FIELD CANCERISATION OF THE UPPER AERODIGESTIVE TRACT: SCREENING FOR SECOND PRIMARY CANCERS OF THE OESOPHAGUS IN CANCER SURVIVORS

***Hans Scherübl,[1] Güllü Cataldegirmen,[2] Jan Eick,[1] Wanda Ring,[1] Christoph Schwertner,[1] Joachim Steinberg,[1] Hermann Herbst[3]**

1. Klinik für Gastroenterologie, GI Onkologie und Infektiologie, Vivantes Klinikum Am Urban, Berlin, Germany
2. Klinik für Viszeral- und Gefäßchirurgie, Vivantes Auguste-Viktoria-Klinikum, Berlin, Germany
3. Institut für Pathologie, Vivantes – Netzwerk für Gesundheit, Berlin, Germany
**Correspondence to hans.scheruebl@vivantes.de*

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ABSTRACT

Tobacco, alcohol, and betel quid are the main causes of squamous cell cancers of the upper aerodigestive tract. These substances can cause multifocal carcinogenesis leading to multiple synchronous or metachronous cancers of the oesophagus, head and neck region, and lungs ('field cancerisation'). Globally there are several million people who have survived either head and neck squamous cell cancer (HNSCC) or lung cancer (LC). HNSCC and LC survivors are at increased risk of developing second primary malignancies, including second primary cancers of the oesophagus. The risk of second primary oesophageal squamous cell cancer (OSCC) ranges from 8-30% in HNSCC patients. LC and HNSCC survivors should be offered endoscopic surveillance of the oesophagus. Lugol chromoendoscopy is the traditional and best evaluated screening method to detect early squamous cell neoplasias of the oesophagus. More recently, narrow band imaging combined with magnifying endoscopy has been established as an alternative screening method in Asia. Low-dose chest computed tomography (CT) is the best evidence-based screening technique to detect (second primary) LC and to reduce LC-related mortality. Low-dose chest CT screening is therefore recommended in OSCC, HNSCC, and LC survivors. In addition, OSCC survivors should undergo periodic pharyngolaryngoscopy for early detection of second primary HNSCC. Secondary prevention aims at quitting smoking, betel quid chewing, and alcohol consumption. As field cancerisation involves the oesophagus, the bronchi, and the head and neck region, the patients at risk are best surveilled and managed by an interdisciplinary team.

Keywords: Squamous cell carcinoma, second malignancy, lung, head and neck, endoscopy, surveillance, tobacco, alcohol, betel, neoplasm, tumour, computed tomography.

EPIDEMIOLOGY AND INCREASED CANCER SURVIVORSHIP

Oesophageal cancer (OEC) is the eighth-most common cancer globally with approximately 456,000 new cases per year. Globally the incidence of oesophageal squamous cell cancer (OSCC) clearly outweighs that of oesophageal adenocarcinoma but there are marked epidemiological differences between Western countries and Central Asia and China. Head and neck squamous cell cancer (HNSCC) accounts for approximately 600,000 new cases annually worldwide. With almost 1,825,000 new cases annually, lung cancer (LC) is the most common cancer in the world.[1] The topic of cancer survivorship is becoming increasingly important in current cancer management. Both HNSCC and LC survivors are at risk of developing second primary cancers, including OSCC.[2-5] Long-term survivors of HNSCC or LC are increasing and may amount to 3-5 million persons globally. OSCC survivors

are increasing too; they are at increased risk of second primary HNSCC or LC.[6-8] This review addresses the OSCC risk of people who survived either head and neck cancer (HNC) or LC and gives recommendations for surveillance.

RISK FACTORS: TOBACCO, ALCOHOL, AND BETEL QUID

Tobacco and Alcohol

Smoking and alcohol are well-known risk factors not only of OSCC but also of HNC;[4,8-11] tobacco being the main culprit of LC. Tobacco and alcohol use can cause 'field cancerisation' of the upper aerodigestive tract (UADT) and the lungs.[12] The development of multiple primary squamous cell cancers and widespread epithelial oncogenic alterations, including carcinoma *in situ,* dysplasia, and hyperkeratosis, have long been recognised as the field cancerisation phenomenon.[8,12] Field cancerisation can lead to multiple synchronous and/or metachronous cancers of the oesophagus, lungs, and head and neck region (i.e. oral cavity, oropharynx, hypopharynx, or larynx). 90% of the tumours in head and neck are squamous cell carcinomas, and at least 75% of them are attributable to the combination of tobacco and alcohol consumption. The odds ratio of OSCC may be as high as 50.1 for those who are both heavy smokers and heavy drinkers in comparison to people who neither drink nor smoke.[13] It has been estimated that a history of smoking, alcohol consumption, and diets low in fruits and vegetables account for almost 90% of OSCC cases in the USA. Tobacco and alcohol synergistically increase OSCC risk.[8]

Betel Quid

In Central, Southern, and Southeastern Asia chewing of areca nut or betel quid is prevalent. Unfortunately, the use of areca nut or betel quid (areca nuts wrapped in betel leaves) is associated with an increased risk of oral and oropharyngeal cancer (ORC) as well as of OSCC. The combination of betel nut chewing with tobacco smoking synergistically potentiates the risks of oral, oropharyngeal, or oesophageal squamous cell cancers.[14-16]

Interestingly, the cancer risk from mouth, pharynx, oesophagus, to larynx increases with alcohol and cigarette consumption, but decreases with betel consumption. Tobacco, alcohol, and betel quid act synergistically in OSCC tumourigenesis and are independent risk factors for distinct cancers of the UADT.[9] In Taiwanese men the lifetime risk of UADT cancer was calculated to be 9.42% versus 1.65% for betel chewers versus non-chewers, 3.22% versus 1.21% for cigarette smokers versus non-smokers, and 4.77% versus 1.85% for alcohol drinkers versus non-drinkers. The lifetime UADT cancer risk reached 17.2% in men who chewed more than 20 betel quids a day.[9]

Mutations of the Enzyme Aldehyde Dehydrogenase (ALDH)

Alcohol drinking results in exposure to acetaldehyde, derived from the beverage itself and formed endogenously. Acetaldehyde is a genotoxic compound that is detoxified by ALDH. The presence of the *ALDH2-2* allele encodes ALDH2, an inactive enzyme. Carriers of the *ALDH2-2* allele accumulate acetaldehyde and have higher relative risks of alcohol-related OEC and HNCs as compared with individuals with wild-type alleles. The International Agency for Research of Cancer stated in 2009 that acetaldehyde derived from alcoholic beverages could cause cancer and that alcohol consumption, i.e. ethanol in alcoholic beverages, was classified as a group 1 carcinogen.[17] A strong linkage of inactive ALDH2 to increased susceptibility to multiple cancers was reported in male Japanese drinkers with OEC or ORC. A similar association between inactive ALDH2 and the risk of multiple intraoesophageal and OEC accompanied by oropharyngolaryngeal or stomach cancers (or all) was described in Japanese male alcoholics. These reports indicate that inactive ALDH2 plays an important role in susceptibility of the UADT to multiple cancers.[18-20]

INFECTION WITH HUMAN PAPILLOMA VIRUS (HPV)

The aetiologic factors of HNSCC in patients who have never used tobacco or consumed alcohol are not yet well understood. Multiple lines of evidence indicate that nowadays HPV infection contributes to tumourigenesis in up to 70% of ORC in North America and Europe.[21] Approximately 30% of all HNSCC patients are infected with HPV, mostly with high-risk type HPV-16. Interestingly, oropharyngeal HNSCC patients with HPV infection show fewer synchronous second primary tumours

compared with HPV-negative HNSCC.[22] The reason appears to be the absence of carcinogen-induced early genetic changes in the epithelium and the development of multifocal tumours as known for heavy smokers and alcohol abusers. About 25% of OSCC cases are HPV-positive. It is unclear if having HPV alone is sufficient to cause OEC or if other factors such as tobacco and alcohol interact with HPV to trigger carcinogenesis. At present the role of HPV infection in OSCC carcinogenesis is not well understood.[23,24] A recent study suggests that HPV-16 infection may be involved in OSCC tumourigenesis in Xinjiang Kazakh patients in China.[25]

RISK OF SECOND PRIMARY OEC

12-19% of LCs are diagnosed at tumour Stage 1.[4] When screening for LC is done by using low-dose computed tomography (CT), the percentage of LC being detected at early stages rises to 47.5%.[26] Thanks to curative treatment options the majority of Stage 1 (non-small-cell) LC patients become long-term LC survivors. LC survivors carry a significantly increased risk of developing second primary OEC (odds ratio 2.29).[4] Endoscopic surveillance of the oesophagus should be considered in these patients.[4,27]

HNSCC patients have quite a good outlook: 5-year disease-specific survival of HNSCC patients now reaches 66% in the USA[5] and steps up to 80% or even 90% in patients with Stage 2 or Stage 1 HNSCC. Second primary malignancies (SPM) have been recognised as the leading long-term cause of death in patients surviving HNC.[2,3,5,28] SPM in HNSCC survivors mainly develop in the lungs and oesophagus but also in the head and neck region itself.[28-30] In Western literature, the overall incidence of SPM in HNSCC patients has been reported to range from 9.1-19.0%, with an annual incidence ranging from 3.2-4.0%.[5] Globally HNSCC patients carry a risk of second primary oesophageal squamous cell neoplasias (OSCN) of 8.9-30.4%; the odds ratios or excess absolute risks may be as high as 240.96 or 72.5.[28,31-36] Unfortunately, the OSCC prognosis is generally dismal, with a 5-year survival rate of approximately 10-16% in Western countries.[8] Quitting smoking reduces the risk of SPM.[37]

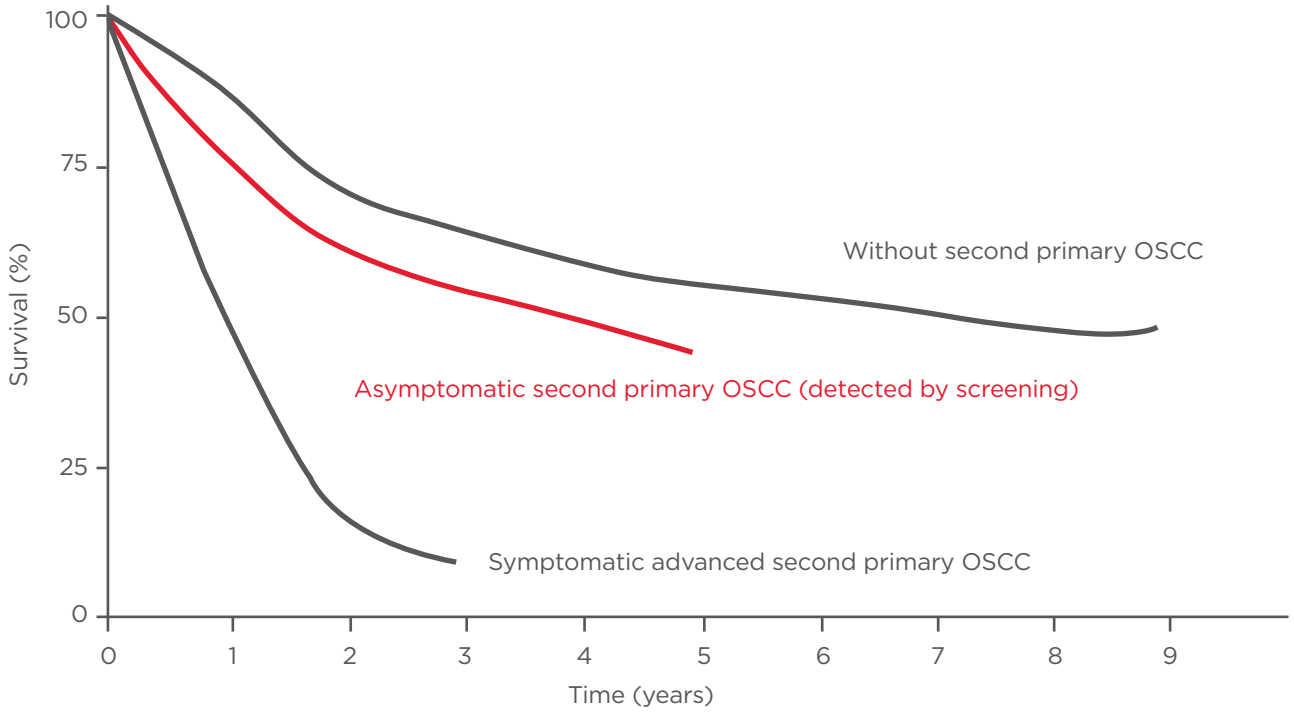

Figure 1: Perspective relative survival of HNSCC patients with and without second primary oesophageal squamous cell cancer (OSCC).
Asymptomatic oesophageal squamous cell neoplasias are detected by screening at an early stage (red line). Symptomatic second primary OSCC is generally diagnosed at advanced stages.
HNSCC: head and neck squamous cell cancer.
With permission from Scherübl et al.[38]

ENDOSCOPIC SCREENING FOR EARLY OSCN

The aim of surveillance is to detect asymptomatic OSCC at very early stages, where both endoscopic and surgical resection generally result in long-term survival. However, when symptomatic OSCC is diagnosed in HNSCC or LC survivors, advanced OSCC stages are prevalent and the outlook is very poor. Overall survival of HNSCC or LC survivors with second primary cancer, in particular second primary OSCC, is significantly lower (5-year survival rate of only 6%) than the overall survival of those without SPM.[2,3,5,38] (Figure 1).

The recommendation that HNSCC and LC survivors undergo periodic endoscopic surveillance is based upon the assumption that on the one hand OSCC adversely affects survival and on the other, surveillance can reduce mortality by detecting OSCN at a very early stage.[38-41] Several lines of evidence suggest that OSCC is diagnosed in routinely screened HNSCC patients more commonly than in those not screened.[29,31-36,39-41] In routinely screened HNSCC patients, OSCC cases are detected at earlier cancer stages.[35,38] Nowadays, OSCC limited to the upper layers of the mucosa (T1a: m1, m2) can be treated effectively by endoscopic resection and thereby with low morbidity and very low mortality. OSCC invading the lamina muscularis mucosae (m3) or the upper layer of the submucosa (<500 μm: sm1) has a higher risk of lymph node metastases and in Europe is generally only chosen for endoscopic resection if no further risk factors are present, such as poor grade of differentiation, angioinvasion, or a higher grade of tumour cell dissociation.[27] OSCC invading the deeper layers of submucosa (sm2, sm3) should be managed surgically and/or by chemoradiotherapy. In elderly patients with very significant comorbidities an endoscopic approach may be considered even in sm2 or sm3 cancers. Therefore, the aim of surveillance is to detect second primary oesophageal neoplasias at (very) early stages, i.e. intraepithelial neoplasias or m1/m2 intramucosal cancers.

LUGOL CHROMOENDOSCOPY OF EARLY OSCC

Chromoendoscopy with Lugol's solution (1-2%) used to be the traditional and reference procedure to screen for early OSCC in high-risk patients. Multicentric squamous neoplasias of the oesophagus can be visualised by Lugol chromoendoscopy as Lugol-voiding lesions (LVL), because dysplastic or hyperkeratotic epithelium does not stain with Lugol iodine solution and appears white or pink, whereas normal epithelium is stained brown. Multiple LVL have been associated with a very high risk of multiple cancers arising in the oesophagus, as well as in the head and neck region.[7,38,39] The sensitivity and specificity of Lugol chromoendoscopy to detect OSCC in high-risk groups amounts to about 80-96% and 63-72%, respectively.[29] The French Ear, Nose and Throat (ENT) Society suggests using flexible white-light, high-resolution video oesophagoscopy combined with targeted biopsies of any suspected oesophageal lesion. In addition, it recommends applying Lugol chromoendoscopy as this technique diagnoses more early-stage preneoplastic and neoplastic lesions with better definition of local extension of more advanced OECs.[42] (Figure 2).

NARROW-BAND IMAGING (NBI) AND MAGNIFYING ENDOSCOPY (ME)

NBI is a novel optical technique that enhances the diagnostic capability of gastrointestinal endoscopy by highlighting the intraepithelial papillary capillary loops of the squamous mucosa by means of light passed through filters that narrow the spectral bandwidths, incorporated into a red-green-blue sequential illumination system. NBI combined with ME has been demonstrated to further improve the detection rate and accuracy of early OSCC in HNSCC patients.[33] In a recent study NBI endoscopy with ME was reported to be the ideal screening tool to search for early oesophageal squamous neoplasias; the respective sensitivity, specificity, and accuracy amounted to 97.3%, 94.1%, and 96.3%.[29] These observations go in line with an Asian-Pacific consensus conference on early-stage oesophagogastric cancer in 2011; that consensus conference stated that NBI could replace chromoendoscopy in routine examination because it is easy to use and adds much information to conventional white light imaging, but it cannot eliminate chromoendoscopy when we make a final diagnosis for treatment decision making (Figure 3).[43] Both due to unpleasant side-effects and low specificity of Lugol chromoendoscopy, high-resolution flexible video oesophagoscopy with NBI may well become the

preferred routine screening technique for second primary OSCN in the near future. In most countries of Western Europe NBI endoscopy is generally available and widely used.

SCREENING RECOMMENDATIONS OF NATIONAL HEALTHCARE SOCIETIES

Risks of second primary malignancies differ among LC or HNSCC survivors of different countries and regions. Therefore, there are no generally and worldwide accepted recommendations of screening for second primary OSCC. The recent guidelines of the French ENT Society recommend upper-gastrointestinal endoscopy in the initial workup of hypopharyngeal squamous cell cancer and in all chronic alcoholics with HNSCC,[42] corresponding to the great majority of HNSCC patients in France. Similarly, healthcare specialists in Taiwan pointed out that the odds ratios for second primary OSCC were 18.41, 40.49, and 240.96 in patients suffering from malignancy of the oral cavity, oropharynx, and hypopharynx, respectively.[34] They recommend periodic OSCC screening according to the individual risk stratification.[35] Still, most national ENT, gastroenterology, and cancer societies have yet to make up their minds and have to balance possible survival benefits resulting from screening against economic restraints. Efforts to reduce heavy alcohol and tobacco consumption as well as betel quid chewing are generally recommended and often supported by national campaigns.

OSCC SURVIVORS: SURVEILLANCE FOR SECOND PRIMARY CANCERS OF THE HEAD AND NECK, AND THE LUNGS

Risk of developing a second malignancy should be anticipated after curative treatment of OSCC. Common risk factors including lifestyle and genetic alterations may explain both the pattern and the increased incidence of second primary cancers in OSCC survivors. Because of the high mortality of OEC itself, not much attention was previously paid to the development of SPM. Due to promising results of a recent prospective study of the National Lung Screening Trial research team, today LC screening has become the focus of increasing interest in high-risk groups.[26]

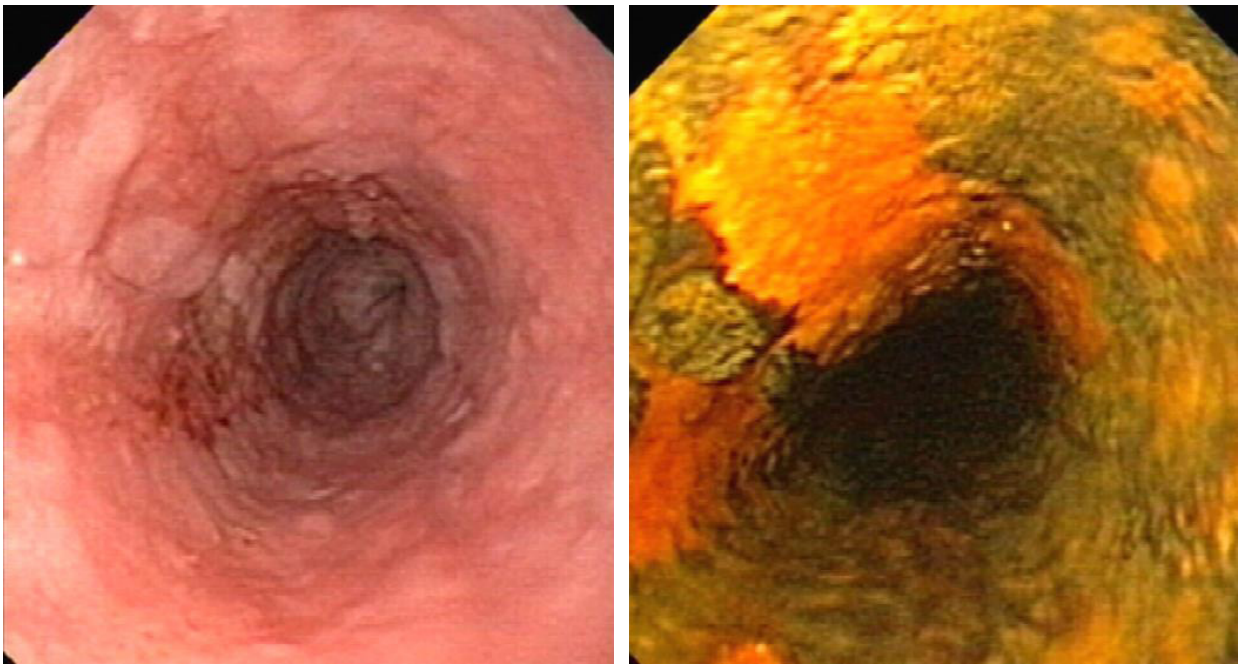

Figure 2: Oesophageal squamous cell cancer (OSCC) in a HNSCC patient.
Left panel: Videoendoscopic image of an OSCC (Stage T1aN0M0) at 25 cm from the incisors. 29 months ago the patient had been treated for a squamous cell cancer of the oral cavity. Right panel: The same tumour after staining with Lugol dye solution to delineate the tumour margins.
HNSCC: head and neck squamous cell cancer.
With permission from Scherübl et al.[40]

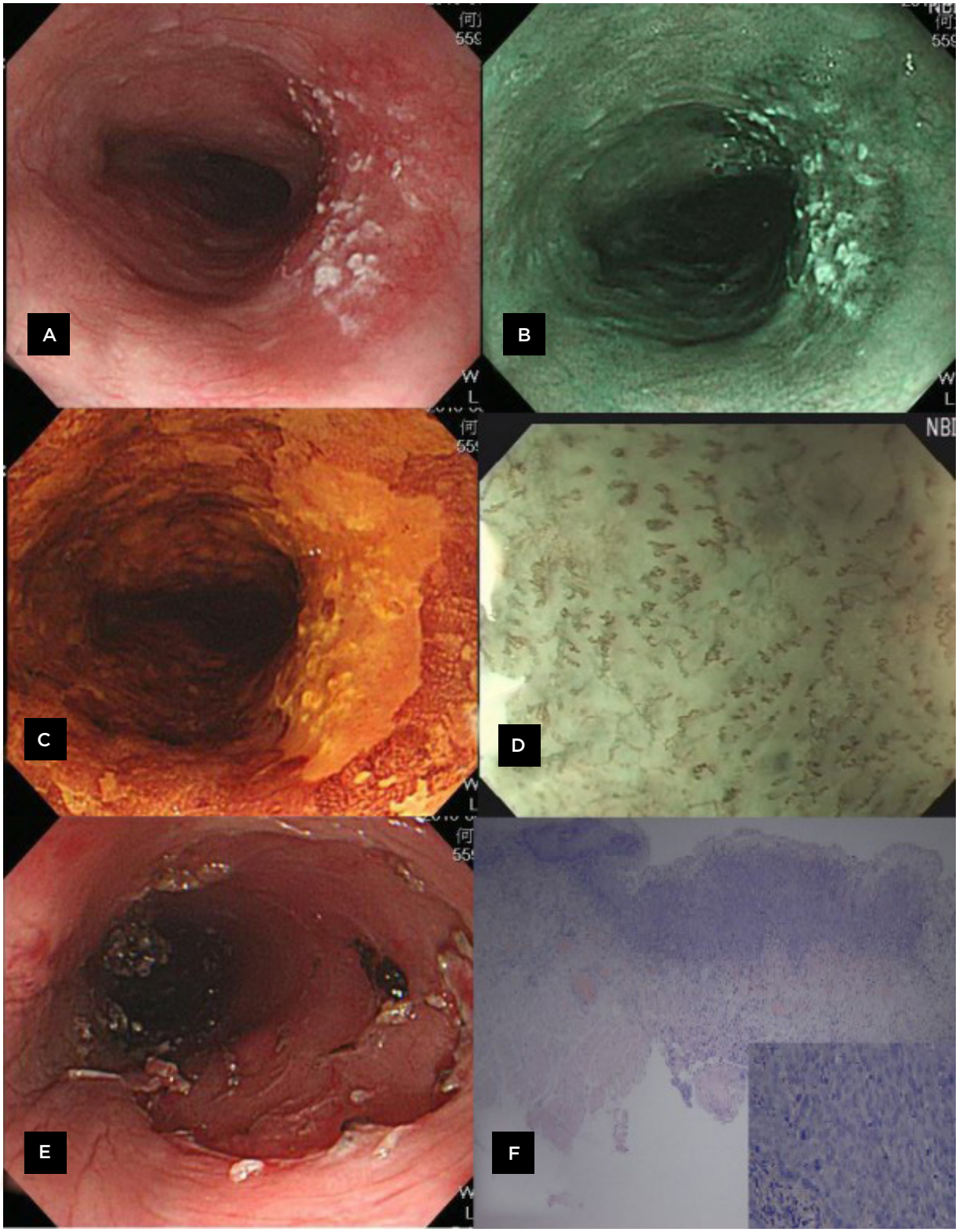

Figure 3: Endoscopic surveillance and management of synchronous high-grade intraepithelial neoplasia of oesophagus in a laryngeal cancer patient.

A: A flat superficial neoplasia with hyperaemia in white-light imaging system. B: A superficial neoplasia with brownish discolouration under narrow-band imaging system. C: Lugol-voiding of the neoplasia after spraying a 1.5% Lugol's solution. D: Abnormal intraepithelial capillary loops under narrow-band imaging system with magnifying endoscopy. E: Endoscopic submucosal dissection of the superficial neoplasia. F: Mucosal cancer invading the lamina propria (main picture: H&E stain, 40x; right bottom: H&E stain, 100x). H&E: haematoxylin and eosin.

With permission from Chung et al.[29]

Superficial HNCs

OSCC patients have a risk of 8.3-27.1% of developing SPM.[8] Due to common risk factors such as tobacco and alcohol, OSCC shows a particularly high association with LC and HNC. Matsubara et al.[44] reported that OSCC patients are at very high risk for the development of both HNC and LC after oesophagectomy and that the early detection of second cancers allowed less invasive treatment with favourable outcomes.

Patients with OSCC, particularly alcohol drinkers, current smokers, and those with the *ALDH-2* allele and multiple LVL of the oesophageal mucosa, have an increased risk of superficial squamous cell cancer within the head and neck region. As Lugol chromoendoscopy is not applicable to the head and neck region, NBI in combination with ME is the preferred technique to search for early (i.e. superficial) HNSCC in OSCC patients.[7,8] The ability to detect a second primary cancer at a (very) early stage is of benefit for patients at high risk of superficial HNSCC. However, controlled prospective studies that provide evidence for a survival benefit of endoscopic surveillance in OSCC survivors have yet to be performed.[6]

Lung Cancer

LC is the largest single cause of death from cancer in the world. As the number of long-term OEC survivors continues to increase worldwide, the incidence of second primary cancers including LC will increase. Detecting and treating SPM appear to be effective in OSCC patients. Thus, recent evidence suggests similar overall survival rates in OEC patients with or without SPM.[8] Both early asymptomatic LC and superficial HNSCC are amenable to curative treatment.[4,7] Detection of early LC is best achieved by low-dose chest CT. Periodic, low-dose CT screening leads to a shift to detection of earlier-stage non-small-cell LC and thereby reduces LC mortality.[26] Nowadays, both HNSCC and OSCC survivors should be considered for regular screening for early LC by low-dose chest CT.

CONCLUSION

As field cancerisation involves the oesophagus, the bronchi, and the head and neck region, the patients at risk are best surveilled and managed by an interdisciplinary team.

REFERENCES

1. Stewart BW, Wild CP (eds.), World Cancer Report (2014), World Health Organization.

2. Chen MC et al. Impact of second primary esophageal or lung cancer on survival of patients with head and neck cancer. Oral Oncol. 2010;46(4):249-54.

3. Liao LJ et al. The impact of second primary malignancies on head and neck cancer survivors: a nationwide cohort study. PLoS One. 2013;8(4):e62116.

4. Surapaneni R et al. Stage I lung cancer survivorship: risk of second malignancies and need for individualized care plan. J Thorac Oncol. 2012;7(8):1252-6.

5. Baxi SS et al. Causes of death in long-term survivors of head and neck cancer. Cancer. 2014;120(10):1507-13.

6. Zhu G et al. Risk of second primary cancer after treatment for esophageal cancer: a pooled analysis of nine cancer registries. Dis Esophagus. 2012;25(6): 505-11.

7. Katada C et al. Risk of superficial squamous cell carcinoma developing in the head and neck region in patients with esophageal squamous cell carcinoma. Laryngoscope. 2012;122(6):1291-6.

8. Nandy N, Dasanu CA. Incidence of second primary malignancies in patients with esophageal cancer: a comprehensive review. Curr Med Res Opin. 2013;29(9):1055-65.

9. Hsu WL et al. Lifetime risk of distinct upper aerodigestive tract cancers and consumption of alcohol, betel and cigarette. Int J Cancer. 2014;135(6): 1480-6.

10. Li Y et al. Alcohol drinking and upper aerodigestive tract cancer mortality: a systematic review and meta-analysis. Oral Oncol. 2014;50(4):269-75.

11. Druesne-Pecollo N et al. Alcohol drinking and second primary cancer risk in patients with upper aerodigestive tract cancers: a systematic review and meta-analysis of observational studies. Cancer Epidemiol Biomarkers Prev. 2014;23(2):324-31.

12. Slaughter DP et al. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer. 1953;6(5):963-8.

13. Morita M et al. Alcohol drinking, cigarette smoking, and the development of squamous cell carcinoma of the esophagus: epidemiology, clinical findings, and prevention. Int J Clin Oncol. 2010;15(2):126-34.

14. Sharan RN et al. Association of betel nut with carcinogenesis: revisit with a clinical perspective. PLoS One. 2012;7(8):e42759.

15. Akhtar S. Areca nut chewing and esophageal squamous-cell carcinoma risk in Asians: a meta-analysis of case-control studies. Cancer Causes Control. 2013;24(2):257-65.

16. Huang SF et al. Association of HPV infections with second primary tumors in early-staged oral cavity cancer. Oral Dis. 2012;18(8):809-15.

17. Testino G, Borro P. Alcohol and gastrointestinal oncology. World J Gastrointest Oncol. 2010;2(8):322-5.

18. Lee CH et al. Carcinogenetic impact of ADH1B and ALDH2 genes on squamous cell carcinoma risk of the esophagus with regard to the consumption of alcohol, tobacco and betel quid. Int J Cancer. 2008;122(6):1347-56.

19. Muto M et al. Risk of multiple squamous cell carcinomas both in the esophagus and the head and neck region. Carcinogenesis. 2005;26(5):1008-12.

20. Duan F et al. [Genetic polymorphisms of ADH1B and ALDH-2 associated with risk of esophageal cancer: a meta-analysis].

Wei Sheng Yan Jiu. 2012;41(5):723-9.

21. Curado MP, Boyle P. Epidemiology of head and neck squamous cell carcinoma not related to tobacco or alcohol. Curr Opin Oncol. 2013;25(3):229-34.

22. Jain KS et al. Synchronous cancers in patients with head and neck cancer: risks in the era of human papillomavirus-associated oropharyngeal cancer. Cancer. 2013;119(10):1832-7.

23. de Villiers EM et al. Esophageal squamous cell cancer in patients with head and neck cancer: prevalence of human papillomavirus DNA sequences. Int J Cancer. 2004;109(2):253-8.

24. Hardefeldt HA et al. Association between human papillomavirus (HPV) and oesophageal squamous cell carcinoma: a meta-analysis. Epidemiol Infect. 2014;142(6):1119-37.

25. Chen WG et al. Gene chip technology used in the detection of HPV infection in esophageal cancer of Kazakh Chinese in Xinjiang Province. J Huazhong Univ Sci Technolog Med Sci. 2014;34(3):343-7.

26. Aberle DR et al; National Lung Screening Trial Research Team. Results of the two incidence screenings in the National Lung Screening Trial. N Engl J Med. 2013;369(10):920-31.

27. Pech O et al. Endoscopic resection of superficial esophageal squamous-cell carcinomas: Western experience. Am J Gastroenterol. 2004;99:1226-32.

28. Lee DH et al. Second cancer incidence, risk factor, and specific mortality in head and neck squamous cell carcinoma. Otolaryngol Head Neck Surg. 2013;149(4):579-86.

29. Chung CS et al. Risk factors for second primary neoplasia of esophagus in newly diagnosed head and neck cancer patients: a case-control study. BMC Gastroenterol. 2013;13:154.

30. Morris LG et al. Anatomic sites at elevated risk of second primary cancer after an index head and neck cancer. Cancer Causes Control. 2011;22(5):671-9.

31. Scherübl H, Zeitz M. Esophageal cancer. N Engl J Med. 2004;350(13): 1363-4.

32. Priante AV et al. Second primary tumors in patients with head and neck cancer. Curr Oncol Rep. 2011;13(2):132-7.

33. Lee CT et al. Narrow-band imaging with magnifying endoscopy for the screening of esophageal cancer in patients with primary head and neck cancers. Endoscopy. 2010;42(8):613-9.

34. Hung SH et al. Routine endoscopy for esophageal cancer is suggestive for patients with oral, oropharyngeal and hypopharyngeal cancer. PLoS One. 2013;8(8):e72097.

35. Su YY et al. Effect of routine esophageal screening in patients with head and neck cancer. JAMA Otolaryngol Head Neck Surg. 2013;139(4):350-4.

36. Scherübl H et al. Head and neck cancer. N Engl J Med. 2002;346(18): 1416-7.

37. Tabuchi T et al. Tobacco smoking and the risk of subsequent primary cancer among cancer survivors: a retrospective cohort study. Ann Oncol. 2013;24(10):2699-704.

38. Scherübl H et al. Coincidental squamous cell cancers of the esophagus, head, and neck: risk and screening. HNO. 2008;56(6):603-8.

39. Horiuchi M et al. Survival benefit of screening for early esophageal carcinoma in head and neck cancer patients. Digestive Endoscopy. 1998;10:110–5.

40. Scherübl H et al. Screening for oesophageal neoplasia in patients with head and neck cancer. Br J Cancer. 2002;86(2):239-43.

41. Wang WL et al. The benefit of pretreatment esophageal screening with image-enhanced endoscopy on the survival of patients with hypopharyngeal cancer. Oral Oncol. 2013;49(8):808-13.

42. de Monès E et al; Socéité Française de l'Otorhinolaryngologie. Initial staging of squamous cell carcinoma of the oral cavity, larynx and pharynx (excluding nasopharynx). Part 2: Remote extension assessment and exploration for secondary synchronous locations outside of the upper aerodigestive tract. 2012 SFORL guidelines. Eur Ann Otorhinolaryngol Head Neck Dis. 2013;130(2):107-12.

43. Uedo N et al. Role of narrow band imaging for diagnosis of early-stage esophagogastric cancer: current consensus of experienced endoscopists in Asia-Pacific region. Dig Endosc. 2011;23 Suppl 1:58-71.

44. Matsubara T et al. Risk of second primary malignancy after esophagectomy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol. 2003;21(23):4336-41.