

Clinical studies of indicative biopsies in opportunistic screening in high risk population of oesophageal cancer.

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Abstract

This research is aimed to improve detectable rate of early oesophageal cancer and precancerous lesion with opportunistic screening and indicative biopsies guided by different doses of iodine staining/NBI (Narrow Band Imaging) in high risk population of oesophageal cancer. Local patients aged 40 to 69 treated in our digestive system department were screened. Following randomized grouping, high-risk patients were stained with different doses of iodine (low: 5~7 ml; high: 10~15 ml) for endoscopy and NBI endoscopy, and indicative biopsies was conducted in suspicious esophageal lesions; Pathology results were considered as the final diagnosis. Diagnostic criteria are divided into: mild dysplasia, moderate dysplasia, severe dysplasia and (or) carcinoma *in situ*, intramucosal carcinoma, submucosal carcinoma and invasive cancer. The results indicated that in first stage: In 2014, a total of 1624 people attended opportunistic screening for esophageal cancer. Among them, detectable rate of early esophageal cancer was 1.23%, accounting for 20.41% of all esophageal cancer, improved significantly compared with that in 2013 ($\chi^2=5.511$, $P=0.019$). The second stage: in 2015, a total of 1948 people participated in esophageal opportunistic screening. There was no significant difference between detectable rates of early esophageal cancer and precancerous lesion with different esophageal endoscopies ($P>0.05$), a higher incidence of adverse reactions can be seen in low-dose iodine staining group compared with high-dose group ($\chi^2=6.566$, $P=0.01$). In conclusion, the combination of opportunistic screening and indicative biopsies guided by different doses of iodine staining/NBI can effectively improve the detectable rate of early esophageal cancer and precancerous lesion, wherein the low-dose iodine staining endoscopy is more suitable for mass screening.

Keywords: Esophageal cancer, Precancerous lesion, Opportunistic screening, Chromoendoscopy, Narrow band imaging.

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Introduction

Esophageal cancer is a common human gastrointestinal cancer. In China, new cases of esophageal cancer accounted for about half cases of new global development, which possesses characteristics in high morbidity (ranked 4th) and mortality (ranked 5th) [1]. Although the treatment of esophageal cancer in our country was in rapid spread and improved to save a large number of esophageal cancer patients or prolong their survival time, 5-year survival rate of early and advanced esophageal cancer patients after operation was only about 10% [2]. Moreover, 5-year survival rate of patients with early esophageal cancer treated with feasible endoscopy was more than 95% [3,4]. Thus, screening and early diagnosis of esophageal cancer is the key to reduce the incidence of esophageal cancer and improve survival rate. In this study, patients treated in the hospital joined in opportunistic screening, and indicative biopsies were conducted in high risk

population, which was desirable to improve the detectable rate of early esophageal cancer and precancerous lesions and the prognosis of the patients. This research is aimed to improve detectable rate of early esophageal cancer and precancerous lesion with opportunistic screening and indicative biopsies guided by different doses of iodine staining/NBI (Narrow Band Imaging) in high risk population of esophageal cancer.

Objects and Methods

Objects

Based on China esophageal cancer early diagnosis and early treatment project [5], 3572 of the local patients aged 40 to 69 years treated in our hospital in 2014.1~2015.11 were ultimately confirmed as risk population of esophageal cancer through the investigation of health factors, including 1879 male patients and 1693 female patients.

Opportunistic screening for high risk population

According to the principle of esophageal cancer early diagnosis and early treatment project, trained medical personnel in digestive system department distributed publicity materials about screening for esophageal cancer, held esophageal promotional lectures, and mobilize high-risk population to endoscopy and filling out the questionnaire.

Endoscopy

Depending on the different endoscopic techniques, the study was divided into two stages: the first phase was from January 2014 to December 2014. After determination of high risk population by the opportunistic screening, specialized digestive physician took endoscopy examination for them. Routine iodine staining endoscopic observation was chose for patients without contraindications. Then, indicative biopsies were conducted for the suspicious esophageal lesions. The effect of combination of opportunistic screening and indicative biopsies on the indicative rate of early cancer detection was observed.

The second stage: On the basis of the preliminary work in 2015, indicative biopsy was further improved. Endoscopy in high-risk patients was randomly divided into 3 groups: First group: 5~7 ml iodine solution named low-dose group; Second group: 10~15 ml iodine solution named high-dose group; third group: high-definition endoscopic NBI named NBI group. The detectable rate and incidence of adverse reactions of early esophageal cancer and precancerous lesions with different methods were compared, and screening efficiency, advantages and disadvantages of different methods were evaluated.

Gastroscope techniques

(1) After insertion, the gastroscope should be slowly forward. Every subtle change in the esophageal mucosa should be carefully observed. (2) After observation of esophagus, gastroscope slipped by stomach and duodenum slowly, regular checks were done to the stomach and duodenum. (3) When observation is completed and endoscopy retreated to cardia, the color, shapes and motion status of the esophagus mucous membrane, as well as abnormal vascular texture submucosal were noticed. (4) The endoscopy will retreat about 20 cm from the front of esophageal, then be ready for iodine staining. (5) After the above work completed, indicative biopsy of unstained area lightly stained area were carried out. NBI group would be operated with NBI-guided biopsy after keeping graphs.

Quality control

Guided with China esophageal cancer early diagnosis and early treatment project, endoscopy and pathology diagnosis of esophageal cancer were performed, the detectable rate of biopsy of esophageal lesions was above 120% (biopsy tissue/total number of screening). All the equipment were cleaned and disinfected in strict accordance with the "cleaning and disinfection of endoscopic techniques Practice 2004 Edition". Once screening completed, all questionnaires and report cards

were checked and in statistical process by dedicated staff in opportunistic screening study group of esophageal endoscopy room. This research was approved by ethical committee of Dongying People's Hospital, and the approval number is DPH-2015-11.

Data analysis and statistical process

The statistics was analysed with SPSS/19.0, expressed in (Mean \pm Standard Deviation). $\alpha=0.05$ was considered as the test standard in chi-square test.

Results

The study results of the first phase

From January 2014 to December, a total of 1624 patients participated in esophageal opportunistic screening, including 838 males and 786 females. Mild dysplasia of esophagus was screened in 98 patients, 32 were moderate dysplasia, 9 were severe dysplasia (or *in situ* cancer), 7 were intramucosal carcinoma, 4 were submucosal carcinoma and 78 were invasive cervical cancer. Their detectable rates were 6.03%, 1.97%, 0.55%, 0.43%, 0.25% and 4.8%, respectively. Among them, the detectable rate of early esophageal cancer was 1.23%, accounting for 20.41% of all esophageal cancer cases (20/98).

In 2014, the opportunistic screening and indicative biopsy of esophageal cancer were applied successfully in our hospital. Gastroenterology esophageal carcinoma were found in 78 cases, a total of 20 cases were early cancer, which diagnosis rate was 20.41% (20/98); However, before screening, 64 cases of advanced esophageal cancer were detected, including five cases of early esophageal cancer, which early diagnosis of esophageal cancer was 7.25% (5/69) in 2013. The diagnosis rate of early esophageal cancer in 2014 was higher than in 2013 (Table 1).

Table 1. Comparison of detectable rate of esophageal cancer in 2013 and 2014 (n).

	Early cancer	esophageal Advanced cancer	esophageal	χ^2	P
2013	5	64		5.511	0.019
2014	20	78			

The study results of the second phase

From January 2015 to November 2015, a total of 1948 patients participated in esophageal opportunistic screening, including 1041 males and 907 females. Mild dysplasia of esophagus was screened in 122 patients, 62 were moderate dysplasia, 15 were severe dysplasia/*in situ* cancer, 14 were intramucosal carcinoma, 12 were submucosal carcinoma and 117 were invasive cervical cancer. Their detectable rates were 6.26%, 3.18%, 0.77%, 0.72%, 0.62% and 6.01%, respectively. And the detection rate of early cancer was 25.95% (41/158). The

detectable rate of esophageal cancer and precancerous lesion was shown in Table 2 below.

Table 2. The detectable rate of esophageal cancer and precancerous lesion (n).

Pathological diagnosis	Cases	Percent (%)
Mild dysplasia	122	6.26
Moderate dysplasia	62	3.18
Severe dysplasia/ <i>in situ</i> cancer	15	0.77
Intramucosal carcinoma	14	0.72
Submucosal carcinoma	12	0.62
Invasive cervical cancer	117	6.01

The detectable rate of early cancer with indicative biopsies guided by different endoscopic staining

All patients were randomly assigned to low-dose (5~7 ml) iodine staining group, high-dose (10~15 ml) iodine staining group and NBI group, including 647, 665 and 636 patients, respectively. There was no statistical meaning in the detectable rate of esophageal lesion with three different methods in Table 3.

Table 3. The detectable rate of esophageal lesion with different staining does (n).

	Benign	Low grade neoplasia	Early carcinoma	Advanced carcinoma	χ^2	P
Low-dose	532	64	13	38	0.316	0.999
High-dose	549	62	14	40		
NBI	525	58	14	39		

As shown in Table 4, there was no statistically meaning in the detectable rate of early cancer with three different methods.

Table 4. The detectable rate of early cancer with three different methods (n).

	Early carcinoma	Advanced carcinoma	χ^2	P
Low-dose	13	38	0.012	0.994
High-dose	14	40		
NBI	14	39		

Table 5 indicated that there was no statistically meaning in the detectable rate of low grade neoplasia with three different methods.

Table 5. The detectable rate of low grade neoplasia with three different methods (n).

	Low neoplasia	grade	Precancerous conditions	χ^2	P
Low-dose	64		532	0.217	0.897

High-dose	62	549
NBI	58	525

In the patients with iodine staining, 2.63% of the low dose group (17/647) suffered from heartburn, upper abdominal pain and other adverse reactions; 5.41% of high doses group (36/665) had discomfort as mentioned above. After staining, the gastric lumen remained visible stains in high-dose group, while little or no stain remaining in low does group. After administration of sodium thiosulfate for de-iodination, most discomfort can be quickly alleviated, a few need symptomatic treatment.

The different incidence of adverse reactions in patients with different-dose iodine staining endoscopic can be seen in Table 6.

Table 6. The incidence of adverse reactions in patients with different-dose iodine staining endoscopic.

	Yes	No	χ^2	P
Low-dose	17	630	6.566	0.01
High-dose	36	629		

Comparison of the detectable rate of esophageal cancer in the two stage

In 2014, the opportunistic screening and indicative biopsy of esophageal cancer were applied successfully in our hospital. Gastroenterology esophageal carcinoma were found in 78 cases, a total of 20 cases were early cancer, which diagnosis rate was 20.41% (20/98). From Jan to Nov in 2015, 117 cases of advanced esophageal cancer were detected, 41 cases of early esophageal cancer. The diagnostic rate of early cancer was 25.95% (41/158) in 2015, which was higher than 2014, but the difference between groups was not statistically significant (Table 7).

Table 7. Comparison of the detectable rate of esophageal cancer in 2014 and 2015 (n).

	Early esophageal cancer	Advanced esophageal cancer	χ^2	P
2014	20	78	0.312	0.336
2015 (1-11 month)	41	117		

Discussion and Conclusion

In our country, high incidence and mortality of esophageal cancer is largely due to the low detectable rate of early esophageal cancer, which was attributable to a variety of reasons including two significant aspects: lack of health awareness of patients and the weak ability of identifying early esophageal cancer of endoscopists. In the past, Shen performed the screening and monitoring of high-risk population with the application esophageal balloon cytology techniques in the high

incidence of esophageal cancer, and achieved gratifying results [6]. Nevertheless, this method is no longer applicable for the current status; at present, the rate of missed diagnosis by main endoscopy is up to 40% [7]. Based on the previous studies, we employed opportunistic screening combining iodine staining endoscopy and NBI endoscopy [8,9] to guide indicative biopsy and improve the detection rate of esophageal cancer and precancerous lesions.

In 1624 people screened in 2014, mild dysplasia of esophagus were found in 98 cases, 32 were moderate dysplasia, 9 were severe dysplasia (or *in situ* cancer), 7 were intramucosal carcinoma, 4 were submucosal carcinoma and 78 were invasive cervical cancer. Their detectable rates were 6.03%, 1.97%, 0.55%, 0.43%, 0.25% and 4.8%, respectively. Among them, the detectable rate of early esophageal cancer was 1.23%, accounting for 20.41% of all esophageal cancer cases (20/98). Among the early detection of esophageal cancer was 1.23% (20/1624), accounting for 20.41% of all esophageal cancer (20/98). From mild dysplasia of esophagus to the submucosal cancer, the detectable rate of screening population decreased gradually, which was closed to census results of esophageal cancer in many areas [10-12]. The higher detectable rate of precancerous lesions than that in high risk population in multiple areas with high incidence of esophageal cancer may be due to opportunistic screening targeting for patients, while the census for the majority of residents, including a large number of those who are asymptomatic and without treatment. But, detectable rate of invasive cancer was significantly higher than the high incidence area, because the patient attending opportunistic screening was the crowds for treatment, while the census contained a lot of healthy people and people without symptoms. Early esophageal cancer often has no obvious clinical manifestations. The onset of symptoms generally indicates that esophageal cancer has entered advanced stage, which is consistent with the patient's clinic situation.

In 2014, 78 cases of advanced cancer were detected, and 20 cases were early cancer, which diagnosis rate was 20.41% (20/98); yet, in 2013, it was found in 64 cases of advanced esophageal cancer, including five cases of early esophageal cancer, which diagnosis rate was 7.25% (5/69). The diagnosis rate of early esophageal cancer was significantly higher in 2014 than that in 2013. There are a few reasons accounting for this: Firstly, in accordance with national esophagus early detection and treatment programs, we conducted opportunistic screening for patients and improved inspection efficiency, which was significantly more effective than the census. Secondly, staining endoscopy enhanced the contrast of lesion and normal esophageal mucosa, provided clearer scope, so as to improve the ability to identify the lesion with the naked eye, guide biopsy and improve detection rate. Early esophageal cancer and precancerous lesions, which are usually difficult to observe with naked eye, can be found in this way.

On the basis of our previous work, the endoscopy method is modified in 2015. Iodine staining endoscopy is divided into the low-dose group (5~7 ml) and high-dose group (10~15 ml), and

esophageal NBI observation is increased; Precision biopsy guided with different doses of iodine staining endoscopy and NBI endoscopy improved detection rate of early cancer. Modified methods and improved endoscopic diagnosis promoted 122 cases of mild dysplasia (detection rate of 6.26%) detected, moderate dysplasia were 62 cases (detection rate of 3.18%), severe dysplasia/*in situ* were 15 cases (detection rate of 0.77%), 14 were intramucosal carcinoma (detection rate of 0.72%), 12 cases were submucosal cancer (detection rate of 0.62%), and 117 cases were invasive cervical cancer (the detection rate of 6.01%). The detection rate of early cancer was 25.95% (41/158). Early cancer's detection rate was higher compared with ever before, but the difference was not statistically significant compared with 2014. In the study, we found three methods can effectively improve the detection rate of esophageal small lesions, precancerous lesions and early esophageal cancer, no significant difference between the three different methods in low-grade neoplasia, esophageal esophagitis and precancerous diseases was distinguished; Although, the effect on guiding indicative biopsy and improving detection rate of early esophageal cancer was the same, NBI inspection was obviously easier than the iodine staining endoscopy without additional pain. NBI endoscopy requires better standard in endoscopic host, source and endoscopy itself, so endoscopy must be high-definition, endoscopy should in high-quality inspection, at the same time the light source must be in useful life. In addition, physicians need for professional learning to interpret NBI image, which resulted in the promotion of technical limitations. NBI combining with zoom endoscopy can achieve a qualitative diagnosis and staging judge of esophageal cancer and precancerous lesions, whereas the higher cost contributed to inapplicability for screening, there is still important significance in detailed inspection before treatment of esophageal cancer. Different doses of iodine staining endoscopy were not statistically significant in the detectable rate of early esophageal cancer and precancerous lesions. Fewer adverse reactions, such as heartburn, cough and other complications [13], occurred in patients in low-dose group, no or only a small amount of dye staining retained in stomach for cleaning up. While high-dose iodine staining endoscopy strongly stimulated the patients with severe stomach inflammation and reflux esophagitis, the incidence of abdominal pain, heartburn and other adverse reactions was higher than the low-dose group, which most patients were able to afford. After administration of sodium thiosulfate for de-iodination, most discomfort can be quickly alleviated. We believe that low-dose iodine staining endoscopy can reach the goal of the indicative biopsy and fewer adverse reactions occurred, which can be used as the preferred screening mean. It is more helpful in the diagnosis combining NBI endoscopy and comprehensive application of a variety of means.

Opportunistic screening associated with for indicative biopsy technique not only improves the detection rate of early esophageal cancer, but also can reduce the arbitrariness of biopsy and subjectivity of endoscopist through obvious

indication, which is significantly superior to endoscopy in white light with naked-eye observation, worth of promoting.

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