28. Chiba T, Marusawa H, Seno H, et al. Mechanism for gastric cancer development by Helicobacter pylori infection. J Gastroenterol Hepatol 2008;23:1175–1181.
29. Jemal A, Center MM, DeSantis C, et al. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev 2010;19:1893–1907.

Received May 28, 2011. Accepted August 11, 2011.

Reprint requests

Address requests for reprints to: Manabu Muto, MD, PhD, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. e-mail: mmuto@kuhp.kyoto-u.ac.jp; fax: (81) 75-751-4303.

Acknowledgments

Gastric NBI Study Investigators in Japan include the following: Noriya Uedo, Yoji Takeuchi (Osaka Medical Cancer for Cancer and Cardiovascular Diseases, Osaka); Hisashi Doyama, Yoshibumi Kaneko, Kenichi Takemura, Kazuhiro Miwa, Shinya Yamada (Ishikawa Prefectural Central Hospital, Ishikawa); Yutaka Saito, Ichiro Oda, Shigetaka Yoshinaga, Satoru Nonaka, Shusei Fukunaga (National Cancer Center Hospital, Tokyo); Manabu Muto, Yasumasa Ezoe, Shuko Morita, Takahiro Horimatsu (Kyoto University, Kyoto); Kenshi Yao, Takashi Nagahama, Hiroshi Tanabe, Takahiro Beppu, Yoichiro Ono, Masao Takeichi (Fukuoka University Chikushi Hospital, Fukuoka); Kazuhiro Kaneko, Tomonori Yano, Hiroaki Kon, Shinya Tsuruta (National Cancer Center Hospital East, Chiba); Yoshiro Kawahara, Toshio Uraoka, Seiji Kawano, Keisuke Hori (Okayama University Hospital, Okayama); Chizu Yokoi, Naoyoshi Nagata (National Center for Global Health and Medicine, Tokyo); Yasushi Sugiura (Kitano Hospital, Osaka); Hideki Ishikawa (Kyoto Prefectural University of Medicine, Kyoto); and Tomoko Aoyama (Medical Research Support, Osaka).

Conflicts of interest

The authors disclose no conflicts.

Funding

Supported by a part of grant-in-aid for cancer research from the Ministry of Health (H21-009), Labor, and Welfare of Japan.

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

Manabu Muto, MD, PhD, Hironaga Satake, MD, Tomonori Yano, MD, Keiko Minashi, MD, Ryuichi Hayashi, MD, Satoshi Fujii, MD, PhD, Atsushi Ochiai, MD, PhD, Atsushi Ohtsu, MD, PhD, Shuko Morita, MD, Takahiro Horimatsu, MD, Yasumasa Ezoe, MD, Shinichi Miyamoto, MD, PhD, Ryo Asato, MD, PhD, Ichiro Tateya, MD, PhD, Akihiko Yoshizawa, MD, PhD, Tsutomu Chiba, MD, PhD

Kyoto, Japan

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.

DISCLOSURE: *Dr Muto was supported in part by grants-in-aid for cancer research from the Ministry of Health (H21-1), Labor, and Welfare of Japan. The other authors disclosed no financial relationships relevant to this publication.*

0016-5107/$36.00
doi:10.1016/j.gie.2011.04.027

Received November 18, 2010. Accepted April 19, 2011.

Current affiliations: Department of Gastroenterology and Hepatology (M.M., S. Morita, T.H., Y.E., S. Miyamoto, A.Y., T.C.), Department of Head and Neck Surgery (I.T., R.A.), Department of Pathology (A.Y.), Kyoto University Graduate School of Medicine, Kyoto, Japan, Division of Gastrointestinal Oncology and Endoscopy (H.S., T.Y., K.M., A. Ohtsu), Division of Head and Neck Surgery (R.H.), Division of Pathology (S.F., A. Ochiai), National Cancer Center Hospital East, Kashiwa, Japan.

Reprint requests: Manabu Muto, MD, PhD, Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.

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

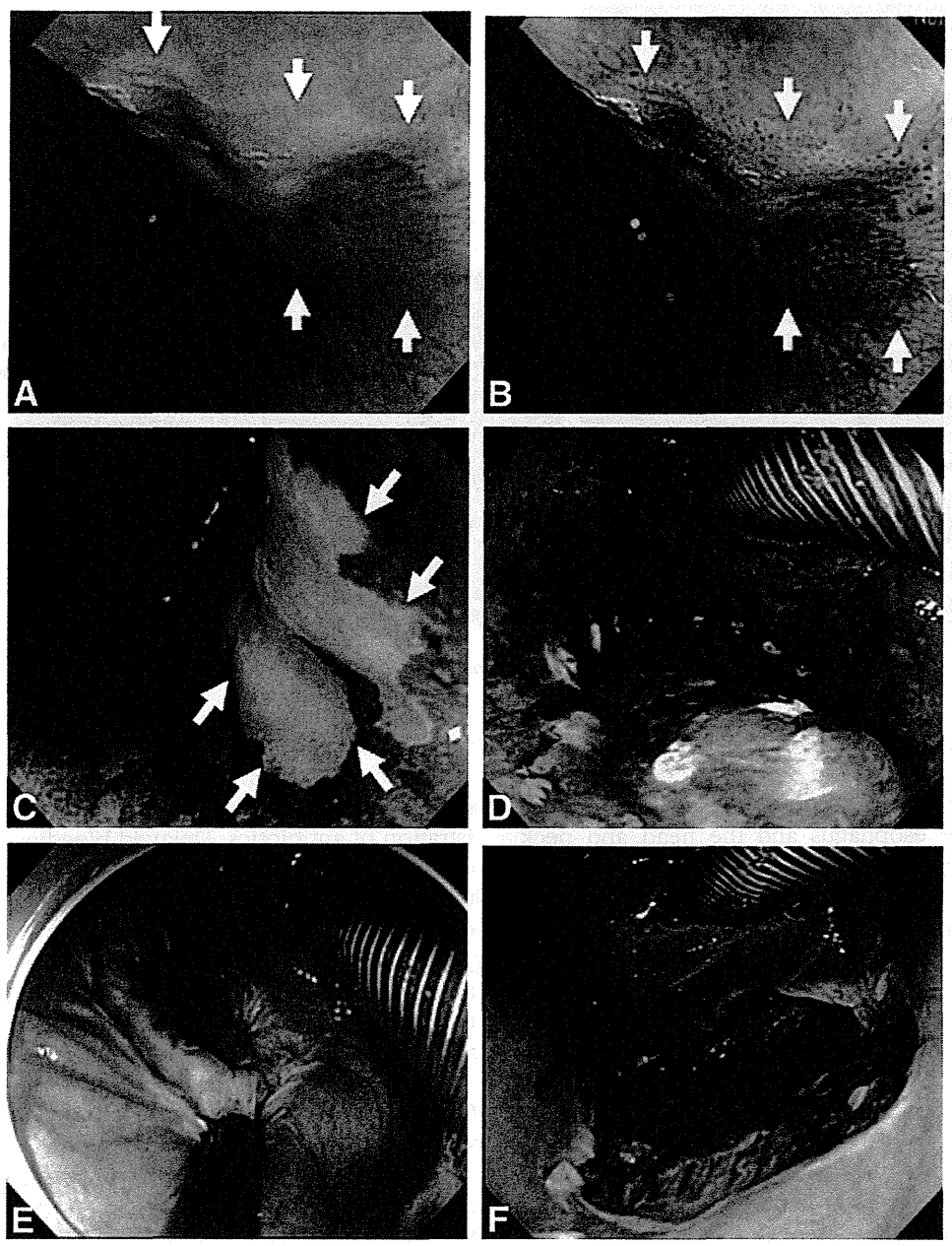

Figure 1. TOPER for superficial pharyngeal cancer. **A,** Endoscopic photograph showing the right piriform sinus with superficial pharyngeal cancer. The slight reddish-color mucosa is the neoplastic lesion (*arrows*). **B,** Narrow-band imaging corresponding with **A** showing well-demarcated brownish 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

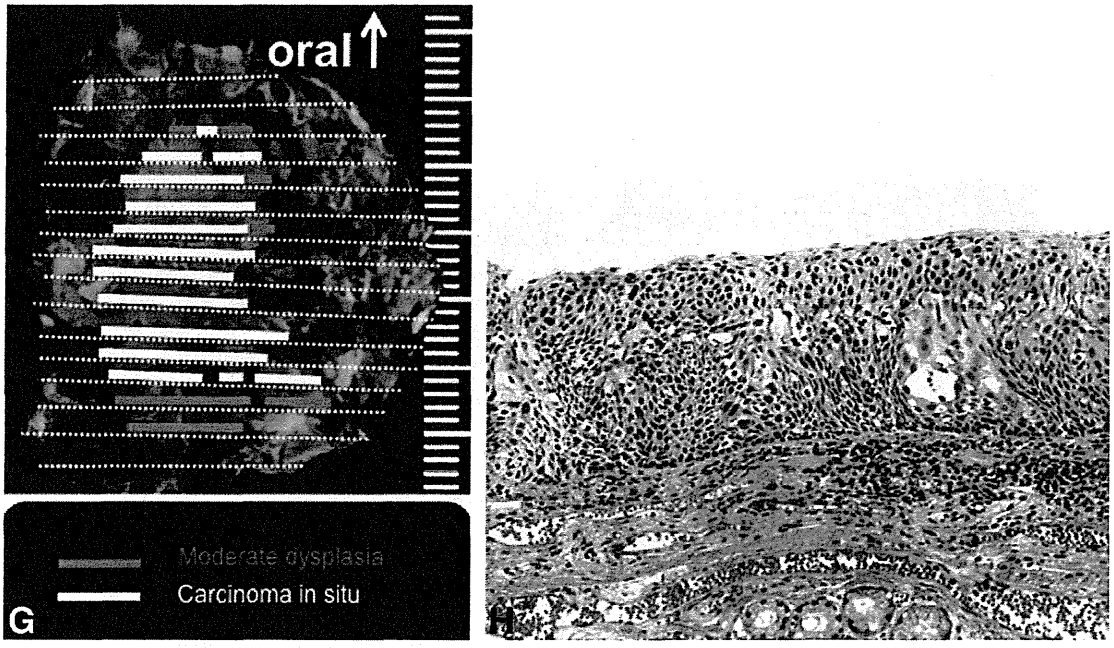

Figure 1. (*continued*)

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[13] 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.

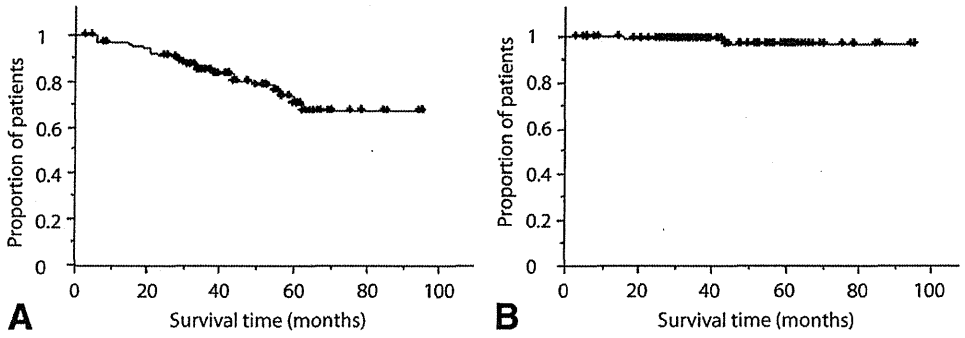

Figure 2. Overall survival (**A**) and cause-specific survival (**B**) after TOPER for superficial pharyngeal cancer.

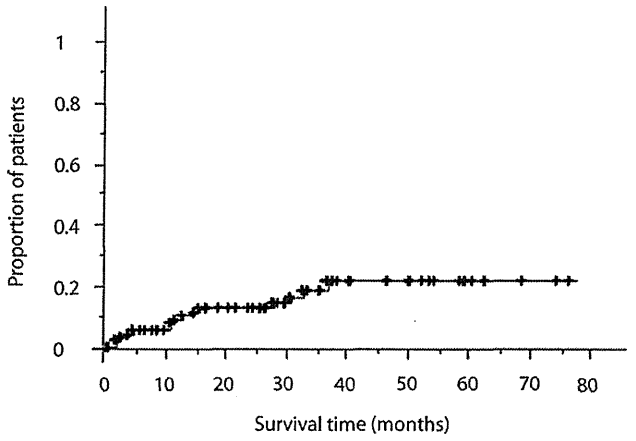

Figure 3. Metachronous development of superficial pharyngeal cancer after TOPER.

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

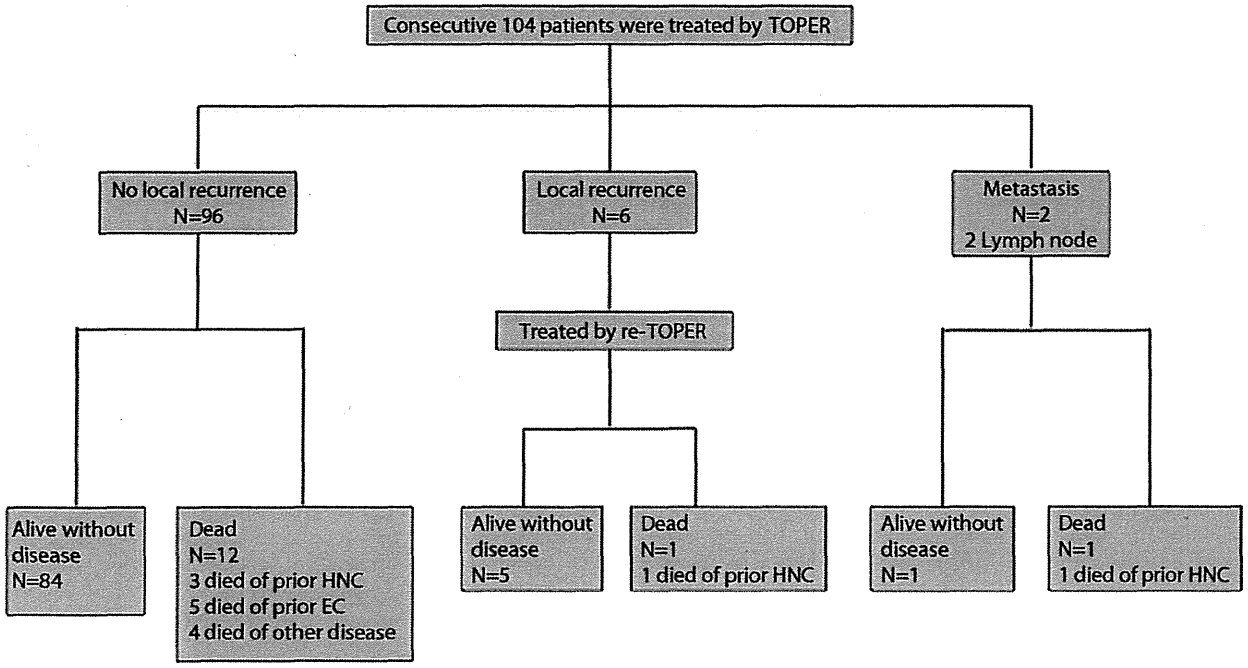

Figure 4. Clinical outcomes after TOPER for superficial pharyngeal cancer.

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.

J Gastroenterol (2011) 46:998–1002
DOI 10.1007/s00535-011-0419-5

ORIGINAL ARTICLE—ALIMENTARY TRACT

Differences of image enhancement in image-enhanced endoscopy: narrow band imaging versus flexible spectral imaging color enhancement

Manabu Muto · Hirokazu Higuchi · Yasumasa Ezoe · Takahiro Horimatsu · Shuko Morita · Shin-ichi Miyamoto · Tsutomu Chiba

Received: 25 January 2011 / Accepted: 21 April 2011 / Published online: 26 May 2011

Abstract
Background Narrow band imaging (NBI) can emphasize images of the surface microvasculature of lesions, because the central wavelengths of the NBI filter are 415 and 540 nm and these wavelengths are well absorbed by hemoglobin. Flexible spectral imaging color enhancement (FICE) increases the contrast in depictions of mucosal lesions. However, quantitative evaluation of the image enhancement shown by NBI and FICE has not been reported. The aim of this study was to measure and compare the degrees of image enhancement in NBI and FICE.
Methods We compared the visibility of human blood diluted with distilled water between that shown by white-light imaging (WLI) and that shown by NBI or FICE. One milliliter of human blood was plated onto a 12-well transparent plastic plate to set up doubling dilutions, from 1/2 to $1/2^{23}$. High-definition endoscopes were used for each imaging method. A total of 11 endoscopists independently evaluated the visibility of the diluted blood. The median dilution was defined as the limit of visibility in each image.
Results NBI enabled clearer visualization of the presence of blood compared with conventional WLI. NBI recognized blood contamination up to a $1/2^{14}$ dilution, whereas conventional WLI recognized blood contamination up to a $1/2^{11}$ dilution. In contrast, FICE did not improve the visualization of diluted blood and recognized blood contamination up to a $1/2^{10}$ dilution.
Conclusions NBI more effectively enhanced images of diluted blood compared to conventional WLI, while FICE did not improve the visualization of the diluted blood. These data suggest the usefulness of NBI for the early detection of gastrointestinal neoplasia, which is accompanied by abundant neovascularization.

Keywords Image-enhanced endoscopy · Narrow band imaging · Flexible spectral imaging color enhancement

Introduction

Image-enhanced endoscopy (IEE) can be divided into dye-based and equipment-based approaches; the latter is a newly developed technology [1]. The diagnostic accuracy of equipment-based IEE is expected to improve in combination with magnifying endoscopy. In particular, narrow band imaging (NBI) is an equipment-based IEE approach that uses optical technology and depends on hemoglobin absorption wavelengths of 415 and 540 nm exclusively [2, 3]. The combination of NBI with magnifying endoscopy enables the clear visualization of very small mucosal structures and the microvasculature [4].

Superficial cancers in the head and neck region and in the esophagus show neovascularization and morphological changes in microvascular architecture, and novel endoscopic diagnosis by NBI has been established for such cancers [4–9]. We recently showed that NBI provided superior detection and higher diagnostic accuracy compared with conventional white-light imaging (WLI) for lesions in the head and neck region and the esophagus [10].

M. Muto (✉) · H. Higuchi · T. Horimatsu · S. Morita · S. Miyamoto · T. Chiba
Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, 54 Kawahara Cho, Syogoin, Sakyo-ku, Kyoto 606-8507, Japan
e-mail: mmuto@kuhp.kyoto-u.ac.jp

Y. Ezoe
Department of Multidisciplinary Cancer Treatment, Kyoto University Graduate School of Medicine, 54 Kawahara Cho, Syogoin, Sakyo-ku, Kyoto 606-8507, Japan

Most pharyngeal and esophageal superficial cancers can be recognized as well-demarcated brownish areas which are associated with the development of irregular microvessels. Confirmation of this finding leads to a cancer diagnosis with very high accuracy. However, no reports have objectively quantified the impact of red blood cells contained in the lesions on the acquisition of the images.

Flexible spectral imaging color enhancement (FICE) is also an equipment-based IEE that employs image post-processing technology to increase the contrast of the depictions of mucosal lesions [11]. However, there are no reports documenting the superiority of FICE over conventional WLI for the detection and diagnosis of cancers in the head and neck region and in the esophagus. Additionally, images acquired using FICE require processing, but are not influenced by the amounts of red blood cells or hemoglobin. However, color enhancement in the absorption range for hemoglobin is possible in FICE images; thus, visualization of the vasculature should be facilitated with FICE. However, objective quantitative evaluation of the image enhancement shown by FICE compared with that shown by NBI has not been reported.

In the present study, we measured the degree of image enhancement in samples with different amounts of red blood cells in diluted water, comparing the results among WLI, NBI, and FICE.

Methods

To measure differences in the degree of image enhancement between IEE and conventional WLI, we compared endoscopic images of human blood diluted with distilled water. Endoscopic WLI and IEE images of diluted blood were taken under the same conditions in a dark room.

Dilution series

One milliliter of human blood (containing 5×10^7 red blood cells per μL) was plated onto a 12-well transparent plastic plate (Cellstar; Greiner Bio-one, Tokyo, Japan) to set up doubling dilutions, from 1/2 to $1/2^{23}$ (Fig. 1). The human blood was taken from one healthy volunteer (H.H.) and was divided into two experimental samples, to be used for NBI and FICE.

Endoscopic systems

High-definition endoscopes (H260Z; Olympus Medical Systems, Tokyo, Japan, and EC-590ZW; Fujifilm Medical, Tokyo, Japan) were used, with corresponding light sources (LUCERA; Olympus Medical Systems and ADVANCIA; Fujifilm), respectively. The magnifying function was not used in this study, because this study aimed to evaluate the overall visibility.

WLI and IEE conditions

WLI

Color enhancement was employed at level 0 for WLI in the Olympus system. In the Fujifilm Medical system, color enhancement was not set for WLI. While the function of the color enhancement by the Olympus system indicates hemoglobin enhancement, that of the Fujifilm system indicates enhancement of color tone. In this study, to avoid the influence of color enhancement on the results, the color enhancement function was not set in either system.

NBI

Color tone was employed at level 1 for NBI. This setting is recommended for the visualization of microvessels in the upper gastrointestinal tract in the Olympus instruction manual.

FICE

The red, green, and blue (RGB) settings for FICE were $R = 525$ nm (gain 3), $G = 495$ nm (gain 4), and $B = 495$ nm (gain 3). This setting was one of the best recommendations for the enhancement of microvascular architecture provided in the Fujifilm instruction manual.

Evaluation of the endoscopic images

The WLI endoscopic images provided by both Olympus and Fujifilm Medical; NBI; and FICE were independently reviewed by 11 endoscopists who were blinded to the information on each imaging method. The median dilution that was estimated as the limitation of the visibility of diluted blood by each endoscopist was defined as the limitation of visibility with each imaging method.

Results

In general, NBI yielded darker images than WLI in the Olympus system (Fig. 1). However, NBI enabled clear visualization of the presence of blood, which was not visible by WLI (Fig. 1). In contrast, the brightness of FICE was similar to that of WLI in the Fujifilm system (Fig. 2) and the presence of blood was also similarly observable with WLI and FICE (Fig. 2).

In the Olympus system, blood dilutions up to around $1/2^{11}$ were recognizable by WLI; however, it was difficult

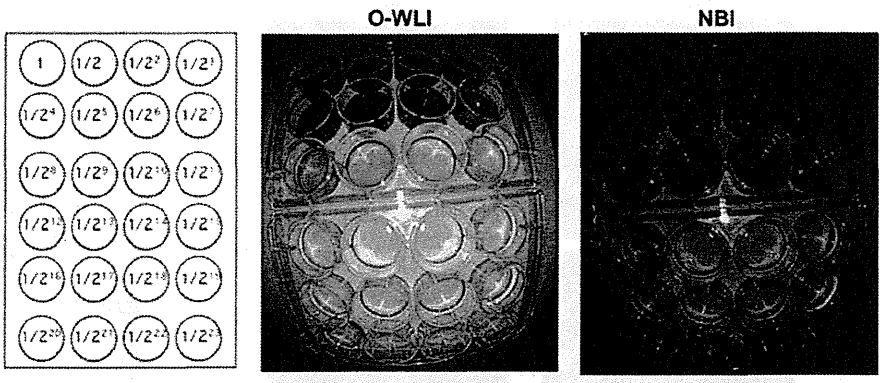

Fig. 1 Comparison of the visibility of blood diluted with distilled water using narrow band imaging (*NBI*) and conventional white light imaging (*WLI*) in the Olympus system. *O-WLI* WLI by Olympus system

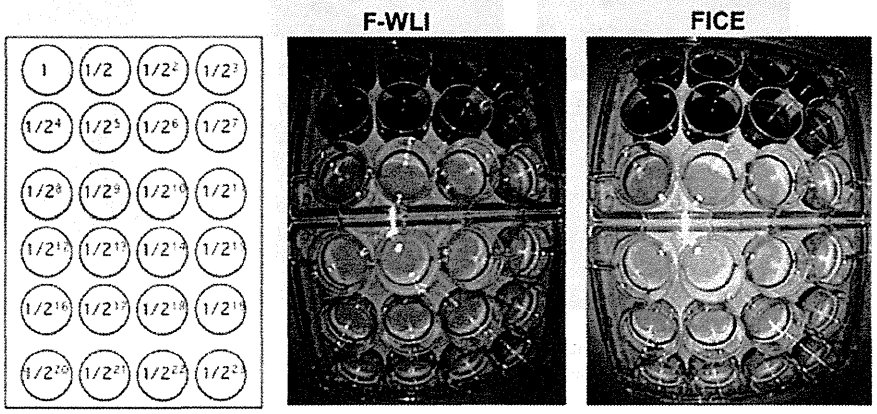

Fig. 2 Comparison of the visibility of blood diluted with distilled water using flexible spectral imaging color enhancement (*FICE*) and conventional WLI in the Fujifilm system, *F-WLI* WLI by Fujifilm system

to detect blood contamination at greater dilutions. In contrast, blood contamination up to a dilution of around $1/2^{14}$ was visualized using NBI (Fig. 1). The limit of visibility of the diluted blood in the water was $1/2^{11}$ and $1/2^{14}$ by WLI and NBI, respectively (Fig. 3). Thus, there was a 2^3-fold difference in sensitivity between these two methods.

To avoid any undesirable effect due to curved endoscopic images, we selected the demonstrable images around the limit of the visibility (Fig. 4). At a dilution of $1/2^9$, blood contamination was recognized in a relatively easy manner by WLI, but the detection was clearer using NBI. At a dilution of $1/2^{10}$, blood contamination was only marginally recognizable by WLI; in contrast, it was clearly observable using NBI. Furthermore, at a dilution of $1/2^{11}$, blood contamination was barely detectable by WLI, whereas it remained clearly visible using NBI. In addition, the presence of blood in distilled water was indicated by a brownish color in NBI images.

In the Fujifilm system, blood dilutions up to around $1/2^{10}$ were recognizable by both WLI and FICE; however, it was difficult to detect blood contamination at greater dilutions by FICE (Fig. 2). The limit of visibility of the diluted blood in the water was $1/2^{10}$ with both WLI and FICE (Fig. 3).

Similar to the Olympus system, to avoid any undesirable effect due to curved endoscopic images, we selected the

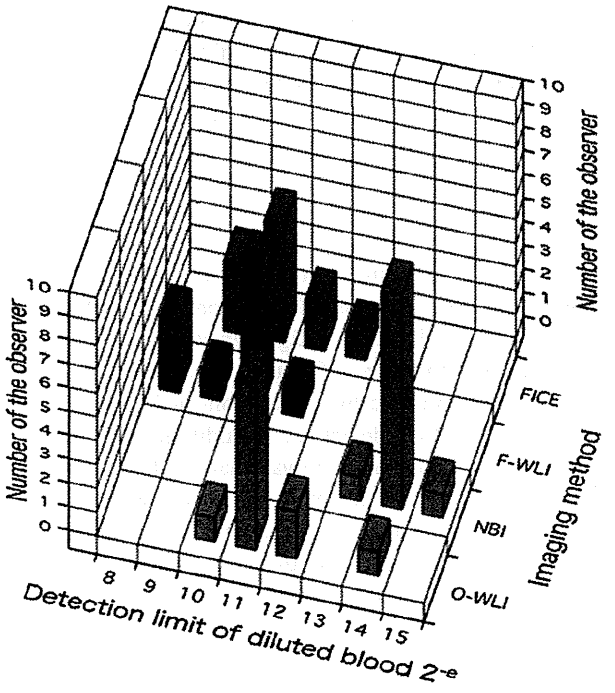

Fig. 3 Estimation of the limitation of the visibility of diluted blood by each endoscopist. *O-WLI* WLI by Olympus system, *F-WLI* WLI by Fujifilm system, $2^{-e} = 2^{-8 \sim 15}$

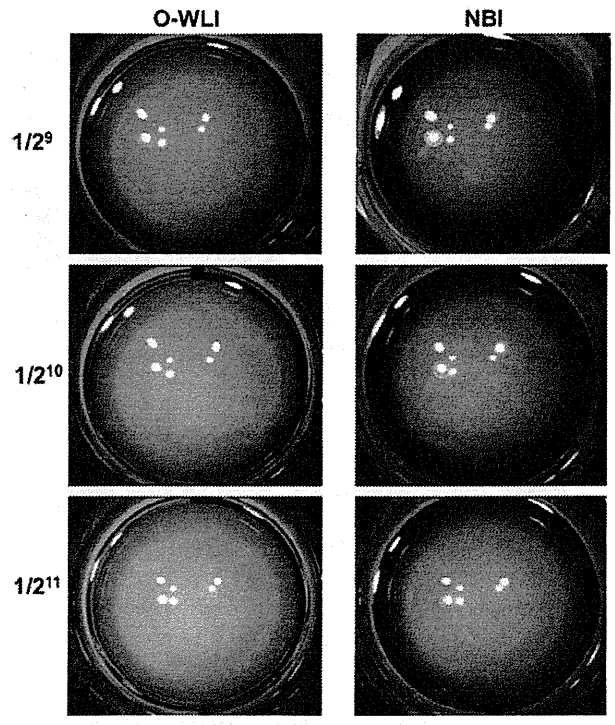

Fig. 4 Comparison of the visibility of blood dilutions from $1/2^9$ to $1/2^{11}$ using NBI and conventional WLI

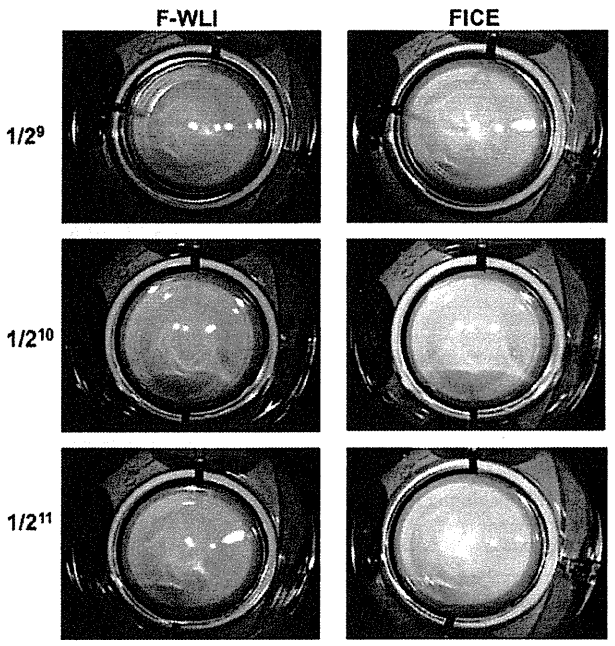

Fig. 5 Comparison of the visibility of blood dilutions from $1/2^9$ to $1/2^{11}$ using FICE and conventional WLI

demonstrable images around the limit of the visibility (Fig. 5). At a dilution of $1/2^9$, blood contamination was marginally recognized by both WLI and FICE. At a dilution of $1/2^{10}$, blood contamination was difficult to detect by both WLI and FICE. Indeed, at dilutions of $1/2^9$–$1/2^{11}$, FICE failed to provide better visualization than NBI (Figs. 4, 5).

Discussion

In this study, by using a quantitative approach, we demonstrated for the first time that the presence of blood was detectable by NBI with a high sensitivity, which was 2^3 times greater than that of conventional WLI. Since NBI light is well absorbed by hemoglobin, it follows that NBI will enhance blood detection. In addition, as blood is the content of the human microvasculature, NBI could theoretically enhance the detection of microvessels.

As cancer arising from squamous cell epithelia in the head and neck region and in the esophagus is accompanied by abundant neovascularization, the present results suggest the usefulness of NBI for the sensitive detection of these cancers [10]. Furthermore, abnormal microvessels are also observed in early cancers of the stomach and colorectum, and NBI with magnification endoscopy has been reported to be more useful for cancer diagnosis than WLI in these regions [12–14]. The present data may also confirm such clinical usefulness.

In contrast to the findings with NBI, when using FICE we did not detect blood with greater sensitivity compared with that for WLI. While the FICE preset mode in this study was one of the best recommendations for the imaging of microvessels, this result might suggest that FICE has limitations for diagnoses based on neovascularization and morphological changes in the microvascular architecture.

In general, the evaluation of visibility is subjective and varies among different individuals. Therefore, in the present study, the visibility of the diluted blood in the sterilized water was independently evaluated by a total of 11 endoscopists. While seven of them (63.6%) evaluated that the limit of visibility of the diluted blood was $1/2^{11}$ in the WLI Olympus system, nine of them (81.8%) evaluated the limit at $1/2^{14}$ with NBI. This means that visibility was objectively improved by NBI. In contrast, evaluation of the visibility of the diluted blood was similar for WLI and FICE. This means that visibility was not objectively improved by FICE.

Most superficial squamous cell carcinomas in the head and neck region and in the esophagus are recognized as brownish areas by NBI. The reason for this remains unclear. In the present study, diluted blood in distilled water was recognized as a brownish color by NBI, even at the dilution level at which the identification of blood contamination was difficult with conventional WLI. One possibility may be that most squamous cell carcinomas in

these regions exhibit marked neovascularization, and the lesions are supplied by abundant red blood cells; as a result, the lesions may be recognized as brownish areas.

The limitation of this study was that the evaluation was performed in vitro. In the human body, cancerous lesions contain not only red blood cells but also collagen tissue, inflammatory cells, and so on. Furthermore, a patient's movement and the existence of mucus will influence the image. Therefore, the possibility cannot be denied that the content of other materials in the tissue and the light condition affect the advantages of NBI. However, there are no structural components that will be absorbed by specialized light as well as NBI. And the patient's condition can be managed in the clinical setting. Thus, the presence of blood might be a strong enhancer for the visualization provided by NBI.

The disadvantage of NBI is its darkness. However, when we visualize the microvascular architecture, the magnifying function is necessary and therefore the darkness will be omitted in the conditions of close observation. Thus, the clinical implications of the present results might not be influenced for the detection but for the detailed observation by magnifying function. Also the present results could provide a plausible explanation for the better visibility of microvessels shown by NBI.

In conclusion, this study demonstrated that NBI is superior to WLI for the identification of diluted blood in an in vitro assay, whereas FICE did not have better visibility of diluted blood than WLI. These results deepen our understanding of the superiority of NBI compared to conventional WLI and also support the evidence that NBI provides better visibility of changes in the microvascular architecture of gastrointestinal neoplasia [9], which is accompanied by abundant neovascularization. Conversely, the data suggest that the visualization of a lesion lacking vascularization would not be improved by NBI.

References

1. Kaltenbach T, Sano Y, Friedland S, Soetikno R. American Gastroenterological Association (AGA) Institute technology assessment on image-enhanced endoscopy. Gastroenterology. 2009;134:327–40.
2. Gono K, Yamazaki K, Doguchi N, Nonami T, Obi T, Yamaguchi M, et al. Endoscopic observation of tissue by narrow band illumination. Opt Rev. 2003;10:211–5.
3. Gono K, Obi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, et al. Appearance of enhanced tissue feature in narrow-band endoscopic imaging. J Biomed Opt. 2004;9:568–77.
4. Muto M, Katada C, Sano Y, Yishida S. 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, Sano Y, Ohtsu A, Esumi H, et al. Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites. Cancer. 2004;101:1375–81.
6. Muto M, Ugumori T, Sano Y, Ohtsu A, Yoshida S. Narrow band imaging combined with magnified endoscopy for the cancer at the head and neck region. Dig Endosc. 2005;17:S23–4.
7. Yoshida T, Inoue H, Usui S, Satodate H, Fukami N, Kudo SE. Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. Gastrointest Endosc. 2004;59:288–95.
8. Watanabe A, Taniguchi M, Tsujie H, Hosokawa M, Fujita M, Sasaki S. The value of narrow band imaging endoscope for early head and neck cancers. Otolaryngol Head Neck Surg. 2008;138:446–51.
9. Ugumori T, Muto M, Hayashi R, Hayashi T, Kishimoto S. Prospective study of early detection of pharyngeal superficial carcinoma with the narrowband imaging laryngoscope. Head Neck. 2009;31:189–94.
10. Muto M, Minashi K, Yano T, Saito Y, Oda I, Nonaka S, 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.
11. Pohl J, May A, Rabenstein T, Pech O, Ell C. Computed virtual chromoendoscopy: a new tool for enhancing tissue surface structures. Endoscopy. 2007;39:80–3.
12. Nakayoshi T, Tajiri H, Matsuda K, Kaise M, Ikegami M, Sasaki H. Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: correlation of vascular pattern with histopathology. Endoscopy. 2004;36:1080–4.
13. Sumiyama K, Kaise M, Nakayoshi T, Kato M, Mashiko T, Uchiyama Y, 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. 2004;60:79–84.
14. Machida H, Sano Y, Hamamoto Y, Muto M, Kozu T, Tajiri H, et al. Narrow-band imaging in the diagnosis of colorectal lesions: a pilot study. Endoscopy. 2004;36:1094–8.

Cancer Chemother Pharmacol (2011) 68:263–266
DOI 10.1007/s00280-011-1633-9

SHORT COMMUNICATION

Pharmacokinetics of oxaliplatin in a hemodialytic patient treated with modified FOLFOX-6 plus bevacizumab therapy

Takahiro Horimatsu · Shin'ichi Miyamoto · Shuko Morita · Yoko Mashimo · Yasumasa Ezoe · Manabu Muto · Tsutomu Chiba

Received: 14 February 2011 / Accepted: 22 March 2011 / Published online: 16 April 2011

Abstract
Purpose To establish an appropriate administration schedule for oxaliplatin in FOLFOX plus bevacizumab therapy for a hemodialytic patient.
Methods A 50-year-old man on chronic hemodialysis was treated for colon cancer and synchronous hepatic metastasis with modified FOLFOX-6 plus bevacizumab therapy every 3 weeks. The plasma concentration of free platinum was measured at eight points, before and within the first 50 h after oxaliplatin administration. A dose escalation study of oxaliplatin was performed at doses of 60, 70, and 85 mg/m^2. A 4-h dialysis session was begun at the end of the oxaliplatin treatment.
Results The pharmacokinetics of free platinum showed a bimodal pattern at each dose: The serum concentration decreased rapidly soon after dialysis, then increased, and remained at a high level for 24 h. The areas under the curves (AUC) for free platinum were 17.6, 23.6, and 32.6 μg h/mL after doses of 60, 70, and 85 mg/m^2 oxaliplatin, respectively. These exceeded the AUC when 90 mg/m^2 was given to a patient with normal renal function (7.9 μg h/mL). Treatment was safely continued for 6 months without severe toxicity.
Conclusion FOLFOX plus bevacizumab therapy can be given safely to hemodialytic patients with no reduction in the dose of oxaliplatin if hemodialysis is performed soon after the administration of oxaliplatin and the dosing interval is extended to 3 weeks.

Keywords Colorectal cancer · Renal failure · Hemodialysis · FOLFOX plus bevacizumab · Oxaliplatin

Introduction

The number of long-lived hemodialytic patients has been increasing with improvements in dialysis treatments. However, hemodialytic patients are potentially at increased risk of cancer for several reasons, including the presence of chronic infection, a weakened immune system, nutritional deficiencies, and altered DNA repair [1].

Colorectal cancer is the third leading cause of cancer deaths, and its incidence is also increasing yearly in Japan [2]. FOLFOX plus bevacizumab is a chemotherapeutic regimen consisting of oxaliplatin and infusional 5-Fluorouracil (5-FU)/levofolinate plus bevacizumab and is accepted widely as an initial treatment for unresectable colorectal cancer, with an objective response in up to 50% of patients treated [3]. However, there have been few reports of the use of oxaliplatin in hemodialytic patients [4–6], and little is known about the safety/efficacy of FOLFOX plus bevacizumab therapy or its optimum dosage in this patient population. Here, we report the case of a hemodialytic patient with metastatic colon cancer, successfully treated with modified FOLFOX-6 plus bevacizumab therapy.

T. Horimatsu · S. Miyamoto (✉) · S. Morita · Y. Mashimo · M. Muto · T. Chiba
Department of Gastroenterology and Hepatology,
Kyoto University Graduate School of Medicine,
54 Shogoinkawaharacho, Sakyo-ku, Kyoto 606-8507, Japan
e-mail: shmiyamo@kuhp.kyoto-u.ac.jp

Y. Ezoe
Department of Multidisciplinary Cancer Treatment,
Kyoto University Graduate School of Medicine,
54 Shogoinkawaharacho, Sakyo-ku, Kyoto 606-8507, Japan

Materials and methods

A 50-year-old Japanese man with gouty nephropathy had been maintained on hemodialysis since 2006. A computed tomography (CT) scan showed more than 20 metastases (up to 3 cm in diameter) scattered throughout both lobes of his liver. A colonoscopy showed a protuberant type of tumor located on the sigmoid colon. After the surgical resection of the primary tumor to prevent intestinal obstruction and bleeding, the patient received systemic chemotherapy. Chemotherapy was initiated with the modified FOLFOX-6 (mFOLFOX-6) regimen plus bevacizumab, given every 3 weeks. After bevacizumab was administered by infusion over 90 min, oxaliplatin and levofolinate were administered simultaneously for 2 h. 5-FU was then administered as a bolus injection, followed by its continuous infusion for 46 h with a pump after a 4-h dialysis session (Fig. 1). The starting dose of oxaliplatin was 60 mg/m^2 (70% of the standard dose of 85 mg/m^2) because oxaliplatin is known to be primarily excreted in the urine and was expected to be eliminated by hemodialysis alone in this patient [7]. The dose of oxaliplatin was increased to 70 and 85 mg/m^2, while possible adverse events were monitored. The starting dose of 5-FU was set at the standard dose, because 5-FU is largely (80%) eliminated by the hepatic metabolism and secreted into the bile [8]. Many previous reports have shown that there is no need to adjust its dose in dialysis patients [9]. During each course of mFOLFOX-6 plus bevacizumab therapy, a 4-h dialysis session was begun immediately after the administration of oxaliplatin, using a polysulfonate hollow-fiber dialyzer (APS-21SA) and acetic acid-free dialysate (Carbostar P). The blood flow rate was set at 250 mL/min and the dialysate flow rate at 600 mL/min. The patient's free platinum levels were measured. Blood samples were collected at the following eight points: before the start of oxaliplatin administration, 2 (just before dialysis), 2.25, 2.5, 3, 6, 26, and 50 h after oxaliplatin administration (the last collection was just before the second dialysis session). The blood samples were immediately centrifuged at 1,700×g for 10 min, and the serum thus obtained was further centrifuged at 1,700×g for 20 min in an ultrafiltration tube. The ultrafiltrate sample was then stored in a freezer until the platinum concentration was assayed by flameless atomic absorption spectrometry (NAC Co., Ltd, Tokyo, Japan). The area under the curve (AUC) for platinum in the ultrafiltrate was calculated from time 0 to 50 h after the start of oxaliplatin administration, using the trapezoidal method.

Results

Table 1 shows the C_{max} and AUC data for free platinum in the serum of a hemodialytic patient receiving mFOLFOX-6 plus bevacizumab therapy. Figure 2 shows the time course of the free platinum concentration. The level of free platinum, which is related to the antitumor activity and toxicity of oxaliplatin, decreased soon after dialysis. It subsequently increased for 26 h after the administration of oxaliplatin and thereafter remained at the same level for 24 h. These findings differ considerably from those previously reported for patients with normal renal function who received 90 mg/m^2

Table 1 Pharmacokinetic parameters of platinum in plasma ultrafiltrate

	60 mg/m^2 $n = 1$	70 mg/m^2 $n = 1$	85 mg/m^2 $n = 3$	90 mg/m^2 ($n = 3$*)
C_{max} (ng/mL)	500	600	863	963.3
AUC_{0-50} (μg h/mL)	17.6	23.6	32.6	7.9

AUC area under the plasma concentration–time curve

* Shirao et al. [10]

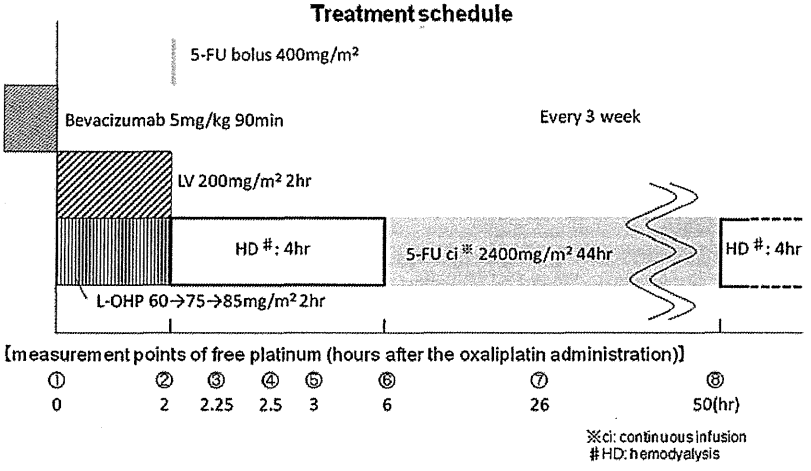

Fig. 1 Treatment schedule

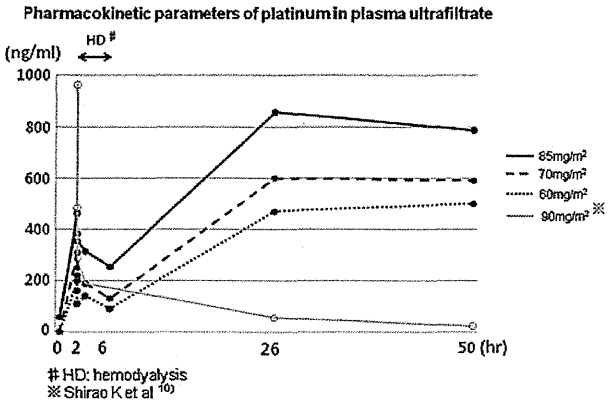

Fig. 2 Concentration of platinum in plasma ultrafiltrate

oxaliplatin (free platinum C_{max} was 963.3 ng/mL and AUC was 7.9 μg h/mL) [10]. The tolerability data and pharmacokinetic profiles obtained during each cycle were used to optimize the dose of each drug and the dosing intervals for the subsequent cycles. The free platinum AUCs were 17.6, 23.6, and 32.6 μg h/mL at doses of 60, 70, and 85 mg/m^2, respectively, which are about 2–4 times greater than that obtained with 90 mg/m^2 oxaliplatin in patients with normal renal function [11]. Therefore, a longer dose interval of 3 weeks was set for the subsequent cycles, instead of the standard interval of 2 weeks for mFOLFOX-6 plus bevacizumab therapy. The free platinum C_{max} values measured in this patient were 500, 600, and 863 ng/mL at oxaliplatin doses of 60, 70, and 85 mg/m^2, respectively, which are about 50–90% of that obtained with a dose of 90 mg/m^2 oxaliplatin in patients with normal renal function [10]. Therefore, a standard dose of 85 mg/m^2 was given during the subsequent five cycles. In all, eight courses of mFOLFOX-6 plus bevacizumab therapy (a total of 815 mg/m^2 oxaliplatin) were completed, although grade 1 peripheral neuropathy by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 3) criteria was observed. A CT scan showed no changes in the number or sizes of the metastatic liver tumors.

Discussion

To the best of our knowledge, this is the first report of a hemodialytic patient with metastatic colon cancer successfully treated with mFOLFOX-6 plus bevacizumab therapy. In the patient reported here, the free platinum level showed a bimodal pattern, with peaks appearing at 2 and 26 h after the start of oxaliplatin administration. The second peak was as high as the first peak. In patients treated with oxaliplatin, the serum-free platinum concentration reflects the biological activity of the drug, i.e., it determines both its antitumor activity and its toxicity [11, 12]. Previous studies have shown that most circulating platinum molecules derived from oxaliplatin are immediately bound to plasma proteins (primarily albumin) and irreversibly inactivated [13, 14]. The free platinum in the blood is serially excreted by the kidneys, and its excretion is delayed in patients with impaired renal function [15]. A second peak in the free platinum concentration between hemodialyses has also been observed in hemodialytic patients treated with cisplatin [16]. This might be caused by the dissociation of the platinum bound to plasma proteins and blood cells or by platinum in the tissues returning to the blood [17]. In patients with normal renal function, it is likely that free platinum is rapidly eliminated by renal excretion, so no second peak is observed [10].

In our patient, who was given 60 mg/m^2 oxaliplatin, the AUC of free platinum was about twofold greater than that observed after an oxaliplatin dose of 90 mg/m^2 in patients with normal renal function. Although the relationship between the AUC of free platinum and the antitumor activity of oxaliplatin is poorly understood, it has been reported that the antitumor activities of cisplatin and carboplatin correlate with the AUC of free platinum [12]. Takimoto et al. [9] reported that reductions in the dose of single-agent oxaliplatin are unnecessary, even in patients with impaired renal function, suggesting that the AUC of free platinum does not correlate with the toxicity of oxaliplatin, regardless of the patient's renal function. They proposed the hypothesis that after the administration of oxaliplatin, the majority of free platinum is in the inactive form in low molecular weight conjugates, which are cleared by glomerular filtration. Therefore, the increase in systemic platinum exposure associated with renal impairment does not increase the drug-related toxicity [18].

Giacchetti et al. [19] compared the antitumor activity and hematological toxicity of oxaliplatin in two regimens: four daily doses versus continuous infusion for 48 h. They reported that hematological toxicity was three times more frequent with the former regimen than with the latter regimen, whereas a similar tumor response was achieved with both regimens. These findings suggest that the antitumor activity of oxaliplatin does not correlate with the AUC of free platinum, whereas its hematological toxicity correlates with its C_{max}.

In our patient, treatment with the standard dose of oxaliplatin in the mFOLFOX-6 plus bevacizumab regimen resulted in a larger AUC with a lower C_{max} for free platinum than those observed with the standard dose of oxaliplatin in patients with normal renal function. This pharmacokinetic profile might explain the significant tumor response achieved with relatively mild toxicity.

Recently, Kawazoe et al. reported that long-term FOLFOX-6 therapy given every 2 weeks with the standard dose of oxaliplatin in patients with mild renal dysfunction led to

accumulated renal toxicity, and the patients were forced to undergo dialysis [20]. However, in the patient reported here, the concentration of free platinum before the administration of oxaliplatin increased gradually (<30, 40, 50, and 80 ng/mL in the second, third, fifth, and seventh courses, respectively). The 3-week dosing interval set for this patient may have been optimal, but it is essential to monitor the serum concentration of free platinum before the administration of oxaliplatin in each course.

In contrast, it has been reported that the clearance rate of bevacizumab by hemodialysis was 0 mL/min and that the pharmacokinetic parameters in hemodialytic patients were similar to those in patients with normal renal function [21].

In conclusion, mFOLFOX6 plus bevacizumab therapy can be used safely for hemodialytic patients, with no dose reduction in oxaliplatin, if hemodialysis is performed soon after the administration of oxaliplatin and the dosing interval is extended to 3 weeks. The cumulative toxicities and long-term outcomes remain to be established. Larger studies of hemodialytic patients with longer follow-up periods are required.

Acknowledgments We thank Dr. Shigemi Matsumoto, Dr. Takafumi Nishimura, and Dr. Yoshiharu Sakai for their invaluable support in the conduct of this study.

References

1. Maisonneuve P, Agodoa L, Gellert R et al (1999) Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet 354:93–99
2. Hyodo I, Suzuki H, Takahashi K et al (2010) Present status and perspectives of colorectal cancer in Asia: colorectal cancer working group report at the 30th Asia-Pacific cancer conference. Jpn J Clin Oncol 40(Suppl 1):i38–i43
3. Hochster HS, Hart LL, Ramanathan RK et al (2008) Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. J Clin Oncol 26:3523–3529
4. Shitara K, Munakata M, Muto O et al (2007) Hepatic arterial infusion of oxaliplatin for a patient with hepatic metastases from colon cancer undergoing hemodialysis. Jpn J Clin Oncol 37:540–543
5. Matoba S, Sawada T, Toda S et al (2008) Modified FOLFOX6 in a patient on hemodialysis with metastatic colorectal cancer. Gan To Kagaku Ryoho 35:673–675 (in Japanese)
6. Watayo Y, Kuramochi H, Hayashi K et al (2010) Drug monitoring during FOLFOX6 therapy in a rectal cancer patient on chronic hemodialysis. Jpn J Clin Oncol 40:360–364
7. Takimoto CH, Remick SC, Sharma S et al (2003) Administration of oxaliplatin to patients with renal dysfunction: a preliminary report of the National Cancer Institute Organ Dysfunction Working Group. Semin Oncol 30:20–25
8. Heggie GD, Sommadossi JP, Cross DS, Huster WJ, Diasio RB (1987) Clinical pharmacokinetics of 5-fluorouracil and its metabolites in plasma, urine, and bile. Cancer Res 47:2203–2206
9. Takimoto CH, Remick SC, Sharma S et al (2003) Dose-escalating and pharmacological study of oxaliplatin in adult cancer patients with impaired renal function: a National Cancer Institute Organ Dysfunction Working Group Study. J Clin Oncol 21:2664–2672
10. Shirao K, Matsumura Y, Yamada Y et al (2006) Phase I study of single-dose oxaliplatin in Japanese patients with malignant tumors. Jpn J Clin Oncol 36:295–300
11. Schellens JHM, Ma J, Planting AST et al (1996) Relationship between the exposure to cisplatin, DNA-adduct formation in leucocytes and tumour response in patients with solid tumours. Br J Cancer 73:1569–1575
12. Jodrell DI, Egorin MJ, Canetta RM et al (1992) Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. J Clin Oncol 10:520–528
13. Graham MA, Lockwood GF, Greenslade D et al (2000) Clinical pharmacokinetics of oxaliplatin: a critical review. Clin Cancer Res 6:1205–1218
14. Calvert H, Judson I, van der Vijgh WJ (1993) Platinum complexes in cancer medicine: pharmacokinetics and pharmacodynamics in relation to toxicity and therapeutic activity. Cancer Surv 17:189–217
15. Massari C, Brienza S, Rotarski M et al (2000) Pharmacokinetics of oxaliplatin in patients with normal versus impaired renal function. Cancer Chemother Pharmacol 45:157–164
16. Watanabe R, Takiguchi Y, Moriya T et al (2003) Feasibility of combination chemotherapy with cisplatin and etoposide for haemodialysis patients with lung cancer. Br J Cancer 88:25–30
17. Levi F, Metzger G, Massari C, Milano G (2000) Oxaliplatin: pharmacokinetics and chronopharmacological aspects. Clin Pharmacokinet 38:1–21
18. Takimoto CH, Graham MA, Lockwood G et al (2007) Oxaliplatin pharmacokinetics and pharmacodynamics in adult cancer patients with impaired renal function. Clin Cancer Res 13:4832–4839
19. Giacchetti S, Bjarnason G, Garufi C et al (2006) Phase III trial comparing 4-day chronomodulated therapy versus 2-day conventional delivery of fluorouracil, leucovorin, and oxaliplatin as first-line chemotherapy of metastatic colorectal cancer: the European Organisation for Research and Treatment of Cancer Chronotherapy group. J Clin Oncol 24:3562–3569
20. Kawazoe H, Sugishita H, Watanabe S et al (2010) Nephrotoxicity induced by repeated cycles of oxaliplatin in a Japanese colorectal cancer patient with moderate renal impairment. Gan To Kagaku Ryoho 37:1153–1157
21. Garnier-Viougeat N, Rixe O, Paintaud G et al (2007) Pharmacokinetics of bevacizumab in haemodialysis. Nephrol Dial Transplant 22:975

Case Report

Epidermoid Metaplasia of the Esophagus: Endoscopic Feature and Differential Diagnosis

Yasumasa Ezoe[1], Satoshi Fujii[2], Manabu Muto[1], Atsushi Ochiai[2] and Atsushi Ohtsu[1]
[1]Division of Digestive Endoscopy and Gastrointestinal Oncology, and [2]Pathology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Chiba, Japan
Corresponding Author: Yasumasa Ezoe, MD, Department of Multidisciplinary Cancer Treatment, Graduate School of Medicine, Kyoto University, 54 Kawara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan
Tel: +81757514319, Fax: +81757514303, E-mail: yasuzoe@kuhp.kyoto-u.ac.jp

ABSTRACT

Background/Aims: Despite the recent improvement of endoscopic diagnostic accuracy, there remain many undiscovered lesions in the GI tract. One such lesion is epidermoid metaplasia of the esophagus. The aim of this study is to clarify the endoscopic and pathological characteristics of epidermoid metaplasia of the esophagus.
Methodology: We reviewed all histological records of gastrointestinal endoscopic biopsy specimens obtained in our institution from September 2003 to August 2006 and identified five lesions from four patients with characteristic pathological findings of epidermoid metaplasia.
Results: All four patients were heavy drinkers and had a synchronous or metachronous squamous cell carcinoma. Three of them had multiple lugol-voiding lesions in the background esophageal mucosa. Endoscopic examination revealed common findings in these lesions: clear demarcation, slightly elevated shape, translucent white color, scaly or shaggy surface, and unstained appearance after Lugol's iodine staining. These endoscopic findings resembled those of superficial esophageal cancer. The pathological features of these lesions were uniform in hyperkeratotic and distinct granular layers of the epithelium and were very similar to those of normal epidermis of the skin.
Conclusions: Since the endoscopic features of epidermoid metaplasia resemble those of superficial esophageal cancer, we must pay enough attention to this new entity at the endoscopic examination.

KEY WORDS: Esophagus; Epidermoid metaplasia; Esophageal cancer; Differential diagnosis; GERD

ABBREVIATIONS: Multiple Lugol–Voiding Lesions (m–LVLs); Endoscopic Mucosal Resection (EMR); Gastro–Esophageal Reflux Disease (GERD); Gastrointestinal (GI)

INTRODUCTION

Despite the recent improvement of endoscopic diagnostic accuracy, it is likely that there are many undiscovered lesions in GI tract. One such lesion is epidermoid metaplasia, which we describe in this report. To our knowledge, there are only two previous reports of epidermoid metaplasia. In 1997, Nakanishi *et al.* reported similar characteristic pathological features, which they termed "epidermization" (1), detected as an irregularly shaped area that was unstained by Lugol's iodine in a surgically resected specimen of esophageal cancer; however, they did not publish an endoscopic picture of the lesion. In 2006, Fukui *et al.* briefly reported a minor lesion with the features of an epidermoid metaplasia located proximal to the gastroesophageal junction (2). This was the only previous report to describe both the endoscopic and pathological appearance of an epidermoid metaplasia. However, the specific characteristics of their endoscopic findings have not been clarified. To clarify the specific gross features of these lesions, it is important to find the common characteristics by reviewing a certain number of cases with epidermoid metaplasia.

METHODOLOGY

We reviewed all histological records of gastrointestinal endoscopic biopsy specimens obtained in our institution from September 2003 to August 2006 and identified five lesions from four patients with characteristic pathological findings diagnosed as epidermoid metaplasia. Thereafter, we reviewed all recorded endoscopic pictures and biopsy specimens obtained from these patients with epidermoid metaplasia.

RESULTS

The clinical background of each patient and the endoscopic findings of each lesion are summarized in **Table 1**. The four patients were two men and two women, whose ages ranged from 48 to 71 years. All reported high alcohol consumption but no special eating habits. All four patients had a concomitant or previous history of squamous cell carcinoma: three patients had a history of esophageal squamous cell carcinoma, and one had oropharyngeal squamous cell carcinoma. None of the patients had any other disease history or concomitant disease.

In two patients (patients 1 and 2), endoscopic examination was performed for the detailed evaluation of the esophageal cancer. Patient 3 was evaluated by routine follow-up after endoscopic mucosal resection (EMR) for superficial esophageal cancer, and patient 4 was evaluated by screening of the upper gastrointestinal tract before multimodal treatment for oropharyngeal cancer detected at another

Hepato-Gastroenterology 2011; 58:809-813

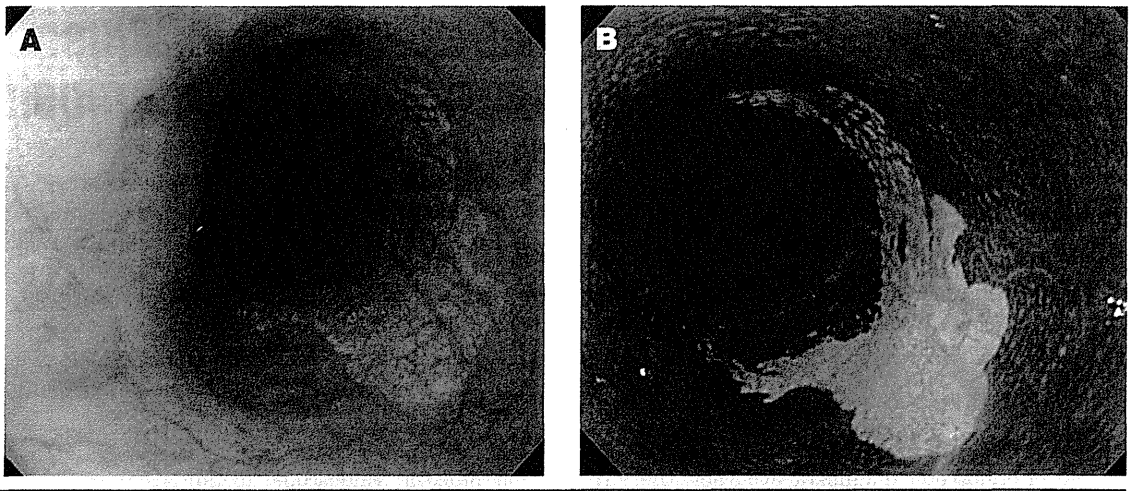

FIGURE 1
Patient 1. Endoscopic images of the large epidermoid metaplasia on the oral side of the cancerous lesion. **A**: A well–demarcated, translucent white scaly lesion that involved one half of the luminal circumference. **B**: Well–demarcated unstained area seen with Lugol's iodine staining.

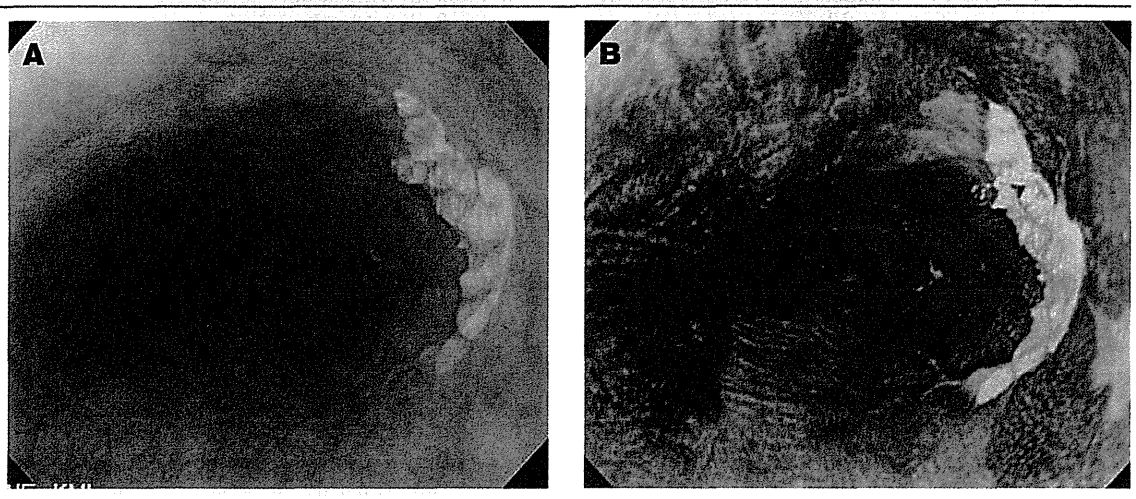

FIGURE 2
Patient 2. Endoscopic images of the small epidermoid metaplasia. **A**: A well–demarcated, white shaggy lesion that measured 15mm on its major axis. **B**: A clearly demarcated, unstained area after Lugol's iodine staining. Multiple Lugol–voiding lesions are seen all over the esophagus without any relation to the epidermoid metaplasia.

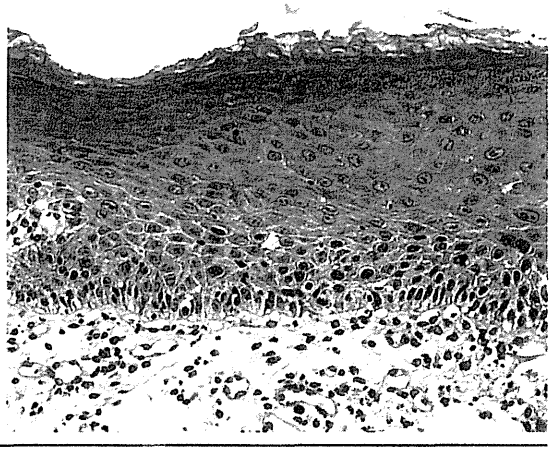

FIGURE 3
Histological features of epidermoid metaplasia (HE). There are hyperkeratotic and distinct granular layers in the epithelium and granulation tissue, with abnormal infiltration of inflammatory cells in the subepithelial layer.

hospital. The lesions were located in the middle or lower esophagus, and the size of the major axis ranged from 6 to 40mm. Patient 1 had two lesions and the others each had one lesion.

Endoscopic examination revealed common findings of the lesions: clear demarcation, slightly elevated shape, translucent white colour, scaly or shaggy surface without erosion or ulceration, and unstained appearance after Lugol's iodine staining (**Figures 1** and **2**). These endoscopic features differed from those associated with other esophageal abnormalities (**Table 2**), and these features seem to be specific to epidermoid metaplasia. In three patients, endoscopic examination had been performed previously. Therefore, we reviewed all of the recorded endoscopic pictures and biopsy specimens taken from the lesions and used this information to determine that both endoscopic and histological findings had not changed during the course of follow-up. In addition, there were multiple Lugol-voiding lesions (m-LVLs (3-5)) all through the entire esophagus in three of four patients. No patient had gastro-esophageal reflux disease (GERD). The pathological features of these lesions were uniform in both the hyperkeratotic and distinct granular layers of the epithelium (**Figure 3**). These histological findings differed considerably from other known histological findings in various esophageal abnormalities, but appeared very similar to normal epidermis of the skin and were also consistent with the microscopic findings in two previous reports of epidermoid metaplasia (1, 2). Accordingly, we regarded these findings as epidermoid metaplasia. In addition, one biopsy specimen obtained from the lesion contained granu-