Original Article - Evaluative Study

Lugol Chromoscopy in the Follow-up of Head and Neck Carcinoma

Cesar Augusto Simões, Marcelo Doria Durazzo, Flávia Caló de Aquino Xavier[1], Marina Helena Cury Gallottini[1], Sílvia Vanessa Lourenço[1], Décio dos Santos Pinto Júnior[1], Natália Martins Magacho de Andrade, Aline Paterno Miazaki, Rogério Aparecido Dedivitis, Cláudio Roberto Cernea

Department of Head and Neck Surgery, Hospital das Clínicas, University of São Paulo School of Medicine, [1]Department of Stomatology, University of São Paulo Dental School, São Paulo, Brazil

Abstract

Introduction: Lugol is helpful in identifying early second primary tumors (SPTs) during oroscopy and pharyngoscopy, but this technique has not been assessed during follow-up visits with these patients. **Aim:** The aim of this study is to describe the use of Lugol (a low-cost method) to diagnose SPTs in the oral cavity and oropharynx. **Methods:** Patients treated for squamous cell carcinoma of the head and neck were randomly assigned to two groups. Group A was examined with routine oroscopy and pharyngoscopy without Lugol, and Group B was examined with routine oroscopy and pharyngoscopy without stain and with Lugol. A total of 211 patients were included during 4 years. **Results:** Six oral and oropharynx carcinomas were detected in Group A. Eighteen oral and oropharynx carcinomas were detected in Group B, twelve of which were not seen without chromoscopy but were detected with Lugol. **Conclusion:** Lugol increases the detection of malignant lesions compared to routine examination alone.

Keywords: Coloring agents, low-cost diagnostic, Lugol, mouth neoplasms, prospective studies, squamous cell carcinoma

Introduction

Smokers and drinkers with squamous cell carcinoma of the head and neck have a high risk of developing a second primary tumor (SPT)[1-6] based on the theory of field cancerization, proposed in 1946.[7-9] According to the literature, the most frequent region of SPT development is the head and neck region.[10-14]

Published guidelines suggest the following methods can be used during follow-up visits with patients with head and neck cancer for early detection of lesions in the mouth or oropharynx: routine visual inspection of the oral cavity, use of toluidine blue to detect neoplastic and preneoplastic lesions not visible to the naked eye, use of fluorescent dyes for diagnosis of injuries, and exfoliative cytology or biopsy of suspected cancerous areas.[15-21] Despite these guidelines, no studies have comprehensively assessed the advantages of each method of detecting SPT.[22] Promising results with a method developed to detect the spectrum of light refraction of preneoplastic and neoplastic lesions have been shown;[23-25] however, this technique is not so employed in some centers due to the cost of equipment. Despite the prevalent diagnostic use of Lugol solution for the early detection of cervical cancer[26] and esophageal cancers,[27-35] its ability to detect malignant tumors or premalignant lesions of the mucosa of the head and neck has not been thoroughly addressed. A recent study in which Lugol solution was used to detect SPT in the mouth and oropharynx suggested that this solution may potentially be used to identify malignant and premalignant lesions that are not detected during routine inspections;[36] however, a more detailed and complete study is necessary to determine whether Lugol chromoscopy results in increased survival.

The aim of this study is to verify the impact of Lugol chromoscopy of the mouth and oropharynx on identification of SPTs during follow-up visits with patients with squamous cell carcinoma of the head and neck.

Methods

After obtaining Ethics Committee approval and informed consent of the patients involved, we evaluated 211 patients with

Access this article online

Quick Response Code:

Website: www.amsjournal.com

DOI: 10.4103/ams.ams_95_17

Address for correspondence: Dr. Cesar Augusto Simões, Praça Amadeu Amaral, 47, Conjunto 41, São Paulo, Brasil. E-mail: simoesccp@terra.com.br

How to cite this article: Simões CA, Durazzo MD, de Aquino Xavier FC, Gallottini MH, Lourenço SV, Pinto Júnior Dd, *et al*. Lugol chromoscopy in the follow-up of head and neck carcinoma. Ann Maxillofac Surg 2017;7:188-93.

primary cancer of the oral cavity, oropharynx, hypopharynx, and larynx during 4 years. These patients had histopathologically confirmed squamous cell carcinoma and were included in the study regardless of the stage of their cancer or the length and modality of treatment they had received. We separated the patients into two groups by drawing lots to assess whether Lugol increases the diagnosis of SPT. Patients were randomly assigned – Group A and B.

The exclusion criteria were allergy to iodine, anatomical changes that would allow Lugol aspiration during the test, difficult to the examination such as trismus, presence of ulcerated tumors that could cause intense pain upon Lugol application, history of gastrointestinal bleeding within 30 days before the examination that predisposed patients to further episodes due to the irritant effects of Lugol in the esophageal mucosa, and who did not have a known diagnosis at the time of examination (the index tumor result of pathological analysis). Attempting these criteria 19 patients were excluded from the study.

In Group A, without the use of Lugol, lesions that could potentially form SPTs were detected by routine examination with artificial lighting.

In addition to the routine examination in Group B, we applied 2% Lugol solution (iodine - potassium iodide solution) in all mucosa of the mouth and oropharynx at an approximate dose of 3–5 ml each one with the aid of a hand sprayer, without any previous preparation and enough to color mucosa [Figure 1] and expose hypocolored lesions [Figures 2 and 3]. We reexamined 2 min after the spray application and always ask the patient to keep the solution in the oral cavity for about 1 min, chewing it, and them swallowing.

In both groups, biopsies of regions classified as potentially cancerous or "suspect" were performed. In Group B, additional biopsies of hypopigmented (suspect) areas and normal (control) areas were performed.

In Group B, Lugol staining reached the optimal point for evaluation after one to 2 min of spraying and the mucosa remained colored for about 8 min. During this period, the appearance of the mucosa was assessed, lesions that were completely unstained or hypopigmented were treated with Lugol again to confirm the findings, and biopsies of hypopigmented and unstained areas [Figures 4-7] were performed with a conventional Burke biopsy forceps. The biopsies were always conducted at the center of the hypopigmented area.

We compared the gender, age, tumor-node-metastasis stage, and quantity and duration of alcohol and tobacco consumption of the patients in the two groups. Tobacco consumption was assessed using the Brinkman index.[37,38]

Diagnosis of dysplasia and malignant lesions was based on a classification suggested by Kujan *et al.*, in 2006.[39,40] The biopsies were referred to for histopathological examination at the Department of Pathology of the Hospital das Clínicas, University of São Paulo School of Medicine, with descriptions of the original localization of the specimen and chromoscopy test characteristics. The slides were prepared using routine techniques and stained with H and E. Only one surgeon performed endoscopy and Lugol application. Two pathologists to avoid discrepancies in diagnostic criteria analyzed samples separately.

Results

Group A (patients examined without Lugol) was composed of 106 patients, whereas Group B (patients examined with Lugol) was composed of 105 patients. A total of nineteen patients were excluded from the study. Eight of those patients were excluded because had large ulcerated lesions in the mouth that could cause great discomfort during Lugol application, two were excluded because did not give a good visualization of the oral cavity because of trismus secondary to the treatment of the tumor index (scar retraction in the masticatory space), and nine patients who did not have a known diagnosis at the time of examination were also excluded from the study.

Patients in Group A were followed up for an average of 25.2 months and those in Group B were followed up for an average of 24.9 months.

The characteristics of Group A and B were compared statistically using the Q^2 test and both are comparable. Patients in Group A ranged in the age from 41 years to 94 years, with an average age of 61.73 ± 10.98 years and a median age of 60.95 years. Patients in Group B ranged in the age from 40 years to 81 years, with an average age of 59.32 ± 9.6 years and a median age of 58 years ($P = 0.61$). In Group A, 96 patients were men and ten were women. In Group B, 94 patients were men and 11 were women ($P = 0.80$).

Most patients in both groups had stage IV cancer. The most common sites of primary cancer were the mouth (11 patients in Group A and 19 patients in Group B) and the larynx (13 patients in Group A and 12 patients in Group B).

The rate of alcohol use was defined as the number of units of ethanol (1 IU of alcohol = 28 g) consumed per day multiplied by the number of years of consumption.[37] The two groups had statistically similar rates of alcohol usage ($P = 0.181$). The Brinkman index (defined as the number of cigarettes smoked per day multiplied by the number of years of consumption) was used to quantify smoking exposure,[37,38] and this measure was also statistically similar in both groups ($P = 0.118$).

Fifty-five patients in Group B underwent biopsy of lesions that were hypopigmented after Lugol application. Of those biopsies, 11 were invasive carcinomas [Figures 8 and 9], one was carcinoma *in situ* [Figures 10 and 11], six were high-risk dysplasias, 27 were low-risk dysplasias, and 10 were normal tissues. No cancer was detected in pathological analysis of the random control biopsies, which showed 20 normal, 18 low-risk dysplasias, and 2 high-risk dysplasias.

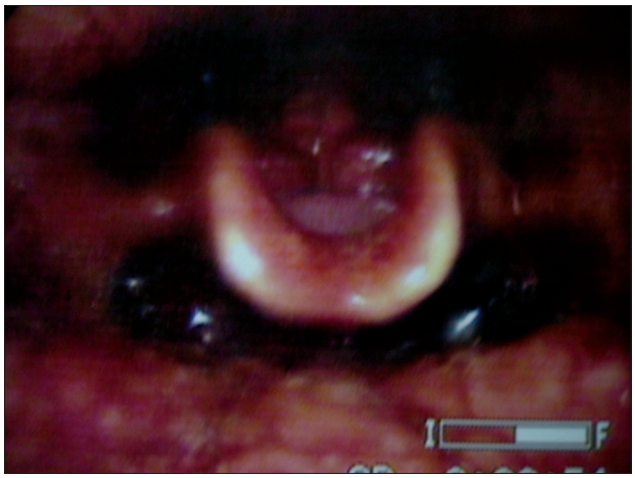

Figure 1: Aspect of the normal coloration in the oropharynx region extending up to the hypopharynx

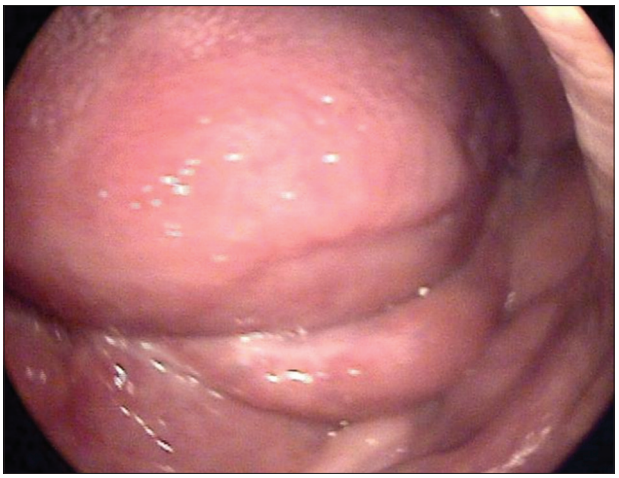

Figure 2: Example of examining the oral cavity of a patient from group B without the dye

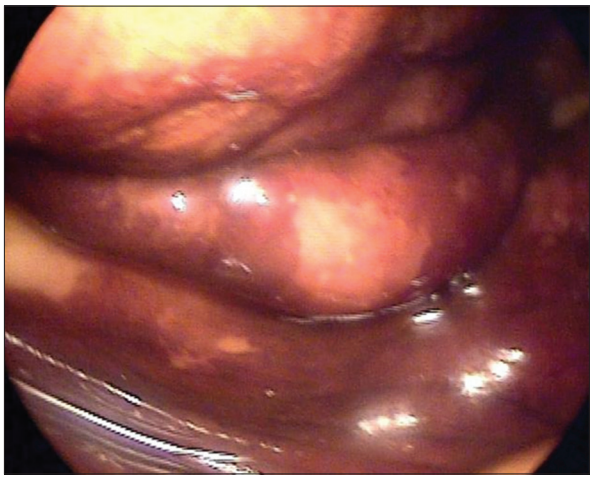

Figure 3: The same patient of figure 2 with Lugol dye. The biopsy of this patient in the hypocored área near the center showed invasive carcinoma

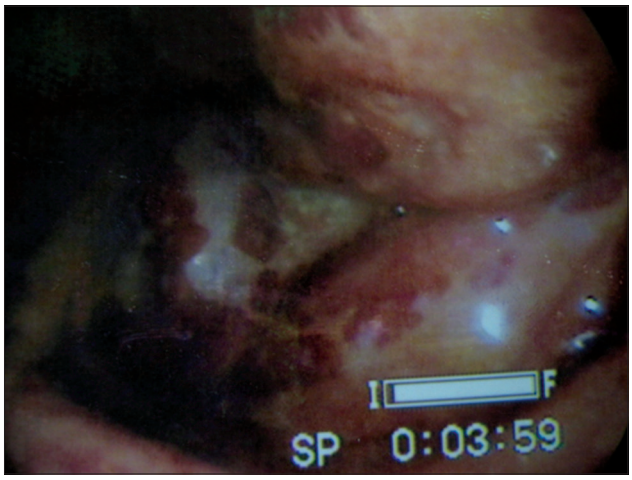

Figure 4: Hypocored floor lesion photograph whose pathological examination showed invasive carcinoma

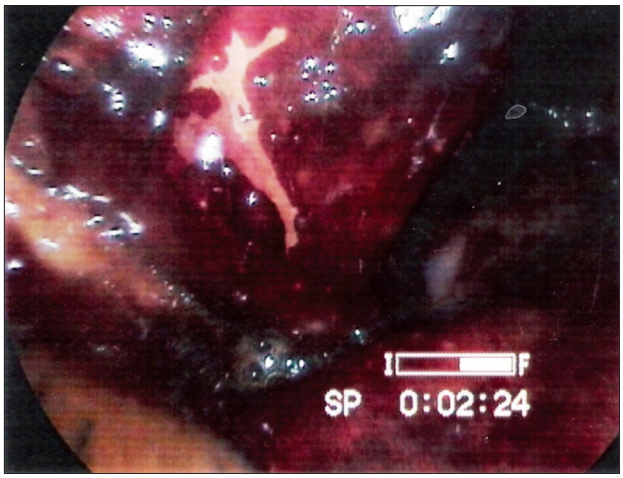

Figure 5: Aspect of hypocored lesion in the right oral tongue, whose pathological examination showed invasive carcinoma

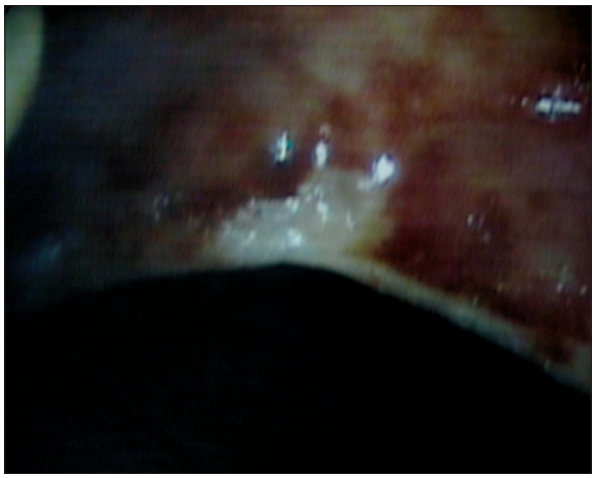

Figure 6: Photograph of lesion hypocored innerface commissure labial and whose pathology examination was low-risk dysplasia

Considering that hypopigmented areas contained both true-positive (cancerous) and false-positive (noncancerous) tissues and normal areas contained true-negative (noncancerous) and false-negative (cancerous) tissues, we determined that the

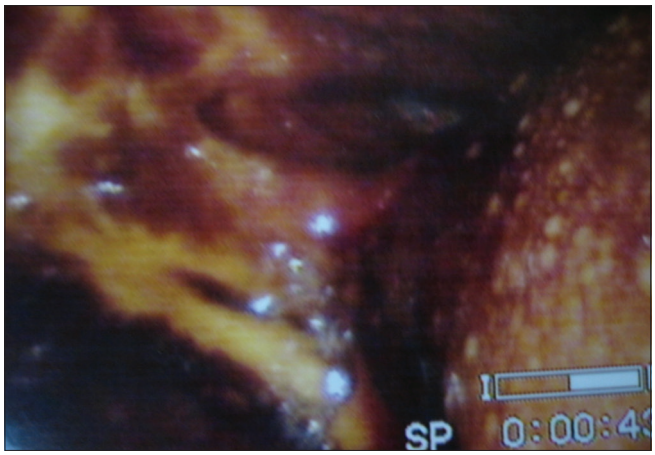

Figure 7: Photograph of hypocored lesion Jugal D whose pathological anatomical examination was low-risk dysplasia

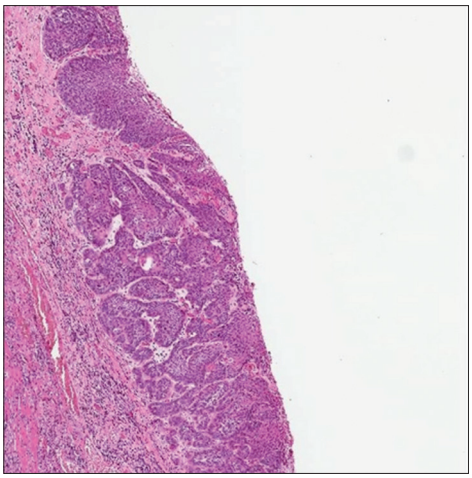

Figure 8: H and E of the biopsy of patient in Figures 2 and 3 with invasive carcinoma

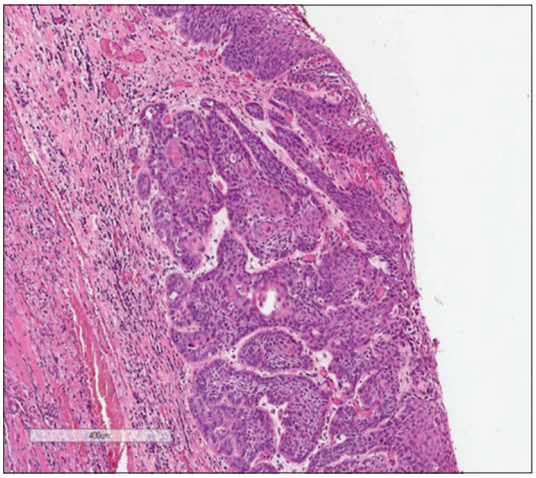

Figure 9: H and E of the biopsy of patient in Figures 2 and 3 with invasive carcinoma

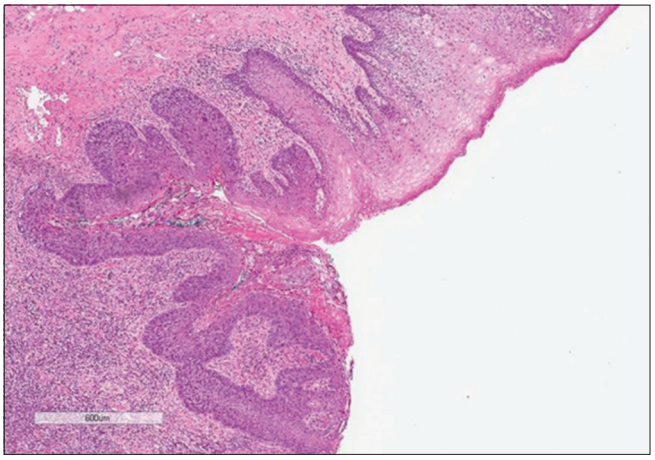

Figure 10: H and E of an hypocored area showed *in situ* carcinoma

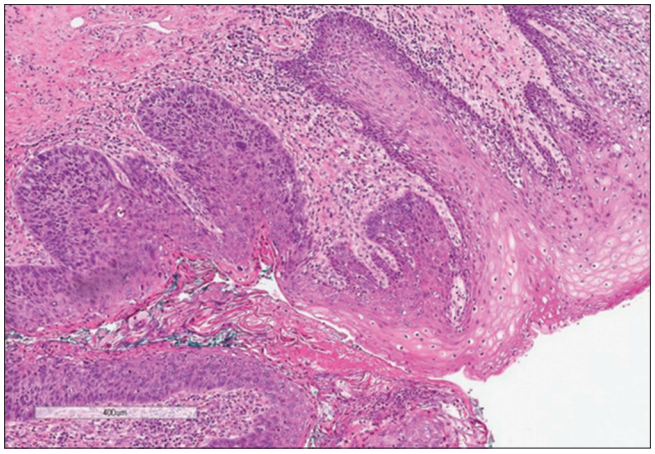

Figure 11: H and E of an hypocored area showed *in situ* carcinoma

sensitivity of this method was 1 (one), the specificity was 0.48, the accuracy was 0.55, the positive predictive value was 0.21, and the negative predictive value was 1 (one). All of these hypopigmented areas also noted to appear abnormal on traditional unstained endoscopy.

Within 6 months of follow-up, more SPTs were identified in patients in Group B than those in Group A; 12 patients in Group B (85.7%) and two patients in Group A (14.2%) had detectable injuries. We observed the emergence of six head and neck tumors in Group A between 3 and 37 months of follow-up. The average time at which these tumors were detected was 15.66 (±12.51) months after the study enrollment and the median time of detection was 12.5 months after study enrollment. In Group B, we detected 6 (six) tumors without Lugol and 12 tumors with Lugol. Of these tumors, the SPT were detected between 3 and 25 months after the first test. The average time at which these tumors were detected was 12.85 (±3.43) months after study enrollment, and the median time of detection was 8 (eight) months after the study enrollment.

Fourteen patients in Group A died and 10 (ten) of those deaths were related to the index tumor and no other tumor being found in these patients. Seventeen patients in Group B died and seven of those deaths were related to the index tumor, no other tumor

being found in these patients. No deaths during the follow-up period were related to SPTs of the head and neck.

In Group A, the site most commonly affected by SPT was the mouth (5 cases, 25% of SPT), followed by the esophagus (3 cases, 15%). In Group B, the oropharynx and mouth were the most commonly affected sites; eight cases of SPT were detected at each site (34.78% of SPT).

Discussion

The increased number of SPT detected in patients in Group B can be attributed to the employment of Lugol, which allowed early diagnosis of ten tumors, similar as used in esophagus.[30-33] Furthermore, the lesions that were hypopigmented with Lugol appeared normal on unstained visual inspection.

We have shown that Lugol chromoscopy is of great value in diagnosis.[41] It allowed the examiner to detect hypopigmented areas that were shown to be early carcinomas in 10.4% of all patients who underwent biopsy. The sensitivity of oropharyngeal chromoscopy with Lugol is high (100%) and the specificity is moderate (48%). This level of specificity is not better than random chance (50%), and thus, this technique could lead to a significant number of unnecessary negative biopsies.

At the end of the study, we diagnosed six carcinomas in patients with head and neck SPT without Lugol; however, when we employed Lugol, 18 carcinomas in the mouth and oropharynx were identified, resulting in a relevant increase in the number of malignant diagnoses. Additional time, expense, and discomfort (causing several patients to be excluded from the study) are worth the additional detection of lesions that may be subclinical.[41]

During the follow-up period, Lugol chromoscopy in the mouth and oropharynx did not impact the survival of the patients as it does in esophagus.[42]

The group examined with Lugol had higher mortality than the group that underwent routine examination and no deaths were related to SPTs; however, it was a short period for conclusions. Additional studies could recommend how lead-time bias may affect these results. It is worth mentioning that longer follow-up may allow to detect further changes in mortality between the two groups as well as to detect additional SPT.

Tests for the presence or not of human papillomavirus infection were not done,[43,44] but this is a possible future study using Lugol for diagnosis. The low cost of this method may be a good alternative to the use of narrow-band image.[41-46]

The value of this technique for subclinical detection of cancer is undeniable, so a potential application of this is to study molecular alterations in subclinical cancer form to understand better the mechanism of a clinical presentation form.[47]

Other use of Lugol staining described may lead to a reduction in local recurrence, and improved survival is to assist excision of dysplasias and carcinomas *in situ* at mucosal resection margins of oral and oropharyngeal squamous cell.[48] This early application of the dye at time of resection in our view may have results similar to ours without impact on the survival and cause larger resections with worse quality of life.

Conclusion

The chromoscopy examination with Lugol's iodine is an important complement in the detection of primary tumors in the mouth and oropharynx, due to its high sensitivity. The prevalence of STP increased after the examination was held with Lugol's iodine.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Jones AS, Morar P, Phillips DE, Field JK, Husband D, Helliwell TR, *et al.* Second primary tumors in patients with head and neck squamous cell carcinoma. Cancer 1995;75:1343-53.
2. Warren S, Gates S. Multiple primary malignant tumors. J Cancer 1932;16:1358-414.
3. Grossman TW, Toohill RJ, Lehman RH, Duncavage JA, Malin TC. Role of esophagoscopy in the evaluation of patients with head and neck carcinoma. Ann Otol Rhinol Laryngol 1983;92:369-72.
4. Schwartz LH, Ozsahiin M, Zhang GN, Touboul E, De Vataire F, Andolenko P, *et al*. Synchronous and metachrounous head and neck carcinomas. Ann Cancer 1994;74:1933-8.
5. Riboli E, Kaaks R, Estève J. Nutrition and laryngeal cancer. Cancer Causes Control 1996;7:147-56.
6. Marshall JR, Boyle P. Nutrition and oral cancer. Cancer Causes Control 1996;7:101-11.
7. Slaughter DP. Multicentric origin of intraoral carcinoma. Surgery 1946;20:133-46.
8. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 1953;6:963-8.
9. Hong WK, Lippman SM, Itri LM, Karp DD, Lee JS, Byers RM, *et al.* Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck. N Engl J Med 1990;323:795-801.
10. León X, Quer M, Diez S, Orús C, López-Pousa A, Burgués J, *et al.* Second neoplasm in patients with head and neck cancer. Head Neck 1999;21:204-10.
11. Herranz González-Botas J, Sarandeses García A, Martínez Vidal J, Vázquez Barro C, López Amado M. Second primary tumors in patients with carcinoma of the head and neck. Acta Otorrinolaringol Esp 2000;51:149-53.
12. Guardiola E, Pivot X, Dassonville O, Poissonnet G, Marcy PY, Otto J, *et al.* Is routine triple endoscopy for head and neck carcinoma patients necessary in light of a negative chest computed tomography scan? Cancer 2004;101:2028-33.
13. Kawata LT, Biazolla ER, Durazzo MD, Ferraz AR. Second primary tumor in patients with squamous cell carcinoma in the mouth. Rev Pós Grad 2006;13:20-4.
14. Cernea CR, de Araújo Filho VJ, Brandão LG, dos Santos LR, Yano OJ, Ferraz AR, *et al.* [Second primary tumors: The role of the head and neck surgeon]. Rev Paul Med 1988;106:201-4.
15. Mashberg A, Samit AM. Early detection, diagnosis, and management of oral and oropharyngeal cancer. CA Cancer J Clin 1989;39:67-88.
16. Epstein JB, Oakley C, Millner A, Emerton S, van der Meij E, Le N, *et al.* The utility of toluidine blue application as a diagnostic aid in patients previously treated for upper oropharyngeal carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;83:537-47.

17. Cristofaro MG, Cafaro D, Lazzaro F, Onofrio L, Savino N, Macchione B, *et al.* Chromoendoscopy in the diagnosis of precancerous lesions of the esophagus. Our experience. Ann Ital Chir 2001;72:405-9.
18. Feaver GP, Morrison T, Humphris G. A study to determine the acceptability in patients and dentists of toluidine blue in screening for oral cancer. Prim Dent Care 1999;6:45-50.
19. Mashberg A. Tolonium (toluidine blue) rinse – A screening method for recognition of squamous carcinoma. Continuing study of oral cancer IV. JAMA 1981;245:2408-10.
20. Zhang L, Williams M, Poh CF, Laronde D, Epstein JB, Durham S, *et al.* Toluidine blue staining identifies high-risk primary oral premalignant lesions with poor outcome. Cancer Res 2005;65:8017-21.
21. Robinson PN, Mickelson AR. Early diagnosis of oral cavity cancers. Otolaryngol Clin North Am 2006;39:295-306.
22. Kujan O, Glenny AM, Duxbury AJ, Thakker N, Sloan P. Screening programmes for the early detection and prevention of oral cancer. Cochrane Database Syst Rev 2003;4:CD004150.
23. Poh CF, Ng SP, Williams PM, Zhang L, Laronde DM, Lane P, *et al.* Direct fluorescence visualization of clinically occult high-risk oral premalignant disease using a simple hand-held device. Head Neck 2007;29:71-6.
24. Chu PY, Tsai TL, Tai SK, Chang SY. Effectiveness of narrow band imaging in patients with oral squamous cell carcinoma after treatment. Head Neck 2012;34:155-61.
25. Piazza C, Cocco D, De Benedetto L, Bon FD, Nicolai P, Peretti G, *et al.* Role of narrow-band imaging and high-definition television in the surveillance of head and neck squamous cell cancer after chemo- and/or radiotherapy. Eur Arch Otorhinolaryngol 2010;267:1423-8.
26. Schiller W. Early diagnosis of carcinoma of the cervix. Surg Gynecol Obstet 1933;56:210-22.
27. Kitamura K, Kuwano H, Yasuda M, Sonoda K, Sumiyoshi K, Tsutsui S, *et al.* What is the earliest malignant lesion in the esophagus? Cancer 1996;77:1614-9.
28. Nothmann BJ, Wright JR, Schuster MM. *In vivo* vital staining as an aid to identification of esophagogastric mucosal junction in man. Am J Dig Dis 1972;17:919-24.
29. Okumura T, Aruga H, Inohara H, Matsunaga T, Shiozaki H, Kobayashi K, *et al.* Endoscopic examination of the upper gastrointestinal tract for the presence of second primary cancers in head and neck cancer patients. Acta Otolaryngol Suppl 1993;501:103-6.
30. Freitag CP, Barros SG, Kruel CD, Putten AC, Dietz J, Gruber AC, *et al.* Esophageal dysplasias are detected by endoscopy with Lugol in patients at risk for squamous cell carcinoma in Southern Brazil. Dis Esophagus 1999;12:191-5.
31. Yamamuro EM, Cecconello I, Iriya K, Tomishigue T, Oliveira MA, Pinotti HW, *et al.* Lugol dye endoscopy for analysis of esophageal mucosa in achalasia. Hepatogastroenterology 1999;46:1687-91.
32. Meyer V, Burtin P, Bour B, Blanchi A, Oberti F, Person B, *et al*. Endoscopic detection of early esophageal cancer in a high risk population. Does the Lugol coloration improve the results of vide-endoscopic examination? Gastrointest Endosc 1995;41:356.
33. Adachi Y, Kitamura K, Tsutsui S, Ikeda Y, Matsuda H, Sugimachi K, *et al.* How to detect early carcinoma of the esophagus. Hepatogastroenterology 1993;40:207-11.
34. Lambert R. Esophageal cancer: Which stent, who places it, and where? Endoscopy 1995;27:509-11.
35. Simões CA, Durazzo MD, Sampaio MA, Kulcsar MA, Brandão LG, Ferraz AR. Lugol chromoscopy for early diagnosis of second primary tumors in patients treated for carcinoma of the head and neck. Oral Oncol 2007;2 (Suppl):195-6.
36. Launoy G, Milan CH, Faivre J, Pienkowski P, Milan CI, Gignoux M, *et al.* Alcohol, tobacco and oesophageal cancer: Effects of the duration of consumption, mean intake and current and former consumption. Br J Cancer 1997;75:1389-96.
37. Chyou PH, Nomura AM, Stemmermann GN. Diet, alcohol, smoking and cancer of the upper aerodigestive tract: A prospective study among Hawaii Japanese men. Int J Cancer 1995;60:616-21.
38. Elwood JM, Pearson JC, Skippen DH, Jackson SM. Alcohol, smoking, social and occupational factors in the aetiology of cancer of the oral cavity, pharynx and larynx. Int J Cancer 1984;34:603-12.
39. Kujan O, Oliver RJ, Khattab A, Roberts SA, Thakker N, Sloan P, *et al.* Evaluation of a new binary system of grading oral epithelial dysplasia for prediction of malignant transformation. Oral Oncol 2006;42:987-93.
40. Kujan O, Khattab A, Oliver RJ, Roberts SA, Thakker N, Sloan P, *et al.* Why oral histopathology suffers inter-observer variability on grading oral epithelial dysplasia: An attempt to understand the sources of variation. Oral Oncol 2007;43:224-31.
41. Morita FH, Bernardo WM, Ide E, Rocha RS, Aquino JC, Minata MK, *et al.* Narrow band imaging versus lugol chromoendoscopy to diagnose squamous cell carcinoma of the esophagus: A systematic review and meta-analysis. BMC Cancer 2017;17:54.
42. Gong EJ, Kim DH, Ahn JY, Choi KS, Jung KW, Lee JH, *et al.* Routine endoscopic screening for synchronous esophageal neoplasm in patients with head and neck squamous cell carcinoma: A prospective study. Dis Esophagus 2016;29:752-9.
43. Hoffmann M. Relevance of HPV infections in head and neck cancers: Highlights of the 2016 ASCO annual meeting. HNO 2016;64:731-5.
44. Pringle GA. The role of human papillomavirus in oral disease. Dent Clin North Am 2014;58:385-99.
45. Fang TJ, Li HY, Liao CT, Chiang HC, Chen IH. Office-based narrow band imaging-guided flexible laryngoscopy tissue sampling: A cost-effectiveness analysis evaluating its impact on Taiwanese health insurance program. J Formos Med Assoc 2015;114:633-8.
46. Davies K, Connolly JM, Dockery P, Wheatley AM, Olivo M, Keogh I, *et al.* Point of care optical diagnostic technologies for the detection of oral and oropharyngeal squamous cell carcinoma. Surgeon 2015;13:321-9.
47. Muto M, Takahashi M, Ohtsu A, Ebihara S, Yoshida S, Esumi H, *et al.* Risk of multiple squamous cell carcinomas both in the esophagus and the head and neck region. Carcinogenesis 2005;26:1008-12.
48. McCaul JA, Cymerman JA, Hislop S, McConkey C, McMahon J, Mehanna H, *et al.* LIHNCS – Lugol's iodine in head and neck cancer surgery: A multicentre, randomised controlled trial assessing the effectiveness of Lugol's iodine to assist excision of moderate dysplasia, severe dysplasia and carcinoma *in situ* at mucosal resection margins of oral and oropharyngeal squamous cell carcinoma: Study protocol for a randomised controlled trial. Trials 2013;14:310.