

ORIGINAL PAPERS

# Diagnostic accuracy of lugol chromoendoscopy in the oesophagus in patients with head and neck cancer

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## ABSTRACT

**Background and aim:** patients with head and neck squamous cell malignancies have a higher risk of oesophageal squamous cell carcinomas. Lugol chromoendoscopy in oesophagus is a simple technique with a high diagnostic yield in premalignant lesions. The objective was to analyze its diagnostic accuracy in dysplasia and carcinoma of the oesophagus in high-risk patients.

**Methods:** prospective study from April/2008 to January/2012 using lugol chromoendoscopy with biopsies of suspicious lugol voiding areas  $\geq 5$  mm. Patients with head and neck malignancies were included, except the ones with iodine allergy, oesophageal varices and contra-indications to standard endoscopy. The reference method was histopathology.

**Results:** 89 patients were enrolled (mean age  $62.8 \pm 13.3$  years, 87 % men). Primary tumour was located in oropharynx in 37 (41.6 %), in oral cavity in 29 (32.6 %) and in the larynx in 23 (25.8 %) cases. 40.4 % patients had previous treatments and 87 % reported alcohol or tobacco addition. All exams performed without anaesthesia or complications. Nine suspicious lugol voiding areas were observed and biopsied. Histopathological analysis revealed high-grade dysplasia in 2 (2.2 %) and inflammation or normal findings in the others. The sensitivity and specificity for detecting high-grade dysplasia were 100 % and 92 % (95 % CI: 87-97), respectively. Diagnostic accuracy of the test was 92 % (95 % CI: 86-98).

**Conclusion:** lugol staining of the oesophagus during endoscopy seems to be a feasible, safe and justified procedure in high-risk population as it enhances the detection of premalignant lesions.

**Key words:** Oesophageal cancer. Squamous cell carcinoma. Lugol solution. Gastrointestinal Endoscopy. Chromoendoscopy.

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## INTRODUCTION

Oesophageal cancer is the eighth most common cancer worldwide and the sixth more common cause of death from cancer (1,2). Squamous cell carcinoma is still the most frequent type, but the incidence of adenocarcinoma is rising in developed countries, becoming the most frequent type in these regions (3,4).

Important risk factors for oesophageal squamous cell carcinoma (OSCC) includes alcohol and tobacco addiction (1). Others less frequent risk factors are achalasia, caustic injury, previous radiotherapy for breast cancer, thylosis, ingestion of a hot beverage called *maté* (particularly in South America) and exposure to polycyclic aromatic hydrocarbons (5).

The risk of OSCC is also increased in patients with head and neck squamous cell carcinoma (HNSCC), and the incidence in this set varies from 1-17 % (6,7). The presence of multiple cancers is a phenomenon well described and a consequence of a theory called "field cancerization", where repeated exposure to carcinogens leads to accumulation of genetic alterations resulting in the development of independent cancers (8). This association is related to a poorer disease control and survival rates of both tumours (9).

The prognosis of the disease is poor, with a low 5-year survival rate, mainly because the majority is diagnosed at advanced stages. The early detection of precursor lesions can improve the prognosis of these tumours.

Lugol chromoendoscopy is a complementary method to standard endoscopy that can enhance the diagnosis of OSCC at earlier stages of dysplasia and non-invasive cancer. It can be particularly important in screening high-risk groups of patients and in follow-up after OSCC treatment (6,9-12). It can be used also to delineate lesions prior to endoscopic mucosal resection (EMR) and to detect recurrences at the EMR scar.

Normal oesophageal mucosa has glycogen that reacts with lugol iodine solution and forms a brown-green colour.

On the contrary, dysplastic or malignant tissue is immature and loses glycogen-rich granules, remaining unstained and appearing white or pink (11,13). Areas of leukoplakia are also unstained but remain yellow.

This method has a high sensitivity (91-100 %), but the specificity may be lower (40-95 %) (14,15) because other benign lesions like oesophagitis, ectopic mucosa and Barrett oesophagus can appear as unstained areas.

In addition, several studies have reported that the presence of multiple and irregular shaped lugol voiding lesions is related to the presence of synchronous and metachronous OSCC (9,16,17), and these patients should be carefully monitored.

The aim of this study was to determine the diagnostic accuracy of lugol chromoendoscopy combined with biopsy to diagnose oesophageal squamous cell carcinoma and high-grade dysplasia in high-risk patients with previous or present head and neck squamous cell carcinoma.

## METHODS

### Study population

A prospective study was carried out from April/2008 to January/2012 in consecutive patients with previous or present HNSCC referred for endoscopy.

Exclusion criteria were iodine allergy, presence of oesophageal varices and patients with contra-indications to standard endoscopy or biopsy, like those uncooperative or with serious coagulation abnormalities.

Written informed consent was obtained from all patients.

All exams were performed in our Department that belongs to a referral Oncology Hospital and were performed by three Gastroenterologists with an average of 5 years endoscopic experience with conventional chromoendoscopy and performing around 20 lugol staining per year.

Patients were included if referred to endoscopy as a screening strategy in patients with present HNSCC or based on symptoms and a positive personal history of HNSCC.

Patient's data recorded were alcohol and tobacco consumption, local of HNSCC, date of diagnosis, previous treatments and presence of digestive symptoms.

### Endoscopy

The exam started with a regular endoscopy performed with standard videoendoscopes (Olympus GIF-160) without any magnification, virtual enhancement or sedation, with careful visualization of oesophagus, stomach and duodenum and description and biopsy of any suspicious area. Antispasmodic drugs were not administered.

After that 20 mL of a 2 % lugol iodine solution for staining were sprayed over the entire oesophageal mucosa with a catheter (Olympus PW-205V). A second examination of the oesophagus was performed 1-2 minutes later. If a well

demarcated, isolated, suspicious lugol voiding lesion (LVL) sized 5 mm or more was identified, at least 2 biopsies were taken with a standard 7mm biopsy forceps (Olympus FB-15K-1). The chromoendoscopic part of the exam took on average 3 minutes.

Data was collected about the macroscopic characteristics of the oesophageal lesions seen before lugol staining, the modifications after staining and the macroscopic characteristics of the oesophageal lesions seen exclusively after lugol staining. For lesions location we divided the oesophagus into three regions: proximal, medium and distal.

Histopathological analysis, which was considered the gold standard, was done by pathologists with several degree of differentiation and the specimens were classified into the following categories: normal, inflammation, low-grade dysplasia, high-grade dysplasia (HGD) and squamous cell carcinoma. Pathologists were blinded to the endoscopic appearance of the lesions concerning lugol.

### Statistical analysis

Continuous data are described by mean and standard deviation, if the distribution is normal, or by median and interquartile range if skewed. Diagnostic accuracy measures (sensitivity, specificity, positive and negative predictive values) were obtained comparing the presence of LVL detected in the endoscopic index test with the histological result from the biopsy as the reference test. Values were determined from 2x2 tables, after dichotomization into cases and controls and positive and negative tests, using 95 % confidence intervals (CI).

## RESULTS

A total of 89 patients underwent lugol chromoendoscopy (Table I). Mean age was  $62.8 \pm 13.3$  years and 78 (88 %) patients were men. Endoscopy was performed in median 7 (3; 31) weeks after the diagnosis of HNSCC.

The median alcohol intake was 40 (20; 70) g/day in 77 (87 %) patients, and the median tobacco consumption was 37 (5.8; 52.5) pack-years in 74 (83 %) patients.

Regarding local of the HNSCC, 37 (41.6 %) were in the oropharynx, 29 (32.6 %) in oral cavity and 23 (25.8 %) in the larynx.

Eighty one (91 %) patients had single carcinomas.

Digestive symptoms were present in 8 (9 %) patients: 4 (4.5 %) with dysphagia, 1 (1.1 %) with dysphagia and heartburn, 1 (1.1 %) with heartburn, 1 (1.1 %) with odynophagia and 1 (1.1 %) with odynophagia and heartburn.

Previous treatment targeting the primary tumour had been made in 36 (40.4 %) patients: 19 (21.3 %) were submitted to surgery, 27 (30.3 %) were submitted to radiotherapy and 14 (15.7 %) to chemotherapy.

All the exams were performed without anaesthesia and there were no complications reported.

**Table I. Baseline characteristics of the patients**

Age (years)	62.8 ± 13.3*
Male sex, no. (%)	78 (87 %)
Time of endoscopy after HNSCC diagnosis (weeks)	7 (3; 31)**
Alcohol intake (g/day)	40 (20; 70)**
Tobacco consumption (pack-years)	35 (5.8; 52.5)**
Local of HNSCC	
Oropharynx, no. (%)	37 (41.6 %)
Oral cavity, no. (%)	29 (32.6 %)
Larynx, no. (%)	23 (25.8 %)
Presence of digestive symptoms previous to endoscopy, no. (%)	8 (9 %)
Previous treatment to HNSCC, no. (%)	36 (40.4 %)

\*Mean ± SD. \*\*Median (IQR: p25; p75). HNSCC: Head and neck squamous cell carcinoma.

At standard endoscopy, 22 (24.7 %) of the patients had hiatal hernia, 10 (11.2 %) had oesophagitis and 4 (4.5 %) had other lesions: 1 Schatzki ring, 1 gastric heterotopy, 1 cardiac polyp and one invasion of the upper oesophageal sphincter by the head and neck malignancy. None had Barrett oesophagus.

In the 89 exams, white light identified one suspicious area with 7 mm. After lugol spraying, 9 LVL with more than 5 mm were identified which means that 8 suspicious LVL were additionally seen with lugol staining. The mean size of the LVLs was 8 ± 0.5 mm (from 5 to 20 mm). Concerning location, 5 (55.6 %) were in the distal oesophagus, 3 (33.3 %) in the medium oesophagus and 1 (11.1 %) in the proximal oesophagus.

From these 9 LVL, histopathology revealed two cases (2.2 %) of HGD, 6 (6.7 %) cases with inflammation and one (1.1 %) normal sample. The two cases of HGD were not described before lugol staining. There were no cases of carcinoma.

The two lesions with HGD had 7 and 20 mm of diameter and characteristics of the two patients are shown in table II. The two cases of HGD were not described before lugol staining, although, if we look at them retrospectively, there was some mucosal irregularity on conventional endoscopy (Fig. 1 –lugol staining of patient 2–; Fig. 2 –histology of patient 1–). The patient with the 20 mm lesion was submitted to endoscopic mucosal resection, after performing endoscopic ultrasonography that confirmed absence of submucosal involvement or presence of lymph nodes. The pathology revealed HGD limited to the mucosa, and the patient is free of recurrence at 1 and 2-year controls. The other patient had an advanced stage of the primary oropharyngeal malignancy, and is currently being submitted to palliative chemotherapy.

According to these results, the sensitivity and specificity of white light endoscopy plus lugol staining in detecting HGD were 100 % and 92 % (95 % CI: 87-97), respectively (Table III). The predictive positive value was 22 % (95 % CI: 0-50), the predictive negative value was

**Table II. Characteristics of the two patients with high-grade dysplasia**

	Patient 1	Patient 2
Age (years)	49	40
Sex	Male	Male
Local of the primary tumour	Larynx	Oropharynx
Previous treatment to primary tumour	Yes	Yes
Alcohol intake	40 g/day	70 g/day
Smoking	Yes	Yes
Digestive symptoms	No	No
Concomitant oesophageal disease	Oesophagitis	Hiatal hernia
<i>Lugol voiding lesion:</i>		
Suspicious lesion before Lugol	No	No
Size	7 mm	20 mm
Local	Proximal	Mild
	oesophagus	oesophagus
Type of relation	Metachronous	Synchronous

100 % and the diagnostic accuracy of the test was 92 % (95 % CI: 86-98).

There were no cases of indeterminate or missing results.

## DISCUSSION

In our experience lugol chromoendoscopy revealed to be a safe and well tolerated procedure. Although reports available about the allergenic potential of lugol are poor, we decided to consider history of iodine allergy a contraindication to the exam.

Other adverse events reported are oesophageal spasm, bronchospasm, increased duration of endoscopic examination (10), retrosternal discomfort (18) and rarely acute esophageal and gastric mucosal damage (19). Although the length of the exam was prolonged in about 3 minutes, we did not report any of the other complications.

A multicenter study (10) of endoscopic screening with lugol staining revealed a prevalence of 3.2 % of OSCC in high-risk patients (head and neck or traqueobronchial squa-

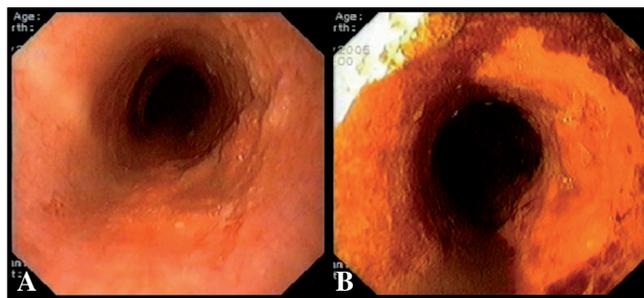


Fig. 1. A. White light conventional endoscopy showing a very slight irregularity difficult to define. B. Chromoendoscopic image with lugol showing a clearly demarcated 20 mm suspicious lugol-voiding area.

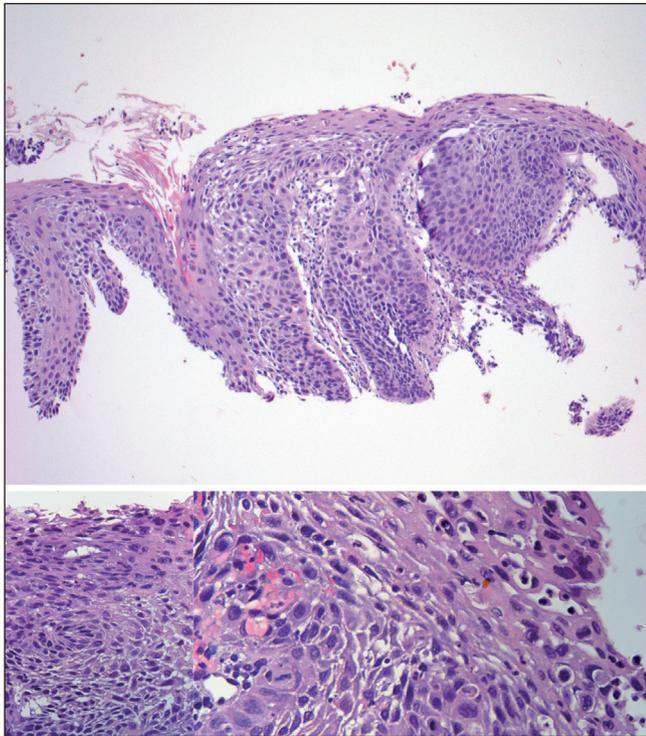


Fig. 2. Histology images (haematoxylin-eosin) (40x upper image, 400x lower image). Fragment of squamous epithelium of the oesophagus with high grade dysplasia.

mous cell carcinoma, alcohol and tobacco addiction) and a higher diagnostic yield in the earlier lesions, assuming the important role of the technique in detecting precursor lesions of OSCC. Moreover, was demonstrated that about 20 % of the cancers were detected only after lugol staining.

In our study the incidence of HGD of the oesophagus in a high-risk population with HNSCC was 2.2 % and lugol staining allowed the diagnosis of all the previously undescribed lesions. This percentage is in accordance with other series that reports frequencies varying from 0.5 to 8 % (7,10,12).

As described in the literature, we verified sensitivity and predictive negative values of 100 %, and a high diagnostic accuracy of 92 %. The specificity and predictive undescrbed value were affected by the presence of benign lesions like oesophagitis, which can appear as suspicious LVL.

One drawback of our study might be the threshold of 5 mm used to perform biopsies, because some smaller dysplastic areas can be missed. We used this value because is the cut-off most frequently described to traduce areas with premalignant alterations. Another limitation for the assessment of sensibility of the technique is that we did not biopsied non-suspicious areas in regular non-lugol staining areas and we cannot be sure if there was any cancer in a non stained segment of oesophageal mucosa. Furthermore, we do not have yet the follow up endoscopies of all the patients that might reveal more false negative results and result in a lower sensitivity.

In this work, probably because of the small number of patients included, we did not had any case of multiple LVL

**Table III. Diagnostic accuracy of lugol chromoendoscopy**

		<i>Histopathological diagnosis</i>	
		High-grade dysplasia (n = 2)	Inflammation or normal (n = 7)
<i>Presence of lugol voiding lesion</i>	Yes (n = 9)	2	7
	No (n = 80)	0	80

and so we didn't analyse its relation with increased risk of multiple cancers. In a recent study (17) it was demonstrated that more than 20 LVLs of  $\geq 10$  mm were independent risk factors for synchronous and metachronous cancer in the oesophagus and head and neck region.

Recently new methods of narrow-band imaging (NBI) with magnifying endoscopy have been used in the diagnosis of early precursor lesions of OSCC (20). Sensitivity appears to be similar to lugol staining, but specificity can be higher (21,22). Although some possible advantages, further prospective and multicenter studies are needed to clarify its role and importance in cancer screening.

In conclusion, despite some limitations previously described, including the lack of follow-up and absence of comparison with other diagnostic techniques like NBI, results from this present cohort study support a potential usefulness for lugol staining (albeit not statistically significant and in probably less than 2 % of cases) in clinical practice, potentially enhancing the detection of early malignant lesions in high-risk populations.

Although there are no current guidelines for OSCC screening, some high-risk patients can benefit with the use of lugol chromoendoscopy like the ones with HNSCC.

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