P = 0.008$). In contrast, other noncancerous diseases or unknown sudden death which might be late toxicity of RT for ESCC were more frequent in group A [27 (11%) *vs* 8 (2.6%), $P < 0.001$].

DISCUSSION

This is the first study to investigate the clinical significance of early detection and intervention to second primary HNSCC in ESCC patients. The innovation of NBI has allowed for the early diagnosis of head and neck cancer. The NBI technique could significantly improve the efficacy of screening and surveillance of HN region, especially the lesions at oropharyngeal and hypopharyngeal mucosal sites. In previous reports, NBI screening was undertaken for the HN region (10%-13%) in ESCC patients[3,4]. In this study, we classified into two groups whether intervention of NBI surveillance was present or not, and detection rate of superficial HNSCC was clarified. Few superficial HNSCCs were detected using conventional endoscopy with white light illumination alone, however, many superficial HNSCCs were detected synchronously (3.9%) and metachronously (9.4%) after commencement of NBI surveillance. Furthermore, multiple metachronous HNSCCs were also detected. One of the main reason of lower HNSCC detection rate is considered that we did not perform NBI surveillance with magnifying endoscopy in all cases. One important point was that almost all of metachronous HNSCC could be detected as superficial cancer by NBI surveillance once from six months to one year.

Furthermore, early detection of second primary HNSCC in ESCC patients brought to minimally invasive treatment, such as peroral ER. In this study, ER was performed in 83% of second primary HNSCCs due to NBI surveillance, and these patients did not lose laryngeal function. In contrast, most of the second primary HNSCCs were detected as advanced cancers in no NBI surveillance from 1992 to 2000, 60% of patients lost laryngeal function due to invasive treatment. Several studies have reported that peroral ER of superficial HNSCC is a feasible and effective treatment with curative intent[9,15,16]. Muto *et al*[9] reported that local recurrence or distant metastasis after ER or superficial pharyngeal cancer were only 8% and patients who underwent ER had an excellent prognosis, with a 5-year cause-specific survival rate of 97% (95%CI: 93%-100%). We believe development of ER for cancer of oral cavity would progress along with early detection of superficial HNSCC. Loss of laryngeal function is a serious problem, and decreases quality of life in patients with second primary HNSCC. In contrast, we clarified that second primary advanced HNSCC could become the risk of death if superficial HNSCC was not detected. HNSCC was 2.4% of various death factors in no NBI surveillance,

however, there was no HNSCC related death after NBI surveillance. In this study, while two groups were different periods (1992-2000 *vs* 2006-2008), we compared the detection rate of early HNSCC, and the number of serious adverse events related to metachronous advanced HNSCC, in periods before and after the commencement of NBI surveillance for the head and neck region. We suggested that early detection of metachronous HNSCC in ESCC patients led to minimally invasive ER without loss of laryngeal function, and avoided HNSCC related death. Regarding follow-up periods, NBI surveillance was performed in 6 mo for ER and CRT and in 1 year for operation. In our present results, 5 years have passed through NBI surveillance, however, advanced HNSCC was not detected. We believe that 6 mo follow-up periods would be appropriate.

Limitations of this retrospective study are that the data are taken from only a single institution, and historical background, the medical backgrounds of the ESCC patients, are different in each group. Moreover, it is uncertain whether the approximately 5 years of follow up in the present study is long enough to verify the serious events due to metachronous HNSCC. However, it seems impossible to conduct a randomized control study since the usefulness of endoscopic surveillance with NBI has been demonstrated.

In conclusion, endoscopic surveillance using NBI for the HN region improved detection of both synchronous and metachronous superficial HNSCC in patients with ESCC. The early detection and intervention for HNSCC might lead to the reduction of serious adverse events and the risk of death related to HNSCC.

COMMENTS

Background

Most of patients with esophageal squamous cell carcinoma (ESCC) have a high prevalence of second primary head and neck squamous cell carcinoma (HNSCC). The innovation of narrow-band imaging (NBI) has allowed for the early diagnosis of head and neck cancer. However, it has not been yet clarified whether prompt detection and intervention for early HNSCC in patients with ESCC would decrease the death rate or the serious events related to metachronous advanced HNSCC. In this study, the authors compared the detection rate of early HNSCC, and the number of serious adverse events related to metachronous advanced HNSCC, in periods before and after the commencement of NBI surveillance for the head and neck region.

Research frontiers

NBI is useful to detect the early HNSCC and minimally invasive treatment, such as peroral endoscopic resection (ER) of early HNSCC, is a feasible and effective treatment with curative intent. This results of this study contribute to clarifying the clinical impact of early intervention to metachronous NHSCCs in patient with ESCC.

Innovations and breakthroughs

In this study, many HNSCCs were detected synchronously (3.9%) and metachronously (9.4%) after commencement of NBI surveillance, and all 53 lesions could be detected as early stage. These results are in agreement with previous reports. Minimally invasive treatment (ER) was performed in 83% of these second primary HNSCCs due to NBI surveillance and these patients did not lose laryngeal function or death related to HNSCC. In contrast, most of the second primary HNSCCs were detected as advanced cancers in no NBI surveillance from 1992 to 2000, 60% of patients lost laryngeal function and were died due to invasive treatment.

Applications

This study suggested that early intervention for metachronous HNSCC is useful to reduce the serious adverse events and the risk of death related to HNSCC in patient with ESCC.

Terminology

NBI: A video endoscopic imaging technique that enhances the display of the microstructures and capillaries in the superficial mucosal layer using narrow band filters that change the spectral features of the observation light.

Peer-review

This study investigated the clinical usefulness of surveillance of head and neck cancer in patients with esophageal squamous cell carcinoma. Although the study is retrospectively performed, the results are well analyzed and clearly presented.

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ORIGINAL ARTICLE

Retrospective Study

Second-line bismuth-containing quadruple therapy for *Helicobacter pylori* eradication and impact of diabetes

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Author contributions: Kim SE interpreted and analyzed the data and wrote the manuscript; Park MI designed, organized, and supervised writing of the manuscript; Park SJ and Moon W helped with data interpretation that was used in the current study; Kim JH and Jung K provided input and organized the data for statistical analysis; Kim HK and Lee YD helped with data analysis; all authors approved the final version of the manuscript.

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Abstract

AIM

To investigate *Helicobacter pylori* (*H. pylori*) eradication rates using second-line bismuth-containing quadruple therapy and to identify predictors of eradication failure.

METHODS

This study included 636 patients who failed first-line triple therapy and received 7 d of bismuth-containing quadruple therapy between January 2005 and December 2015. We retrospectively demonstrated *H. pylori* eradication rates with respect to the year of therapy as well as demographic and clinical factors. *H. pylori* eradication was confirmed by a ^{13}C-urea breath test or a rapid urease test at least 4 wk after the completion of bismuth-based quadruple therapy: proton pump inhibitor, metronidazole, bismuth, and tetracycline.

RESULTS

The overall eradication rates by intention-to-treat analysis and per-protocol analysis were 73.9% (95%CI: 70.1%-77.4%) and 94.5% (95%CI: 92.4%-96.5%), respectively. Annual eradication rates from 2005 to 2015 were 100.0%, 92.9%, 100.0%, 100.0%, 100.0%, 97.4%, 100.0%, 93.8%, 84.4%, 98.9%, and 92.5%, respectively, by per-protocol analysis. A multivariate analysis showed that diabetes mellitus (OR = 3.99, 95%CI: 1.56-10.20, P = 0.004)

was associated with *H. pylori* eradication therapy failure.

CONCLUSION

The second-line bismuth-containing quadruple therapy for *H. pylori* infection is still effective in Korea, and diabetes mellitus is suggested to be a risk factor for eradication failure.

Key words: *Helicobacter pylori*; Disease eradication; Treatment failure; Bismuth; Diabetes mellitus

Core tip: This study investigated the efficacy of 7 d of second-line bismuth-containing quadruple therapy for *Helicobacter pylori* (*H. pylori*) infection and identified risk factors for eradication failure in South Korea. The overall eradication rate per-protocol analysis was 94.5% in the current study. Additionally, diabetes mellitus was related to *H. pylori* eradication therapy failure. Therefore, second-line bismuth-containing quadruple therapy for *H. pylori* infection is still worth considering in South Korea, and diabetes mellitus is suggested to be a risk factor for eradication failure.

Kim SE, Park MI, Park SJ, Moon W, Kim JH, Jung K, Kim HK, Lee YD. Second-line bismuth-containing quadruple therapy for *Helicobacter pylori* eradication and impact of diabetes. *World J Gastroenterol* 2017; 23(6): 1059-1066 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i6/1059.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i6.1059

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a global pathogen that causes gastritis, peptic ulcers, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer[1]. The International Agency for Research on Cancer, a branch of the World Health Organization, has declared that *H. pylori* is a definite gastric carcinogen (group I)[2,3]. Therefore, *H. pylori* eradication is crucial to maintain public health, especially in high *H. pylori* and gastric cancer prevalence areas.

Various combination therapies are recommended for *H. pylori* eradication due to a decrease in eradication rates. According to the Maastricht IV/Florence consensus report, clarithromycin-containing therapy (comprised of a proton pump inhibitor (PPI), amoxicillin, and clarithromycin) is recommended for first-line eradication treatment, and bismuth-containing quadruple therapy (comprised of a PPI, metronidazole, bismuth, and tetracycline) is recommended for second-line eradication treatment if first-line eradication therapy fails[4]. Guidelines for the treatment of *H. pylori* infection in South Korea are similar to recommendations in the Maastricht IV/Florence consensus report. Specifically, clarithromycin-containing triple therapy is the recommended first-line eradication therapy, and bismuth-containing quadruple therapy is recommended for the second-line eradication treatment if the clarithromycin-based triple therapy fails[5].

In general, clarithromycin-containing therapy is recommended for first-line eradication treatment in low (< 20%) clarithromycin resistance areas[4]. However, the eradication rates for clarithromycin-containing triple therapy have been decreasing significantly in Korea in recent years due to increased *H. pylori* antibiotic resistance[6,7]. In addition, there is controversy about the role of bismuth-containing quadruple therapy as a second-line therapy for *H. pylori* eradication due to a decrease in eradication rates for bismuth-containing quadruple therapy in Korea[8,9].

The aims of the present study were to identify the effects of second-line eradication therapy using bismuth-containing quadruple therapy at a single center over the past 11 years, and to evaluate risk factors associated with the failure of second-line eradication therapy.

MATERIALS AND METHODS

Study population

Patients who failed clarithromycin-containing triple therapy and received second-line bismuth-containing quadruple therapy at Kosin University Gospel Hospital from January 2005 to December 2015 were retrospectively enrolled in this study. *H. pylori* positivity was identified using a ^{13}C-urea breath test or a rapid urease test before and after eradication therapy. Patients lost to follow-up were defined as patients who received the second-line bismuth-containing quadruple therapy with unknown results regarding eradication success or failure. Compliance was classified as good or poor by pill count in the medical records. Patients who took 80% or more of the prescribed medicine were included in the good compliance group, and those who took less than 80% of the prescribed medicine were placed in the poor compliance group.

We investigated demographic features: area of residence, smoking and alcohol habits, diabetes mellitus, hypertension, endoscopic findings, and adverse effects of eradication therapy. Rural or urban residence was regarded as living or not living in the metropolitan cities of Korea, respectively. All patients underwent endoscopy, and endoscopic findings [such as gastric ulcers, duodenal ulcers, gastric and duodenal ulcers, a previous endoscopic submucosal dissection (ESD) state due to adenoma or early gastric cancer (EGC), MALT lymphoma, nodular gastritis, dyspepsia, gastric polyps, and intestinal metaplasia] were identified by endoscopy or by endoscopy with biopsy. Adverse effects after eradication therapy were identified by verification in the medical records. The Institutional Review Board (IRB) of Kosin University Gospel Hospital

Table 1 Baseline characteristics of the patients *n* (%)

Variable	Patients (n = 636[1])
Age (yr, mean ± SD)	54.6 ± 11.6
Gender	
Male	354 (55.7)
Female	282 (44.3)
Residence	
Rural	126 (19.8)
Urban	510 (80.2)
Cigarette smoking	174/605 (28.8)
Alcohol intake	279/605 (46.1)
Diabetes mellitus	61/605 (10.1)
Hypertension	121/605 (20.0)
Endoscopic findings	
Gastric ulcer	205 (32.2)
Duodenal ulcer	193 (30.3)
Gastric ulcer + Duodenal ulcer	40 (6.3)
Post ESD due to adenoma or EGC	91 (14.3)
Nodular gastritis	29 (4.6)
Others[2]	78 (12.2)

[1]Total number of enrolled patients; missing values are not included. The number behind the dash is the total number of subjects who answered each question. [2]Others include MALT lymphoma, dyspepsia, gastric polyp and intestinal metaplasia. ESD: Endoscopic submucosal dissection; EGC: Early gastric cancer; MALT lymphoma: Mucosa-associated lymphoid tissue lymphoma.

approved this study (IRB file No. 2015-03-018).

H. pylori eradication therapy and follow-up

Patients who failed the first-line clarithromycin-containing triple therapy (standard-dose PPI, 1.0 g amoxicillin, and 0.5 g clarithromycin twice daily for 7 d) were recommended for second-line eradication therapy. The latter was comprised of 20 mg rabeprazole twice daily, 500 mg metronidazole three times daily, 300 mg tripotassium dicitrato bismuthate, and 500 mg tetracycline four times daily for 7 d. Afterwards, a ^{13}C-urea breath test or a rapid urease test was conducted to assess *H. pylori* eradication at least 4 wk after the treatment completion, and at least 2 wk after cessation of PPIs or histamine (H_2) receptor antagonists.

^{13}C-urea breath test

Patients fasted for at least 4 h before the first breath sample was collected. Then, participants took tablets including 100 mg of ^{13}C-urea (UBiTkit™, Otsuka Pharmaceutical, Tokyo, Japan) with 100 mL of water orally, and the second breath sample was obtained 20 min after taking the tablets. *H. pylori* infection was analyzed using the ^{13}C-urea breath test (UBiT-IR300®; Otsuka Electronics, Osaka, Japan) on the collected breath samples. The cut-off value in the current procedure was set at 2.5‰.

Rapid urease test

To identify *H. pylori* infection with the rapid urease test (CLOtest®; Delta West, Bentley, WA, Australia), an endoscopic biopsy was conducted at the gastric mucosa. The site of gastric mucosal biopsy was antrum and/or corpus, and normal or near-normal gastric mucosa with little atrophy or intestinal metaplasia was removed. The tissue sample was immersed in rapid urea reagent. The result was positive when the reagent color changed from yellow to red at least 12 h later, and the result was negative when there was no change in reagent color.

Statistical analysis

All statistical analyses were conducted with the Statistical Package for the Social Sciences software version 20.0 (SPSS, Chicago, IL, United States). The *H. pylori* eradication rate was demonstrated by intention-to-treat (ITT) and per-protocol (PP) analyses. The trend in *H. pylori* eradication rates was analyzed with linear association. Patients lost to follow-up or those with poor compliance were excluded when we performed the PP analysis and univariate and multivariate logistic regression analyses. Categorical variables were analyzed using a χ^2-test, and continuous variables were analyzed using the Student's *t*-test. Univariate and multivariate logistic regression tests were used for the analysis of risk factors, which were expressed as an OR and 95%CI. A P value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

Between January 2005 and December 2015, 636 patients received 7 d of second-line bismuth-containing quadruple therapy after *H. pylori* eradication failure with clarithromycin-based triple therapy. Average age (mean ± SD) was 54.6 ± 11.6 years (range, 17-86 years), and 354 patients (55.7%) were male. Table 1 shows the clinical data and demographic information for enrolled patients. Among 636 patients receiving second-line bismuth-containing quadruple therapy, 138 patients were lost to follow-up, and three patients exhibited poor compliance. Finally, a total of 495 patients were included as subjects for PP analysis and multivariate logistic regression (Figure 1).

H. pylori eradication rates

In terms of eradication therapy success or failure, 468 patients achieved successful eradication. The eradication rates by ITT and PP analyses were 73.9% (95%CI: 70.1%-77.4%) and 94.5% (95%CI: 92.4%-96.5%) for second-line quadruple therapy, respectively. Annual eradication rates from 2005 to 2015 were 100.0%, 92.9%, 100.0%, 100.0%, 100.0%, 97.4%, 100.0%, 93.8%, 84.4%, 98.9% and 92.5%, consecutively by PP analysis. The eradication rate for first-line triple therapy decreased over the years (P = 0.01). Figure 2 presents the annual eradication rates for the last 11 years.

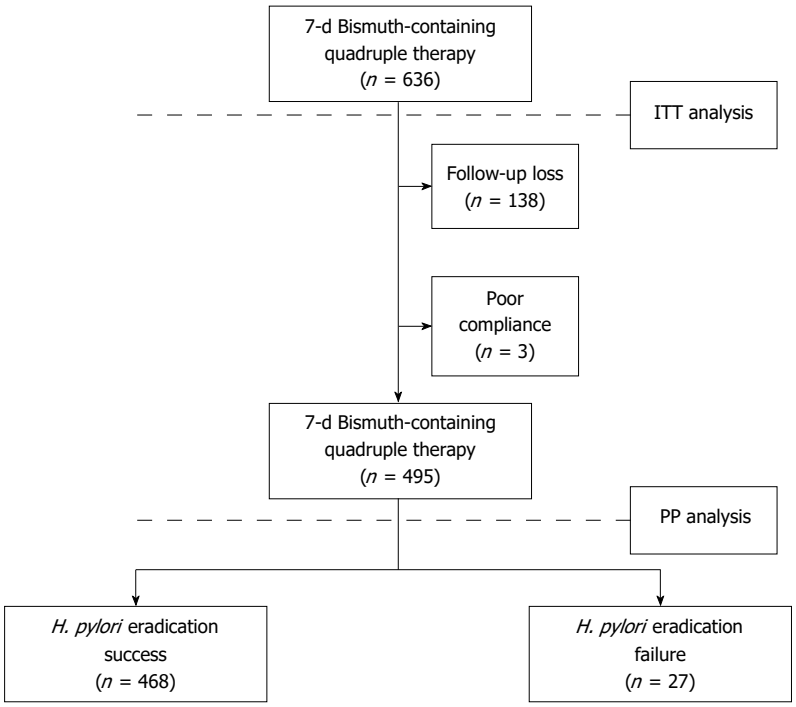

Figure 1 Flowchart of the study participants. ITT: Intention-to-treat; PP: Per-protocol; *H. pylori*: *Helicobacter pylori*.

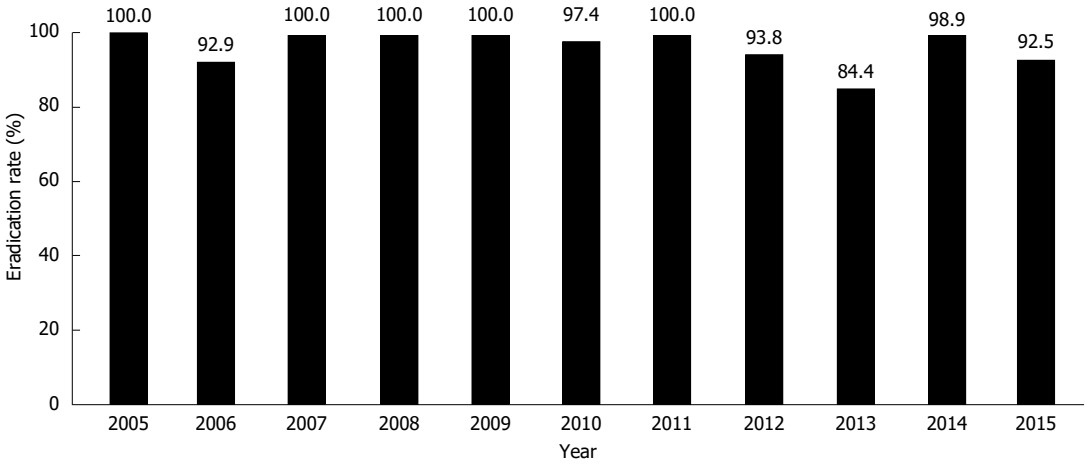

Figure 2 *Helicobacter pylori* eradication rates of second-line bismuth-based quadruple therapy according to years ($P = 0.01$).

Table 2 Adverse effects after bismuth-based quadruple therapy *n* (%)

	Patients (*n* = 495)
Side effect	74 (14.9)
Diarrhea	16 (3.2)
Bloating or abdominal pain	22 (4.4)
Nausea or vomiting	26 (5.3)
Others[1]	10 (2.0)

[1]Others include myalgia, headache and bitter sensation in the mouth.

Adverse effects of eradication therapy

Of the 495 patients, 74 patients (14.9%) complained of adverse events after bismuth-based quadruple therapy; fortunately, the adverse events were mild or moderate. Adverse events possibly related to treatment were diarrhea in 16 patients (3.2%), bloating or abdominal pain in 22 patients (4.4%), nausea or vomiting in 26 patients (5.3%), and others (such as myalgia, headache, and bitter sensation in the mouth) in 10 patients (2.0%; Table 2).

Associated factors for eradication failure

Associated factors for eradication failure are summarized in Table 3. Univariate and multivariate analyses demonstrated that only diabetes mellitus (OR = 3.99, 95%CI: 1.56-10.20, $P = 0.004$) was significantly related to eradication failure. There was no statistically significant relationship between eradication failure and

Table 3 Related factors about eradication failure of bismuth-based quadruple therapy *n* (%)

Variable	Eradication Success (*n* = 468[1])	Eradication Failure (*n* = 27[1])	*P* value[a]	*P* value[c]	Adjusted OR (95%CI)[c]
Age (yr)					
< 50	124 (95.4)	6 (4.6)			
⩾ 50	344 (94.2)	21 (5.8)	0.822	0.752	1.17 (0.44-3.09)
Gender					
Male	248 (93.2)	18 (6.8)			
Female	220 (96.1)	9 (3.9)	0.233	0.240	0.57 (0.22-1.46)
Residence					
Rural	90 (94.7)	5 (5.3)			
Urban	378 (94.5)	22 (5.5)	1.000	0.783	1.16 (0.41-3.24)
Cigarette smoking					
No	341 (95.0)	18 (5.0)			
Yes	111 (92.5)	9 (7.5)	0.359	0.435	1.48 (0.56-3.93)
Alcohol intake					
No	252 (94.4)	15 (5.6)			
Yes	200 (94.3)	12 (5.7)	1.000	0.522	0.74 (0.29-1.89)
Diabetes mellitus					
No	408 (95.6)	19 (4.4)			
Yes	44 (84.6)	8 (15.4)	0.005	0.004	3.99 (1.56-10.20)
Hypertension					
No	361 (94.5)	21 (5.5)			
Yes	91 (93.8)	6 (6.2)	0.806	0.638	0.78 (0.28-2.18)

[1]Total number of analyzed patients. Missing values are not included. [a]$P < 0.05$, univariate logistic regression test; [c]$P < 0.05$, multivariate logistic regression test. Logistic model including terms of age, gender, residence, cigarette smoking, alcohol intake, diabetes mellitus and hypertension.

other factors including age, gender, residence, smoking, alcohol, and hypertension.

DISCUSSION

In the current study, the *H. pylori* eradication rate for bismuth-containing quadruple therapy given for 7 d was < 80% by ITT analysis, but was > 90% by PP analysis in patients who failed clarithromycin-containing triple therapy. The frequency of adverse effects was less than 15%, which is consistent with the results of previous studies using bismuth-containing quadruple therapy[9,10].

As a second-line therapy, the effect of bismuth-containing quadruple therapy is controversial. Our PP eradication rate result was consistent with earlier studies, which reported that bismuth-containing quadruple therapy produced a high eradication rate in patients that failed *H. pylori* eradication therapy using clarithromycin-containing triple therapy. A recent multinational study in Europe reported the eradication rates for bismuth-containing quadruple therapy as rescue therapy for 10 d were 93.2%-93.8% by ITT analysis and 94.7%-95.0% by PP analysis[11]. Results with bismuth-containing quadruple therapy in China also demonstrated a 10-d bismuth-containing quadruple therapy eradication rate of 88.9% by ITT analysis and 90.9%-91.6% by PP analysis in patients that failed *H. pylori* eradication therapy[12,13]. However, eradication rates using second-line bismuth-containing quadruple therapy revealed diverse results in South Korea. Yoon *et al*[14] suggested that a 7-d bismuth-containing quadruple therapy might be as efficient as a 14-d bismuth-containing quadruple therapy for second-line eradication therapy, because a 7-d bismuth-containing quadruple therapy produced 83.5% and 87.7% eradication rates by ITT and PP analyses, respectively, and a 14-d bismuth-containing quadruple therapy produced 87.7% and 88.9% eradication rates by ITT and PP analyses, respectively. In contrast, another study reported that ITT eradication rates for a 7-d bismuth-containing quadruple therapy were 67.4%, and PP eradication rates were 78.2%, whereas ITT eradication rates for a 14-d bismuth-containing quadruple therapy were 72.8%, and PP eradication rates were 84.1%[9]. Usually, *H. pylori* eradication rates correlate with patient drug compliance and *H. pylori* antibiotic resistance. Unfortunately, studies to evaluate antibiotic resistance between different areas in South Korea are rare, and one small study determined there was no significant regional difference between *H. pylori* metronidazole and tetracycline resistance in South Korea[15]. Therefore, the reason for the high PP eradication rate in the current study is unclear. Although regional differences in antibiotic resistance may exist, bismuth-containing quadruple therapy achieved a more than 90% ITT eradication rate in patients who had *H. pylori* resistant to metronidazole (32.7%) and clarithromycin (63.3%)[11]. Thus, bismuth-containing quadruple therapy for second-line eradication therapy might even be effective in patients with antibiotic-resistant *H. pylori*.

In terms of adverse effects, most patients in the current study complained of gastrointestinal symptoms including nausea, vomiting, bloating, abdominal pain, or diarrhea. The symptoms were well tolerated, and no serious adverse events were observed. Only one patient wanted to be hospitalized for supportive care

due to nausea. With regard to neurologic symptoms, three patients complained of headache or dizziness, but the symptoms were mild. Severe neurological symptoms, such as bismuth-related encephalopathy, were not observed[11,16,17]. In accordance with previous studies, bismuth-containing therapy for the eradication of *H. pylori* is considered safe and well tolerated[9,18].

Several factors have been postulated as the cause of eradication failure, including age, gender, smoking, alcohol, and specific drug history (*e.g.*, aspirin)[6,19-22]. However, there was no significant relationship between these factors and eradication failure in the current study, except for diabetes mellitus. Diabetes mellitus has been presumed to be a risk factor for *H. pylori* eradication failure based on a recent meta-analysis (RR = 2.19, 95%CI: 1.65-2.90)[23]. It is hypothesized that microcirculatory complications related to diabetes mellitus could induce gastroparesis and reduce the absorption of antibiotics into the gastric mucosa, thereby influencing the effect of eradication therapy[24,25]. In addition, drug binding was revealed to be decreased by glycosylation, which was presumed to be associated with levels of blood glucose[26]. Concerning antibiotic resistance, the frequent use of antibiotics might increase antibiotic resistance[23,27]. A recent Danish nationwide cohort study found that the rates for community-based antibiotic prescriptions were higher in patients with diabetes mellitus compared to the general population[28]. Therefore, a more careful choice of *H. pylori* eradication therapy is needed for patients with diabetes mellitus.

Limitations of the present study are that it was performed at a single center and many patients were lost to follow-up, which might have influenced results of the ITT analysis. In addition, antibiotic susceptibility tests were not conducted in this study. Culturing *H. pylori* is difficult, and the response rates for antibiotic susceptibility tests are relatively low. Therefore, this was hard to inspect in all enrolled patients, and there were no standard criteria for identifying antibiotic resistance[9]. Furthermore, we did not diagnose *H. pylori* by histology before and after eradication therapy, as most patients underwent the ^{13}C-urea breath test or the rapid urease test for confirmation of *H. pylori* presence before and after therapy. These limitations could affect the eradication rate. According to the manufacturer, sensitivity and specificity of the rapid urease test were 90% to 95% and 95% to 100%, respectively. A recent meta-analysis reported that sensitivity and specificity of the ^{13}C-urea breath test were 95% to 97% and 91% to 94%, respectively, and that this test only rarely provided false-positive results[29-32]. We found that eradication rates based on the ^{13}C-urea breath test and the rapid urease test were 95.1% (327/344) and 93.4% (141/151), respectively (P = 0.519). Therefore, there was no significant difference between the two methods. The accuracy of both tests is high and very practical for clinical use[33], thus the absence of histology is unlikely to have had a significant effect on this study.

In conclusion, bismuth-containing quadruple therapy might be effective in patients that failed *H. pylori* eradication using clarithromycin-containing triple therapy, and might be worthy of consideration as a useful second-line therapy for *H. pylori* eradication in South Korea. Additionally, patients with diabetes mellitus are at higher risk for eradication failure with bismuth-containing quadruple therapy. Further studies on a larger scale evaluating the effects of second-line bismuth-containing quadruple therapy are needed in the near future in South Korea.

COMMENTS

Background

Helicobacter pylori (*H. pylori*) has been classified as a definite gastric carcinogen (group I) by the International Agency for Research on Cancer. Therefore, *H. pylori* eradication is important to protect public health, especially in areas with high *H. pylori* prevalence. However, the eradication rate for proton pump inhibitor (PPI)-containing triple therapy has decreased worldwide, and an effective rescue treatment is needed.

Research frontiers

There is controversy about the role of bismuth-containing quadruple therapy as a second-line therapy for *H. pylori* eradication due to a decrease in eradication rates for bismuth-containing quadruple therapy in South Korea. In addition, risk factors related to the failure of second-line eradication therapy are obscure.

Innovations and breakthroughs

This retrospective study was performed to investigate the effects of second-line eradication therapy using bismuth-containing quadruple therapy at a single center over the past 11 years, and to evaluate the risk factors associated with the failure of second-line eradication therapy. According to the high eradication rate and low adverse effects of the therapy, bismuth-containing quadruple therapy is worthy of consideration as a useful second-line therapy for *H. pylori* eradication in South Korea. Additionally, diabetes mellitus is suggested to be a risk factor for eradication failure.

Applications

This retrospective study's design and findings may be helpful for planning further prospective studies on a larger scale which can evaluate the effects of second-line bismuth-containing quadruple therapy and clarify additional risk factors for eradication failure.

Terminology

H. pylori: A global pathogen that causes gastritis, peptic ulcers, mucosa-associated lymphoid tissue lymphoma, and gastric cancer. Eradication of *H. pylori* infection is crucial to maintaining public health, especially in high *H. pylori* and gastric cancer prevalence areas.

Peer-review

This is a well-designed, although retrospective study including a high number of patients. The methods used are appropriate, the statistics is sound. The difference between intention-to-treat and per-protocol eradication rates reflects the real life, while a proportion of patients lost to follow up is high.

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