Feasibility of Standardized Procedures of White Light Gastroscopy for Clinical Practice: A Multiple Center Study in China

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Research Article

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Abstract

Background: There is no standardized operation procedure for white light gastroscopy (WLG) in China. We aimed to establish a standardized procedure of white light gastroscopy for clinic patients screening, to verify its effect and its feasibility in clinical practice.

Methods: We applied the standardized procedure for WLG to out-patients at 9 tertiary hospitals in Beijing. All of the clinical information and operation procedure were recorded.

Results: We set a standardized operation procedure for WLG. 1051 patients were enrolled in the base-line survey stage between March 2014 and December 2015. 2156 patients were enrolled in the WLG standardized operation stage from January 2016 to June 2017. The median durations of standardized procedure group were significantly longer than that of the base-line group (prolonged 60.3 seconds averagely, P=0.003). The taken picture numbers in the standardized procedure group were significantly higher than that in the base-line group (17 pictures more averagely, P<0.001). The overall detection rate of gastric mucosal lesions in the standardized procedure group was significantly higher than that in the base-line group (52.5% vs. 38.4%, P<0.01). Both the patient and endoscopist satisfaction scores in the standardized procedure group were all significantly improved than those in the base-line group.

Conclusions: The standardized procedure for WLG can improve the detection rate of gastric lesions significantly, and also improve the satisfaction of patients and endoscopists despite prolonged duration. The standardized procedure for white light gastroscopy is effective and feasible in clinical practice with the present endoscopy equipment in China.

Background

Gastric cancer (GC) is the fifth most common malignancy and the third leading cause of cancer mortality in the world [(1)]. In China, GC was the second commonly diagnosed cancer and the second leading cause of cancer death in 2015 [(2)]. The five-year survival rate was nearly 10%~20% for advanced stage GC patients, while it was over 90% for early stage patients [(3, 4)]. It is the effective strategy with early detection, diagnosis and treatment to reduce mortality of GC. The early GC detection rate is defined as the ratio of the number of early GC to the total number of GC, which is a crucial indicator for cancer screening program evaluating. The early GC detection rate was over 80% in Japan [(5)], while it was lower than 10% in many hospitals of China [(6)]. Most GC patients in China were in advanced stage at the time of diagnosis, therefore, they had to afford a heavy cost burden for treatment with poor prognosis. In order to earlier diagnose GC, WLG contributes to search the suspected lesions by endoscopists and confirm the characters of lesions by enhancing endoscopy or biopsy. In China, there is no standardized operation procedure for WLG at present, which leads to misdiagnose for many early GC and precancerous lesions [(7)]. In this study, we set the standardized operation procedure of white light gastro endoscopy for clinic patients screening, based on the endoscopy procedure experience of endoscopy in China and systematic screening protocol for the stomach (SSS) in Japan [(8)]. Through the prospective multi-center registry study,
we verified the effect to improve the detection rate of gastric lesions and early gastric cancers after using the standard procedure. We also confirmed the feasibility of the standard procedure by satisfaction survey for both patients and endoscopists.

**Methods**

**Study Populations**

This prospective controlled, open-label, multicenter feasibility study was conducted at 9 hospitals in Beijing, China. This study was conducted according to the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) initiative ([7]) and the Declaration of Helsinki. Out-patients aged 40 years or older at each center between March 2014 and June 2017 were considered for enrollment in this study. We excluded patients who underwent gastrectomy, had got the diagnosis of GC before, refused to take part in the study, and couldn't accept the examination.

Informed consent was obtained from each participant, and the study was approved by the institutional review board of each participating hospital (2014/8/25-2014/9/30). Moreover, the study were registered in Chinese Clinical Trial Register (ChiCTR:2000028733).

**Study Design**

Firstly, we surveyed the current status of conventional WLG procedures as the base-line data at each center. All clinical information and procedure details were collected, including preparation before examination, the time during operation (from insert into pharynx to withdrawal from pharynx), and photos taken during examination. Patients and endoscopists filled in the satisfaction questionnaire for each endoscopy examination. The endoscopically detected gastric lesions were recorded, as well as their pathological results including inflammation, intestinal metaplasia, intraepithelial neoplasia, and early and advanced staged GC.

Based on the endoscopy procedure experience and SSS in Japan, we set a standardized operation procedure for WLG after the discussion by more than endoscopy experts from all of the 9 centers. The standardized procedure can map the entire stomach without blind spots. The procedure includes 3 steps: 1) Preparation before the endoscopy. Patients were asked for fasting and water deprivation for more than 6 hours. Fifteen minutes before the procedure, patients were asked to drink a mixture of mucolytic and defoaming agents, which was 50ml water mixed with 8000U chymotrypsin or 10000U pronase, 1 g sodium bicarbonate, and 5 ml simethicone. They also took the lidocaine mucilage for local pharyngeal anaesthesia before examination. 2) Rinsing out the mucus and froth from gastric mucosa during the endoscopic examination. 3) Standard operation procedure. Endoscopists were asked to take at least 34 + 1 pictures with careful observation during the entire examination. All the pictures included: 2 pictures for laryngeal part of pharynx when entry and exit. 5 + 1 pictures for esophagus, each for introitus oesophagi, upper segment (22 cm from incisor), middle segment (28 cm from incisor), lower segment (34 cm from incisor), and cardia (including
dental line). +1 meant an esophagogastric junction picture when dental line migrating upward. 22 pictures for stomach (Fig. 1), including 4 quadrants of gastric antrum, lower body, middle-upper body with the antegrade view and fundus-cardia with retroflex view, and 3 quadrants of middle-upper body, incisura with retroflex. 5 for duodenum, including 4 quadrants of duodenal bulb and one picture of descending duodenum with papilla. These were the minimum required standard. If lesions were found in the examination, additional pictures could be taken.

Then we applied the standard procedure for white light endoscopy to out-patients at each center. All clinical and operation information were recorded. The endoscopically detected gastric lesions and the pathological results were recorded as mentioned above. Patients and endoscopists filled in the satisfaction questionnaires after each endoscopy examination. The satisfaction was graded into 5 scales, which were “very satisfied, satisfied, general, not satisfied, very dissatisfied” respectively and endowed 5,4,3,2,1 points. We made the comparative analysis between the base-line data and standard procedures.

**Endoscopy Examination**

All examinations were performed by endoscopic specialists who had been trained for more than two years on endoscopy in 9 institutes. All patients were offered local pharyngeal anesthesia with lidocaine mucilage before examination, without intravenous sedation drugs. We used the same types of endoscopy (GIF-XQ260, GIF-H260, Olympus Medical Systems, Tokyo, Japan) and high-resolution liquid-crystal monitors. We used a fixed structure enhancement setting and color tone for the video processor.

**Pathologic Evaluation**

Specimens for histological analysis were placed in 10% formalin solution and processed in the routine manner. The biopsy specimens were evaluated using H&E staining. The pathologist was blinded to the clinical and endoscopic findings. Histologic evaluation and diagnoses were performed at each center by two experienced pathologists according to WHO criteria for tumors \(^9\) and the updated Sydney system for gastritis \(^10\). We used a central system of consultation with a main expert pathologist (Wei-xun Zhou). If an indeterminate lesion was encountered, it was scheduled to be reviewed by this consulting pathologist in making a final diagnosis.

**Statistical Analysis**

Statistical analysis was performed using SPSS version 17 software (SPSS, Chicago, IL). The continuous variables were expressed as mean ± standard deviation for normal distribution data or medians (25%, 75% quantile) for non-normal distribution data. Continuous data were compared using the independent sample  \(t\) test or the Mann-Whitney  \(U\) test. Categoric data were compared using the Pearson \(\chi^2\) test (continuity corrected \(\chi^2\) when minimum expected count was < 5; Fisher’s exact test was used when minimum expected count was < 1). All \(P\) values were two-tailed, and \(P\) value < 0.05 was considered statistically significant.
Results

During the base-line survey stage for conventional WLG endoscopy procedure, 1051 patients were enrolled in the study between March 2014 and December 2015. Then, during the standardized operation stage for WLG endoscopy procedure, 2156 patients were enrolled in the study from January 2016 to June 2017. All patients completed the endoscopic procedures. There were no serious adverse events directly related to the endoscopies.

Table 1 shows the clinical features of patients from the base-line group and standardized group. There was no difference between the two groups and sex, age, family history of gastric cancer, fecal occult blood examination, and symptoms (epigastric pain, heartburn, dysphagia, weight loss and melena). As to the eating habits for fresh vegetables and pickled foods, no significant difference was found between the base-line group and standardized group patients (Table 2).

| Clinical features                        | Base-line group | Standardized procedure group | P value |
|------------------------------------------|-----------------|-------------------------------|---------|
| N                                        | 1051            | 2156                         |         |
| Sex M:F                                  | 1: 1.4          | 1: 1.2                       | 0.379   |
| Age                                      | 56.0 ± 9.5      | 55.8 ± 9.1                   | 0.677   |
| Family history of gastric cancer         | 11.0%           | 11.9%                        | 0.709   |
| Epigastric pain                          | 41.4%           | 36.6%                        | 0.184   |
| Heartburn                                | 40.8%           | 34.1%                        | 0.056   |
| Dysphagia                                | 15.0%           | 13.6%                        | 0.585   |
| Weight loss                              | 29.3%           | 26.2%                        | 0.337   |
| Melena                                   | 8.6%            | 6.4%                         | 0.230   |
| Fecal occult blood positive              | 9.4%            | 6.1%                         | 0.077   |
We analyzed the median durations and picture numbers in the endoscopy procedure of the two groups (Table 3). The median durations of standardized procedure group were $455.3 \pm 188.9$s, which were significantly longer than that of the base-line group ($395.0 \pm 172.4$s), and the average total procedure time was prolonged for $60.3$s ($p = 0.003$). The picture numbers taken in the standardized procedure group were $38.2 \pm 6.9$, which were higher than that in the base-line group ($21.3 \pm 6.0$), with averagely increased 17 pictures after the standard procedure ($p < 0.001$). Table 4 showed all kinds of mucosal lesions detected in the stomach before and after the standardized endoscopic procedure. The overall detection rate of gastric mucosal lesions in the standardized procedure group was 52.5%, which was significantly higher than that in the base-line group (38.4%, $p < 0.001$). Although the early gastric cancer rate in the standardized procedure group (36.4%) was higher than that in the base-line group (14.3%), there was no significant difference between the two groups ($p = 0.225$).

### Table 2

Eating habits of patients of the base-line group and standardized procedure group

|                  | Base-line group (%) | Standardized procedure group (%) | P value |
|------------------|---------------------|----------------------------------|---------|
| Fresh vegetables |                     |                                  | 0.211   |
| Never            | 1.2                 | 0.7                              |         |
| < 3–4 times/week | 11.2                | 13.4                             |         |
| 3–4 times/week   | 42.2                | 38.9                             |         |
| > 5–7 times/week | 45.3                | 47.0                             |         |
| Pickled foods    |                     |                                  | 0.612   |
| Never            | 7.0                 | 14.5                             |         |
| < 3–4 times/week | 75.5                | 66.2                             |         |
| 3–4 times/week   | 13.2                | 15.3                             |         |
| > 5–7 times/week | 4.3                 | 4.0                              |         |

### Table 3

Duration and picture number in endoscopy procedure of the base-line group and standardized procedure group

|                  | Base-line group | Standardized procedure group | P value |
|------------------|-----------------|------------------------------|---------|
| N                | 1051            | 2156                         |         |
| Median duration(s) | $395.0 \pm 172.4$ | $455.3 \pm 188.9$  | 0.003   |
| Picture number   | $21.3 \pm 6.0$  | $38.2 \pm 6.9$              | < 0.001 |
Table 4
Gastric lesions detected in the base-line group and standardized procedure group

|                               | Base-line group | Standardized procedure group | P value |
|-------------------------------|-----------------|------------------------------|---------|
| N                             | 1051            | 2156                         |         |
| Detection rate of gastric lesions |                 |                              | < 0.001|
| Noncancerous lesions          |                 |                              |         |
| Simple inflammation           | 222 (21.1%)     | 431 (20.0%)                  | 0.455   |
| Intestinal metaplasia         | 159 (15.1%)     | 360 (16.7%)                  | 0.257   |
| LGIN                          | 4 (0.4%)        | 17 (0.8%)                    | 0.179   |
| Cancerous lesions             |                 |                              |         |
| EGC                           | 2 (0.2%)        | 8 (0.4%)                     | 0.514   |
| AGC                           | 12 (1.1%)       | 14 (0.6%)                    | 0.144   |
| Early gastric cancer rate     | 14.3%           | 36.4%                        | 0.255   |

LGIN: low-grade intraepithelial neoplasia; EGC: early gastric cancer, including high-grade intraepithelial neoplasia and tumor confined to the mucosa or submucosa (T1); AGC: advanced gastric cancer

Table 5 showed the patient satisfaction before and after the standardized endoscopic procedure. The patient satisfaction scores in the standardized procedure group on operation time, tolerance for endoscopy, privacy protection during examination, attitude of medical staff, and technical level of operation, were all significantly improved than that in the base-line group (p < 0.001). As to the willingness for patients to undergo gastroscopy again, or to recommend others to gastroscopy, there was no difference between the two groups. Table 6 showed the endoscopist satisfaction before and after the standardized endoscopic procedure. There are significantly improved for endoscopist satisfaction scores including impression of operation, patient coordination, preparation before endoscopy, and the residual condition of mucus and froth in stomach in the standardized procedure group than those in the base-line group.
|                                | Base-line group | Standardized procedure group | \( P \) value |
|--------------------------------|----------------|-------------------------------|--------------|
| N                              | 1051           | 2156                         |              |
| Tolerance for endoscopy        | 4.34 ± 0.53    | 4.58 ± 0.51                  | < 0.001      |
| Operation time                 | 3.82 ± 0.46    | 3.94 ± 0.34                  | < 0.001      |
| Privacy protection             | 4.38 ± 0.59    | 4.53 ± 0.54                  | < 0.001      |
| Attitude of medical staff      | 4.47 ± 0.59    | 4.65 ± 0.51                  | < 0.001      |
| Technical level of operation   | 4.51 ± 0.57    | 4.69 ± 0.48                  | < 0.001      |
| Willingness for gastroscopy again (rate) | 95.8% | 94.7%                       | 0.478        |
| Recommending others to gastroscopy (rate) | 91.7% | 93.7%                       | 0.265        |
|                                | Base-line group | Standardized procedure group | P value  |
|--------------------------------|----------------|-----------------------------|---------|
| **Patients**                   |                |                             |         |
| N                              | 1051           | 2156                        |         |
| Tolerance for endoscopy        | 4.34 ± 0.53    | 4.58 ± 0.51                 | < 0.001 |
| Operation time                 | 3.82 ± 0.46    | 3.94 ± 0.34                 | < 0.001 |
| Privacy protection             | 4.38 ± 0.59    | 4.53 ± 0.54                 | < 0.001 |
| Attitude of medical staff      | 4.47 ± 0.59    | 4.65 ± 0.51                 | < 0.001 |
| Technical level of operation   | 4.51 ± 0.57    | 4.69 ± 0.48                 | < 0.001 |
| Willingness for gastroscopy again (rate) | 95.8% | 94.7% | 0.478 |
| Recommending others to gastroscopy (rate) | 91.7% | 93.7% | 0.265 |
| **Endoscopist**                |                |                             |         |
| General impression of operation| 3.91 ± 0.55    | 4.39 ± 0.59                 | < 0.001 |
| Patient coordination           | 3.82 ± 0.70    | 4.41 ± 0.63                 | < 0.001 |
| Preparation before endoscopy   | 3.87 ± 0.59    | 4.57 ± 0.56                 | < 0.001 |
| Mucus residual                 | 3.62 ± 0.76    | 4.55 ± 0.68                 | < 0.001 |
| Froth residual                 | 3.66 ± 0.67    | 4.56 ± 0.60                 | < 0.001 |
| Operation time                 | 3.78 ± 0.66    | 4.42 ± 0.69                 | < 0.001 |
| Taken pictures                 | 3.97 ± 0.37    | 4.36 ± 0.53                 | < 0.001 |
| Lesion observation             | 3.71 ± 0.60    | 4.38 ± 0.60                 | < 0.001 |
Table 6
Endoscopist satisfaction scores in the base-line group and standardized procedure group

|                                | Base-line group | Standardized procedure group | P value |
|--------------------------------|----------------|------------------------------|---------|
| N                              | 1051           | 2156                         |         |
| General impression of operation| 3.91 ± 0.55    | 4.39 ± 0.59                  | < 0.001 |
| Patient coordination           | 3.82 ± 0.70    | 4.41 ± 0.63                  | < 0.001 |
| Preparation before endoscopy   | 3.87 ± 0.59    | 4.57 ± 0.56                  | < 0.001 |
| Mucus residual                 | 3.62 ± 0.76    | 4.55 ± 0.68                  | < 0.001 |
| Froth residual                 | 3.66 ± 0.67    | 4.56 ± 0.60                  | < 0.001 |
| Operation time                 | 3.78 ± 0.66    | 4.42 ± 0.69                  | < 0.001 |
| Taken pictures                 | 3.97 ± 0.37    | 4.36 ± 0.53                  | < 0.001 |
| Lesion observation             | 3.71 ± 0.60    | 4.38 ± 0.60                  | < 0.001 |

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Discussion

In recent years, much attention has been paid on early GC with the wildly use of magnifying endoscopy and image enhancement endoscopy. Otherwise, conventional white-light imaging endoscopy remains the standard endoscopic examination modality worldwide. Up to now, most endoscopic equipment has not been magnifying function in many hospital of China. In this study, we aimed to set the standardized WLG operation procedure for clinic patients screening based on existing equipment. Meanwhile, we verified the
effectiveness of this procedure for diagnosis and also the acceptability for both patients and endoscopists.

Doctors in primary hospitals have insufficient understanding about the endoscopic manifestation of early GC. The practicability for diagnosing early GC in routine gastroscopy screening is limited. The key point of this study is to find a way to improve the detection rate of gastric lesions and early GC by white light endoscopy, without changing the current limited endoscopy equipment conditions.

There is no standardized method of mapping the entire stomach that is accepted worldwide. There are no common reviews for the preparation before examination, duration of procedure, and picture numbers of gastroscopy in China. The rates of missed gastric lesion by endoscopic examination have been reported to be about 10%-15%\textsuperscript{[11, 12]}. Rate of missing diagnosis were influenced by many factors including the skill and experience of endoscopists, preparation before examinations (use of mucolytic agents or injection of anti-spasmodic agent), use of high-resolution endoscopy with image-enhanced modalities and double check system on the recorded images\textsuperscript{[13]}. The ideal gastroscopy procedure should extend the gastric wall by air insufflation, and map the entire stomach without blind spots, in terms of getting rid of mucus and froth from gastric mucosa\textsuperscript{[14]}. The guideline of European Society of Gastrointestinal Endoscopy (ESGE) for image documentation in upper GI endoscopy recommended only four pictures of the stomach\textsuperscript{[15]}, which was adopted by many endoscopists in China. It has been reported that the rate of lesion detection could be improved by taking more pictures, longer examinations, and experienced endoscopists\textsuperscript{[16]}. Professor Kenshi Yao proposed a “systematic screening protocol for the stomach”\textsuperscript{[14]}. Otherwise, if we increase too many pictures or prolong the duration time excessively, we might decrease the working quantity within the limited period of time, and patients might also feel suffering from lengthy examination. Therefore, when we try to increase the detection rate of lesions, we must pay attention to the feelings and satisfaction degree of patients and endoscopists.

In this study, although the duration of endoscopy was prolonged in the standardized procedure, the degree of patients’ satisfaction was improved. Patients believed that effect of examination could be improved by extended procedure time and more carefully examination, which also implied the serious working attitude of the medical staff. Patients who had ever took the conventional endoscopy examinations before, were easier to recognize the advantage of standardized procedure compared with the previous examinations. These patients would like to accept the prolonged duration for examination, try to cooperate with the operation and be tolerant to the discomfort of endoscopy. To some extent, they might be willing to recommend others to take the standardized gastroscopy. Although they prolonged the duration of each endoscopy for more than one minute and increased the picture numbers, endoscopists were ready to adopt the standardized procedure. Endoscopists considered that adequate preparation before examination could make the patients cooperate with the examination, and the use of mucolytic and antifoam agents could make the visual field of stomach much better. These improvements enhanced the satisfaction of endoscopists for operation and observation. Therefore, the prolonged duration of standardized procedure is clinically acceptable for both patients and endoscopists.
In our study, detection rate of gastric lesions can be improved by the standardized procedure for WLI. Nevertheless, an accurate early diagnosis of gastric mucosal cancer is difficult with conventional WLI \[^{17}\]. Some early GC are difficult to discover because of lacking special manifestations under white-light imaging observation, and distinguish from benign abnormalities, such as inflammations. The most commonly applied system in clinical practice for endoscopic diagnosis of early GC is the VS (vessel plus surface) classification system based on magnifying endoscopy with narrow-band imaging (M-NBI) \[^{18,19}\]. The diagnosis criteria is based on the analysis of the demarcation line, microvascular and microsurface patterns of the gastric lesions, which is hard to identify with conventional white-light imaging endoscopy. If only white-light imaging endoscopies are used for screening examinations without magnifying imaging equipment, histologic evaluation of biopsy specimens from suspicious lesions is conventionally used to confirm a diagnosis. Theoretically, with the improvement of the detection rate for gastric lesions by standardized white-light imaging endoscopy procedure, the detection rate of early GC will be improved correspondingly.

Out study has some limitations. First, the patients were enrolled from class A hospitals of grade III, which were the highest-level hospitals in China. Patients of these hospitals were selected to some extent, and might be different from gastroscopy screening in primary hospitals. The detection rate and spectrum of gastric lesions of community people and primary hospital patients may vary from our study. Second, the number of early GC was small in our study. We used the white-light imaging endoscopy without magnifying and image enhancement equipment, which was difficult to diagnosis early GC directly. Many patients were referral from lower grade hospitals, and those patients who had got the diagnosis of gastric cancer before were excluded. These might be the reasons for small numbers of early gastric cancers. Further studies should be done in primary hospitals for community people. Third, in our routine examinations, we often used image enhancement endoscopy, such as narrow-band imaging, and dye-based imaging, such as indigo carmine or acetic acid. The detection rate of lesions might be higher if we used these imaging methods. Otherwise, if we added these imaging methods in our study, the required sample size would need to be enlarged and the study design and statistical analyses would be excessively complex. In addition, this study was open labeled because endoscopists and even some patients knew which procedure was used, and it was impossible for a blinded study.

**Conclusions**

It is lack for a standardized procedure of white-light imaging endoscopy in China. The missing diagnosis rate is high for gastric lesions, especially early gastric cancers. In this study, we established the standardized operation procedure for white-light imaging endoscopy, verified its effect to improve the detection rate of gastric lesions, and confirmed its feasibility in clinical practice. This standardized gastroscopy procedure is suitable for Chinese current national conditions, and can be promoted in nationwide hospitals with the present endoscopy equipment.

**Abbreviations**
WLG: white light gastroscopy, GC: Gastric cancer.

Declarations

Ethics approval and consent to participate: This study was approved by the ethical committee of the Peking Union Medical College Hospital (Reference Number: S-730; August 25, 2014). All patients gave written informed consent for this study.

Consent for publication: Written informed consent was obtained from those patients. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no conflicts of interest.

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Author Contributions: Experiments were conceived, designed by Qiang Wang and Aiming Yang. Gastrointestinal endoscopy was performed by Qiang Wang, Shengyu Zhang, Xi Wu, Fang Yao, Ning-li Chai, Shu-tian Zhang, Jianyu Hao, Jing Wu, Jichang Zhang, Baohong Xu, Lixia Hu, Fang Yao. Pathological diagnosis were performed by Weixun Zhou. Data were analyzed and interpreted by Shengyu Zhang, Xi Wu, Fang Yao. The paper was written by Qiang Wang. All authors reviewed and provided feedback on the manuscript.

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