Evaluating Synchronous Esophageal Cancer in Head and Neck Cancer Patients Using Lugol Dye Chromoendoscopy

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Objective: *Routine screening for esophageal cancer in head and neck cancer patients in Thailand is controversial, because of concerns regarding the screening methods and cost effectiveness. Since Lugol dye chromoendoscopy is an effective technique for early detection of squamous cell carcinoma of the esophagus, the objectives of the present study are to evaluate the synchronous esophageal cancer in head and neck cancer patients and the effectiveness of Lugol dye chromoendoscopy for routine screening.*

Material and Method: *All diagnosed patients with head and neck cancer between September 1, 2009 and June 30, 2011 were enrolled into the study. Both conventional esophagoscopy and Lugol dye chromoendoscopy were done. The incidence of esophageal cancer was calculated. A diagnostic statistical analysis was done to compare the diagnostic properties between conventional esophagoscopy and Lugol dye chromoendoscopy. Univariate and multivariate logistic regression analyses were used to find significant factors associated with esophageal cancer in this study.*

Results: *Eighty-nine head and neck cancer patients were enrolled in this study. The incidence of esophageal cancer in head and neck cancer patients was 12.4% (11/89). Conventional esophagoscopy found a highly suspicious malignant lesion in only six patients, while the Lugol dye chromoendoscopy detected all 11 esophageal cancers. The sensitivity and specificity for conventional esophagoscopy were 54.5% and 100%, respectively, and for Lugol dye chromoendoscopy were 100% and 70.5%, respectively. The three significant factors that increased the likelihood of synchronous esophageal cancer from univariate analysis were age less than 50 years, presence of dysphagia, and an unstained Lugol dye area ≥10 mm. However, these factors were not statistically significant by multivariate analysis.*

Conclusion: *Lugol dye chromoendoscopy is a promising tool to enhance the diagnosis of esophageal cancer among head and neck cancer patients.*

Keywords: *Esophageal cancer, Head and neck cancer, Lugol dye chromoendoscopy*

J Med Assoc Thai 2014; 97 (11): 1164-70
Full text. e-Journal: *http://www.jmatonline.com*

Squamous cell carcinoma of the esophagus is a common cancer in southern Thailand[1]. There are various treatments for this cancer, such as surgery, chemotherapy, radiation, targeted therapy or a combination of treatments. However, the prognosis of this disease is still poor because it is usually diagnosed in the later stages of disease. Several risk factors have been studied in an attempt to find some way to identify this disease in the early stages when treatment might be more effective. Some risk factors that are common to various illnesses and cancers such as tobacco smoking or excessive consumption of alcohol might cause of esophageal cancer, but routine screening in patients with these habits is not cost effective.

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The causation between squamous cell carcinoma of head and neck and esophageal cancer were better explained by the "field cancerization theory"[2]. According to various reports, the incidence of esophageal cancer in patients with head and neck cancer has been found to range from 1.7% to 11.5%[3-8]. Routine screening for esophageal cancer in head and neck patients is controversial. One report suggested esophagoscopy had low yield[9] and should be considered only for symptomatic patients such as those with dysphagia because of limited resources for investigations. However, other reports suggested benefits from screening for esophageal cancer in all patients with head and neck cancer[10,11].

In general, esophageal cancer has a much worse prognosis than other head and neck cancers. Therefore, if we diagnose early and treat esophageal cancer, the prognosis of these patients would be much better. Lugol dye chromoendoscopy is one beneficial

technique for early detection of squamous cell carcinoma of the esophagus among head and neck cancer patients[8,10,12,13].

Currently, in Thailand there is no routine screening protocol for esophageal cancer in head and neck cancer patients. The objectives of the present study aimed to determine the incidence of esophageal cancer in patients newly diagnosed with head and neck cancer using the Lugol dye technique and compare the diagnostic efficacy between Lugol dye chromoendoscopy and conventional endoscopy in the early diagnosis of esophageal cancer.

Material and Method

All new cases of head and neck cancer diagnosed between September 1, 2009 and June 30, 2011 at the head and neck cancer clinic were enrolled into this study. The exclusion criteria were patients with nasopharyngeal cancer, allergy to iodine, hyperthyroidism, coagulopathy and thrombocytopenia, esophageal varices, congestive heart failure (NYHA class III/IV), chronic renal failure, pregnant or lactating women, trismus or tumor obstruction, and those who did not wish to participate. After enrollment, these patients were sent to the surgical endoscopy unit, where endoscopy was performed by the same doctor in all subjects to diagnose by both conventional esophagoscopy and Lugol dye chromoendoscopy for every patient. Conventional esophagoscopy was done first and then Lugol dye chromoendoscopy. If abnormal lesions were noted from conventional esophagoscopy, a biopsy was performed before continuing with the Lugol dye chromoendoscopy. For the chromoendoscopy, a 2% Lugol's solution was spray-injected into the esophageal lumen at a rate of about 10 ml per 10 cm of esophageal length from the distal esophagus to the proximal esophagus and the stained area was checked. Theoretically, Lugol's solution contains iodine and potassium iodide, which stain the normal squamous cell epithelium of the esophagus. Iodine binds with intracellular glycogen so the color stain ranges from dark green to black. Because of a reduced level of glycogen in cancer cells, unstained areas become visible with the Lugol chromoendoscopy. Random biopsies were done on tissues taken from an area in the esophagus with little or no staining for histopathology confirmation. In cases of multiple unstained areas, biopsies were done in one or two of the largest and most defined areas. After the procedure finished, the residual amount of Lugol's solution remaining in the tract was aspirated to reduce iodine exposure.

The study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University and all patients gave informed consent.

Data collection included demographic data of the patients and habits that may increase the risk of esophageal and head and neck cancer for example, tobacco smoking, alcohol drinking, and betel nut chewing. All habits were considered significant in patients with continuous use of more than 10 years. Other data included type and staging of head and neck cancer, findings from standard esophagoscopy and Lugol dye chromoendoscopy and the pathological results if a biopsy was done. The incidence of esophageal cancer in the head and neck cancer patients was calculated. The diagnostic statistical analysis was done to compare the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy between conventional esophagoscopy and Lugol dye chromoendoscopy. Univariate and multivariate logistic regression analyses were used to find significant factors associated with esophageal cancer in this study. The odds ratio and 95% confidence interval were calculated and values of $p<0.05$ were considered significant.

Results

Between September 1, 2009 and June 30, 2011, 89 head and neck cancer patients were included in the present study. The majority of the patients were male and the median age was 61 years old. The most common type of head and neck cancer was oropharyngeal cancer and most patients were in stage IV. Most patients had a significant history of tobacco smoking and alcohol drinking. All demographic characteristics are shown in Table 1.

In pathologically proved squamous cell carcinoma of the esophagus, the overall incidence of esophageal cancer among head and neck cancer patients in this study was 12.4% (11/89 cases). Conventional esophagoscopy found a highly suspicious malignancy in only six patients (55%), while the Lugol dye chromoendoscopy detected all 11 esophageal cancers (100%). There were eighty-three normal mucosa findings from conventional esophagoscopy. After application of the Lugol staining technique, five of these normal finding cases were malignant and six cases were dysplasia (Fig. 1, 2). For Lugol dye chromoendoscopy, 34 cases (38.2%) had unstained area following the application of the Lugol dye. The histopathology results showed squamous cell carcinoma

in 11 cases, dysplasia in six cases, chronic inflammation, or ulcer in nine cases and normal squamous epithelium in eight cases.

The diagnostic properties for esophageal cancer detection between conventional esophagoscopy and Lugol dye chromoendoscopy are shown in Table 2.

The study was recorded and analyzed for a correlation between the size of the unstained area and the malignancy. Ten of the 11 histopathologically confirmed squamous cell carcinomas had unstained area ≥10 mm. In contrast, only one of the 18 unstained areas <10 mm was a case of squamous cell carcinoma (Table 3). The median unstained diameter in cancer patients was 20 mm (8-80 mm) and in non-cancer patients, it was 5 mm (3-50 mm).

None of the patients developed complications from the Lugol's solution such as esophagitis, gastritis, or aspiration into the airway.

The univariate analysis found three significant factors that increased the likelihood of synchronous esophageal cancer in head and neck cancers, less than 50 years old, presence of dysphagia and unstained Lugol dye area ≥10 mm (Table 4). However, in the multivariate analysis, these risk factors were not statistically significant.

Table 1. Baseline characteristics of patients

Age (years), mean ± SD	61.36±11.38
Male, n (%)	82 (92.1)
Significant history of tobacco smoking, n (%)	82 (92.1)
Significant history of alcoholic drinking, n (%)	68 (76.4)
Significant history of betal nut chewing, n (%)	28 (31.5)
Dysphagia symptom, n (%)	6 (6.7)
Types of head and neck cancer, n (%)	
Oral cavity cancer	19 (21.3)
Oropharyngeal cancer	46 (51.7)
Hypopharyngeal cancer	14 (15.7)
Laryngeal cancer	10 (11.2)
Stage of head and neck cancer, n (%)	
Stage I	8 (9.0)
Stage II	18 (20.2)
Stage III	18 (20.2)
Stage IV	45 (50.6)

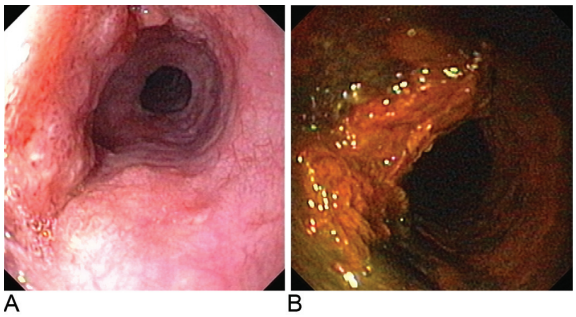

Fig. 1 Endoscopic findings in the same patient: (A) conventional esophagoscopy showed a mass at the left side of the esophageal lumen (highly suspicious cancer), (B) Lugol dye chromoendoscopy showed an unstained area and the subsequent histopathology found squamous cell carcinoma.

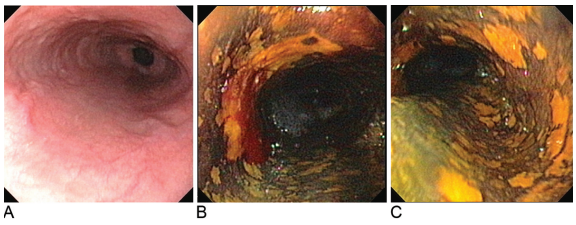

Fig. 2 Endoscopic findings in the same patient: (A) conventional esophagoscopy showed normal esophageal mucosa, (B) and (C) Lugol dye chromoendoscopy showed many unstained areas with the largest one of the unstained mucosa area; histopathology found squamous cell carcinoma.

Discussion

The incidence of synchronous esophageal cancer in head and neck cancer patients in the present study was quite high (12.4%). This is comparable with other studies, which found the incidence to vary from 1.7% to 11.5%[3-8]. Squamous cell carcinoma of the esophagus is usually associated with a poorer outcome than head and neck cancers. Therefore, the physician should attempt to identify synchronous esophageal

Table 2. Comparison of diagnostic properties between conventional esophagoscopy and Lugol dye chromoendoscopy

Diagnostic properties	Lugol dye chromoendoscopy	Conventional esophagoscopy
Sensitivity	100%	54.5%
Specificity	70.5%	100%
Positive predictive value	32.4%	100%
Negative predictive value	100%	94.0%
Accuracy	74.2%	94.4%

Table 3. Relationship between the diameter of Lugol dye unstained area and histopathology

Lugol staining	Number of patients	Number of normal epithelium	Number of chronic inflammation/ulcer	Number of dysplasia	Number of esophageal cancer
Normal staining	55	55 (100%)	0	0	0
Unstained area <10mm	18	8 (44.44%)	8 (44.44%)	1 (5.55%)	1 (5.55%)
Unstained area ≥10 mm	16	0	1 (6.25%)	5 (31.25%)	10 (62.5%)

Table 4. Analysis of risk factors for developing synchronous esophageal and head and neck cancers

Factors	Synchronous esophageal cancer, n (%)	Odds ratio	95% confidence interval	*p*-value
Male	10 (90.9)	0.83	0.09-7.66	0.87
Age ≤50 years	6 (54.5)	6.00	1.59-22.64	0.004*
Dysphagia	4 (36.4)	21.71	3.36-140.27	0.001*
Tobacco smoking	10 (90.9)	0.83	0.09-7.66	0.87
Alcoholic drinking	10 (90.9)	3.45	0.42-28.66	0.23
Betal nut chewing	3 (27.3)	0.80	0.19-3.26	0.75
Type of head and neck cancer (oral cavity and oropharynx vs. hypopharynx and larynx)	8 (72.7)	0.98	0.24-4.06	0.98
Stage of head and neck cancer (stage III and IV vs. stage I and II)	3 (27.3)	1.12	0.27-4.58	0.88
Unstained area ≥10 mm	10 (90.9)	26.67	2.78-255.76	0.001*
Number of unstained area ≥4 lesion	2 (18.2)	0.76	0.12-4.70	0.76

cancer in this group of patients as early as possible, which will improve the chances of a better outcome.

Conventional esophagoscopy using only white light is the standard procedure to check for synchronous esophageal cancer in head and neck cancer patients. However, this procedure can easily miss superficial invasive squamous cell carcinoma or dysplastic epithelium as these lesions often show normal or minimal abnormal mucosa. Lugol dye chromoendoscopy is a good method for early detection of esophageal cancer because it can demonstrate an unstained esophageal mucosa in esophageal cancer that otherwise would not be identified by conventional esophagoscopy. The present study found that conventional esophagoscopy could detect only six out of 11 patients with esophageal cancer. However, Lugol dye chromoendoscopy had a higher detection rate that could identify all patients with esophageal cancer. The present study also found that conventional esophagoscopy had a sensitivity of 54.5% and a specificity of 100%. Because of low sensitivity, conventional esophagoscopy should not be used for esophageal cancer screening. Lugol dye chromoendoscopy had a sensitivity of 100%, specificity of 70.5%, and 74.2% accuracy, which was comparable to other studies. Dawsey et al found Lugol dye chromoendoscopy had a sensitivity of 96% and a specificity of 63%[14]. Similarly, the study from Lee et al found 88.9% sensitivity, 72.2% specificity, and 77.8% accuracy[15].

There are many methods to enhance the likelihood of detection of esophageal cancer including primarily the use of Lugol dye chromoendoscopy, narrow band imaging, and autofluorescence imaging. Previous studies found that conventional esophagoscopy had 55.6% to 62.9% sensitivity and 97.2% specificity, which were similar to the present study. Narrow band imaging had 88.9% to 100% sensitivity and 95.4% to 97.2% specificity; autofluorescence imaging had 71% sensitivity and 25% positive predictive value[16-23]. Nevertheless, only narrow band imaging was excellent in both sensitivity and specificity. However, this technique is more expensive and requires more skill. Therefore, since the Lugol's solution technique has very good sensitivity and fair specificity, this technique is appropriate as a screening test. Furthermore, this method does not require an experienced endoscopist, is performed easily with the equipment available in most settings, is inexpensive, and has no major lasting side effects. The main drawback is that it cannot

differentiate between non-neoplastic lesions from neoplastic lesions very well. The advantages more than offset the relatively small disadvantage of not being able to distinguish between neoplastic and non-neoplastic lesions. Therefore, this technique is appropriate for a developing country such as Thailand and should be a standard work-up in all head and neck cancer patients.

From univariate analysis, we noted that larger unstained areas showed more aggressive lesions as earlier studies also found. The present study found that an unstained area larger than 10 mm was strongly associated with squamous cell carcinoma or dysplastic epithelium. Similar to the studies from Boller et al, the sensitivity and specificity to detect high grade dysplasia or carcinoma in situ in unstained lesions ≥2 cm were 100% and 96.5%, respectively[24]. Hori et al found that an unstained area more than 10 mm was an independent risk factor for esophageal cancer[25]. Some earlier studies found a large number of unstained lesions were related with more aggressive lesions; however, the present study did not find this correlation[25-27]. The present study found that age less than 50 years was also a risk factor for developing esophageal cancer. The study from Wang WL et al also demonstrated this finding[28]. Actually, this disease is common in the elderly; however, the high incidence of synchronous cancer in younger patients may be explained by molecular factors that need further study.

Conclusion

Lugol dye chromoendoscopy is a promising tool for enhanced diagnosis of esophageal cancer. Because of the high prevalence of synchronous esophageal cancer in head and neck cancer patients, we recommend a routine esophagoscopy with Lugol dye chromoendoscopy in these patients.

What is already known on this topic?

The incidence of esophageal cancer in patients with head and neck cancer has been found to range from 1.7% to 11.5%; however, routine screening for esophageal cancer in head and neck patients is controversial because of various screening methods and cost effectiveness.

What this study adds?

The present study found that the size of an unstained area of Lugol dye chromoendoscopy was associated with aggressiveness and histopathology findings, especially if the size was equal to or more than 10 mm. Furthermore, this study found a high incidence of synchronous esophageal cancer. Therefore, routine esophagoscopy with Lugol dye chromoendoscopy is recommended for all head and neck cancer patients.

Acknowledgement

The authors wish to thank Mr. Glenn Shingledecker for checking and editing the English in this study.

Potential conflicts of interest

None.

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การศึกษาถึงการเกิดโรคมะเร็งหลอดอาหารร่วมในผู้ป่วยโรคมะเร็งศีรษะและลำคอโดยการใช้สารละลายลูกอลย้อมสีระหว่างทำการส่องกล้องหลอดอาหาร

ศุภฤกษ์ เลาหวิริยะกมล, สมเกียรติ สรรพวีรวงศ์, วิฑูร ลีลามานิตย์, โกวิทย์ พฤกษานุศักดิ์, วัฒนา สินกิจเจริญชัย

วัตถุประสงค์: *การตรวจคัดกรองหาโรคมะเร็งหลอดอาหารในผู้ป่วยโรคมะเร็งศีรษะ และลำคอเป็นประจำในประเทศไทยยังมีความเห็นไม่ชัดเจน เนื่องจากมีความหลากหลายในวิธีการตรวจ และความคุ้มค่า พบว่าการใช้สารละลายลูกอลย้อมสีระหว่างทำการส่องกล้องหลอดอาหารสามารถตรวจพบมะเร็งตั้งแต่ระยะเริ่มต้นได้ ดังนั้นวัตถุประสงค์ของการศึกษานี้คือเพื่อตรวจหาการเกิดโรคมะเร็งหลอดอาหารร่วมในผู้ป่วยโรคมะเร็งศีรษะ และลำคอโดยใช้สารละลายลูกอลย้อมสีระหว่างทำการส่องกล้องหลอดอาหาร*

วัสดุและวิธีการ: *เก็บข้อมูลผู้ป่วยใหม่ที่เป็นโรคมะเร็งศีรษะ และลำคอ ตั้งแต่วันที่ 1 กันยายน พ.ศ. 2552 ถึง 30 มิถุนายน พ.ศ. 2554 ผู้ป่วยทุกรายได้รับการส่องกล้องทั้งแบบมาตรฐาน และโดยย้อมสารละลายลูกอล เพื่อคำนวณหาอุบัติการณ์ของโรคมะเร็งหลอดอาหาร และทำการวิเคราะห์ทางสถิติเปรียบเทียบระหว่างวิธีการส่องกล้องแบบมาตรฐาน กับการส่องกล้องโดยย้อมสารละลายลูกอล รวมทั้งหาปัจจัยเสี่ยงของการเกิดโรคมะเร็งหลอดอาหารร่วม*

ผลการศึกษา: *ผู้ป่วยในการศึกษามีจำนวน 89 ราย พบอุบัติการณ์ของโรคมะเร็งหลอดอาหารร้อยละ 12.4 (11 ใน 89 ราย) การส่องกล้องหลอดอาหารโดยวิธีมาตรฐานสามารถตรวจพบมะเร็งหลอดอาหารได้เพียง 6 ราย ขณะที่การส่องกล้องโดยใช้สารละลายลูกอลย้อมสามารถตรวจพบมะเร็งหลอดอาหารได้ทั้งหมด 11 ราย ความไวและความจำเพาะของการส่องกล้องหลอดอาหารโดยวิธีมาตรฐานมีค่าเท่ากับร้อยละ 54.5 และ 100 สำหรับความไวและความจำเพาะของการส่องกล้องหลอดอาหารโดยย้อมสารละลายลูกอลมีค่าเท่ากับร้อยละ 100 และ 70.5 จากการวิเคราะห์ถดถอยเอกนามพบว่าปัจจัยเสี่ยงที่ทำให้เกิดโรคมะเร็งหลอดอาหารได้แก่ อายุผู้ป่วยน้อยกว่า 50 ปี อาการกลืนติด และพื้นที่ของเยื่อบุหลอดอาหารที่ไม่ติดสีสารละลายลูกอลขนาดมากกว่าหรือเท่ากับ 10 มิลลิเมตร อย่างไรก็ตามปัจจัยเหล่านี้ไม่มีนัยสำคัญทางสถิติเมื่อทำการวิเคราะห์ถดถอยแบบพหุนาม*

สรุป: *การส่องกล้องหลอดอาหารโดยใช้สารละลายลูกอลย้อมเป็นวิธีการที่มีแนวโน้มว่าสามารถเพิ่มการวินิจฉัยโรคมะเร็งหลอดอาหารในผู้ป่วยโรคมะเร็งศีรษะและลำคอ*