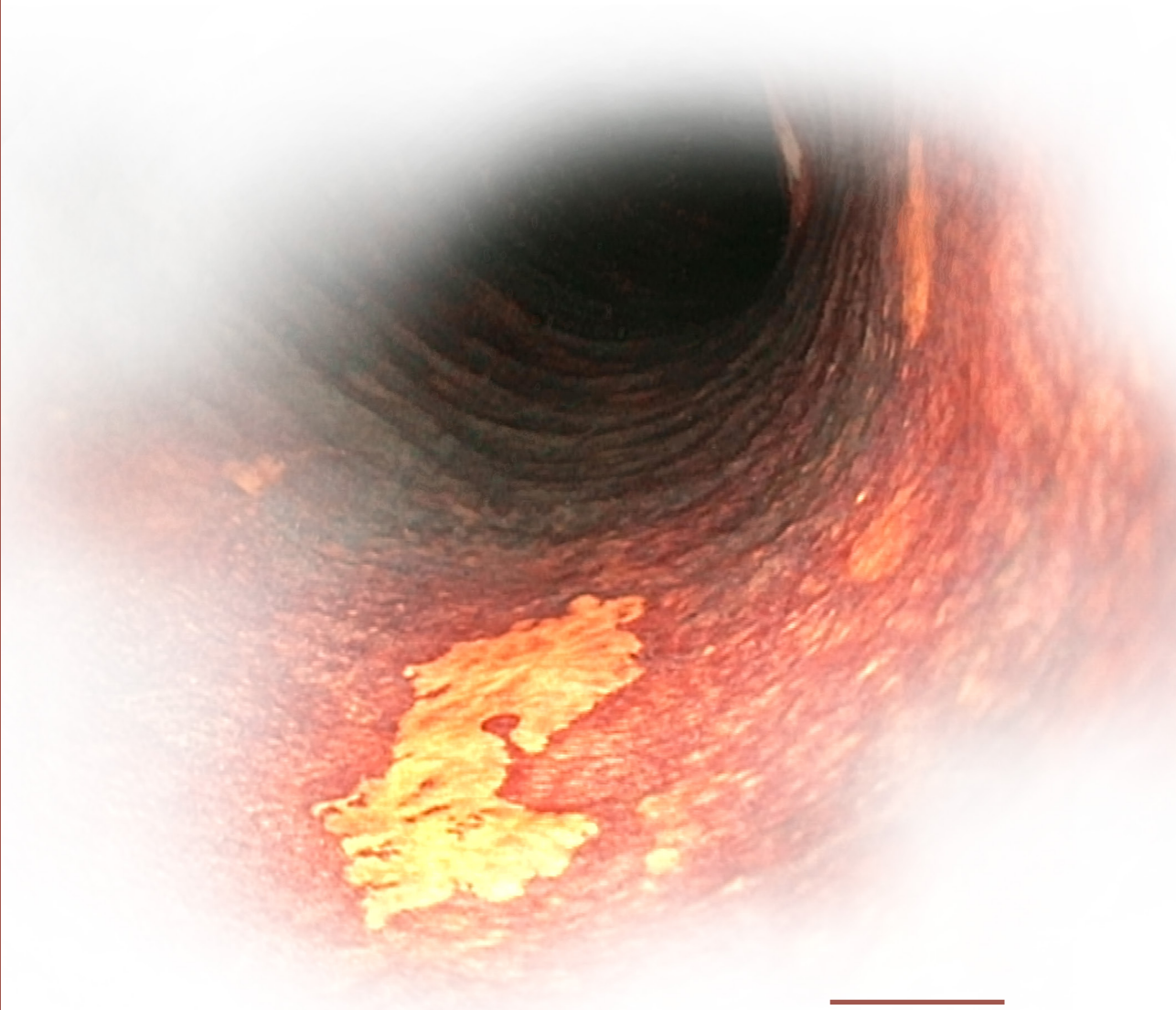
Steffi E.M. van de Ven



# Diagnosis and treatment of early esophageal carcinoma and second primary tumors in the upper aerodigestive tract

# Diagnosis and Treatment of Early Esophageal Carcinoma and Second Primary Tumors in the Upper Aerodigestive Tract

Steffi Elisabeth Maria van de Ven

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# Diagnosis and Treatment of Early Esophageal Carcinoma and Second Primary Tumors in the Upper Aerodigestive Tract

Diagnostiek en behandeling van vroegcarcinomen in de slokdarm en tweede primaire tumoren in de luchtwegen en het bovenste deel van het spijsverteringskanaal

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## Introduction

# CHAPTER 1.1

## General introduction

# General introduction

### Epidemiology and etiology of esophageal cancer

The incidence of esophageal cancer (EC) has increased over the past few decades.[1, 2] EC is the eight most common cancer and the sixth most common cause of death worldwide.[3] The incidence of EC was approximately 2,500 in the Netherlands, in 2018.[2]

There are two main types of EC; esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Although ESCC is the most common histologic type worldwide, EAC predominates in the Netherlands.[2] Likewise, EAC is the most common type in West and North Europe and in the United States.[4] In contrast, the prevalence of ESCC is highest in East Asia and Africa.[4]

These two types of EC differ in certain aspects. ESCC is most often located in the upper and middle part of the esophagus while EAC is located in the lower part of the esophagus and the gastroesophageal junction (GEJ). In developed countries, smoking and alcohol are risk factors for ESCC.[5] Besides smoking and alcohol, poor nutritional status (low intake of vegetables and fruits) and drinking high temperature beverages are thought to be risk factors for ESCC in Asian countries.[6] Common risk factors for EAC are obesity, smoking, and the presence of Barrett's esophagus (BE).[7, 8] Unlike ESCC, alcohol is not reported as a risk factor for EAC.[9]

### Clinical presentation, diagnosis and treatment of esophageal cancer

Patients with EC often present with weight loss and progressive dysphagia.[8] Asymptomatic patients might present with iron deficiency anemia due to chronic gastrointestinal blood loss from EC.[8] However, patients with early stage EC usually do not present with any symptoms and EC is therefore often diagnosed in an advanced stage.[8, 10] As a consequence, the 5-year survival rate of EC is only 19%.[11] When EC is detected in an early stage, curative treatment is possible with less morbidity and mortality.[8] A study by Pech et al. about the long-term follow-up results of 1,000 patients who underwent endoscopic mucosal resection (EMR) for early EAC, showed a long-term complete remission rate of 93.8% and a 10-year survival rate of 75%.[12]

Esophagoduodenoscopy (EGD) is the gold standard for EC diagnosis.[8, 13] EGD allows the gastroenterologist to visualize the tumor and take biopsies to confirm EC diagnosis.[8] During EGD, the endoscopist can macroscopically assess the tumor for morphology according to the Paris classification, location, size, and whether EC is suitable for endoscopic resection (ER).[14, 15] The latter, however, has to be performed by an endoscopist with experience in assessing endoscopic resectability of the tumor.

EC staging is based on the American Joint Committee on Cancer's TNM system.[16] Degree of tumor invasion (T), regional lymph node involvement (N), and the presence of distant metastasis (M) are described in this system.[16] Different tumor stages of EC are presented in Figure 1. To determine the TNM-classification for a specific esophageal carcinoma, guidelines recommend endoscopic ultrasound (EUS), computed tomography (CT) scan, and Positron emission tomography (PET).[8, 13] EUS is most often used for tumor staging because it is superior to CT and PET.[17, 18]

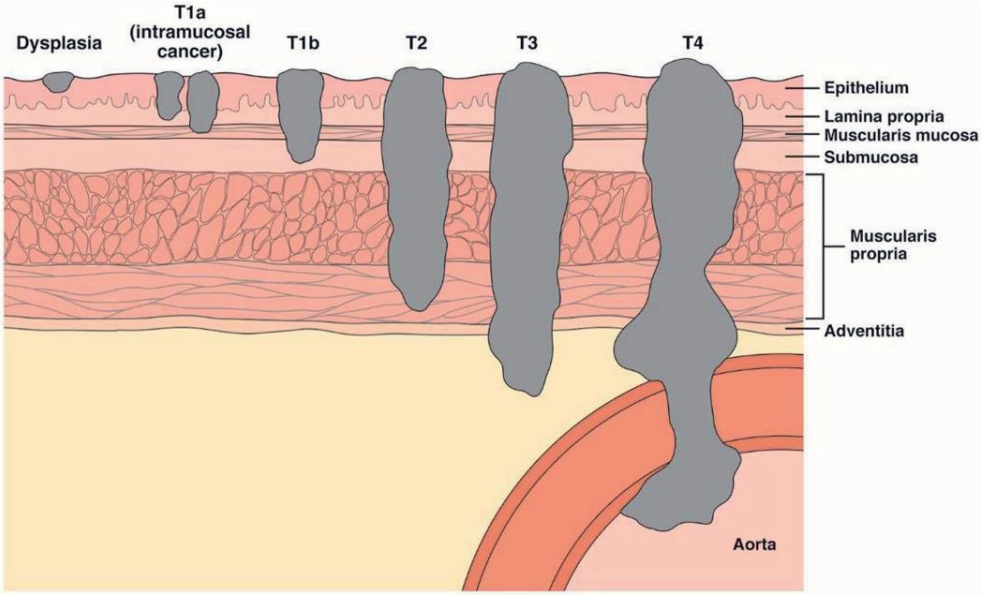


**Figure 1. Esophageal cancer tumor staging** [from Rubenstein JH, Shaheen NJ. *"Epidemiology, diagnosis and management of esophageal adenocarcinoma."* Gastroenterology 2015; 149(2):307, Copyright Elsevier; permission to use this figure].[19]

In patients with EAC, EUS is accurate in staging T3 and T4 EAC, but less accurate in differentiation T1 and T2 EAC (sensitivity 43-55%, specificity 80-85%).[20, 21] As a result, many patients with cT2 EAC are actually pT1 EAC and these patients might receive unnecessary invasive treatment.[14] Accurate tumor staging is crucial since treatment strategies differ for T1 and T2 EAC.

Patients with high grade dysplasia (HGD) / carcinoma-in-situ (Tis) or EAC limited to the mucosa (T1a) have a very low risk of developing lymph node metastasis (LNM) (0-2%).[22] Therefore, ER without adjuvant treatment is justified in these patients.[12, 23, 24] When EAC invades the submucosa (T1b), the risk of LNM is higher; up to 78%.[25-29] However, when pT1b EAC is limited to the upper part of the submucosa (sm1: ≤500 µm) without poor histologic features (e.g. lymphovascular invasion [LVI], poor tumor differentiation), guidelines state that ER could be potentially curative and adjuvant treatment decision should be individualized in these patients.[30]

Additional esophagectomy with lymphadenectomy is only advocated when the risk of LNM outweighs the risk for morbidity and mortality associated with esophagectomy.[31] Current guidelines recommend esophagectomy with loco-regional lymph node dissection (with or without neo-adjuvant chemo-radiotherapy) in patients with pT1b EAC with submucosal invasion ≥sm2 (>500 µm) and in patients with T2 EAC.[31, 32]

However, not every patient with pT1b EAC develops LNM. Although separate histopathological risk factors associated with LNM have been previously described, no clinical tool is available that incorporates all prognostic histopathological parameters to predict the LNM risk on an individual basis. It is not known whether a combination of specific risk factors

improve estimation of LNM risk. A clinical tool is needed for shared decision making whether or not to undergo adjuvant treatment after ER of pT1b EAC.

**Esophageal squamous cell carcinoma and the risk of second primary tumors in the upper aerodigestive tract**

In patients with ESCC, multiple primary tumors (MPTs) frequently develop.[33] Likewise, MPTs can also develop in patients with head and neck squamous cell carcinoma (HNSCC).[34, 35] These MPTs are particularly located in the upper aerodigestive tract (UADT), consisting of the head and neck region, esophagus and lungs.[36] The stomach is another important region at risk for MPT development.[37]

The occurrence of MPTs can be explained by the field cancerization theory, which was first described by Slaughter et al., in 1953.[38] Premalignant histologic and genetic changes can occur around the primary tumor due to carcinogen exposure, such as alcohol and tobacco.[38] These subtle histologic and genetic changes might increase the risk of synchronous and metachronous MPTs.[38] Common risk factors for cancers in the UADT might play a role in the development of MPTs.[37] When MPTs develop within 6 months after diagnosis of the primary tumor, it is defined synchronous. MPTs that develop ≥ 6 months after primary tumor diagnosis are defined metachronous.

Previous studies have reported an MPT incidence in the UADT up to 19.3% in patients with primary ESCC.[33, 39-42] Most of these studies have been performed in Asian populations and data on Western incidences are currently not known. The head and neck region is especially at risk for developing MPTs in patients with ESCC.[37, 42] Although the prognosis of EC is poor because most tumors are diagnosed in an advanced stage, this prognosis is even worse when head and neck second primary tumors (HNSPTs) are detected.[8, 43] A previous study reported a 5-year survival rate of 21.0% in patients with ESCC compared to 9.2% in ESCC patients with HNSPT.[43] Early detection of MPTs is therefore vitally important. Nowadays, The European Society for Medical Oncology Clinical Practice Guidelines for EC recommends head and neck and lung screening to detect MPTs in patients with ESCC who use chronic tobacco and alcohol.[44] However, screening is usually not performed in daily clinical practice and no Western screening studies have been published to date.

MPTs that develop in patients with HNSCC are particularly located in the esophagus.[35, 45] The prevalence of these esophageal MPTs is reported up to 22% in retrospective studies.[46] Early detection of esophageal MPTs is very important since early EC can be treated with minimally invasive ER instead of surgery or (neo-adjuvant) chemo-radiotherapy, which is associated with higher morbidity and decreased quality of life.[47, 48] Although several esophageal screening studies have been performed in Asian patients with HNSCC, there is a lack of screening studies in the Western population.

**Endoscopic detection techniques**

EGD is the gold standard for the detection of (early) EC. EGD can be performed with white light high resolution endoscopy (WLE), narrow band imaging (NBI) and Lugol chromoendoscopy (LCE). Early EC, in particular ESCC, are characterized by flat lesions and these lesions are easily missed with WLE.[49]

LCE is considered by many the gold standard for the detection of superficial ESCC.[50] Lugol iodine binds to glycogen and is applied during EGD to stain the esophagus.[51] Glycogen is abundant in normal epithelium and diminished or absent in dysplastic or neoplastic tissue.[51] Iodine-unstained areas, also called Lugol-voiding lesions (LVL), are therefore characteristic for dysplastic and neoplastic lesions.[49, 51] However, non-dysplastic lesions such as inflammation can also appear unstained wherefore LCE is not very specific.[49] In addition, LCE can cause several side effects, such as chest discomfort, nausea, heartburn and pulmonary aspiration.[52, 53]

NBI is a real-time optical chromoendoscopy technique that was first described in 2004.[54] In contrast to LCE, NBI can be used by simply pressing a button on the endoscope.[52] Intraepithelial papillary capillary loop (IPCL) patterns can be visualized with NBI.[55, 56]

Figure 2 shows the IPCL pattern classification. IPCL type I-III corresponds to benign pathology and low grade neoplasia (LGIN).[56, 57] IPCL type IV corresponds to LGIN or high grade neoplasia (HGIN).[56] IPCL pattern V is a malignant pattern and is classified into four categories.[56] The recommended treatment for these different IPCL patterns is outlined in the last column of Figure 2.

Figure 3 shows abnormal squamous epithelium with HGD; IPCL pattern V1-2 in the left picture with NBI and LVL in the right picture with LCE. Since endoscopic imaging techniques have improved over time and LCE has several side effects, the question arises whether LCE is still necessary to date.

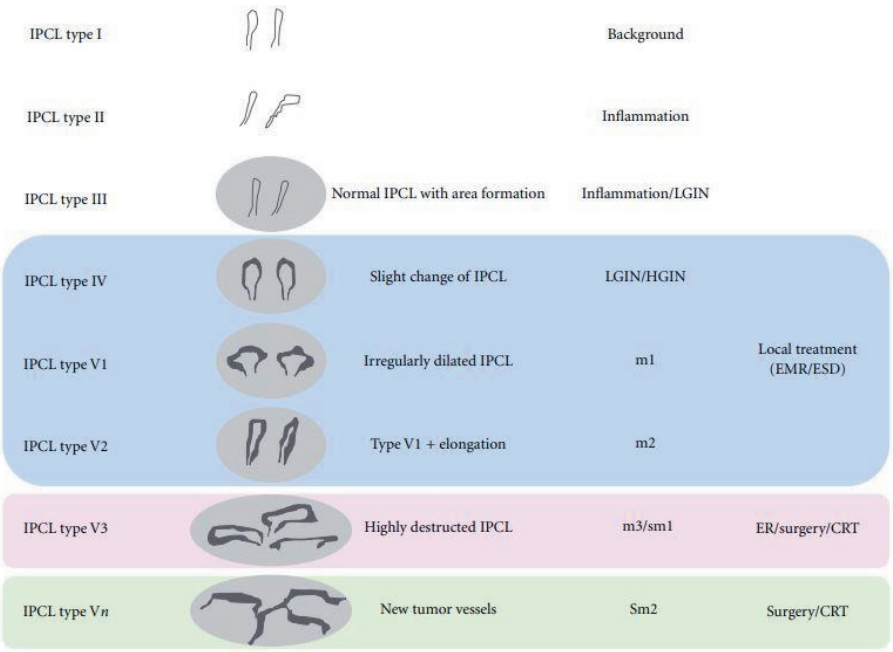


**Figure 2. IPCL pattern classification** IPCL, intraepithelial papillary capillary loop; LGIN, low grade neoplasia; HGIN, high grade neoplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; ER, endoscopic resection; CRT, chemoradiotherapy. [from Minami et al. *"Usefulness of Background Coloration in Detection of Esophago-Pharyngeal Lesions Using NBI Magnification"*, Gastroenterology Research and Practice 2012; permission to use this figure].[57]

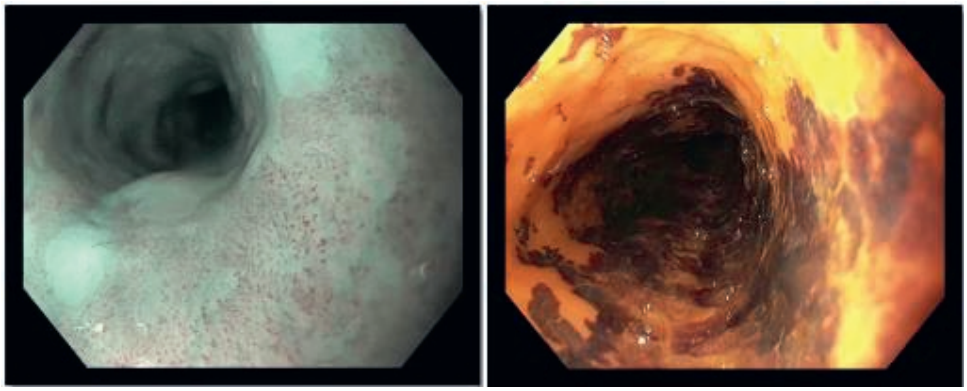

**Figure 3. Abnormal squamous epithelium visible NBI (left picture) and with LCE (right picture)**

**Endoscopic resection of early esophageal cancer**

ER can be used to remove early EC. ER is mostly performed with either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD).

The EMR-cap technique and the EMR band ligation technique are often used for EC resection. EMR-cap: the lesion is sucked into the cap after fluid injection into the submucosa, and the snare is closed at the base of the tumor. EMR band ligation: a rubber band is placed at the base of the tumor to create a 'pseudo polyp', the snare is tightened below the rubber band and the 'pseudo polyp' is subsequently removed.[58]

ESD has a higher curative resection rate than EMR and is used when submucosal invasion of the lesion is suspected.[59, 60] During ESD, a fluid solution with blue dye, usually indigo carmine is injected in the submucosal layer to elevate the lesion from the muscular layer.[58] Afterwards, a circumferential incision is made around the target lesion followed by dissection of the submucosal layer.[58] ESD is a time-consuming procedure that can result in pain and discomfort for the patient.[61, 62] Adequate sedation and analgesia are required to limit complications.[63-65] Although guidelines do not recommend a preferred sedation method during ESD, general anesthesia with endotracheal intubation is most often used during this procedure because of the continuous airway protection which may lead to fewer respiratory problems.[63, 66, 67] However, disadvantages of general anesthesia are higher procedural costs, the need for an anesthesiologist, and prolonged post-procedural hospital stay.[63, 67]

**Strictures rates after endoscopic resection**

A major disadvantage after ER of large esophageal tumors is the high esophageal stricture rate.[68, 69] This risk is especially high when the mucosal defect after ER is more than three quarters of the esophageal circumference. Strictures can result in dysphagia with the need for endoscopic dilations that might decrease patients quality of life.[70] Several methods have been described to prevent these strictures (e.g. preventive balloon dilation, triamcinolone injections, oral prednisolone).[68, 71-73] However, these methods all have several side effects. The optimal preventive treatment strategy has not yet been defined.

## REFERENCES


1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424.
2. IKNL. Netherlands Cancer Registry - The Netherlands Comprehensive Cancer Organisation. https://iknl.nl/nkr-cijfers
3. Napier KJ, Scheerer M, Misra S. Esophageal cancer: A Review of epidemiology, pathogenesis, staging workup and treatment modalities. World J Gastrointest Oncol 2014; 6: 112-120
4. Arnold M, Soerjomataram I, Ferlay J et al. Global incidence of oesophageal cancer by histological subtype in 2012. Gut 2015; 64: 381-387
5. Prabhu A, Obi KO, Rubenstein JH. The synergistic effects of alcohol and tobacco consumption on the risk of esophageal squamous cell carcinoma: a meta-analysis. Am J Gastroenterol 2014; 109: 822-827
6. Engel LS, Chow WH, Vaughan TL et al. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst 2003; 95: 1404-1413
7. Pandeya N, Williams G, Green AC et al. Alcohol consumption and the risks of adenocarcinoma and squamous cell carcinoma of the esophagus. Gastroenterology 2009; 136: 1215-1224, e1211-1212
8. Alsop BR, Sharma P. Esophageal Cancer. Gastroenterol Clin North Am 2016; 45: 399-412
9. Wu AH, Wan P, Bernstein L. A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinomas of the stomach and esophagus (United States). Cancer Causes Control 2001; 12: 721-732
10. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med 2003; 349: 2241-2252
11. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69: 7-34
12. Pech O, May A, Manner H et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology 2014; 146: 652-660 e651
13. Landelijke richtlijn Oesofaguscarcinoom. 2015 Versie 3.1.
14. Gotink AW, Spaander MCW, Doukas M et al. Exploring diagnostic and therapeutic implications of endoscopic mucosal resection in EUS-staged T2 esophageal adenocarcinoma. Endoscopy 2017; 49: 941-948
15. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003; 58: S3-43
16. AJCC Cancer Staging Manual: Esophageal and Esophagogastric Junction (Version 3.2015).
17. Vallbohmer D, Sisic L, Blank S et al. Clinically staged cT2 adenocarcinomas of the gastroesophageal junction: accuracy of staging and therapeutic consequences. Oncol Res Treat 2014; 37: 97-104
18. Choi J, Kim SG, Kim JS et al. Comparison of endoscopic ultrasonography (EUS), positron emission tomography (PET), and computed tomography (CT) in the preoperative locoregional staging of resectable esophageal cancer. Surg Endosc 2010; 24: 1380-1386
19. Rubenstein JH, Shaheen NJ. Epidemiology, Diagnosis, and Management of Esophageal Adenocarcinoma. Gastroenterology 2015; 149: 302-317 e301
20. O'Farrell NJ, Malik V, Donohoe CL et al. Appraisal of staging endoscopic ultrasonography in a modern high-volume esophageal program. World J Surg 2013; 37: 1666-1672
21. Pech O, Gunter E, Dusemund F et al. Accuracy of endoscopic ultrasound in preoperative staging of esophageal cancer: results from a referral center for early esophageal cancer. Endoscopy 2010; 42: 456-461
22. Dunbar KB, Spechler SJ. The risk of lymph-node metastases in patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systematic review. Am J Gastroenterol 2012; 107: 850-862

23. Pouw RE, Beyna T, Belghazi K et al. A prospective multicenter study using a new multiband mucosectomy device for endoscopic resection of early neoplasia in Barrett's esophagus. Gastrointest Endosc 2018; 88: 647-654
24. Bahin FF, Jayanna M, Hourigan LF et al. Long-term outcomes of a primary complete endoscopic resection strategy for short-segment Barrett's esophagus with high-grade dysplasia and/or early esophageal adenocarcinoma. Gastrointest Endosc 2016; 83: 68-77
25. Barbour AP, Jones M, Brown I et al. Risk stratification for early esophageal adenocarcinoma: analysis of lymphatic spread and prognostic factors. Ann Surg Oncol 2010; 17: 2494-2502
26. Sepesi B, Watson TJ, Zhou D et al. Are endoscopic therapies appropriate for superficial submucosal esophageal adenocarcinoma? An analysis of esophagectomy specimens. J Am Coll Surg 2010; 210: 418-427
27. Lee L, Ronellenfitsch U, Hofstetter WL et al. Predicting lymph node metastases in early esophageal adenocarcinoma using a simple scoring system. J Am Coll Surg 2013; 217: 191-199
28. Stein HJ, Feith M, Bruecher BL et al. Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. Ann Surg 2005; 242: 566-573; discussion 573-565
29. Westerterp M, Koppert LB, Buskens CJ et al. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch 2005; 446: 497-504
30. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2015; 47: 829-854
31. Fitzgerald RC, di Pietro M, Ragunath K et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut 2014; 63: 7-42
32. Spechler SJ, Sharma P, Souza RF et al. American Gastroenterological Association technical review on the management of Barrett's esophagus. Gastroenterology 2011; 140: e18-52
33. Lee GD, Kim YH, Kim JB et al. Esophageal Cancer Associated with Multiple Primary Cancers: Surgical Approaches and Long-term Survival. Ann Surg Oncol 2013; 20: 4260-4266
34. Priante AV, Castilho EC, Kowalski LP. Second primary tumors in patients with head and neck cancer. Curr Oncol Rep 2011; 13: 132-137
35. Atienza JA, Dasanu CA. Incidence of second primary malignancies in patients with treated head and neck cancer: a comprehensive review of literature. Curr Med Res Opin 2012; 28: 1899-1909
36. Kagei K, Hosokawa M, Shirato H et al. Efficacy of intense screening and treatment for synchronous second primary cancers in patients with esophageal cancer. Jpn J Clin Oncol 2002; 32: 120-127
37. Chuang SC, Hashibe M, Scelo G et al. Risk of second primary cancer among esophageal cancer patients: a pooled analysis of 13 cancer registries. Cancer Epidemiol Biomarkers Prev 2008; 17: 1543-1549
38. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 1953; 6: 963-968
39. Utada M, Ohno Y, Hori M et al. Incidence of multiple primary cancers and interval between first and second primary cancers. Cancer Sci 2014; 105: 890-896
40. Kumagai Y, Kawano T, Nakajima Y et al. Multiple primary cancers associated with esophageal carcinoma. Surg Today 2001; 31: 872-876
41. Zhu G, Chen Y, Zhu Z et al. Risk of second primary cancer after treatment for esophageal cancer: a pooled analysis of nine cancer registries. Dis Esophagus 2012; 25: 505-511
42. Natsugoe S, Matsumoto M, Okumura H et al. Multiple primary carcinomas with esophageal squamous cell cancer: clinicopathologic outcome. World J Surg 2005; 29: 46-49
43. Lo OS, Law S, Wei WI et al. Esophageal cancers with synchronous or antecedent head and neck cancers: a more formidable challenge? Ann Surg Oncol 2008; 15: 1750-1756

44. Lordick F, Mariette C, Haustermans K et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016; 27: v50-v57
45. Muto M, Hironaka S, Nakane M et al. Association of multiple Lugol-voiding lesions with synchronous and metachronous esophageal squamous cell carcinoma in patients with head and neck cancer. Gastrointest Endosc 2002; 56: 517-521
46. de Mones E, Bertolus C, Salaun PY et al. 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: 107-112
47. Linden PA, Towe CW, Watson TJ et al. Mortality After Esophagectomy: Analysis of Individual Complications and Their Association with Mortality. J Gastrointest Surg 2020, 24(9):1948-1954
48. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med 2011; 364: 2128-2137
49. Goda K, Dobashi A, Yoshimura N et al. Narrow-Band Imaging Magnifying Endoscopy versus Lugol Chromoendoscopy with Pink-Color Sign Assessment in the Diagnosis of Superficial Esophageal Squamous Neoplasms: A Randomised Noninferiority Trial. Gastroenterol Res Pract 2015; 2015: 639462
50. Inoue H, Rey JF, Lightdale C. Lugol chromoendoscopy for esophageal squamous cell cancer. Endoscopy 2001; 33: 75-79
51. Mori M, Adachi Y, Matsushima T et al. Lugol staining pattern and histology of esophageal lesions. Am J Gastroenterol 1993; 88: 701-705
52. Lopes AB, Fagundes RB. Esophageal squamous cell carcinoma - precursor lesions and early diagnosis. World J Gastrointest Endosc 2012; 4: 9-16
53. Dubuc. Endoscopic screening for esophageal squamous-cell carcinoma in high-risk patients: a prospective study conducted in 62 french endoscopy centers. Endoscopy 2006, 38(7): 690-5
54. Gono K, Obi T, Yamaguchi M et al. Appearance of enhanced tissue features in narrow-band endoscopic imaging. J Biomed Opt 2004; 9: 568-577
55. Yoshida T, Inoue H, Usui S et al. Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. Gastrointest Endosc 2004; 59: 288-295
56. Inoue H, Kaga M, Ikeda H et al. Magnification endoscopy in esophageal squamous cell carcinoma: a review of the intrapapillary capillary loop classification. Ann Gastroenterol 2015; 28: 41-48
57. Minami H, Inoue H, Ikeda H et al. Usefulness of Background Coloration in Detection of Esophago-Pharyngeal Lesions Using NBI Magnification. Gastroenterol Res Pract. 2012;2012:529782
58. Nishizawa T, Yahagi N. Endoscopic mucosal resection and endoscopic submucosal dissection: technique and new directions. Curr Opin Gastroenterol 2017; 33: 315-319
59. Imagawa A, Okada H, Kawahara Y et al. Endoscopic submucosal dissection for early gastric cancer: results and degrees of technical difficulty as well as success. Endoscopy 2006; 38: 987-990
60. Weusten B, Bisschops R, Coron E et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy 2017; 49: 191-198
61. Shin S, Park CH, Kim HJ et al. Patient satisfaction after endoscopic submucosal dissection under propofol-based sedation: a small premedication makes all the difference. Surg Endosc 2017; 31: 2636-2644
62. Committee AT, Maple JT, Abu Dayyeh BK et al. Endoscopic submucosal dissection. Gastrointest Endosc 2015; 81: 1311-1325
63. Yamashita K, Shiwaku H, Ohmiya T et al. Efficacy and safety of endoscopic submucosal dissection under general anesthesia. World J Gastrointest Endosc 2016; 8: 466-471

64. Wadhwa V, Issa D, Garg S et al. Similar Risk of Cardiopulmonary Adverse Events Between Propofol and Traditional Anesthesia for Gastrointestinal Endoscopy: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2017; 15: 194-206
65. Lazzaroni M, Bianchi Porro G. Preparation, premedication, and surveillance. Endoscopy 2005; 37: 101-109
66. Yurtlu DA, Aslan F, Ayvat P et al. Propofol-Based Sedation Versus General Anesthesia for Endoscopic Submucosal Dissection. Medicine (Baltimore) 2016; 95: e3680
67. Song BG, Min YW, Cha RR et al. Endoscopic submucosal dissection under general anesthesia for superficial esophageal squamous cell carcinoma is associated with better clinical outcomes. BMC Gastroenterol 2018; 18: 80
68. Shi Q, Ju H, Yao LQ et al. Risk factors for postoperative stricture after endoscopic submucosal dissection for superficial esophageal carcinoma. Endoscopy 2014; 46: 640-644
69. Tsujii Y, Nishida T, Nishiyama O et al. Clinical outcomes of endoscopic submucosal dissection for superficial esophageal neoplasms: a multicenter retrospective cohort study. Endoscopy 2015; 47: 775-783
70. Iizuka T, Kikuchi D, Yamada A et al. Polyglycolic acid sheet application to prevent esophageal stricture after endoscopic submucosal dissection for esophageal squamous cell carcinoma. Endoscopy 2015; 47: 341-344
71. Katada C, Muto M, Manabe T et al. Esophageal stenosis after endoscopic mucosal resection of superficial esophageal lesions. Gastrointest Endosc 2003; 57: 165-169
72. Ono S, Fujishiro M, Niimi K et al. Predictors of postoperative stricture after esophageal endoscopic submucosal dissection for superficial squamous cell neoplasms. Endoscopy 2009; 41: 661-665
73. Lewis JJ, Rubenstein JH, Singal AG et al. Factors associated with esophageal stricture formation after endoscopic mucosal resection for neoplastic Barrett's esophagus. Gastrointest Endosc 2011; 74: 753-760

# CHAPTER 1.2

## Aims and outline of this thesis

# Aims and outline of this thesis



## AIMS

This thesis aims to provide insights in the incidence and risk of second and multiple primary tumors (MPTs) in the upper aerodigestive tract (UADT) in patients with esophageal squamous cell carcinoma (ESCC) and in patients with head and neck squamous cell carcinoma (HNSCC). The second aim of this thesis is to investigate whether screening for these MPTs is recommended.

The third aim of this thesis is to optimize clinical staging and endoscopic resection (ER) of early esophageal cancer (EC) and to develop a prediction model that estimates the risk of lymph node metastasis (LNM) in individual patients with submucosal (pT1b) esophageal adenocarcinoma (EAC).

## OUTLINE OF THE THESIS

This thesis is divided into four parts. **Part I** contains the general introduction (**Chapter 1.1**) and the aims and outline of this thesis (**Chapter 1.2**). In **Chapter 1.1**, a general introduction on EC is outlined including epidemiology, etiology, clinical presentation, diagnosis and treatment of early EC, risk factors for LNM, the risk for second primary tumors (SPTs) in the UADT in patients with ESCC and HNSCC, endoscopic detection techniques, ER techniques, and the prevention of esophageal strictures after ER. **Chapter 1.2** describes the aims and outline of this thesis.

**Part II** of this thesis focusses on screening and diagnosis of MPTs in the UADT in patients with ESCC and HNSCC. **Part II** starts with an overview of the prevalence of MPTs in patients with ESCC in the Netherlands, in **Chapter 2.** In this chapter, the risk of MPTs in patients with ESCC is compared with the general population.

It is currently known that Asian patients with ESCC have a high risk of developing MPTs, compared to the general population. The head and neck region is especially at risk for developing MPTs. Several screening studies have been performed to screen for head and neck SPTs in patients with ESCC. **Chapter 3** describes a systematic review and meta-analysis of studies in which head and neck screening was performed in patients with ESCC. Conversely, patients with HNSCC are also at risk for developing SPTs in the esophagus. **Chapter 4** describes a systematic review and meta-analysis of studies in which esophageal screening was performed by Lugol chromoendoscopy (LCE) to screen for esophageal SPTs in patients with HNSCC.

Most screening studies are performed in the Asian population and there is a lack of well-defined screening studies in the Western population. **Chapter 5** describes a prospective screening study in which patients with HNSCC are screened with esophagogastroduodenoscopy (EGD) for esophageal SPTs. EGD is performed with white light high resolution endoscopy (WLE), narrow-band imaging (NBI) and LCE. LCE is considered by many the gold standard for the detection of early ESCC. However, endoscopic imaging techniques have drastically improved over time. In addition, LCE is associated with several side effects such as nausea or chest discomfort. The question arises whether and

when LCE is still necessary for the detection of ESCC. **Chapter 6** concerns an editorial whether Lugol is still necessary for ESCC detection to date.

While **Part II** of this thesis is about ESCC, **Part III** mainly focusses on early EAC. Endoscopic ultrasound (EUS) is used for clinical staging of early EAC. It is known that the accuracy of EUS is low in differentiating T1 from T2 EAC. **Chapter 7** describes a multicenter prospective cohort study of patients with a clinical (c)T2 EAC. These patients underwent endoscopic reassessment by an experienced interventional endoscopist in order to assess the proportion of cT2 EAC that were downstaged to cT1 EAC.

Early EC can be treated with ER. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are both appropriate ER methods. ESD has a higher curative resection rate than EMR and is used when submucosal invasion of the tumor is suspected or when the tumor cannot be removed by EMR. ESD is, however, time-consuming and minimal patient movement is preferred during the procedure. Therefore, appropriate sedation and analgesia are required to perform a successful ESD. **Chapter 8** describes a retrospective cohort study of patient who underwent ESD for early esophageal or gastric cancer. In this study, analgosedation using propofol and remifentanil without endotracheal intubation was used and endoscopy- and anesthesia-related complications were reported.

When ER is performed in the esophagus, there is a risk of developing esophageal strictures after the procedure. This risk is especially high when the mucosal defect after ER is more than three quarters of the esophageal circumference. Several methods have been described to prevent these strictures. **Chapter 9** describes the effectiveness of a treatment with topical Budesonide for the prevention of esophageal strictures after ESD for EC (both ESCC and EAC).

After ER, the ER specimen is assessed by the pathologist. Adjuvant therapy, such as esophagectomy, is only required when the risk of LNM outweighs the risk for mortality associated with esophagectomy. Although many studies have described separate histopathological risk factors associated with LNM, no clinical tool is available that incorporates these histopathological parameters to predict the LNM risk on an individual basis. **Chapter 10.1** describes a multicenter retrospective cohort study of patients with submucosal (pT1b) EAC that underwent ER or primary surgery. A prediction model was developed, and internally validated, that incorporated all accepted prognostic parameters to accurately predict the LNM risk on an individual basis.

Currently, lymphovascular invasion (LVI) is classified as either present or absent. **Chapter 10.2** describes a multicenter retrospective cohort study that determines whether quantification of LVI provides additional prognostic information for the development of LNM in patients with pT1b EAC.

**Part IV** starts with **Chapter 11.1**, in which the summary of the main findings is outlined. **Chapter 11.2** includes the general discussion and recommendations for further research**.** The conclusion of this thesis is described in **Chapter 11.3**.

# PART II

## Screening and diagnosis of second and multiple primary tumors in the upper aerodigestive tract

# CHAPTER 2

## Increased risk of second primary tumors in patients with esophageal squamous cell carcinoma: A nationwide study in a Western population

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## ABSTRACT

**Background:** Patients with primary esophageal squamous cell carcinoma are at risk of developing multiple primary tumors in the upper aerodigestive tract. To date, most studies are performed in the Asian population. We aimed to evaluate the risk of multiple primary tumors in the upper aerodigestive tract and stomach in patients with esophageal squamous cell carcinoma in a Western population.

**Methods:** We performed a nationwide, retrospective cohort study in collaboration with the Netherlands Cancer Registry. Patients with primary esophageal squamous cell carcinoma, diagnosed between 2000 and 2016, were included. Primary endpoints were synchronous and metachronous multiple primary tumor risk.

**Results**: The cohort consisted of 9,058 patients, diagnosed with esophageal squamous cell carcinoma (male: 57.3%, median age 67 years). In 476 patients (5.3%), 545 multiple primary tumors have been diagnosed. Most of them were located in the head and neck region (49.5%). Among all multiple primary tumors, 329 (60.4%) were diagnosed synchronously (<6 months after esophageal squamous cell carcinoma diagnosis) and 216 (39.6%) metachronously (≥6 months). Patients with esophageal squamous cell carcinoma had a significantly increased risk of both synchronous (standardized incidence ratio 10.95, 99% confidence interval 9.40-12.53) and metachronous multiple primary tumors (standardized incidence ratio 4.36, 99% confidence interval 3.56-5.10), compared to the general population. The median interval to metachronous second primary tumor diagnosis was 3.0 years (interquartile range 1.8-5.9).

**Conclusion**: Approximately one in 20 patients with primary esophageal squamous cell carcinoma have a second primary tumor in the upper aerodigestive tract or stomach, either at the time of esophageal squamous cell carcinoma diagnosis or at a later stage. As second primary tumors occur at an increased risk compared to the general population, prospective studies are necessary to investigate the yield and survival benefit of screening for second primary tumors in patients with esophageal squamous cell carcinoma.

## INTRODUCTION

Squamous cell carcinoma is the most common histologic type of esophageal cancer worldwide, and has the highest incidence in Eastern Asia.[1, 2] Multiple primary tumors (MPTs) frequently develop in patients with esophageal squamous cell carcinoma (ESCC), especially in the upper aerodigestive tract (UADT).[3, 4]

Since survival of patients with esophageal cancer has improved over the last years due to better treatment options, the risk of developing MPTs may increase.[5] These MPTs affect the prognosis and survival of patients with ESCC, and the choice of ESCC treatment in case of synchronous second primary tumor (SPT) detection.[6] It is therefore important to detect MPTs at an early stage, when curative treatment is still possible.

The development of MPTs in the UADT particularly occurs in patients with squamous cell carcinomas, and can be explained by the 'field cancerization' theory.[7] This theory states that premalignant epithelial changes can occur around the primary tumor, due to exposure to common carcinogens.[7] Well-known carcinogens for the development of both ESCC and MPTs, especially in the head and neck region and lungs, are tobacco and alcohol.[8, 9]

In retrospective studies, up to 19.3% of patients with primary ESCC develop MPTs in the UADT.[3, 10-13] Most studies consider the head and neck region, lungs, and esophagus as the UADT, the stomach is another important region to be at risk for MPT development.[3, 12, 14, 15] Most studies about MPT development, however, are performed in Asian populations. There is a lack of Western studies about MPT incidence in ESCC patients.

We therefore conducted a nationwide, retrospective, registry study of patients with primary ESCC to determine the risk of developing MPTs in the UADT and stomach, in a Western country.

## MATERIALS AND METHODS

### Patient and study design

We conducted a nationwide, retrospective, registry study in collaboration with the Netherlands Cancer Registry (NCR; nationwide registry of all cancers). Adult patients diagnosed with ESCC between 1 January 2000 and 31 December 2016 were selected from the NCR. Patients were excluded when ESCC was not the index tumor; defined as another tumor in the UADT or stomach which was diagnosed >180 days prior to ESCC diagnosis. This study was approved by the Medical Ethical Review Committee of the Erasmus Medical Centre [MEC-2018-1631] on 7 January 2019. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's Human Research Committee.

### Data collection

Anonymous patient data were obtained from the NCR. The following data were available and collected: year and age at ESCC diagnosis, sex, ESCC tumor characteristics, the presence of metastases, and ESCC treatment. Tumor characteristics included histology, location in the

esophagus (cervical part; <18 cm from the incisors, upper third; 18-24 cm from the incisors, middle third; 24-32 cm from the incisors, lower third of the esophagus; 32-40 cm from the incisors, or overlapping locations; between two parts of the esophagus), differentiation grade, clinical and histopathological Tumor, Node, Metastasis (TNM) stage according to the 5th (2000-2002), 6th (2003-2009) and 7th (2010-2016) TNM stage classification.[16-18] For final analysis, we converted all different TNM classifications into the 7th TNM classification. cM1A classification was considered as M0 according to the 7th TNM classification. Information about vital state (alive or not) was collected until 31 January 2018.

We collected the following data of patients with MPTs: MPT location in the UADT (defined as: head and neck region, lungs, and esophagus) and in the stomach, age at MPT diagnosis, year of MPT diagnosis, time between ESCC and MPT diagnosis, tumor characteristics and MPT treatment. No information was available about how MPTs were detected (e.g. CT-scan, endoscopy). Diagnosis of MPTs was based on information in medical records in accordance with the Warren and Gates criteria: an MPT (a) must be malignant on histological examination, (b) must be separated from the index tumor by normal mucosa, and (c) may not be a metastasis of the index tumor.[19] An MPT was defined synchronous when it developed within 6 months before or after ESCC diagnosis, and as metachronous when it developed ≥6 months after ESCC diagnosis. This six month cut-off value was used in most other studies about MPT development in the UADT.[20-22] Pathology information was available in the NCR to verify that MPTs were not metastases of the primary tumor. All MPTs were identified, also whether patients had more primary tumors (second, third etc.). The first MPT was also called the SPT. During the study period of 16 years, no MPT screening programs were performed.

**Study endpoints**

The primary endpoint was the risk of MPTs in patients with primary ESCC compared with the general population. Secondary endpoints were; (a) MPT localization in the UADT and stomach, (b) MPT histology, (c) the proportion of synchronous and metachronous MPTs, (d) the cumulative incidence of SPTs, (e) the difference in survival between ESCC patients with low (stage 0/I/II) and high (stage III/IV) stage metachronous SPTs, and (f) risk factors associated with MPT development.

**Statistics**

Continues variables were expressed as mean (± standard deviation (SD)) and median (interquartile range (IQR) and range) for normally and skewed distributed variables, respectively. For risk factor analysis, a multivariate Cox proportional hazards model was used. Hazard ratios (HRs) and 95% confidence intervals (CIs) with a time-dependent covariate (follow-up time until development of an SPT, death or the last date of follow-up) were calculated in this model.

To assess the MPT risk in patients with primary ESCC, the standardized incidence ratio (SIR) was calculated with 99% CIs, assuming a Poisson probability distribution for the occurrence of SPTs. The SIR was defined as the total number of observed MPTs (the study cohort) divided by the total number of expected cancers in that same group of patients based on the specific age, gender, year and type of cancer incidence in general population. The SIR was calculated for different groups, separately for synchronous or metachronous MPTs, and stratified in accordance with sex, cancer location, age in 20 year intervals, and cancer treatment. Cancer

incidence data from the general population were acquired from the NCR. The cumulative incidence of SPTs was estimated with death as competing risk. STATA (v. 14) was used for this analysis.

Survival analysis was determined by Kaplan-Meier analysis, and we performed log-rank analysis using SPSS. SIRs were calculated with SAS 9.2 software (SAS Institute Inc., Cary, North Caroline, USA), all other analysis were carried out using IBM SPSS version 25. For SIRs, a two-sided test with a *p*-value of <0.01 was considered significant. For all other analysis, a two-sided test with a *p*-value of <0.05 was considered significant.



## RESULTS

### Patient characteristics

We identified a total of 9,810 patients with ESCC diagnosis between 1 January 2000 and 31 December 2016 in the NCR. In total, 752 patients were excluded because ESCC was not the index tumor (Figure 1). The study cohort consisted of 9,058 patients with primary ESCC. The median age at ESCC diagnosis was 67 years (IQR 60-75), most patients were male (57.3%) (baseline characteristics are shown in Table 1). The total follow-up consisted of 17,072 person-years with a median follow-up time of 9.8 months (IQR 4.2-23.8 months). The median survival after ESCC diagnosis was 9.9 months (IQR 9.6-10.3). The overall five-year survival rate of the total cohort was 15.9%.

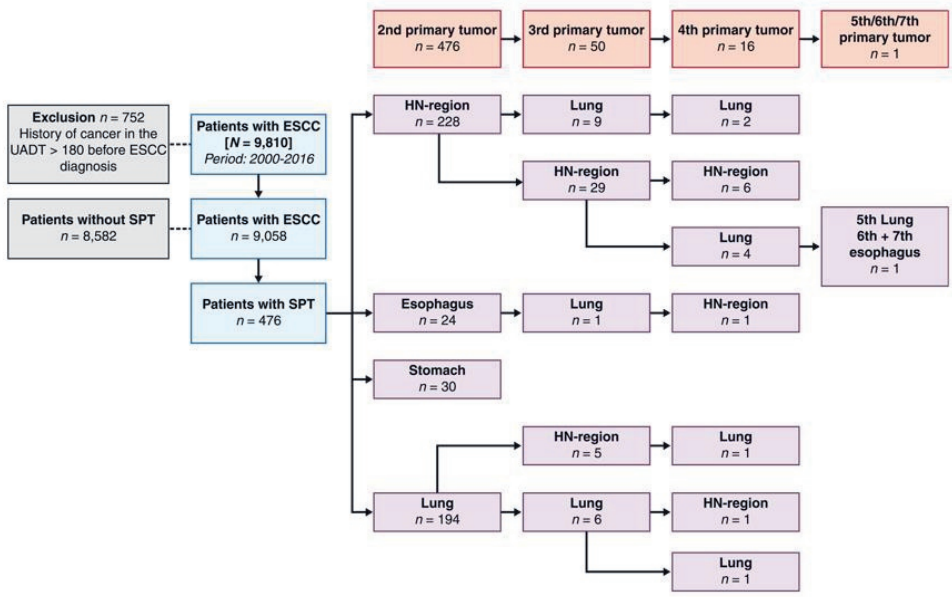



**Figure 1. Flow-chart patient selection and MPT development**
ESCC, esophageal squamous cell carcinoma; HN, head and neck; SPT, second primary tumor; UADT, upper aerodigestive tract.

**Table 1. Baseline and tumor characteristics of patients with esophageal squamous cell carcinoma**

| **Characteristics** | (N=9,058) |
|---|---|
| **Gender**, n(%) | |
| Male | 5,193 (57.3%) |
| **Median age** (years) (IQR) | 67 (60-75) |
| **Follow-up** | |
| Person-years at risk (years) | 17,072 |
| Median follow-up (months) (IQR) | 9.8 (4.2-23.8) |
| **Vital status** (31-01-2018), n (%) | |
| Alive | 1,358 (15.0%) |
| Dead | 7,700 (85.0%) |
| **Median overall survival after ESCC diagnosis** (months) (95% CI) | 9.9 (9.6-10.3) |
| **Anatomical sub-location**, n (%) | |
| Cervical esophagus | 276 (3.0%) |
| Upper third esophagus | 1,236 (13.6%) |
| Middle third esophagus | 3,301 (36.4%) |
| Lower third esophagus | 3,501 (38.7%) |
| Esophagus overlapping or unspecified | 744 (8.3%) |
| **ESCC clinical tumor stage**, n(%) | |
| 0 | 73 (0.8%) |
| 1 | 591 (6.5%) |
| 2 | 1,717 (19.0%) |
| 3 | 2,428 (26.8%) |
| 4 | 2,620 (28.9%) |
| *Missing* | *1,629 (18.0%)* |
| **Differentiation grade**, n (%) | |
| Grade 1 (good) | 298 (3.3%) |
| Grade 2 (moderate) | 2,739 (30.2%) |
| Grade 3 (poor) | 2,594 (28.6%) |
| Grade 4 (undifferentiated) | 8 (0.1%) |
| *Missing* | *3,419 (37.8%)* |
| **Distant metastasis at diagnosis (cM stage)**, n (%) | 2,372 (26.2%) |
| **ESCC treatment,** n (%) | |
| Endoscopic resection | 116 (1.3%) |
| Surgical resection | 734 (8.1%) |
| Chemotherapy | 479 (5.3%) |
| Radiotherapy | 2,163 (23.9%) |
| Chemotherapy + radiotherapy | 1,812 (20.0%) |
| neoadjuvant chemotherapy + surgery | 267 (2.9%) |
| Chemotherapy +radiotherapy + surgery | 1,021 (11.3%) |
| Surgery + radiotherapy | 25 (0.3%) |
| Other [a] | 61 (0.7%) |
| No therapy | 2,380 (26.2%) |

ESCC, esophageal squamous cell carcinoma; CI, confidence interval; IQR, interquartile range. [a] other treatment combinations with either endoscopic or surgical resection combined with (neo)adjuvant chemo and/or radiotherapy.

**ESCC characteristics**

The majority of ESCCs were located in the middle (36.4%) and lower third (38.7%) of the esophagus (Table 1). ESCC tumor stage was low in 26.3% and high in 55.7% of patients. Pathological assessment of ESCCs revealed good or moderate differentiation grade (G1/G2) in 33.5%, and poor or undifferentiated grade (G3/G4) in 28.7%. In total, 2,372 patients (26.2%) had distant metastasis at time of diagnosis (cM stage). In total, 2,163 patients (23.9%) were treated with radiotherapy for ESCC, 1,812 patients (20.0%) with chemo-radiotherapy, and 1,288 (14.2%) patients received neoadjuvant therapy followed by surgery.

**MPTs**

A total of 545 MPTs were registered in 476 (5.3%) patients. Of these 476 patients, 50 patients developed a third primary tumor, 16 patients a fourth primary tumor, and one patient developed another fifth, sixth and seventh primary tumor (Figure 1). Of all MPTs (545), 329 (60.4%) were diagnosed synchronously and 216 (39.6%) metachronously (Table 2). The majority of both synchronous and metachronous MPTs were located in the head and neck region (270/545; 49.5% ) and lungs (219/545; 40.2%). MPT tumor stage was low (stage 0/I/II) in 39.6%, and high (stage III/IV) in 43.5% of the tumors, which was roughly the same for synchronous and metachronous MPTs. Of all MPTs, 160/545 (29.4%) were treated with radiotherapy and 170/545 MPTs (31.2%) did not receive any treatment. Squamous cell carcinoma (337/545; 61.8%) was the most prevalent histologic MPT type (Table 2).

**SIRs**

In total, 545 MPTs were detected during the observation period. Patients with ESCC had a significantly increased risk of both synchronous (SIR 10.95, 99% CI 9.40-12.53) and metachronous MPTs (SIR 4.36, 99% CI 3.56-5.10) compared to the general population (Table 3). Sub-analyses showed that patients with ESCC had the highest risk of developing synchronous (SIR 36.33, 99% CI 29.44-44.30) and metachronous (SIR 14.17, 99% CI 10.41-17.52) MPTs in the head and neck region. Patients aged 41-60 years at ESCC diagnosis had a highest SIR of 32.07 (99% CI 24.71-40.77) for developing synchronous MPTs, and patients aged 18-40 years at ESCC diagnosis had a highest SIR of 70.87 (99% CI 2.72-329.97) for developing metachronous MPTs. In order to determine whether radiotherapy had influence on MPT development compared to other treatments, we stratified the MPT risk for different treatment groups. The MPT risk was high for all different treatment groups compared to the general population. We were unable to address any influence of previous radiotherapy on MPT development; of patients who developed metachronous MPTs >10 years after ESCC diagnosis (n=15), only four patients received radiotherapy for ESCCs. For all sub-analyses, females had the highest SIR compared to males (Table 3).

**Metachronous SPT**

Of all patients who were alive 6 months after ESCC diagnosis (n=5,715), 191 patients developed metachronous MPTs. Of these patients, 16 had already developed a synchronous SPT. In total, 175 patients developed a metachronous SPT. Figure 2 shows the cumulative incidence of metachronous SPTs. Fifteen years after ESCC diagnosis, the cumulative incidence of metachronous SPTs was 19.7%. Cumulative incidences of different SPT sub-locations is shown in the Supplementary Tables S1-S4, Figures S1 and S2. The median time between ESCC diagnosis and metachronous SPT diagnosis was 3.0 years (IQR 1.8 – 5.9).

The median time between ESCC and metachronous head and neck SPT diagnosis was 2.8 years (IQR 2.2 – 3.4) and for lung SPT diagnosis 3.2 years (IQR 1.9 – 4.5). SPT stage was high (stage III/IV) in 57.4% of the patients with metachronous SPTs. These patients had a significantly worse two-year survival after SPT diagnosis than low stage SPTs (stage 0/ I/II) (15.1% vs 51.9%, $p$<0.01) (Figure 3).

**Cumulative incidence of MPTs in patients with low-stage ESCC**

Subgroup analysis was performed in patients with low-stage ESCC (n=2,381). The 15-year cumulative incidence for this subgroup was 21.7% (Supplementary Table S5 and Figure S3).

**Table 2. Tumor characteristics of all multiple primary tumors**

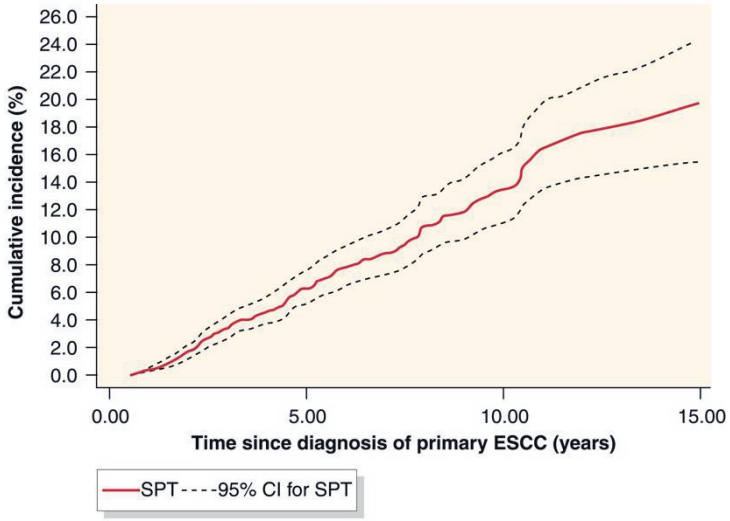
| Characteristics | Total (545) | Synchronous (329) | Metachronous (216) |
|---|---|---|---|
| **MPT location**, n (%) | | | |
| Head and neck region | 270 (49.5%) | 167 | 103 |
| Lung | 219 (40.2%) | 123 | 96 |
| Esophagus | 26 (4.8%) | 14 | 12 |
| Stomach | 30 (5.5%) | 25 | 5 |
| **Histology**, n (%) | | | |
| Squamous cell carcinoma | 337 (61.8%) | 196 | 141 |
| Adenocarcinoma | 79 (14.5%) | 50 | 29 |
| Carcinoid | 2 (0.4%) | 2 | 0 |
| Neoplasm and carcinoma * | 127 (23.3%) | 81 | 46 |
| **Tumor stage**, n (%) | | | |
| 0 | 11 (2.4%) | 6 | 5 |
| 1 | 149 (32.9%) | 86 | 63 |
| 2 | 56 (12.4%) | 37 | 19 |
| 3 | 65 (14.3%) | 38 | 27 |
| 4 | 172 (38.0%) | 94 | 78 |
| *Missing* | *92* | *68* | *24* |
| **MPT Treatment**, n (%) | | | |
| Endoscopic resection | 20 (3.7%) | 8 | 12 |
| Surgical resection | 60 (11.0%) | 32 | 28 |
| Chemotherapy | 45 (8.3%) | 22 | 23 |
| Radiotherapy | 160 (29.4%) | 90 | 70 |
| Chemotherapy + radiotherapy | 72 (13.2%) | 54 | 18 |
| Chemo + surgery | 1 (0.2%) | 1 | 0 |
| Chemo + radio + surgery | 2 (0.4%) | 2 | 0 |
| Surgery + radio | 13 (2.4%) | 5 | 8 |
| Surgery + chemo + radio | 1 (0.2%) | 1 | 0 |
| Endoscopic resection +radio | 1 (0.2%) | 0 | 1 |
| No treatment | 170 (31.2%) | 114 | 56 |

MPT, multiple primary tumor; * unspecified

**Table 3. Standardized Incidence Ratio (SIR) for synchronous and metachronous multiple primary tumors**

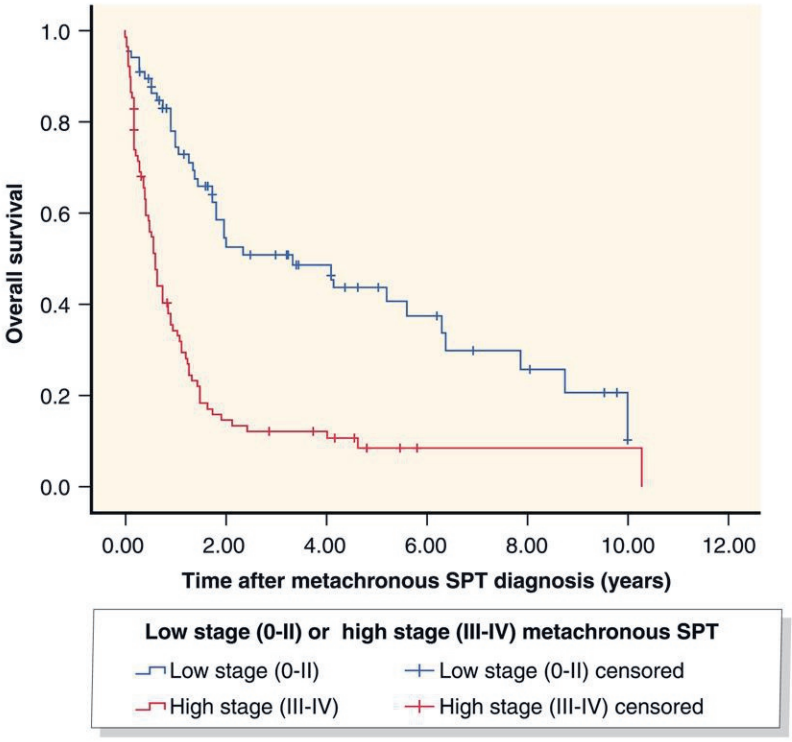
| Characteristics | Observed (n) | Expected (n) | SIR (99% CI) Total | SIR (99% CI) Male | SIR (99% CI) Female |
|---|---|---|---|---|---|
| **Synchronous MPTs** | | | | | |
| **All cancers** | 329 | 30.05 | 10.95 (9.40-12.53) | 9.82 (8.20-11.65) | 14.07 (10.79-17.98) |
| Head and neck | 164 | 4.51 | 36.33 (29.44-44.30) | 34.69 (27.05-43.76) | 41.51 (27.29-60.29) |
| Lungs | 123 | 19.17 | 6.42 (5.02-8.06) | 5.35 (3.90-7.14) | 9.48 (6.29-13.66) |
| Stomach | 25 | 3.16 | 7.92 (4.43-12.99) | 7.75 (3.84013.83) | 8.37 (2.40-20.52) |
| Esophagus | 17 | 4.04 | 4.21 (2.04-7.63) | 3.14 (1.00-7.30) | 10.64 (3.05-26.08) |
| **Age at ESCC diagnosis** (yrs) | | | | | |
| 41-60 | 110 | 3.43 | 32.07 (24.71-40.77) | 28.26 (20.21-38.35) | 40.86 (26.43-60.09) |
| 61-80 | 202 | 22.57 | 8.95 (7.41-10.70) | 8.15 (6.49-10.09) | 11.56 (8.10-15.95) |
| >80 | 17 | 4.04 | 4.21 (2.04-7.63) | 4.99 (2.21-9.56) | 2.44 (0.25-8.96) |
| **Treatment ESCC** | | | | | |
| Chemo + radiotherapy | 100 | 9.85 | 10.15 (7.73-13.08) | 9.25 (6.58-12.61) | 12.53 (7.68-19.21) |
| Chemotherapy | 22 | 2.15 | 10.23 (5.47-17.31) | 7.99 (3.54-15.32) | 20.09 (6.39-46.71) |
| Radiotherapy | 88 | 8.59 | 10.24 (7.75-13.55) | 9.49 (6.69-13.03) | 13.34 (7.56-21.69) |
| No chemo- or radiotherapy | 119 | 9.48 | 12.60 (9.98-16.08) | 11.72 (8.65-15.48) | 15.74 (10.00-23.48) |
| **Metachronous MPTs** | | | | | |
| **All cancers** | 216 | 49.51 | 4.36 (3.56-5.10) | 3.84 (3.03-4.79) | 5.25 (3.87-6.93) |
| Head and neck | 106 | 7.48 | 14.17 (10.41-17.52) | 12.85 (9.19-17.44) | 15.55 (9.53-23.85) |
| Lungs | 96 | 31.95 | 3.00 (2.22-3.82) | 2.50 (1.71-3.53) | 3.81 (2.45-5.62) |
| Stomach | 5 | 4.56 | 1.10 (0.23-3.11) | 0.94 (0.10-3.46) | 1.45 (0.06-6.76) |
| Esophagus | 9 | 5.53 | 1.63 (0.78-4.12) | 1.42 (0.36-3.70) | 3.86 (0.81-10.95) |
| **Age at ESCC diagnosis** (yrs) | | | | | |
| 18-40 | 2 | 0.03 | 70.87 (2.72-329.97) | 157.62 (6.05-733.84) | 0.00 |
| 41-60 | 95 | 11.02 | 8.62 (6.35-10.96) | 6.94 (4.65-9.93) | 11.10 (7.26-16.18) |
| 61-80 | 115 | 36.17 | 3.18 (2.42-3.96) | 2.99 (2.18-4.00) | 3.44 (2.15-5.18) |
| >80 | 4 | 2.30 | 1.74 (0.28-5.50) | 2.12 (0.22-7.79) | 1.13 (0.00-8.46) |
| **Treatment ESCC** | | | | | |
| Chemo + radiotherapy | 112 | 24.89 | 4.50 (3.44-5.67) | 3.87 (2.77-5.25) | 5.88 (3.82-8.61) |
| Chemotherapy | 19 | 6.05 | 3.14 (1.47-5.31) | 2.87 (1.22-5.62) | 3.30 (0.69-9.36) |
| Radiotherapy | 26 | 5.68 | 4.58 (2.46-7.22) | 3.58 (1.59-6.88) | 6.18 (2.42-12.82) |
| No chemo- or radiotherapy | 59 | 12.89 | 4.58 (3.12-6.26) | 4.45 (2.75-6.78) | 4.58 (2.49-7.67) |

*MPT, Multiple Primary Tumor; ESCC, esophageal squamous cell carcinoma; CI, confidence interval; SIR, standardized incidence ratio*




| Interval | Begin total (n) | SPT (n) | Death (n) | 95% CI |
|---|---|---|---|---|
| 0-5 years | 5715 | 119 | 4719 | 6.3% (5.1-7.5) |
| 5-10 years | 877 | 41 | 549 | 13.3% (10.9-15.8) |
| 10-15 years | 287 | 14 | 214 | 19.7% (15.5-24.4) |

**Figure 2. Cumulative incidence of metachronous SPT after ESCC diagnosis**
ESCC, esophageal squamous cell carcinoma; SPT, second primary tumor; CI, confidence interval




| Interval | Number at risk | Death | Lost to follow-up (censored cases) |
|---|---|---|---|
| **Low stage metachrononous SPT** | | | |
| 0-2 years | 66 | 28 | 10 |
| 2-4 years | 28 | 2 | 6 |
| 4-6 years | 20 | 4 | 4 |
| 6-8 years | 12 | 2 | 4 |
| 8-10 years | 6 | 2 | 2 |
| 10-11 years | 2 | 1 | 1 |
| **High stage metachrononous SPT** | | | |
| 0-2 years | 89 | 72 | 4 |
| 2-4 years | 13 | 2 | 3 |
| 4-6 years | 8 | 2 | 5 |
| 6-8 years | 1 | 0 | 0 |
| 8-10 years | 1 | 0 | 0 |
| 10-11 years | 1 | 1 | 0 |

**Figure 3. Survival after SPT diagnosis between low- and high-stage metachronous SPT** SPT, second primary tumor, *n=155; 21 patients were excluded for this analysis as result of missing SPT tumor stages

**Predictive factors for MPTs**

Multivariable Cox proportional hazard analysis showed that being male (HR 1.59, 95% CI 1.29-1.97, *p*<0.001), age <70 years (HR 1.51, 95% CI 1.19-1.90, *p*=0.001), and having a low ESCC tumor stage (stage 0/I/II) at diagnosis (HR 1.50, 95% CI 1.19-1.89, *p*=0.001) were independent predictors for MPT development (Table 4). Analysis with age (HR 0.99, 95% CI 0.98-0.10, *p*=0.022) and tumor stage (HR 0.73, 95% CI 0.64-0.82, *p*<0.001) as continues variables did not alter the outcomes.

**Table 4. Multivariable analysis for MPT development using Cox proportional hazards regression model**

| Variables | Multivariate analysis | |
|---|---|---|
| | HR (95%CI) | p-value |
| **Sex** | | |
| Male | 1.59 (1.29-1.97) | **<0.01** |
| female | Reference | |
| **Age** | | |
| <70 | 1.51 (1.19-1.90) | **<0.01** |
| ≥70 | Reference | |
| **Metastasis** | | |
| Yes | 1.06 (0.79-1.41) | 0.71 |
| No | Reference | |
| **ESCC tumor stage** | | |
| Low (0/I/II) | 1.50 (1.19-1.89) | **<0.01** |
| High (III/IV) | Reference | |

ESCC, esophageal squamous cell carcinoma; HR, hazard ratio

## DISCUSSION

We determined the risk of developing MPTs in the UADT and stomach in patients with primary ESCC. Our study shows that a minimum of one out of 20 patients with primary ESCC develops an SPT, with a 15-year cumulative metachronous SPT incidence of 19.7%. Which means that approximately one in five ESCC patients who survive longer than 6 months will develop an SPT within 15 years. The risk of developing synchronous (SIR 10.95) and metachronous MPTs (SIR 4.36) among patients with primary ESCC was increased compared to the general population, with the highest risk of developing MPTs in the head and neck region. Risk factors associated with MPT development are being male, age <70 years, and low ESCC tumor stage.

In retrospective studies, the incidence of MPTs localized the UADT among patients with primary ESCC ranged between 1.9-19.3%.[3, 10-13] Most studies are performed in the Asian population, where the MPT incidence is reported to be >10%.[3, 11, 13, 23] Studies performed in a Western population reported lower MPT incidences (1.9-6.3%), which is in accordance with our findings.[12, 24, 25] The difference in MPT incidence between Asian and non-Asian populations could possibly be explained by a difference in etiology. While the etiology of ESCC and MPTs in the UADT is clearly linked to smoking and alcohol intake in a Western population, the etiology in an Asian population is also linked to a poor nutritional status.[26, 27] Another explanation might be the difference in genetic polymorphisms in alcohol metabolism between Asian and Western populations.[28, 29]

The increased MPT risk among patients with primary ESCC, as reported in our study, has also been reported in other studies.[12, 15, 30, 31] Chuang et al. reported an increased risk of MPTs in the UADT, especially in the head and neck region (SIR 6.68) and lungs (SIR 1.55), among ESCC patients in 13 different countries.[15] Other studies also reported increased MPT risks.[10, 14, 24, 30, 32] As reported in our study, patients with ESCC diagnosis at a young age showed the highest SIR for developing both synchronous (SIR 32.07) and metachronous MPTs (SIR 70.87). The same results were reported in a study by Chen et al., with a SIR of 36.56 for patients aged between 20-39 years at ESCC diagnosis.[30]

We found the head and neck region to be the most common region for developing MPTs (synchronous; SIR 36.33, metachronous: SIR 14.17), which is also reported in both Asian (SIR 15.83) and Western (SIR 6.68-8.64) studies.[12, 14, 15, 30, 31] Studies from Japan and Korea reported the stomach as their most common MPT location.[3, 4] This could be due to the high incidence of stomach cancer in Japan and Korea.[2] Unfortunately, SIRs were not reported in these studies.[3, 4] For synchronous MPTs, we found the stomach to be the second most common region for MPT development. Less patients had synchronous or metachronous esophageal MPT in our cohort. In case a synchronous esophageal SPT is detected, one could argue that these patients probably had mucosal dysplasia or neoplasia at time of primary ESCC diagnosis. Careful inspection of the esophagus with Lugol chromoendoscopy is therefore very important in cases of curative primary ESCC diagnosis, because early esophageal SPT might be easily overlooked during routine white light endoscopy.[33]

Patients who develop metachronous SPT may potentially benefit from screening programs. The median time between ESCC diagnosis and metachronous SPT detection was 3 years (IQR 1.8-5.9 years), with a cumulative 15-years incidence of 19.7%. Most metachronous SPTs, however, had a high tumor stage (57.4%), with a worse two-year survival compared to low-stage metachronous SPTs (15.1% versus 51.9%, $p<0.01$). Screening for metachronous SPTs could possibly help to increase survival in these patients by detecting these SPTs at an early stage. Patients with high-stage ESCC with poor prognosis will possibly not benefit from screening programs since their prognosis is already determined by the ESCC. Diagnosing MPTs in these patients is probably not clinically relevant. The overall survival of our cohort was 9.9 months, the overall five-year survival was 15.9%. Prospective studies are necessary to investigate the yield of screening for MPTs, and especially whether screening will lead to survival benefit. One could argue that synchronous SPTs already existed at time of index tumor diagnosis but had not yet been detected at that time. The question arises whether routine screening of especially the head and neck region should be performed in curative ESCC patients prior to ESCC treatment.

Asian screening studies to detect head and neck SPTs have been performed in patients with primary ESCC. A systematic review about active screening for head and neck SPTs in patients with primary ESCC showed a pooled prevalence of 6.7% (range 3.0-29.6%).[22] Active screening showed a low SPT tumor stage in most patients (85.7%), and a better survival compared to patients who were not screened.[22, 34] These studies suggest that active screening contributes to an increase in SPT detection and overall survival.[4] Nowadays, no screening studies in patients with ESCC have been performed in Western countries.

Being male was a predictive factor for MPT development in our study, which is in accordance with previous studies.[24, 30, 31] Our study revealed age <70 years as a significant predictive factor, which is also in line with a previous study.[24] Chen et al., however, reported age ≥60

years as a predictive factor for MPT development.[30] Although higher age is reported as a significant risk factor for cancer development in the UADT or stomach in general, one might hypothesize that when patients survive ESCC at a young age they are expected to live longer and might have an increased risk in MPT development. The same might be true for patients with low ESCC tumor stage, they have a more favorable course of their disease and are therefore expected to live longer. We reported low ESCC tumor stage as a predictive factor for MPT development, but this has to be interpreted with caution.

Although this is the largest registry study in Europe with more than 9,000 patients, some limitations need to be acknowledged. First, this is a retrospective cohort study with limited patient information and a substantial amount of missing data. We could therefore not report on risk factors such as smoking or alcohol which are common risk factors for MPT development.[30] This might have caused confounding in our risk factor analysis. In addition, cause of death was not reported in the NCR and this information could be relevant in this patient cohort with a large number of high-stage ESCC and a median survival of only 10 months. Second, since this is a registry study, MPT incidence could be underestimated. Because of the retrospective design of this study, we did not know whether MPTs were diagnosed during regular follow-up or as a result of patients symptoms. As a consequence, no specific advice for time-interval for screening can be drawn from this study.

A minimum of one out of 20 patients with primary ESCC develops an MPT in the UADT or stomach. The majority of these MPTs were detected synchronously, in the head and neck region and in young patients. Survival of patients with ESCC is low. Prospective screening studies are necessary to determine the true MPT incidence and to investigate the yield and benefit of screening for MPTs.

## REFERENCES


1. Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012. Gut. 2015 Mar;64(3):381-7.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424.
3. Lee GD, Kim YH, Kim JB, Choi SH, Kim HR, Kim DK, et al. Esophageal Cancer Associated with Multiple Primary Cancers: Surgical Approaches and Long-term Survival. Ann Surg Oncol. 2013 Dec;20(13):4260-6.
4. Kagei K, Hosokawa M, Shirato H, Kusumi T, Shimizu Y, Watanabe A, et al. Efficacy of intense screening and treatment for synchronous second primary cancers in patients with esophageal cancer. Jpn J Clin Oncol. 2002 Apr;32(4):120-7.
5. van Putten M, de Vos-Geelen J, Nieuwenhuijzen GAP, Siersema PD, Lemmens V, Rosman C, et al. Long-term survival improvement in oesophageal cancer in the Netherlands. Eur J Cancer. 2018 May;94:138-47.
6. Lee JS, Ahn JY, Choi KD, Song HJ, Kim YH, Lee GH, et al. Synchronous second primary cancers in patients with squamous esophageal cancer: clinical features and survival outcome. Korean J Intern Med. 2016 Mar;31(2):253-9.
7. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer. 1953 Sep;6(5):963-8.
8. Henry MA, Lerco MM, Naresse LE, Crema E, Rodrigues MA. Outcome of superficial squamous cell carcinoma of the esophagus: a clinicopathological study. Acta Cir Bras. 2013 May;28(5):373-8.
9. Abiko S, Shimizu Y, Miyamoto S, Ishikawa M, Matsuda K, Tsuda M, et al. Risk assessment of metachronous squamous cell carcinoma after endoscopic resection for esophageal carcinoma based on the genetic polymorphisms of alcoholdehydrogense-1B aldehyde dehydrogenase-2: temperance reduces the risk. J Gastroenterol. 2018 Oct;53(10):1120-30.
10. Utada M, Ohno Y, Hori M, Soda M. Incidence of multiple primary cancers and interval between first and second primary cancers. Cancer Sci. 2014 Jul;105(7):890-6.
11. Kumagai Y, Kawano T, Nakajima Y, Nagai K, Inoue H, Nara S, et al. Multiple primary cancers associated with esophageal carcinoma. Surg Today. 2001;31(10):872-6.
12. Zhu G, Chen Y, Zhu Z, Lu L, Bi X, Deng Q, et al. Risk of second primary cancer after treatment for esophageal cancer: a pooled analysis of nine cancer registries. Dis Esophagus. 2012 Aug;25(6):505-11.
13. Natsugoe S, Matsumoto M, Okumura H, Ishigami S, Uenosono Y, Owaki T, et al. Multiple primary carcinomas with esophageal squamous cell cancer: clinicopathologic outcome. World J Surg. 2005 Jan;29(1):46-9.
14. Mitani S, Kadowaki S, Oze I, Masuishi T, Narita Y, Bando H, et al. Risk of second primary malignancies after definitive treatment for esophageal cancer: A competing risk analysis. Cancer Med. 2019 Nov 15.
15. Chuang SC, Hashibe M, Scelo G, Brewster DH, Pukkala E, Friis S, et al. Risk of second primary cancer among esophageal cancer patients: a pooled analysis of 13 cancer registries. Cancer Epidemiol Biomarkers Prev. 2008 Jun;17(6):1543-9.
16. American Joint Committee on Cancer. AJCC Cancer Staging Manual, 5th edn. Philadelphia/New York: Lippincott-Raven; 1997.
17. American Joint Committee on Cancer. AJCC cancer staging manual, 6th edn. . New York: Springer; 2002.
18. American Joint Committee on Cancer. AJCC cancer staging manual, 7th edn. New York: Springer; 2010.
19. Warren S, Gates O. Multiple primary malignant tumors: A survey of the literature and statistical study. Am J Cancer. 1932;51:1358-414.

20. Bugter O, van de Ven SEM, Hardillo JA, Bruno MJ, Koch AD and Baatenburg de Jong RJ. Early detection of esophageal second primary tumors using Lugol chromoendoscopy in patients with head and neck cancer: A systematic review and meta-analysis. Head Neck. 2019; 41: 1122-30.
21. Bugter O, van Iwaarden DLP, Dronkers EAC, et al. Survival of patients with head and neck cancer with metachronous multiple primary tumors is surprisingly favorable. Head Neck. 2019; 41: 1648-55.
22. van de Ven SEM, Bugter O, Hardillo JA, Bruno MJ, Baatenburg de Jong RJ and Koch AD. Screening for head and neck second primary tumors in patients with esophageal squamous cell cancer: A systematic review and meta-analysis. United European Gastroenterol J. 2019; 7: 1304-11.
23. Nagasawa S, Onda M, Sasajima K, Takubo K and Miyashita M. Multiple primary malignant neoplasms in patients with esophageal cancer. Dis Esophagus. 2000; 13: 226-30.
24. Levi F, Randimbison L, Maspoli M, Te VC and La Vecchia C. Second neoplasms after oesophageal cancer. Int J Cancer. 2007; 121: 694-7.
25. Ribeiro Junior U, Cecconello I, Safatle-Ribeiro AV, Zilberstein B, Pinotti HW. Squamous cell carcinoma of the esophagus and multiple primary tumors of the upper aerodigestive tract. Arq Gastroenterol. 1999 Oct-Dec;36(4):195-200.
26. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011 Mar-Apr;61(2):69-90.
27. Yokokawa Y, Ohta S, Hou J, Zhang XL, Li SS, Ping YM, et al. Ecological study on the risks of esophageal cancer in Ci-Xian, China: the importance of nutritional status and the use of well water. Int J Cancer. 1999 Nov 26;83(5):620-4.
28. Li H, Borinskaya S, Yoshimura K, Kal'ina N, Marusin A, Stepanov VA, et al. Refined geographic distribution of the oriental ALDH2*504Lys (nee 487Lys) variant. Ann Hum Genet. 2009 May;73(Pt 3):335-45.
29. Higuchi S, Matsushita S, Murayama M, Takagi S, Hayashida M. Alcohol and aldehyde dehydrogenase polymorphisms and the risk for alcoholism. Am J Psychiatry. 1995 Aug;152(8):1219-21.
30. Chen SC, Teng CJ, Hu YW, Yeh CM, Hung MH, Hu LY, et al. Secondary primary malignancy risk among patients with esophageal cancer in Taiwan: a nationwide population-based study. PLoS One. 2015;10(1):e0116384.
31. Matsubara T, Yamada K, Nakagawa A. Risk of second primary malignancy after esophagectomy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol. 2003 Dec 1;21(23):4336-41.
32. Hu WS, Liu ZJ, Zhang JB, Wang ZL, Yang N, Xu L, et al. Risk patterns of subsequent primary cancers following esophagectomy in early-stage thoracic esophageal squamous cell cancer patients. Tumori. 2015 May-Jun;101(3):328-33.
33. van de Ven S, Bugter O, Hardillo JA, Bruno MJ, Baatenburg de Jong RJ, Koch AD. Screening for head and neck second primary tumors in patients with esophageal squamous cell cancer: A systematic review and meta-analysis. United European Gastroenterol J. 2019 Dec;7(10):1304-11.
34. Morimoto H, Yano T, Yoda Y, Oono Y, Ikematsu H, Hayashi R, et al. Clinical impact of surveillance for head and neck cancer in patients with esophageal squamous cell carcinoma. World J Gastroenterol. 2017 Feb 14;23(6):1051-8.

## SUPPLEMENATRY

**Table S1. Cumulative incidence for head and neck SPTs in ESCC patients who were alive 6 months after ESCC diagnosis (n=5,715)**

| Interval | Begin total (n) | SPT (n) | death (n) | SPT located in other region | Cumulative incidence (95% CI) |
|---|---|---|---|---|---|
| 0-5 year | 5,715 | 57 | 4,719 | 62 | 2.9% (2.2-3.9) |
| 5-10 year | 877 | 15 | 549 | 26 | 5.3% (3.9-6.9) |
| 10-15 year | 287 | 8 | 214 | 6 | 9.0% (6.3-12.4) |
| 15-16 year | 59 | 0 | 58 | 1 | 9.0% (6.3-12.4) |

**Table S2. Cumulative incidence for metachronous lung SPTs in ESCC patients who were alive 6 months after ESCC diagnosis (n=5,715)**

| Interval | Begin total (n) | SPT (n) | death (n) | SPT located in other region | Cumulative incidence (95% CI) |
|---|---|---|---|---|---|
| 0-5 year | 5,715 | 52 | 4,719 | 67 | 2.8% (2.1-3.8) |
| 5-10 year | 877 | 23 | 549 | 18 | 7.2% (5.4-9.4) |
| 10-15 year | 287 | 4 | 214 | 10 | 9.9% (6.6-14.1) |
| 15-16 year | 59 | 1 | 58 | 0 | 13.6% (7.0-22.4) |

**Table S3. Cumulative incidence for metachronous esophagus SPTs in ESCC patients who were alive 6 months after ESCC diagnosis (n=5,715)**

| Interval | Begin total (n) | SPT (n) | death (n) | SPT located in other region | Cumulative incidence (95% CI) |
|---|---|---|---|---|---|
| 0-5 year | 5,715 | 6 | 4,719 | 113 | 0.4% (0.1-0.9) |
| 5-10 year | 877 | 3 | 549 | 38 | 1.1% (0.4-2.3) |
| 10-15 year | 287 | 1 | 214 | 13 | 1.5% (0.6-3.0) |
| 15-16 year | 59 | 0 | 58 | 1 | 1.5% (0.6-3.0) |

**Table S4. Cumulative incidence for metachronous stomach SPTs in ESCC patients who were alive 6 months after ESCC diagnosis (n=5,715)**

| Interval | Begin total (n) | SPT (n) | death (n) | SPT located in other region | Cumulative incidence (95% CI) |
|---|---|---|---|---|---|
| 0-5 year | 5,715 | 4 | 4,719 | 115 | 0.2% (0.1-0.6) |
| 5-10 year | 877 | 0 | 549 | 41 | 0.2% (0.1-0.6) |
| 10-15 year | 287 | 1 | 214 | 13 | 0.6% (0.1-1.8) |
| 15-16 year | 59 | 0 | 58 | 1 | 0.6% (0.1-1.8) |

**Table S5. Cumulative incidence for all SPTs in patients with low-stage ESCC (n=2,381)**

| Interval | Begin total (n) | SPT (n) | Death (n) | Cumulative incidence (95% CI) |
|---|---|---|---|---|
| 0-5 year | 2,381 | 158 | 1,778 | 8.1% (6.4-10.0) |
| 5-10 year | 445 | 21 | 262 | 15.0% (11.8-18.6) |
| 10-15 year | 162 | 7 | 122 | 21.7% (15.6-28.6) |
| 15-16 year | 33 | 1 | 32 | 27.0% (16.2-38.9) |

CI, confidence interval; ESCC, esophageal squamous cell carcinoma; SPT, second primary tumor

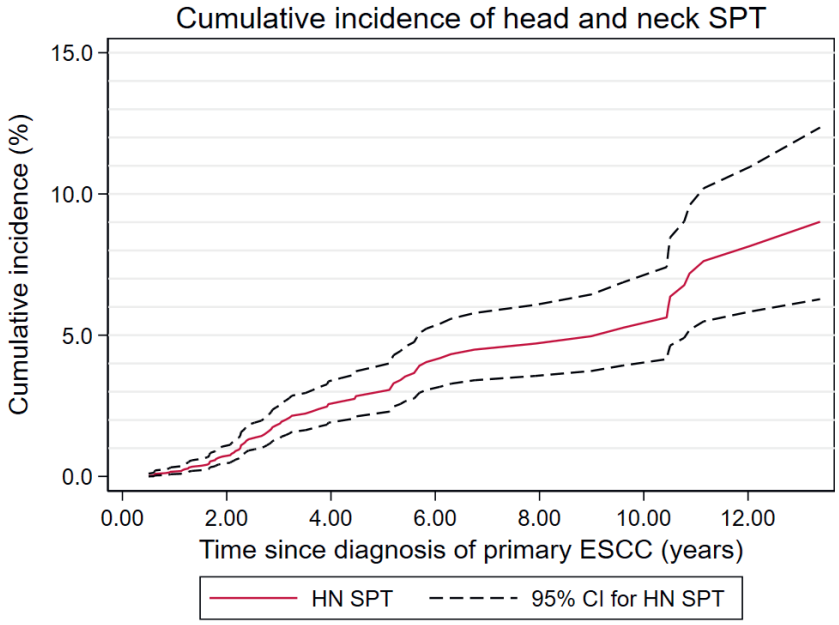



**Figure S1**. **Cumulative incidence of metachronous head and neck SPT after ESCC diagnosis (n=5,715)** HN SPT, head and neck second primary tumor; CI, confidence interval; ESCC, esophageal squamous cell carcinoma

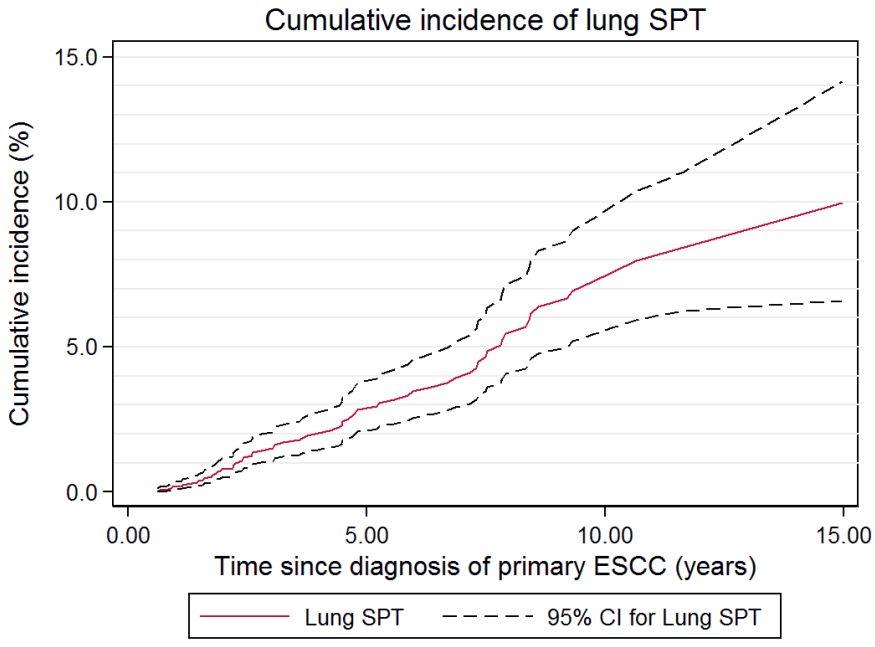



**Figure S2**. **Cumulative incidence of metachronous lung SPT after ESCC diagnosis (n=5,715)** SPT, second primary tumor; CI, confidence interval; ESCC, esophageal squamous cell carcinoma

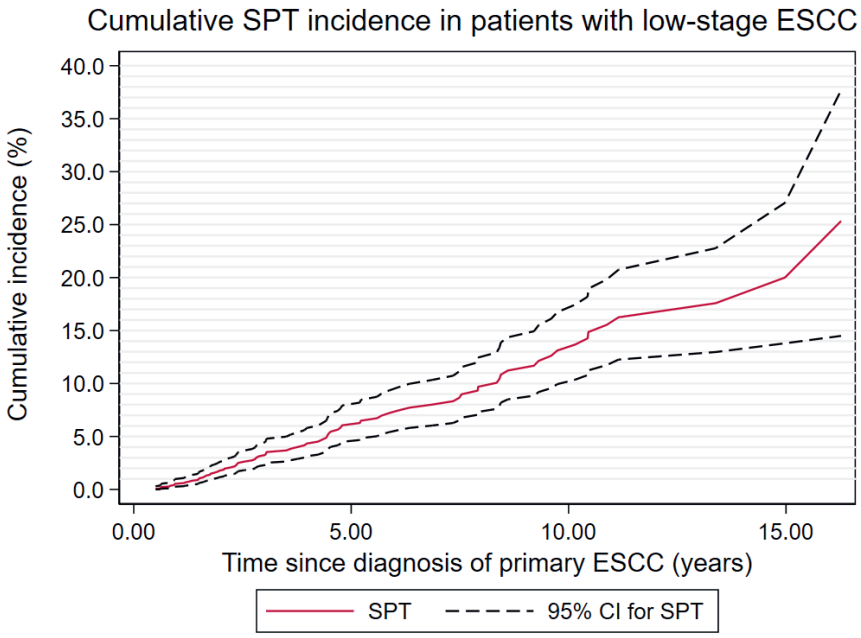



**Figure S3**. **Cumulative incidence of all SPTs in patients with low-stage ESCC diagnosis (n=2,381)**
SPT, second primary tumor; CI, confidence interval; ESCC, esophageal squamous cell carcinoma

# CHAPTER 3

## Screening for head and neck second primary tumors in patients with esophageal squamous cell carcinoma: a systematic review and meta-analysis

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## ABSTRACT

**Background:** Esophageal squamous cell carcinomas (ESCCs) are often accompanied by head and neck second primary tumors (HNSPTs). The prognosis of patients with an additional HNSPT is worse compared to patients with only ESCC. Therefore, early detection of HNSPTs may improve the overall outcome of patients with ESCC. The purpose of this study was to investigate the yield of endoscopic screening for HNSPTs in patients with primary ESCC.

**Methods:** We conducted a systematic literature search of all available databases. Studies were included if ESCC patients were endoscopically screened for HNSPT. The primary outcome was the pooled prevalence of HNSPTs.

**Results:** Twelve studies, all performed in Japan, were included in this systematic review with a total of 6,483 patients. The pooled prevalence of HNSPTs was 6.7% (95% CI: 4.9-8.4). The overall heterogeneity was high across the studies ($I^2$=89.0%, p<0.001). Most HNSPTs were low-stage (85.3%) and located in the hypopharynx (60.3%). The proportion of synchronous (48.2%) and metachronous (51.8%) HNSPTs was comparable.

**Conclusion:** Based on our results, HNSPT screening could be considered in patients with primary ESCC. All studies were performed in Japan, it is therefore not clear if this this consideration applies to the Western world.

## INTRODUCTION

Both esophageal and head and neck (HN) cancer are common malignancies worldwide.[1, 2] Esophageal squamous cell carcinoma (ESCC) is the most common histologic type in the esophagus.[3] Patients with ESCC, frequently develop second primary tumors (SPTs) in the upper aerodigestive tract. Most often in the HN region, but also in the esophagus and lungs.[4, 5] The presence of SPTs can be explained by the "field cancerization" theory: Premalignant epithelial changes can occur because of chronic local exposure to common carcinogens, such as alcohol and tobacco, which contributes to the development of syn- and metachronous SPTs.[6] An important risk factor in Western countries for the development of both ESCC and SPTs is alcohol.[7, 8]



Head and neck second primary tumors (HNSPTs) in patients with primary ESCC are reported up to 7% in retrospective studies.[4, 5] The prognosis and survival of patients with esophageal cancer (EC) is poor because most ECs are diagnosed in advanced stages, when definitive cure is most often not achievable.[9] The long-term prognosis is even worse in patients with an additional HNSPT compared to ESCC alone (five-year survival rate of 9.2% vs. 21.0%).[10] This poor prognosis makes early detection of HNSPTs vitally important, especially for ESCC patients with low-stage tumors that could be treated endoscopically, since they have a considerably higher five year survival rate.[11]

Different endoscopic techniques for HN cancer screening have been studied. Although Lugol chromoendoscopy is often used in the esophagus to detect dysplastic mucosal lesions, it is known to cause side effects in the HN region such as chest pain and aspiration.[12] Narrow-band imaging (NBI) seems to be the best technique for the detection of HNSPTs in patients with primary ESCC.[13] The HNSPT detection rate is significantly higher using NBI (sensitivity 100%, specificity 97.5%) compared to only white light endoscopy (WLE).[13] The sensitivity of fluorodeoxyglucose-positron-emission tomography / computed tomography (CT) for the detection of HNSPTs is 61.5%, more HNSPTs were detected by endoscopy.[14]

The European Society for Medical Oncology Clinical Practice Guidelines for EC recommends endoscopic screening of the HN region and trachea-bronchoscopy to detect SPTs in the upper aerodigestive tract in all ESCC patients with chronic tobacco and alcohol consumption.[15] However, no Western screening studies have been published to date. The Japanese EC guideline recommend appropriate diagnostic measures of other organs (HN, stomach, large intestine) after treatment of ESCC because of the risk of developing SPTs.[16] However, no specific screening recommendations (i.e. diagnostic method and the time of screening) are mentioned.[16]

We have performed a systematic review and meta-analysis of studies that investigated the use of endoscopic screening for the detection of HNSPTs in patients with primary ESCC. Our primary objective was to investigate the yield of endoscopic screening for HNSPTs in patients with primary ESCC. Our secondary objectives were to investigate whether there is evidence to justify endoscopic HN screening in primary ESCC patients in the Western world, and to investigate whether screening should be performed synchronously or metachronously.

## MATERIALS AND METHODS

### Literature search and selection criteria

A systematic literature search was performed in collaboration with the medical library of the Erasmus University Rotterdam, the Netherlands, in February 2019 with no limit on publication date. The search was performed in PubMed, Embase, Medline, Cochrane Central, Google Scholar and Web of Science databases. The full electronic search strategy for the Embase database is provided in Supplementary data. The search was limited to English studies performed on humans. After removing duplicate citations, the remaining articles were reviewed based on title and abstract by two independent reviewers (S.V. and O.B.). Subsequently, the full text of the remaining articles was screened by the same authors and discrepancies were discussed mutually. If there was no agreement, a third party was involved (A.K.). Studies were included if patients with primary ESCC were endoscopically screened for HNSPTs. Studies were excluded if patients with primary head and neck squamous cell carcinoma (HNSCC) were screened for esophageal SPTs, since we investigated the yield of HNSPT screening in patients with primary ESCC. Moreover, these studies are already included in a systematic review about screening for esophageal SPT in patients with primary HNSCC.[17] Studies without full text, case reports, reviews, and studies where only imaging techniques were used to detect HNSPTs were excluded. References of the retrieved studies were manually screened to locate additional studies.

### Study quality

The Methodological Index for Non Randomized Studies (MINORS) was used to test the risk of bias and the methodological quality of the selected studies.[18] The study relevance was determined using a checklist. This checklist includes (1) impact factor of publishing journal (indication of the peer-review quality), (2) data of the HNSPT sub-location, and (3) text clarity (Table 1). The total quality score of the studies was the sum of the MINORS and relevance criteria score. The total scores were classified as low (≤ 10 points), medium (11-14 points) or high (≥ 15 points). Medium and high classified studies were included.

**Table 1. Relevance criteria**

| Criteria | Score | | |
|---|---|---|---|
| | 0 | 1 | 2 |
| Text clarity | Low | Medium | High |
| Sub-location | No | - | Yes |
| Impact factor | < 2 | 2-3.9 | ≥ 4 |

### Data extraction and outcome parameters

Data from included studies were summarized as Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and flow chart.[19] The primary outcome was the prevalence of diagnosed HNSPTs. An HNSPT was defined as a lesion in the HN region classified as carcinoma in situ or carcinoma. With NBI, these lesions can be described as well-demarcated brownish areas without magnification, irregular microvascular patterns, and

increased intraepithelial papillary capillary loops.[20] Secondary outcomes were recorded when possible: (1) HNSPT prevalence per sub-location (upper, middle and lower esophagus) and per tumor stage (0 to IV according to the Vienna classification of gastrointestinal epithelial neoplasia) of the primary ESCC, (2) synchronously (≤ 6 months after diagnosis of primary ESCC) or metachronously (> 6 months after diagnosis of primary ESCC) diagnosed HNSPTs, and (3) tumor stage and sub-location of HNSPTs.[21] Other characteristics of the studies were also recorded: first author, publication year, study design, size and country of the study population.



### Statistical analysis

For each study, the HNSPT prevalence was calculated (total number of HNSPTs divided by the total population that was screened). The standard error (SE) was calculated from the prevalence using the following formula: $\mathrm{SE} = \sqrt{(p \cdot (1-p))/n}$, p = prevalence and n = total number of patients with ESCC that were screened. Estimation of the prevalence was carried out with the aid of a random-effects meta-analysis. Combined estimates and 95% confidence intervals (CIs) for the HNSPT prevalence rates were calculated. The heterogeneity among studies was measured by calculating the inconsistency index ($I^2$), with values from 0% to 100% (maximum heterogeneity). Categories of low, moderate and high were assigned to $I^2$ values of 25%, 50% and 75%, respectively.[22] When $I^2 \geq 50\%$, there was evidence of moderate or high heterogeneity.

## RESULTS

### Study selection and quality assessment

The study selection process and eligibility assessment are outlined in Figure 1. Literature search identified 4,537 citations. After screening, 148 articles were examined by full text review for their eligibility by two reviewers (S.V. and O.B.). Discrepancies were discussed mutually without any final disagreements. One additional study was included after screening the references. Twelve studies were included in our systematic review.[7, 10, 13, 20, 23-30] Exclusion reasons are shown in Figure 1. All twelve included studies were qualified as medium or high (Table 2). The relevance criteria score ranged between 0 and 5 points (maximum possible score is 6). The MINORS-criteria score ranged from 9 to 23 points (maximum possible score of 24).

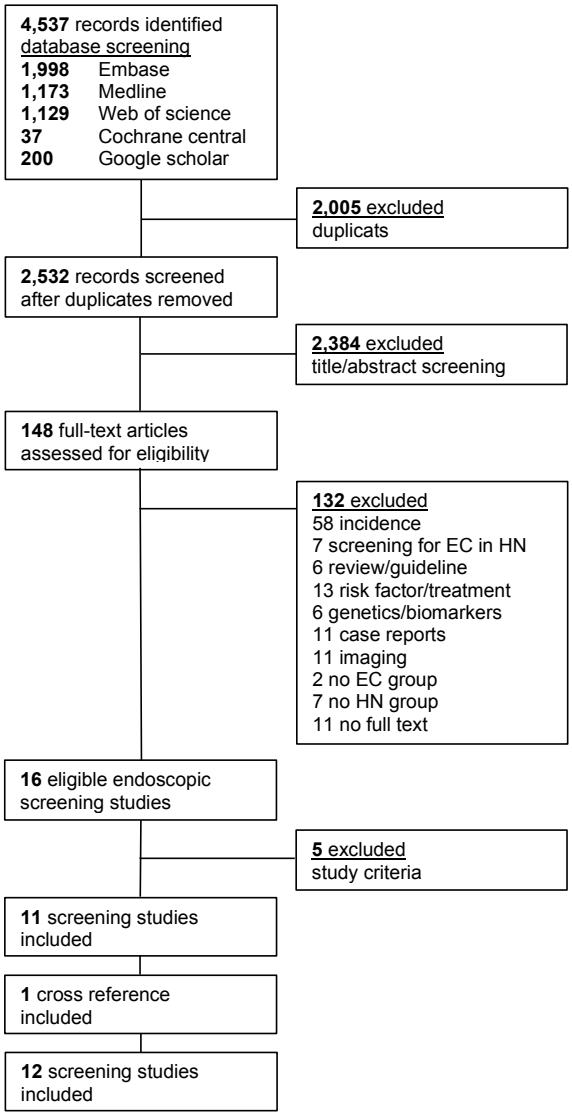


**Figure 1. Study selection process**
EC, esophageal cancer; HN, head and neck cancer

### Study characteristics

The study characteristics are reported in Table 2. All studies were performed in Japan and published between 2002 and 2018. Nine of the 12 studies (75%) collected their data prospectively [7, 10, 13, 20, 24, 25, 27, 28, 30] and three (25%) retrospectively.[23, 26, 29] The total number of included patients was 6,483 (median 313, range 71-1,674). In two studies Lugol iodine was used for screening of the HN region.[24, 28] In five other studies both WLE and NBI were used for screening.[13, 20, 23, 26, 30] In the remaining five studies, only WLE was used for screening.[7, 10,

[25, 27, 29] In only four studies, the entire HN region was screened.[10, 20, 27, 28, 30] Screening was limited to the pharynx and larynx, sub-locations known to be at an increased risk, in most other studies. Eleven of the 12 studies only screened patients with ESCC.[7, 10, 13, 20, 23-26, 28-30] One study screened both patients with ESCC (93%) and esophageal adenocarcinoma (7%).[27] In total, 98% of the esophageal tumors were squamous cell carcinomas and 2% adenocarcinomas. Screening was performed by an otolaryngologist or head and neck surgeon in 5/12 included studies.[7, 24, 25, 27, 28] Screening was performed by a gastroenterologist in 2/12 studies.[20, 29] In these two studies, only the oropharynx and hypopharynx were screened. In 5/12 included studies, however, it was not clearly reported who performed the screening endoscopy of the head and neck region (otolaryngologist or gastroenterologist).[10, 13, 23, 26, 30]



**Pooled SPT prevalence**

The prevalence of HNSPTs in patients with ESCC is shown for each study in Figure 2. In total, 353/6,483 patients were diagnosed with HNSPT. Meta-analysis with a random-effect model was used to calculate the pooled prevalence since the $I^2$ was 89.0%. The pooled prevalence for HNSPTs of the 12 included studies was 6.7% (95% CI: 4.9-8.4%) (Figure 2).

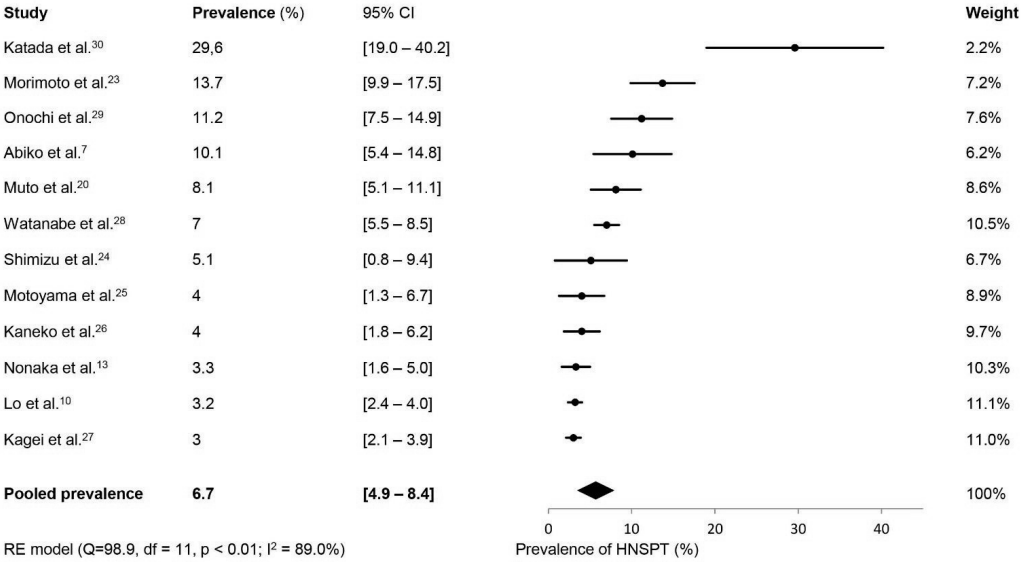


**Figure 2. Forest plot of prevalence of head and neck second primary tumors in patients with esophageal squamous cell carcinoma**

HNSPT, head and neck second primary tumor

**Table 2. Study characteristics and quality of all 12 studies**

| Author [ref] | Year | Design | N | Method | Quality Score | | | Quality | Screening sites |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | MINORS | Rel. | Total | | |
| Abiko et al.[7] | 2018 | Pro | 158 | WLE | 18 | 3 | 21 | High | Larynx |
| Onochi et al.[29] | 2018 | Retro | 285 | WLE | 10 | 3 | 13 | Medium | Oro- hypopharynx |
| Morimoto et al.[23] | 2017 | Retro | 307 | WLE, NBI | 18 | 5 | 23 | High | Oro- hypopharynx, Larynx |
| Kaneko et al.[26] | 2013 | Retro | 348 | WLE, NBI | 9 | 4 | 13 | Medium | Oral cavity, Pharynx |
| Katada et al.[30] | 2012 | Pro | 71 | WLE, NBI | 16 | 5 | 21 | High | Head and neck region [a] |
| Muto et al.[20] | 2010 | Pro | 320 | WLE, NBI | 23 | 4 | 27 | High | Oro- hypopharynx |
| Nonaka et al.[13] | 2009 | Pro | 424 | WLE, NBI | 19 | 5 | 24 | High | Pharynx |
| Lo et al.[10] | 2008 | Pro | 1675 | WLE | 18 | 3 | 21 | High | Head neck region [a] |
| Watanabe et al.[28] | 2007 | Pro | 1118 | Lugol | 10 | 3 | 13 | Medium | Head neck region [a] |
| Shimizu et al.[24] | 2003 | Pro | 99 | Lugol | 18 | 5 | 22 | High | Hypopharynx, Larynx |
| Kagei et al.[27] | 2002 | Pro | 1479 | WLE | 10 | 2 | 12 | Medium | Head and Neck region [a] |
| Motoyama et al.[25] | 2003 | Pro | 200 | WLE | 13 | 4 | 17 | High | Larynx |

MINORS, Methodological Index for Non-Randomized Studies; NBI, narrow-band imaging; Pro, prospective; Rel, relevance; WLE, white light endoscopy; ref, reference. [a] Nasal cavity, oral cavity, naso-, oro-, and hypopharynx and larynx

### Sub-location of HNSPT and tumor stage

The sub-location of the HNSPTs was reported in eight of the twelve studies, for a total of 288 SPTs.[10, 13, 23-26, 28, 30] In one study the sub-location was reported together for primary HN tumors and HNSPTs. Therefore, we excluded the study for this sub-analysis.[10] A total of 234 HNSPTs remained. The combined data showed that 60% (141/234) of all HNSPTs were located in the hypopharynx, 18% (41/234) in the oropharynx, 11% (26/234) in the oral cavity, 9% (22/234) in the larynx and 2% (4/234) in other sub-locations. In total, 405 HNSPTs were detected in 353 patients. Tumor stage of HNSPTs were reported in eight of the 12 studies.[13, 20, 23, 24, 26-28, 30] Morimoto et al. reported tumor characteristics of metachronous HNSPTs only.[23] Combined data showed that tumor stage was available for 62% of the HNSPTs (251/405). Overall, HNSPTs were classified as low-stage (stage 0, I and II) in 85% (214/251) and high-stage (stage III and IV) in 15% (37/251).

### Time to diagnosis

Eight studies performed both syn- and metachronous endoscopic screening of the HN region,[10, 20, 23-25, 28-30] and six studies adequately reported the percentage of detected synchronous and metachronous HNSPTs (Table 3).[10, 23-25, 28, 29] The median time to metachronous HNSPT diagnosis of these six studies ranged from 12 to 48 months. The time to SPT diagnosis in ESCC patients was reported for all SPTs together in Motoyama et al., not separately for HNSPTs.[25] Two studies, only performed HN screening synchronously,[26, 27] and two only metachronously.[7, 13] The HNSPT prevalence in the study by Nonaka and colleagues[13] was 3.3% (14/424) with a median detection period of 27.6 months (range 7.1-143.5) in patients screened with NBI and 101.0 months (range 11.0-134.5) in patients screened with WLE.

**Table 3. Percentages synchronous and metachronous HNSPT**

| Authors [ref] | Total SPTs | Synchronous HNSPTs (%) | Metachronous HNSPTs (%) | Median time to diagnosis (months) (range) |
|---|---|---|---|---|
| Morimoto et al.[23] | 67 | 14 (21%) | 53 (79%) | 31 (7-107) |
| Shimizu et al.[24] | 5 | 0 | 5 (100%) | 37 (15-61) |
| Motoyama et al.[25] | 8 | 0 | 8 (100%) | Not reported |
| Watanabe et al.[28] | 85 | 37 (44%) | 48 (56%) | 48 (12-103) |
| Onochi et al.[29] | 32 | 23 (72%) | 9 (28%) | Not reported |
| Lo et al.[10] | 54 | 47 (87%) | 7 (13%) | 12 (8-110) |
| **Total** | **251** | **121 (48%)** | **130 (52%)** | |

SPTs, second primary tumors; HNSPTs, head and neck second primary tumors; ref, reference

### Primary ESCC tumor characteristics

Only four studies reported the sub-location of the index esophageal tumor.[10, 24, 25, 27] One study only included patients who underwent esophagectomy for thoracic ESCC.[25] The prevalence of HNSPTs in this study was 4.0%. The average percentages of index upper, middle, and lower ESCC of the other three studies were 17.0%, 57.7%, and 25.3% respectively.[10, 24, 27] However, they did not report the prevalence of HNSPT per ESCC sub-location. The tumor

stage of the primary ESCC was reported in nine studies (75%).[7, 10, 20, 23-25, 27, 29, 30] On average, most esophageal lesions were stage 1 (29.0%) and stage 3 (29.8%). Other tumor stages were 0 (high grade dysplasia) (7.3%), 2 (20.2%), and stage 4 (13.6%). The HNSPT prevalence per tumor stage of the primary ESCC was reported in three studies, where only superficial ESCCs (stage 0 and I) were screened.[7, 29, 30]

## DISCUSSION

To our knowledge, this is the first systematic review on endoscopic screening for HNSPTs in patients with primary ESCC. Worldwide, the incidence of HN cancer is more than 550,000 cases annually.[2] We found an HNSPT (pooled) prevalence of 6.7%. Most HNSPTs were located in the hypopharynx (60.3%), and classified as low stage (85.3%). The proportion of synchronous and metachronous HNSPTs was comparable. Although the worldwide incidence cannot be compared directly with the pooled prevalence from this meta-analysis, the concept of endoscopic screening in patients with ESCC bares promise. An increase in early detection of HNSPTs could potentially improve the overall survival of ESCC patients.

Screening in Western countries will possibly show a different HNSPT prevalence because the etiology partly differs among these continents and ESCC and HNSCC have a higher prevalence in Asia.[3, 31] The etiology of ESCC in Asia is, besides smoking and alcohol intake, clearly linked to a lowered fruit and vegetables intake.[32] The overall incidence of HN cancer in Japan was increasing, whereas the incidence in the United States was decreasing.[31, 33] Since the included studies were performed in Japan, it is unlikely that these results can be applied to the contemporary Western population.
Non-screening Asian studies have reported HNSPT prevalence up to 7% in patients with primary ESCC.[4, 5] This is lower than the prevalence of the included studies (3.0%-29.6%). This might indicate that active screening of ESCC patients increase the number of detected HNSPTs.[23] Early diagnosis and treatment of both tumors can increase the survival rate.[23, 24]

Eighty-five percent of the HNSPTs were classified as low-stage, which is higher than in the general HN cancer population.[35] Morimoto et al. reported a higher percentage of low-stage HNSPTs in patients with primary ESCC who were actively screened, and 83% of these HNSPTs could be treated with ER.[23] Furthermore, survival was better in ESCC patients with HNSPTs who were actively screened.[23] ESCC patients could benefit from HN screening because this could result in an increased detection of superficial HN cancer, which can be treated with curative intent.

There is lack of standardization in HN examination protocols among the included studies because different screening techniques are used (WLE, NBI and Lugol). Studies that compared NBI with WLE described a significantly higher detection rate of HNSPTs and a higher sensitivity and accuracy when using NBI.[13, 20, 23, 26] It would therefore be useful to always perform HN screening with WLE and NBI. Lugol chromoendoscopy is not recommended in the HN region because this has to be performed under general anesthesia because of possible side effects.[28]

The average percentage synchronous and metachronous HNSPTs of all studies together is comparable. This could indicate that HN screening in patients with ESCC should be performed during work-up and follow-up. The median detection time of metachronous HNSPTs ranged

from 12-101 months.[10, 13, 23, 24, 28] However, the optimal moment for screening during follow-up has yet to be defined.

Our systematic review showed that 78% of the HNSPTs were located in the pharynx, which suggest that the pharynx has the highest risk of developing SPTs. Moreover, patients with pharyngeal cancer also showed the highest prevalence of esophageal SPTs.[17] The pharynx is the head and neck region that should definitely be screened in patients with primary ESCC. Although 10 of the 12 included studies performed screening of the pharynx, only four studies screened the whole HN region. We are aware of the fact that, of these four studies, only two studies reported the HNSPT sub-location.[28, 30] It was not possible to state if there was a correlation between ESCC tumor stage and the occurrence of HNSPTs since this information was only reported in three studies.[7, 29, 30] In these studies, only superficial ESCCs (stage 0 and I) were screened, which could underestimate the true HNSPT prevalence per ESCC tumor stage.



Some potential limitations about the methodology of the included studies need to be discussed; 1) different screening techniques (i.e. WLE, NBI, Lugol chromoendoscopy) were used. The combination of WLE and NBI has the highest HNSPT detection rate, potential HNSPTs could be missed when using only WLE; 2) One study performed screening with endoscopy and CT-scan.[27] It was not clearly described which proportion of HNSPTs were detected by endoscopic screening. The proportion of HNSPTs detected by endoscopic screening could be lower than reported; 3) a different definition of metachronous and synchronous was used in three studies, whereby the comparison of the different studies was more difficult and the proportion of metachronous SPTs could be higher than reported [7, 27, 28]; 4) only four studies screened the whole HN region. Therefore, we could not easily determine which HN sub-location was at increased risk of developing HNSPTs; 5) this meta-analysis contained both prospective and retrospective data, a significant bias may be present.

In conclusion, the pooled prevalence of HNSPTs in patients with primary ESCC is 6.7%. Most HNSPTs were classified as low-stage. Patients with low-stage HN tumors can be treated curatively with an excellent prognosis. Screening for HNSPTs could therefore be useful in ESCC patients. More screening studies are needed to investigate which type of ESCC (i.e., tumor stage and sub-location) increases the risk of HNSPTs and to report on risk factors associated with HNSPTs. More important, it is necessary to perform Western screening studies to assess the HNSPT prevalence since it is unclear whether the results of Asian studies can be extrapolated into the Western population. Head and Neck examination protocols should be standardized in Japan; screening should be performed during work-up and follow-up with WLE in combination with NBI. The pharynx is the head and neck region which should always be screened.

## REFERENCES


1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.
2. Global Burden of Disease Cancer C, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability,and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2017;3(4):524-48.
3. Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012. Gut. 2015;64(3):381-7.
4. Poon RT, Law SY, Chu KM, Branicki FJ, Wong J. Multiple primary cancers in esophageal squamous cell carcinoma: incidence and implications. Ann Thorac Surg. 1998;65(6):1529-34.
5. Chuang SC, Hashibe M, Scelo G, Brewster DH, Pukkala E, Friis S, et al. Risk of second primary cancer among esophageal cancer patients: A pooled analysis of 13 cancer registries. Cancer Epidemiol Biomarkers Prev. 2008;17(6):1543-9.
6. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer. 1953;6(5):963-8.
7. Abiko S, Shimizu Y, Miyamoto S, Ishikawa M, Matsuda K, Tsuda M, et al. Risk assessment of metachronous squamous cell carcinoma after endoscopic resection for esophageal carcinoma based on the genetic polymorphisms of alcoholdehydrogense-1B aldehyde dehydrogenase-2: temperance reduces the risk. J Gastroenterol. 2018;53(10):1120-30.
8. Henry MACA, Lerco MM, Naresse LE, Crema E, Rodrigues MAM. Outcome of superficial squamous cell carcinoma of the esophagus. A clinicopathological study. Acta Cir Bras. 2013;28(5):373-8.
9. Alsop BR, Sharma P. Esophageal Cancer. Gastroenterol Clin North Am. 2016;45(3):399-412.
10. Lo OSH, Law S, Wei WI, Ng WM, Wong KH, Tong KH, et al. Esophageal cancers with synchronous or antecedent head and neck cancers: A more formidable challenge? Ann Surg Oncol. 2008;15(6):1750-6.
11. Berger A, Rahmi G, Perrod G, Pioche M, Canard JM, Cesbron-Metivier E, et al. Long-term follow-up after endoscopic resection for superficial esophageal squamous cell carcinoma: a multicenter Western study. Endoscopy. 2018.
12. Kondo H, Fukuda H, Ono H, Gotoda T, Saito D, Takahiro K, et al. Sodium thiosulfate solution spray for relief of irritation caused by Lugol's stain in chromoendoscopy. Gastrointest Endosc. 2001;53(2):199-202.
13. Nonaka S, Saito Y, Oda I, Kozu T, Saito D. Narrow-band imaging endoscopy with magnification is useful for detecting metachronous superficial pharyngeal cancer in patients with esophageal squamous cell carcinoma. J Gastroenterol Hepatol. 2010;25(2):264-9.
14. Miyazaki T, Sohda M, Higuchi T, Tanaka N, Suzuki S, Sakai M, et al. Effectiveness of FDG-PET in screening of synchronous cancer of other organs in patients with esophageal cancer. Anticancer Res. 2014;34(1):283-7.
15. Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, Committee EG. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v50-v7.
16. Kuwano H, Nishimura Y, Oyama T, Kato H, Kitagawa Y, Kusano M, et al. Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus April 2012 edited by the Japan Esophageal Society. Esophagus. 2015;12:1-30.
17. Bugter O, van de Ven SEM, Hardillo JA, Bruno MJ, Koch AD, Baatenburg de Jong RJ. Early detection of esophageal second primary tumors using Lugol chromoendoscopy in patients with head and neck cancer: A systematic review and meta-analysis. Head Neck. 2018.

18. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg. 2003;73(9):712-6.
19. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-12.
20. Muto M, Minashi K, Yano T, Saito Y, Oda I. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. J Clin Oncol. 2010 Mar 20;28(9):1566-72.
21. Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut. 2000;47(2):251-5.
22. Haggins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003;327(7414):557-60.
23. Morimoto H, Yano T, Yoda Y, Oono Y, Ikematsu H, Hayashi R, et al. Clinical impact of surveillance for head and neck cancer in patients with esophageal squamous cell carcinoma. World J Gastroenterol. 2017;23(6):1051-8.
24. Shimizu Y, Tsukagoshi H, Fujita M, Hosokawa M, Watanabe A, Kawabori S, et al. Head and neck cancer arising after endoscopic mucosal resection for squamous cell carcinoma of the esophagus. Endoscopy. 2003;35(4):322-6.
25. Motoyama S, Saito R, Kitamura M, Ogawa JI. Outcomes of active operation during intensive followup for second primary malignancy after esophagectomy for thoracic squamous cell esophageal carcinoma. J Am Coll Surg. 2003;197(6):914-20.
26. Kaneko K, Yano T, Minashi K, Kojima T, Ito M, Satake H, et al. Treatment strategy for superficial pharyngeal squamous cell carcinoma synchronously combined with esophageal cancer. Oncology. 2013;84(1):57-64.
27. Kagei K, Hosokawa M, Shirato H, Kusumi T, Shimizu Y, Watanabe A, et al. Efficacy of intense screening and treatment for synchronous second primary cancers in patients with esophageal cancer. Jpn J Clin Oncol. 2002;32(4):120-7.
28. Watanabe A, Hosokawa M, Taniguchi M, Tsujie H, Sasaki S. Head and neck cancer associated with esophageal cancer. Auris Nasus Larynx. 2007;34(2):207-11.
29. Onochi K, Shiga H, Takahashi S, Watanabe N, Fukuda S, Ishioka M, et al. Risk Factors Linking Esophageal Squamous Cell Carcinoma With Head and Neck Cancer or Gastric Cancer. 2018.
30. Katada C, Muto M, Nakayama M, Tanabe S, Higuchi K, Sasaki T, 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.
31. Ioka A, Tsukuma H, Ajiki W, Oshima A. Trends in head and neck cancer incidence in Japan during 1965-1999. Jpn J Clin Oncol. 2005;35(1):45-7.
32. Yokokawa Y, Ohta S, Hou J, Zhang XL, Li SS, Ping YM, et al. Ecological study on the risks of esophageal cancer in Ci-Xian, China: the importance of nutritional status and the use of well water. Int J Cancer. 1999;83(5):620-4.
33. Mourad M, Jetmore T, Jategaonkar AA, Moubayed S, Moshier E, Urken ML. Epidemiological Trends of Head and Neck Cancer in the United States: A SEER Population Study. J Oral Maxillofac Surg. 2017;75(12):2562-72.
34. Hiroshi Saeki, Toh Y, Sakamoto Y, Higaki Y, Morita M, Soejima Y, et al. The treatment outcomes of synchronous and metachronous esophageal squamous cell carcinoma and head and neck squamous cell carcinoma. Esophagus. 2012(9):158–64.
35. Amar A, Altino Franzi S, Rapoport A. Evolution of patients with squamous cell carcinoma of upper aerodigestive tract. Sao Paulo Med J. 2003;121(4):155-8.

## SUPPLEMENTARY

Search strategy

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# CHAPTER 4

## Early detection of esophageal second primary tumors using Lugol chromoendoscopy in patients with head and neck cancer: a systematic review and meta-analysis

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*Head and Neck – 2018*

## ABSTRACT

**Background:** Early detection of esophageal secondary primary tumors (SPT) in head and neck squamous cell carcinoma (HNSCC) patients could increase patient survival. The purpose of this study was to determine the diagnostic yield of esophageal SPTs using Lugol chromoendoscopy.

**Methods:** A systematic review of all available databases was performed to find all Lugol chromoendoscopy screening studies.

**Results:** Fifteen studies with a total of 3,386 patients were included. The average yield of esophageal SPTs in HNSCC patients was 15%. The prevalence was the highest for patients with an index hypopharyngeal (28%) or oropharyngeal (14%) tumor. The esophageal SPTs were classified as high-grade dysplasia in 49% of the cases and as invasive carcinomas in 51%.

**Conclusion:** Our results show that 15% of the HNSCC patients that underwent Lugol chromoendoscopy were diagnosed with an esophageal SPT. Based on these results there is enough evidence to perform Lugol chromoendoscopy, especially in an Asian patient population.

## INTRODUCTION

Part of the mortality of patients treated for head and neck squamous cell carcinoma (HNSCC) is caused by the occurrence of second primary tumors (SPT).[1] Risk factors for their development include alcohol and tobacco use, age, and the sub-location of the index tumor (e.g., hypopharynx).[2] Most SPTs in patients with HNSCC occur in the head and neck region, esophagus, and lungs.[1, 3-6] The risk of esophageal cancer after HNSCC treatment is an 8-fold to 22-fold greater than in the general population.[7-9] These SPTs are often diagnosed in advanced stages, which lead to a very low five year survival rate for affected patients.[6, 10-12] The prevalence of esophageal SPTs in patients with HNSCC is estimated to range from 0-22%.[13]



The occurrence of esophageal SPTs in patients with HNSCC is often explained by field cancerization of the entire upper aerodigestive tract.[14, 15] The theory of field cancerization states that the mucosal field around the index tumor possesses subtle histologic and genetic changes that increase the risk of synchronous and metachronous malignancies. These subtle tissue changes are thought to be the effect of exposure to accumulating carcinogens (e.g., alcohol and tobacco).[10]

Early diagnosis and treatment of an esophageal SPT may improve the overall outcome of patients with HNSCC.[5, 10, 16] It has even been suggested that its treatment will affect patient survival more than the index HNSCC tumor.[5] Esophageal carcinomas can remain asymptomatic for a long time during development. A result of this is that many patients' SPTs only seek medical attention when the tumor is in advanced stages development.[17] Routine screening of the esophagus in the work-up and follow-up of patients with HNSCC could potentially detect more early stage esophageal SPTs.[18-20]

The diagnosis of esophageal SPTs may impact the management of both tumors.[13] Early stage esophageal SPTs may benefit from less invasive endoscopic resection, which can be performed without compromising the treatment of the HNSCC.[21] However, advanced esophageal SPTs are often diagnosed metachronously and will typically be managed by chemoradiotherapy and surgery.[22] The treatment of the index HNSCC could also hinder that of the esophageal cancer due to treatment sequelae or restrictions to therapeutic options. When possible, personalized treatment should be focused on both tumors.[22, 23]

Endoscopic techniques to screen the esophagus have undergone major improvements over the last decades.[10] White light endoscopy is deemed to be insufficient for the detection of superficial cancerous lesions in asymptomatic patients.[9, 10] However, studies with image-enhanced endoscopy, which includes Lugol's stain, have shown very promising results. Lugol's stain isolates abnormal "mucosal islands" within otherwise normal esophageal tissue, enabling targeted biopsy.[9] Lugol chromoendoscopy has a high diagnostic accuracy. When combined with narrow band imaging (NBI), it is reported to have a sensitivity of 94.7% and a specificity of 90.4% to detect early stage esophageal lesions.[24, 25]

Based on these results many clinics in Asia implemented esophageal SPT screening in patients with HNSCC.[10] Recently, the French Society of Otorhinolaryngology recommended routine flexible white-light esophageal endoscopy in the workup of patients with oropharyngeal and hypopharyngeal HNSCC or chronic alcohol use.[13] The addition of Lugol's stain was

recommended. They also suggested to perform routine screening for metachronous esophageal SPTs in the follow-up of HNSCC patients.[9]

Esophageal Lugol chromoendoscopy is not widely used in the management of patients with HNSCC in the Western world. We performed a systematic review on studies that used Lugol chromoendoscopy to detect esophageal SPTs in patients with HNSCC. Our main objective was to investigate the yield of Lugol chromoendoscopy for head and neck cancer patients in general, but also for specific head and neck sub-locations. A second aim was to investigate whether current data from non-Asian patient populations provide enough evidence to justify Lugol chromoendoscopy screening for esophageal SPTs in patients with HNSCC in the Western world.

## MATERIALS AND METHODS

### Literature search and selection criteria

We searched the Embase, Medline (including PubMed), Web of Science, Cochrane, and Google Scholar databases for relevant studies. The search was performed in April 2017 without a limit on publication date. The following keywords were used for the search: “second/ multiple primary tumor”, “esophageal cancer”, and “head and neck cancer”. We limited our search to studies written in English and on humans. Duplicate studies were removed. The remaining citations were reviewed (by O.B.) bases on title and abstract and in second stage on full text. We included studies that investigated the use of Lugol chromoendoscopy to detect esophageal second primary tumors in HNSCC patients. We excluded studies primarily designed as case reports or reviews. The next paragraph presents our full electronic search strategy for the Embase database (see Supplementary file for the search strategy).

(“second cancer”/exp OR “multiple cancer”/de OR (((Metachronous OR Synchronous OR Second* OR Multiple OR double OR triple OR quadruple OR quintuple OR subsequen* OR Simultan*) NEAR/6 ( tumo* OR primary OR malignan* OR carcin* OR neoplas* OR cancer*))):ab,ti) AND (“esophagus tumor”/exp OR “esophagus”/exp OR “esophagus examination”/exp OR (esophag* OR oesophag* OR (upper NEXT/3 (aerodigest* OR digest*))):ab,ti) AND (“head and neck tumor”/exp OR “larynx tumor”/exp OR ((“head”exp OR neck/exp) AND “primary tumor”/de) OR (((lip OR mouth OR oral OR nose OR nasal OR tongue OR tonsil OR nasopharyn* OR oropharyn* OR hypopharyn* OR pharyn* OR laryn* OR head OR neck ) NEAR/10 (tumo* OR primary OR malignan* OR carcin* OR neoplas* OR cancer* OR primar*))):ab,ti) AND [english]/lim NOT ([animals]/lim NOT [humans]/lim).

### Assessment of study quality

The methodological quality and risk of bias of the selected Lugol chromoendoscopy screening studies was tested (by O.B.) with the Methodological Index for Non-Randomized Studies (MINORS).[26] Its relevance to the current topic was determined using a three-criterion checklist, including (1) impact factor of publishing journal and thus an indication of quality of peer-review, (2) data on the prevalence of esophageal SPT per head and neck sub-location, and (3) clarity of the text (Table 1). The total score of both the MINORS scale and relevance criteria was used as a quality score. Based on this score, the quality was classified as low (total score ≤ 10 points), medium (total score 11-14 points) or high (total score ≥ 15 points). Studies of

medium and high quality were included for further analysis and low-quality studies were excluded.

**Table 1. Relevance criteria**

| Criteria | Score | | |
|---|---|---|---|
| | 0 | 1 | 2 |
| Impact factor | < 2 | 2-3.9 | ≥ 4 |
| Sub-location | No | - | Yes |
| Text clarity | Low | Medium | High |



### Data extraction

Data from all included studies were extracted onto record forms (by O.B.) and results were summarized as a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) check list and flow chart.[27] The total prevalence of diagnosed esophageal SPTs were recorded as primary outcome. An esophageal SPT was defined as an esophageal lesion classified as category 4 and 5: high-grade dysplasia (HGD) or carcinoma. When possible three secondary outcomes were recorded : (1) n the SPT prevalence per sub-location of the index head and neck tumor (oral cavity, oropharynx, hypopharynx, larynx, nasopharynx and other) and per tumor stage (0 to 4) of the index tumor; (2) whether the SPTs were diagnosed synchronously (≤ 6 months after diagnosis of index tumor, in some cases simultaneously) or metachronously (> 6 months after diagnosis of index tumor); and (3) in which stage of development the SPTs were according to the Vienna classification of gastrointestinal epithelial neoplasia.[28] Finally, first author, country of study population, year of publication, study design, and population size were also recorded.

### Statistical analysis

Data were reported as counts and percentages. The SPT prevalence was calculated for each study as the total number of detected SPTs divided by the total population that was screening in the particular study. In studies where the Standard Error (SE) was not reported, we calculated it from the prevalence using the following formula: $SE=\sqrt{(p\ (1-p)/\ n)}$; where, p = prevalence and n = total number of patients with ESCC that were screened for head and neck SPTs. Review Manager software (version 5.3) was used for meta-analysis. Random effects model was used to calculate the pooled prevalence. $I^2$ was used to evaluate the level of heterogeneity between studies. Subgroup analyses were performed for specific head and neck cancer sub-locations.

## RESULTS

### Study selection, quality assessment, and characteristics

Results of our search query for eligible qualitative Lugol chromoendoscopy screening studies are presented in Figure 1. The search identified 4,077 citations. After removing duplicates 2,241 citations were reviewed. Based on review of title and abstract, 1,859 citations were excluded. The remaining 382 studies were reviewed for their eligibility by reviewing the full text. This revealed 96 studies that screened a population of patients with HNSCC for

esophageal SPTs. Reasons for exclusion of other studies are mentioned in Figure 1. Review of the 96 screening studies resulted in the selection of 23 Lugol chromoendoscopy screening studies (Table 2).[21, 22, 25, 29-48] Most other screening studies were performed with only white-light endoscopy (e.g., 'triple-endoscopy) or with the use of PET/CT.

The combined quality score of the MINORS and relevance-criteria qualified 15 studies as medium or high quality and these were included in the present review.[21, 22, 25, 29-40] The remaining studies of low quality were excluded. The methodological quality assessment using MINORS resulted in scores ranging from 6 to 11 points, (median 8 and maximal possible score 16). The relevance criteria score ranged from between 0 to 5 points (median 3 and maximal possible score 6). Twelve of the studies included (80%) were performed in Asia (Korea, Japan, and Taiwan) and the remaining three in Switzerland, France, and Brazil. Nine studies were performed within the last decade and all studies within the last two decades. Most studies collected data prospectively (13, 87%). The study populations ranged from 40 to 676 patients (median 171) and the total number of patients was 3,386. All studies used similar methods by applying 10-40 mL of 0.8-3.0% Lugol's solution on the esophageal mucosa.

**Prevalence**

The average prevalence of esophageal SPTs in HNSCC patients of the 15 included studies was 15.2% (413 of 3,386, 95% CI: 11.4-19.0) (Figure 2). The three studies with the highest prevalence included only or mostly patients with a hypopharyngeal index tumor.[21, 22, 33] Two Japanese studies only included patients with oral cavity tumors.[30, 39] The average esophageal SPT prevalence of the 12 Asian studies was 17.7% (358/2627, 95% CI: 12.7-22.7). This was higher than the average of the three non-Asian studies: 6.0% (55/759, 95% CI: 2.3-9.7).

**Prevalence per sub-location**

Nine Asian studies reported data of esophageal SPTs per sub-location of the index HNSCC (Figure 3).[21, 22, 29-32, 38-40] The prevalence of esophageal SPTs was the highest in patients with hypopharyngeal index tumors, followed by patients with oropharyngeal, oral cavity, laryngeal and nasopharyngeal tumors. The average prevalence of esophageal lesions in patients with hypopharyngeal tumors of seven studies was 28.0% (161 of 574, 95% CI: 22.5-33.5)). Five studies reported an average of 14.0% (35 of 308, 95% CI: 5.4-22.5) esophageal SPTs in patients with oropharyngeal tumors. The diagnostic yield of Lugol chromoendoscopy in patients with oral cavity tumors was 7.2% (47 of 637, 95% CI: 3.2-11.2). For patients with laryngeal index tumors the rate of esophageal SPTs was 3.4% (19 of 474, 95% CI: 1.8-5.4). Four studies reported only two esophageal SPTs in 109 patients with nasopharyngeal tumors and none were found in patients with other index tumors (e.g., glandular tumors).

**Time to diagnosis**

Most studies only performed endoscopic screening of the esophagus in the work-up of the index HNSCC tumor and thus only diagnosed synchronous, or even simultaneous, esophageal SPTs. Four studies performed both synchronous and metachronous esophageal endoscopies.[21, 32, 33, 35] Morimoto et al. performed at diagnosis of the HNSCC and annually during follow-up.[21] Eighteen (69.2%) of all SPTs were diagnosed synchronously and 8 (30.8%) metachronously. Fukuhura et al. found a similar distribution between synchronously diagnosed SPTs (n = 17 [60.7%]) and those that were diagnosed metachronously (n = 9

[32.1%]).[32] The two other studies also metachronous endoscopies, but did not separately mention the syn- or metachronous diagnostic yield of Lugol chromoendoscopy.[33, 35]

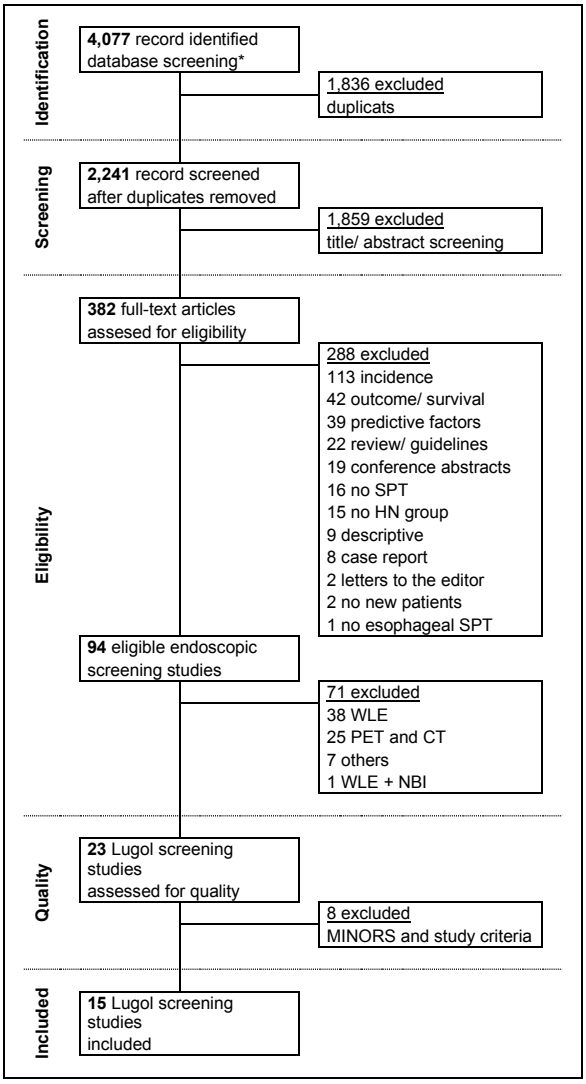


**Figure 1. Study selection process**

* Embase, Medline, Web of Science, Cochrane, and Google Scholar; CT, computed tomography; HN, head and neck; PET, positron emission tomography; NBI, narrow band imaging; SPT, second primary tumor; WLE, white light endoscopy; MINORS, Methodological Index for Non Randomized Studies

**Table 2. Characteristics, MINORS and relevance scores of all 23 Lugol chromoendoscopy screening studies**

| Authors | Country | Year | Design | N | Score | | | Quality |
|---|---|---|---|---|---|---|---|---|
| | | | | | MINORS | Relevance | Total | |
| **Included studies** | | | | | | | | |
| Gong et al.[29] | Korea | 2016 | Pro | 458 | 10 | 5 | 15 | High |
| Wang, CH et al.[25] | Taiwan | 2014 | Pro | 294 | 11 | 3 | 14 | Medium |
| Wang, Wang, et al.[22] | Taiwan | 2013 | Pro | 180 | 9 | 5 | 14 | Medium |
| Ikawa et al.[30] | Japan | 2012 | Pro | 171 | 8 | 4 | 12 | Medium |
| Wang, Lee, et al.[31] | Taiwan | 2011 | Pro | 315 | 11 | 5 | 16 | High |
| Morimoto et al.[21] | Japan | 2010 | Pro | 64 | 7 | 4 | 11 | Medium |
| Fukuhara et al.[32] | Japan | 2010 | Pro | 157 | 8 | 4 | 12 | Medium |
| Lee et al.[33] | Taiwan | 2009 | Pro | 44 | 11 | 4 | 15 | High |
| Boller et al.[34] | Switzerland | 2009 | Pro | 40 | 11 | 3 | 14 | Medium |
| Dubuc et al.[35] | France | 2006 | Pro | 393 | 10 | 3 | 13 | Medium |
| Hashimoto et al.[36] | Brazil | 2005 | Pro | 326 | 10 | 4 | 14 | Medium |
| Muto, Nakane, et al.[37] | Japan | 2002 | Pro | 78 | 9 | 4 | 13 | Medium |
| Tanabe et al.[38] | Japan | 2001 | Retro | 134 | 8 | 3 | 11 | Medium |
| Fukuzawa et al.[39] | Japan | 1999 | Pro | 56 | 7 | 4 | 11 | Medium |
| Horiuchi et al.[40] | Japan | 1998 | Retro | 676 | 7 | 4 | 11 | Medium |
| **Excluded studies** | | | | | | | | |
| Laohawiriyakamol et al.[41] | Thailand | 2014 | Pro | 89 | 10 | 0 | 10 | Low |
| Komínek et al.[42] | Czech R. | 2013 | Pro | 132 | 9 | 0 | 9 | Low |
| Chow et al.[43] | China | 2009 | Retro | 118 | 7 | 2 | 9 | Low |
| Muto, Hironaka, et al.[44] | Japan | 2002 | Retro | 389 | 6 | 1 | 7 | Low |
| Tincani et al.[45] | Brazil | 2000 | Pro | 60 | 7 | 0 | 7 | Low |
| Ina et al.[46] | Japan | 1994 | Pro | 127 | 7 | 2 | 9 | Low |
| Chisholm et al.[47] | China | 1992 | Pro | 37 | 7 | 0 | 7 | Low |
| Shiozaki et al.[48] | Japan | 1990 | Pro | 178 | 7 | 2 | 9 | Low |

N, number of head and neck cancer patients included; Pro, prospective; Retro, retrospective; Year, year of publication

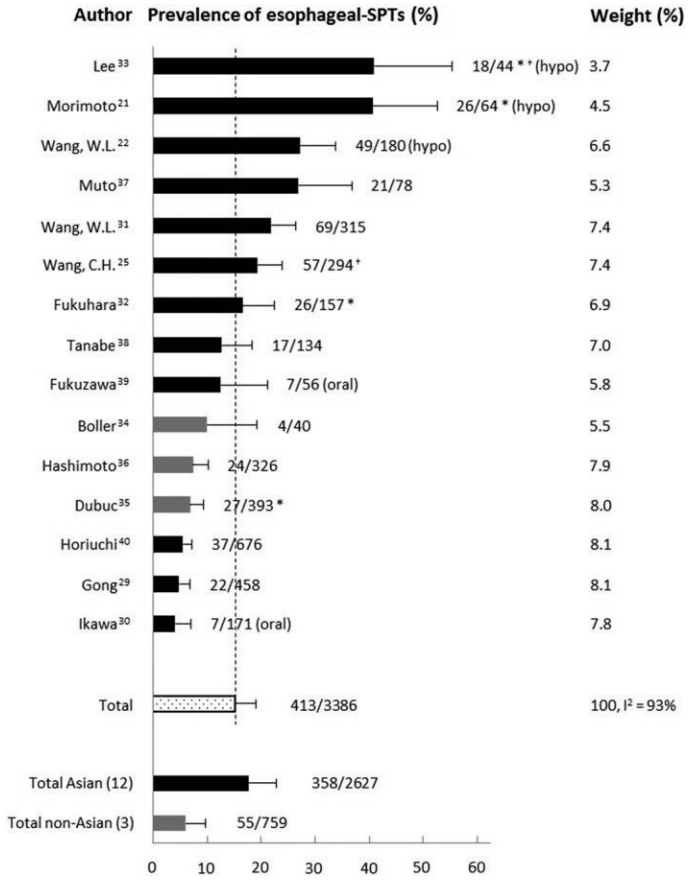


**Figure 2. Overview of prevalence of esophageal SPTs of 15 Lugol chromoendoscopy screening studies**

Hypo, study included only patients with hypopharyngeal tumors; oral, study included only patients with oral cavity tumors; SPT, second primary tumor; *, both synchronous and metachronous screening; †, transnasal Lugol chromoendoscopy. Error bars represent 95% confidence intervals

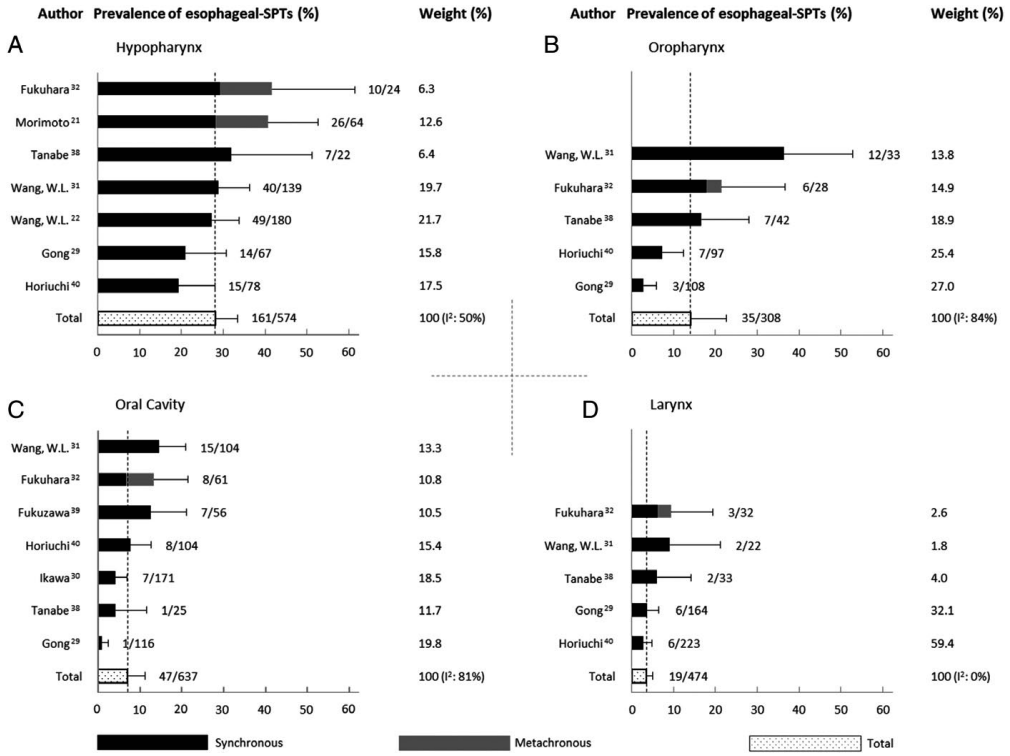


**Figure 3. Overview of prevalence of esophageal SPTs per sub-location of index head and neck squamous cell carcinoma** (A) hypopharynx, (B) oropharynx, (C) oral cavity, and (D) larynx. Nine Asian studies with sub-location specific data. Fukuhara et al. and Morimoto et al. screened both syn- and metachronously. Error bars represent 95% confidence intervals.

### Vienna classification

Eight studies differentiated between esophageal SPTs classified as category 4 (HGD) or 5 (carcinoma).[21, 25, 29, 31, 33-36] The remaining studies either did not mention the category or only mentioned category 5. Almost half of all esophageal SPTs found in these eight studies (48.6%, range 22.2-100.0) were category 4 lesions, HGD. That was approximately the same for Asian (43.3%, n = 5) and non-Asian (57.4%, n = 3) studies. Three of these seven studies also differentiated the esophageal carcinoma's in low- (stage I and II) and high-stage (stage III and IV) esophageal tumors.[21, 29, 31] Their combined data shows that 53.9% (41/76) of all esophageal carcinoma's were classified as low-stage and 46.1% (35/76) as high-stage.

### Prevalence per index tumor stage

Three Asian studies also reported the prevalence of esophageal SPTs in HNSCC patients per tumor stage of the index tumor.[21, 29, 39] There were a total of five (3.1%, 95% CI: 0.3-5.8) esophageal SPTs in 150 patients with stage I HNSCC, 28.8% (95% CI: -5.7-63.3) esophageal SPTs in patients with stage II HNSCC, 5.34% (95% CI: 1.1-9.6) esophageal SPTs in stage III HNSCC, and 22.5% (95% CI: -2.3-47.3) in patents with a stage IV index HNSCC.

## DISCUSSION

To the best of our knowledge, this is the first systematic review on the diagnostic yield of Lugol chromoendoscopy for esophageal second primary tumors in patients with HNSCC. Our main findings show that on average, 15% of the primary HNSCC patients that underwent Lugol chromoendoscopy were diagnosed with an esophageal SPT. We found that the prevalence was the highest for patients with hypopharyngeal index tumors.

There is a large discrepancy between the prevalence of esophageal SPTs in HNSCC patients found with Lugol chromoendoscopy screening (15%, 95% CI: 11-19) and the prevalence of retrospective non-screening studies (1-6%).[6, 7, 49-53] This was also noted by Wang, Lee, et al.[31] This discrepancy could indicate that without an active screening programme esophageal SPTs are underdiagnosed in patients with HNSCC.[7] Multiple studies state that the occurrence of esophageal SPTs negatively influences patient survival, especially in patients with advanced esophageal SPTs.[23, 54-56] Some researchers even claim that SPTs are the leading cause of treatment failure and death in HNSCC patients.[31]



The hypopharynx, and in particular involvement of the piriform sinus, is a well-known risk factor for the development of esophageal SPTs.[57-60] The results from the present review also SPTs underlined this. Wang, WL et al. compared two hypopharyngeal HNSCC cohorts: before and after implementing pretreatment Lugol chromoendoscopy esophagus screening.[22] Active esophageal screening tripled the amount of diagnosed esophageal SPTs (5.3% vs. 15.3%). The present study also found esophageal SPTs in 11% of oropharyngeal cancer patients, which is also a known sub-location to be at risk factor for the development of an esophageal SPT.[60, 61] However, the two largest studies in this review with specific oropharynx data by Horiuchi et al. and Gong et al. found relatively low prevalence of esophageal SPTs (7.2% and 2.8%) in this sub-group of patients.

The finding that up to a third of all esophageal SPTs found in the studies by Morimoto et al. and Fukuhara et al. were diagnosed metachronously during follow-up could indicate that the results of the other synchronous studies underestimate the true prevalence of esophageal SPTs.[21, 32] It is also an indication that esophageal screening of HNSCC patients should also be performed in the follow-up of the index tumor. However, the optimal esophageal screening schedule has yet to be defined.

Approximately 50% of the esophageal lesions found in this review were classified as HGD. Of the remaining lesions classified as invasive carcinoma, about half were early-stage. This is similar to findings from other researchers.[22, 29, 38] Wang, WL et al. showed that an active screening protocol diagnosed more HGD lesions and early-stage carcinomas, which significantly reduced the mortality rate of affected patients.[22] This is possibly the result of adjustments of the treatment strategy aimed at treating two instead of one tumor and less invasive endoscopic treatment of the esophageal lesions. Multiple studies claim that treatment of the esophageal SPT increases the survival, especially in patients with early-stage tumors.[23, 54-56]

Five of the included studies in this review used NBI in addition to Lugol chromoendoscopy.[22, 25, 29, 31, 33] Wang, CH et al. concluded that this combination of both techniques has the highest diagnostic accuracy to detect esophageal lesions: a sensitivity of 95%, a specificity of 90%, and an accuracy of 91% (95% CI 88-94).[25] Several other researchers have investigated the

use of full-body $^{18}$F-FDG-PET/CT. They reported a considerably lower diagnostic esophageal SPT yield that ranged from 0.43% to 4.85%.[62-66] As Kondo et al. also mentioned that PET/CT seems to be an inferior technique for detection of esophageal SPTs because it is not sensitive for early tumors.[62]

Two of the studies included in this review performed transnasal Lugol chromoendoscopy.[25, 33] Tumor-related airway obstruction or post-radiation trismus sometimes make the oropharyngeal passage difficult to reach with conventional endoscopes. The transnasal route bypasses this problem. Transnasal Lugol chromoendoscopy has the additional advantage that it can be performed in unsedated patients and that it even has a higher completion rate than conventional endoscopy.[67]

The prevalence of SPTs after HNSCC in the existing literature varies greatly geographically. In Asia, second primary gastrointestinal tract malignancies are more common after index HNSCC than in the Western world.[2] It is thought that Asians have a higher exposure to risk factors such as smoking and alcohol use. Other risk factor such as hot beverage drinking and betel quid chewing and genetic susceptibility have also been suggested to play a part.[68] As a result, the literature on this topic, including the studies of this review, are mostly from Asian countries. In the present review only three studies were non-Asian. This prohibits us to draw bold conclusions and extrapolate results on the usefulness of Lugol chromoendoscopy in a non-Asian patient population, as also stated by Morimoto et al.[21]

Another limitation is the quality of the included studies. Since the quality of a review greatly relies on the quality of the included data, we excluded studies of low quality. Although the remaining 15 studies were all similar in methodology and research question, there was some heterogeneity among the studies in the sub-sites of the index HNSCC tumors that were included. This might have had an influence on the average prevalence of all studies. However, the four largest studies (n = 326-676) with the highest weight on the average fortunately included all sub-locations. A final potential limitation is that the study selection and quality assessment was performed by one reviewer. The overall study quality could have benefited from an assessment by two independent reviewers.

In conclusion, this review has shown that the prevalence of esophageal second primary tumors in head and neck cancer patients is high, especially for patients with a hypo- and oropharyngeal index tumor. A large percentage of esophageal lesions were found in early stage of development. Literature shows that this group of patients could significantly benefit from dual tumor treatment, resulting in an increased five year survival rate. Based on our results there appears to be strong evidence to perform Lugol chromoendoscopy screening in an Asian patient population. More screening studies are needed to confirm the same for the Western world and Lugol chromoendoscopy holds the potential to increase the overall survival rate of head and neck cancer patients, due a lowered SPT specific mortality.

## REFERENCES


1. Priante AVM, Castilho EC, Kowalski LP. Second primary tumors in patients with head and neck cancer. Curr Oncol Rep 2011;13(2):132-137.
2. Atienza JAS, Dasanu CA. Incidence of second primary malignancies in patients with treated head and neck cancer: A comprehensive review of literature. Curr Med Res Opin 2012;28(12):1899-1909.
3. Shaha AR, Hoover EL, Mitrani M, Marti JR, Krespi YP. Synchronicity, multicentricity, and metachronicity of head and neck cancer. HEAD NECK SURG 1988;10(4):225-228.
4. Morris LGT, Sikora AG, Hayes RB, Patel SG, Ganly I. Anatomic sites at elevated risk of second primary cancer after an index head and neck cancer. Cancer Causes Control 2011;22(5):671-679.
5. Bradley PJ, Bradley PT. Searching for metachronous tumours in patients with head and neck cancer: The ideal protocol! Curr Opin Otolaryngol Head Neck Surg 2010;18(2):124-133.
6. Tiwana MS, Hay J, Wu J, Wong F, Cheung W, Olson RA. Incidence of second metachronous head and neck cancers: Population-based outcomes over 25 years. Laryngoscope 2014;124(10):2287-2291.
7. Schotborgh C, Liu L, Lemmens V, Soerjomataram I, Bergman JJ, Schoon EJ. High incidence of a second primary esophageal squamous cell carcinoma in patients with previous head-and-neck cancer: A nationwide population-based study. Gastroenterology 2011;140(5):S98-S99.
8. Morris LGT, Sikora AG, Patel SG, Hayes RB, Ganly I. Second primary cancers after an index head and neck cancer: Subsite-specific trends in the era of human papillomavirus - Associated oropharyngeal cancer. J Clin Oncol 2011;29(6):739-746.
9. Blanchard D, Barry B, De Raucourt D, et al. Guidelines update: Post-treatment follow-up of adult head and neck squamous cell carcinoma: Screening for metastasis and metachronous esophageal and bronchial locations. Eur Ann Otorhinolaryngol Head Neck Dis 2015;132(4):217-21.
10. Chung CS, Lo WC, Lee YC, Wu MS, Wang HP, Liao LJ. Image-enhanced endoscopy for detection of second primary neoplasm in patients with esophageal and head and neck cancer: A systematic review and meta-analysis. Head Neck 2016;38:E2343-E2349.
11. Dhooge IJ, De Vos M, Van Cauwenberge PB. Multiple primary malignant tumors in patients with head and neck cancer: Results of a prospective study and future perspectives. Laryngoscope 1998;108(2):250-256.
12. Paniello RC, Virgo KS, Johnson MH, Clemente MF, Johnson FE. Practice patterns and clinical guidelines for posttreatment follow-up of head and neck cancers: a comparison of 2 professional societies. Arch Otolaryngol Head Neck Surg 1999;125(3):309-13.
13. De Monès E, Bertolus C, Salaun PY, et al. 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):107-112.
14. Sabharwal R, Mahendra A, Moon NJ, Gupta P, Jain A, Gupta S. Genetically altered fields in head and neck cancer and second field tumor Review. South Asian j cancer 2014;3(3):151-153.
15. Angadi PV, Savitha JK, Rao SS, Sivaranjini Y. Oral field cancerization: current evidence and future perspectives. Oral Maxillofac Surg 2012;16(2):171-80.
16. León X, Quer M, Diez S, Orús C, López-Pousa A, Burgués J. Second neoplasm in patients with head and neck cancer. Head Neck 1999;21(3):204-210.
17. Alsop BR, Sharma P. Esophageal Cancer. Gastroenterol Clin North Am 2016;45(3):399-412.
18. Stoeckli SJ, Zimmermann R, Schmid S. Role of routine panendoscopy in cancer of the upper aerodiaestive tract. Otolaryngol Head Neck Surg 2001;124(2):208-212.
19. Heroiu Cataloiu AD, Danciu CE, Popescu CR. Multiple cancers of the head and neck. Medica 2013;8(1):80-85.

20. Argiris A, Eng C. Epidemiology, staging, and screening of head and neck cancer. Cancer Treat Res 2003;114:15-60.
21. Morimoto M, Nishiyama K, Nakamura S, et al. Significance of endoscopic screening and endoscopic resection for esophageal cancer in patients with hypopharyngeal cancer. Jpn J Clin Oncol 2010;40(10):938-943.
22. Wang WL, Wang CP, Wang HP, 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):808-813.
23. Saeki H, Toh Y, Morita M, et al. The treatment outcomes of synchronous and metachronous esophageal squamous cell carcinoma and head and neck squamous cell carcinoma. Esophagus 2012;9(3):158-164.
24. Makuuchi H, Machimura T, Shimada H, et al. Endoscopic screening for esophageal cancer in 788 patients with head and neck cancers. Tokai J Exp Clin Med 1996;21(3):139-45.
25. Wang CH, Lee YC, Wang CP, et al. Use of transnasal endoscopy for screening of esophageal squamous cell carcinoma in high-risk patients: Yield rate, completion rate, and safety. Dig Endosc 2014;26(1):24-31.
26. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003;73(9):712-6.
27. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62(10):1006-12.
28. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000;47(2):251-5.
29. Gong EJ, Kim DH, Ahn JY, 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(7):752-759.
30. Ikawa H, Tonogi M, Yamane GY, et al. Upper gastrointestinal tract cancers as double-cancers in elderly patients with oral squamous cell carcinoma. Bull Tokyo Dent Coll 2012;53(1):9-16.
31. Wang WL, Lee CT, Lee YC, et al. Risk factors for developing synchronous esophageal neoplasia in patients with head and neck cancer. Head Neck 2011;33(1):77-81.
32. Fukuhara T, Hiyama T, Tanaka S, et al. Characteristics of esophageal squamous cell carcinomas and lugol-voiding lesions in patients with head and neck squamous cell carcinoma. J Clin Gastroenterol 2010;44(2):e27-33.
33. Lee YC, Wang CP, Chen CC, et al. Transnasal endoscopy with narrow-band imaging and Lugol staining to screen patients with head and neck cancer whose condition limits oral intubation with standard endoscope (with video). Gastrointest Endosc 2009;69(3):408-417.
34. Boller D, Spieler P, Schoenegg R, et al. Lugol chromoendoscopy combined with brush cytology in patients at risk for esophageal squamous cell carcinoma. Surg Endosc Interv Tech 2009;23(12):2748-2754.
35. Dubuc J, Legoux J, Winnock M, et al. Endoscopic screening for esophageal squamous-cell carcinoma in high-risk patients: a prospective study conducted in 62 French endoscopy centers. Endoscopy 2006;38(7):690-5.
36. Hashimoto CL, Iriya K, Baba ER. Lugol's dye spray chromoendoscopy establishes early diagnosis of esophageal cancer in patients with primary head and neck cancer. Am J Gastroenterol. 2005;100(2):275-282.
37. Muto M, Nakane M, Hitomi Y, et al. Association between aldehyde dehydrogenase gene polymorphisms and the phenomenon of field cancerization in patients with head and neck cancer. Carcinogenesis 2002;23(10):1759-1765.
38. Tanabe H, Yokota K, Shibata N, Satoh T, Watari J, Kohgo Y. Alcohol consumption as a major risk factor in the development of early esophageal cancer in patients with head and neck cancer. Intern Med 2001;40(8):692-696.

39. Fukuzawa K, Noguchi Y, Yoshikawa T, et al. High incidence of synchronous cancer of the oral cavity and the upper gastrointestinal tract. Cancer Lett 1999;144(2):145-151.
40. Horiuchi M, Makuuchi H, Machimura T, Tamura Y, Sakai M. Survival benefit of screening for early esophageal carcinoma in head and neck cancer patients. Dig Endosc 1998;10(2):110-115.
41. Laohawiriyakamol S, Sunpaweravong S, Leelamanit V, Pruegsanusak K, Sinkijcharoenchai W. Evaluating synchronous esophageal cancer in head and neck cancer patients using Lugol dye chromoendoscopy. J Med Assoc Thailand 2014;97(11):1164-1170.
42. Komínek P, Vítek P, Urban O, et al. Chromoendoscopy to detect early synchronous second primary esophageal carcinoma in patients with squamous cell carcinomas of the head and neck? Gastroenterol Res Pract 2013;2013.
43. Chow TL, Lee DTY, Choi CY, Chan TTF, Lam SH. Prediction of simultaneous esophageal lesions in head and neck squamous cell carcinoma: A multivariate analysis. Arch Otolaryngol Head Neck Surg 2009;135(9):882-885.
44. Muto M, Hironaka S, Nakane M, Boku N, Ohtsu A, Yoshida S. Association of multiple Lugol-voiding lesions with synchronous and metachronous esophageal squamous cell carcinoma in patients with head and neck cancer. Gastrointest Endosc 2002;56(4):517-521.
45. Tincani AJ, Brandalise N, Altemani A, et al. Diagnosis of superficial esophageal cancer and dysplasia using endoscopic screening with a 2% lugol dye solution in patients with head and neck cancer. Head Neck 2000;22(2):170-174.
46. Ina H, Shibuya H, Ohashi I, Kitagawa M. The frequency of a concomitant early esophageal cancer in male patients with oral and oropharyngeal cancer. Screening results using Lugol dye endoscopy. Cancer 1994;73(8):2038-2041.
47. Chisholm EM, Williams SR, Leung JWC, Chung SCS, Van Hasselt CA, Li AKC. Lugol's iodine dye-enhanced endoscopy in patients with cancer of the oesophagus and head and neck. EUR J SURG ONCOL 1992;18(6):550-552.
48. Shiozaki H, Tahara H, Kobayashi K, et al. Endoscopic screening of early esophageal cancer with the Lugal dye method in patients with head and neck cancers. CANCER 1990;66(10):2068-2071.
49. Herranz Gonzalez-Botas J, Varela Vazquez P, Vazquez Barro C. Second primary tumours in head and neck cancer. Acta Otorrinolaringol Esp 2016;67(3):123-129.
50. Andersen AR, Bjerring OS, Godballe C, Detlefsen S, Mortensen MB. Secondary oesophageal or gastric cancer in patients treated for head and neck squamous cell carcinoma. Dan Med J 2016;63(8).
51. Krishnatreya M, Rahman T, Kataki AC, Lahkar K. Synchronous primary cancers in the head and neck region and upper aero digestive tract: Role of triple endoscopy. Indian J Cancer 2015;52(1):53-56.
52. Lee DH, Roh JL, Baek S, et al. Second Cancer Incidence, Risk Factor, and Specific Mortality in Head and Neck Squamous Cell Carcinoma. Otolaryngology-Head and Neck Surgery 2013;149(4):579-586.
53. Kim E, Chandra N, Kim J. Incidence of esophageal cancers among oral cavity and pharynx cancer patients: A review of the SEER database (1973-2007). J Clin Oncol 2011;29(15).
54. Park JW, Lee SW. Clinical outcomes of synchronous head and neck and esophageal cancer. Radiat Oncol J 2015;33(3):172-178.
55. Lim H, Kim DH, Jung HY, et al. Clinical significance of early detection of esophageal cancer in patients with head and neck cancer. Gut Liver 2015;9(2):159-65.
56. Graff P, Schipman B, Desandes E, et al. Management of Patients with Head and Neck Tumours Presenting at Diagnosis with a Synchronous Second Cancer at Another Anatomic Site. Clin Oncol 2011;23(3):174-181.
57. Liu WS, Chang YJ, Lin CL, et al. Secondary primary cancer in patients with head and neck carcinoma: the differences among hypopharyngeal, laryngeal, and other sites of head and neck cancer. Eur J Cancer Care (Engl) 2014;23(1):36-42.

58. Yamamoto E, Shibuya H, Yoshimura RI, Miura M. Site specific dependency of second primary cancer in early stage head and neck squamous cell carcinoma. Cancer 2002;94(7):2007-2014.
59. Kim dH, Gong EJ, Jung HY, et al. Clinical significance of intensive endoscopic screening for synchronous esophageal neoplasm in patients with head and neck squamous cell carcinoma. Scand J Gastroenterol 2014;49(12):1486-1492.
60. Hung SH, Tsai MC, Liu TC, Lin HC, Chung SD. Routine endoscopy for esophageal cancer is suggestive for patients with oral, oropharyngeal and hypopharyngeal cancer. PLoS One. 2013;8(8):e72097.
61. Su YY, Chen WC, Chuang HC, et al. Effect of routine esophageal screening in patients with head and neck cancer. JAMA Otolaryngol Head Neck Surg 2013;139(4):350-354.
62. Kondo N, Tsukuda M, Nishimura G. Diagnostic sensitivity of 18fluorodeoxyglucose positron emission tomography for detecting synchronous multiple primary cancers in head and neck cancer patients. Eur Arch Oto-Rhino-Laryngol 2012;269(5):1503-1507.
63. Wallowy P, Diener J, Grünwald F, Kovács AF. 18F-FDG PET for detecting metastases and synchronous primary malignancies in patients with oral and oropharyngeal cancer. NuklearMedizin 2009;48(5):192-199.
64. Liu FY, Liao CT, Yen TC. Synchronous malignancies in patients with squamous cell carcinomas of the oral cavity. Eur J Nucl Med Mol Imaging 2011;38(6):1020-1028.
65. Krabbe CA, Pruim J, van der Laan BFAM, Rödiger LA, Roodenburg JLN. FDG-PET and detection of distant metastases and simultaneous tumors in head and neck squamous cell carcinoma: A comparison with chest radiography and chest CT. Oral Oncol 2009;45(3):234-240.
66. Chan SC, Wang HM, Yen TC, et al. 18F-FDG PET/CT and 3.0-T whole-body MRI for the detection of distant metastases and second primary tumours in patients with untreated oropharyngeal/hypopharyngeal carcinoma: A comparative study. Eur J Nucl Med Mol Imaging 2011;38(9):1607-1619.
67. Roof SA, Amin MR. Transnasal esophagoscopy in modern head and neck surgery. Current Opinion in Otolaryngology & Head and Neck Surgery 2015;23(2):171-175.
68. Zhang HZ, Jin GF, Shen HB. Epidemiologic differences in esophageal cancer between Asian and Western populations. Chin J Cancer 2012;31(6):281-6.

## SUPPLEMENATRY

**Literature search**

26 April 2017

| | | |
|---|---|---|
| Embase | 1688 | 1659 |
| Medline Ovid | 1122 | 182 |
| Cochrane CENTRAL | 39 | 3 |
| Web of science | 1028 | 277 |
| Google scholar | 200 | 120 |
| **Total** | **4077** | **2241*** |



*after removing duplicates

**Embase.com 1688**

('second cancer'/exp OR 'multiple cancer'/de OR (((Metachronous OR Synchronous OR Second* OR Multiple OR double OR triple OR quadruple OR quintuple OR subsequen* OR Simultan*) NEAR/6 ( tumo* OR primary OR malignan* OR carcin* OR neoplas* OR cancer*))):ab,ti) AND ('esophagus tumor'/exp OR 'esophagus'/exp OR 'esophagus examination'/exp OR (esophag* OR oesophag* OR (upper NEXT/3 (aerodigest* OR digest*))):ab,ti) AND ('head and neck tumor'/exp OR 'larynx tumor'/exp OR (('head'/exp OR neck/exp) AND 'primary tumor'/de) OR (((lip OR mouth OR oral OR nose OR nasal OR tongue OR tonsil OR nasopharyn* OR oropharyn* OR hypopharyn* OR pharyn* OR laryn* OR head OR neck ) NEAR/10 (tumo* OR primary OR malignan* OR carcin* OR neoplas* OR cancer* OR primar*))):ab,ti) AND [english]/lim NOT ([animals]/lim NOT [humans]/lim)

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("Neoplasms, Second Primary"/ OR (((Metachronous OR Synchronous OR Second* OR Multiple OR double OR triple OR quadruple OR quintuple OR subsequen* OR Simultan*) ADJ6 ( tumo* OR primary OR malignan* OR carcin* OR neoplas* OR cancer*))).ab,ti,kf.) AND ("Esophageal Neoplasms"/ OR "esophagus"/ OR (esophag* OR oesophag* OR (upper ADJ3 (aerodigest* OR digest*))).ab,ti,kf.) AND ("Head and Neck Neoplasms"/ OR exp "Mouth Neoplasms"/ OR exp "Otorhinolaryngologic Neoplasms"/ OR (((lip OR mouth OR oral OR nose OR nasal OR tongue OR tonsil OR nasopharyn* OR oropharyn* OR hypopharyn* OR pharyn* OR laryn* OR head OR neck ) ADJ10 (tumo* OR primary OR malignan* OR carcin* OR neoplas* OR cancer* OR primar*))).ab,ti,kf.) AND english.la. NOT (exp animals/ NOT humans/)

**Cochrane CENTRAL 39**

((((Metachronous OR Synchronous OR Second* OR Multiple OR double OR triple OR quadruple OR quintuple OR subsequen* OR Simultan*) NEAR/6 ( tumo* OR primary OR malignan* OR carcin* OR neoplas* OR cancer*))):ab,ti) AND ((esophag* OR oesophag* OR (upper NEXT/3 (aerodigest* OR digest*))):ab,ti) AND ((((lip OR mouth OR oral OR nose OR nasal OR tongue OR tonsil OR nasopharyn* OR oropharyn* OR hypopharyn* OR pharyn*

OR laryn* OR head OR neck ) NEAR/10 (tumo* OR primary OR malignan* OR carcin* OR neoplas* OR cancer* OR primar*))):ab,ti)

**Web of science** **1028**

TS=(((((Metachronous OR Synchronous OR Second* OR Multiple OR double OR triple OR quadruple OR quintuple OR subsequen* OR Simultan*) NEAR/5 ( tumo* OR primary OR malignan* OR carcin* OR neoplas* OR cancer*)))) AND ((esophag* OR oesophag* OR (upper NEAR/2 (aerodigest* OR digest*)))) AND ((((lip OR mouth OR oral OR nose OR nasal OR tongue OR tonsil OR nasopharyn* OR oropharyn* OR hypopharyn* OR pharyn* OR laryn* OR head OR neck ) NEAR/9 (tumo* OR primary OR malignan* OR carcin* OR neoplas* OR cancer* OR primar*)))) ) AND LA=(english)

**Google scholar** **200**

"Metachronous|Synchronous|Second|Multiple|Simultaneous tumor|cancer|primary" esophagus|esophageal|oesophagus|oesophageal "lip |mouth|oral|pharyngeal|larygeal|head|neck tumor|malignancy|carcinma|neoplasms|cancer"

# CHAPTER 5

## Screening for synchronous esophageal second primary tumors in patients with head and neck cancer

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*Diseases of the Esophagus – 2021*

## ABSTRACT

**Background:** Patients with head and neck squamous cell carcinoma (HNSCC) have an increased risk of developing esophageal second primary tumors (ESPTs). We aimed to determine the incidence, stage and outcome of synchronous ESPTs in patients with HNSCC in a Western population.

**Methods:** We performed a prospective, observational, cohort study. Patients diagnosed with HNSCC in the oropharynx, hypopharynx, any other sub-location in combination with alcohol abuse, or patients with two synchronous HNSCCs, between February 2019 and February 2020 underwent screening esophagogastroduodenoscopy (EGD). ESPT was defined as presence of esophageal squamous cell carcinoma (ESCC) or high grade dysplasia (HGD).

**Results:** Eighty-five patients were included. A lesion suspected for ESPT was detected in 14 of 85 patients, which was pathologically confirmed in 5 patients (1 ESCC and 4 HGD). The radiotherapy field was extended to the esophagus in two of five patients, HGD was treated with endoscopic resection in three of five patients. None of the ESPTs were detected on MRI and/or CT-scan prior to EGD. Of the remaining nine patients, three had low grade dysplasia on histology whereas the other six patients had benign lesions.

**Conclusions:** Incidence of synchronous ESPT was 5.9% in our cohort of HNSCC patients. All ESPTs were diagnosed at an early stage and treated with curative intent. We recommend that screening for synchronous ESPTs should be considered in a selected group of patients with HNSCC.

## INTRODUCTION

Patients with head and neck squamous cell carcinoma (HNSCC) are at increased risk of developing second primary tumors (SPTs).[1] The development of SPTs might be explained by the field cancerization theory: premalignant changes of the epithelium around the primary tumor caused by exposure to common carcinogens such as alcohol and tobacco.[2] The esophagus in particular is at increased risk of developing SPTs.[3]

Esophageal cancer is often diagnosed in an advanced stage because these tumors remain asymptomatic for a long period.[4] In general, these patients have to be treated with invasive surgery, associated with high morbidity.[5] If esophageal cancer is detected in an early stage, patients can be treated with minimal invasive endoscopic resection (ER). Therefore, early diagnosis of esophageal second primary tumor (ESPT) in HNSCC patients is crucial to improve survival with minimum morbidity.[6, 7] Screening of the esophagus with esophagogastroduodenoscopy (EGD) has the potential to detect ESPTs at an early stage.[8] In addition, endoscopic screening is reported to be superior to Positron emission tomography (PET).[9]



ESPT is often defined as esophageal squamous cell carcinoma (ESCC) or high grade dysplasia (HGD) of squamous epithelium.[8] Low grade dysplasia (LGD) is a precursor of ESCC, and requires careful follow-up or ER.[10, 11] Therefore, LGD is often included in studies on ESPT.[6, 12]

ESPTs are characterized by flat lesions, which are easily overlooked with white light high resolution endoscopy (WLE).[13] Narrow-band imaging (NBI) improves the identification of these lesions due to the visibility of intraepithelial papillary capillary loop patterns.[14] Still, the gold standard for ESPT detection is Lugol chromoendoscopy (LCE).[8, 15] Lugol iodine binds to glycogen, which is absent or diminished in dysplastic and neoplastic tissue, and therefore highlights ESPT.[16] However, LCE is associated with a high rate of false positive lesions.[17] Combining LCE with NBI improves ESPT detection, with a reported accuracy of 91%.[18]

There are multiple reports on endoscopic screening for ESPTs in HNSCC patients.[8] A recent systematic review with meta-analysis by our research group showed a pooled prevalence of 15.2% (95% confidence interval [CI] 11.4-19.0).[8] However, 12 of 15 included studies were performed in the Asian population.[8] Only very few well-defined screening studies in the Western population exist. The aim of this study was to establish the incidence, stage and outcome of synchronous ESPTs in a selected group of Western patients with HNSCC.

## MATERIALS AND METHODS

### Study design

We performed a prospective, observational cohort study in a tertiary referral center in the Netherlands. This study was approved by the Medical Ethical Review Committee of the Erasmus MC in Rotterdam, the Netherlands (MEC-2018-1243) and is registered in the Netherlands Trial Register (NL7299). Patients diagnosed with HNSCC between February 2019 and February 2020 were eligible for inclusion. To be included in the study, patients had to have an increased risk of ESPT development: HNSCC located in the oropharynx,

hypopharynx, any other head and neck sub-location in combination with alcohol abuse, or the presence of two HNSCCs regardless of location.[8] Alcohol abuse was defined according to the classification for 'risky alcohol use' of The National Institute on Alcohol Abuse and Alcoholism.[19] Patients with history of ESCC, oropharynx carcinoma associated with human papillomavirus infection,[20] or incurable HNSCC at time of diagnosis were excluded. In every patient with oropharynx carcinoma, high-risk human papillomavirus testing was performed with immunohistochemistry for a surrogate p16 marker.

EGD was performed within six months after HNSCC diagnosis. In general, EGD was performed within two weeks after HNSCC diagnosis. All patients underwent routine clinical workup with imaging techniques for HNSCC (i.e., MRI-scan and/or CT-scan). Treatment strategy for HNSCC and ESPT was discussed in a multidisciplinary tumor board meeting consisting of a head and neck surgeon, gastroenterologist, gastrointestinal surgeon, radiotherapist, medical oncologist, and radiologist. If it was deemed impossible to perform EGD during the workup for HNSCC, HNSCC treatment was started and EGD was performed thereafter.

**Screening esophagogastroduodenoscopy**

EGD was performed with WLE, NBI and LCE, by an experienced interventional endoscopist (WG; SN; PJ; MS; and AD). All endoscopists participated in dedicated upper gastrointestinal cancer screening programs and had extensive experience with all three screening techniques. EGD was performed as follows: at first, the duodenum, stomach and esophagus were observed with WLE. Then, the esophagus was observed with NBI for aberrant intraepithelial papillary capillary loop patterns. After observation with NBI, the filter was switched to white light again and LCE was performed. For LCE, the esophagus was stained with 20-30 mL Lugol iodine (1.2%). Incidental findings such as reflux-esophagitis, Barrett's esophagus or erosive gastritis, not related to this study were treated as per standard clinical practice.

Synchronous ESPT was defined as ESCC (category 5) or HGD of squamous epithelium (category 4) according to the Vienna classification, detected within six months after HNSCC diagnosis.[21] A lesion was considered a possible ESPT or LGD if it was suspect on at least one of the three endoscopic detection techniques and had a diameter of at least 5mm. All suspected lesions in the esophagus were systematically assessed for size, location (distance from the incisors), macroscopic appearance according to the Paris Classification, and whether the lesion could be removed by ER.[22] ER was preferably performed for proximal lesions in the esophagus rather than being included in the radiotherapy field for HNSCC because (1) ER provides a more precise histopathological staging of early ESCC, (2) curative ER is superior to radiotherapy alone for ESCC, and (3) extending the radiotherapy field is considered a second best because a larger field might lead to more side effects such as stricture development. If ER was deemed possible, a biopsy was preferably avoided to prevent submucosal fibrosis, which might make ER more difficult. All resected specimens and biopsies were reviewed by an expert gastrointestinal pathologist (Supplementary File 1).[22, 23] All ER specimens were assessed whether they fulfilled the pathological criteria for a curative treatment, according to the ESGE guidelines.[24]

### Study endpoint

The primary endpoint of this study was the incidence of ESPT. Secondary endpoints were: (1) histology and tumor stage of ESPT, (2) the incidence of LGD, (3) treatment and outcome of ESPT and LGD, (4) the number of ESPTs that were not detected with routine imaging techniques for HNSCC workup, and (5) detection rate of ESPT and LGD with WLE, NBI, and LCE.

### Statistical analysis

Continuous data were expressed as mean (± standard deviation) for normally distributed data and as median (interquartile range [IQR]) for skewed data. Categorical data were presented with frequencies and percentages. Follow-up data were retrieved until July 2020. Analyses were performed with IBM SPSS Statistics (Version 25).



## RESULTS

### Baseline characteristics

Out of 129 eligible patients, 92 patients underwent a screening EGD (Figure 1). Seven patients with oropharynx carcinoma who underwent EGD were positive for human papillomavirus infection (no ESPT was detected) and were excluded from further analyses. The remaining 85 patients were included in the final analysis. Baseline and HNSCC characteristics are presented in Table 1. Most HNSCCs were located in the hypopharynx (33%) or oropharynx (29%). Six out of 85 patients died within one year after HNSCC diagnosis.

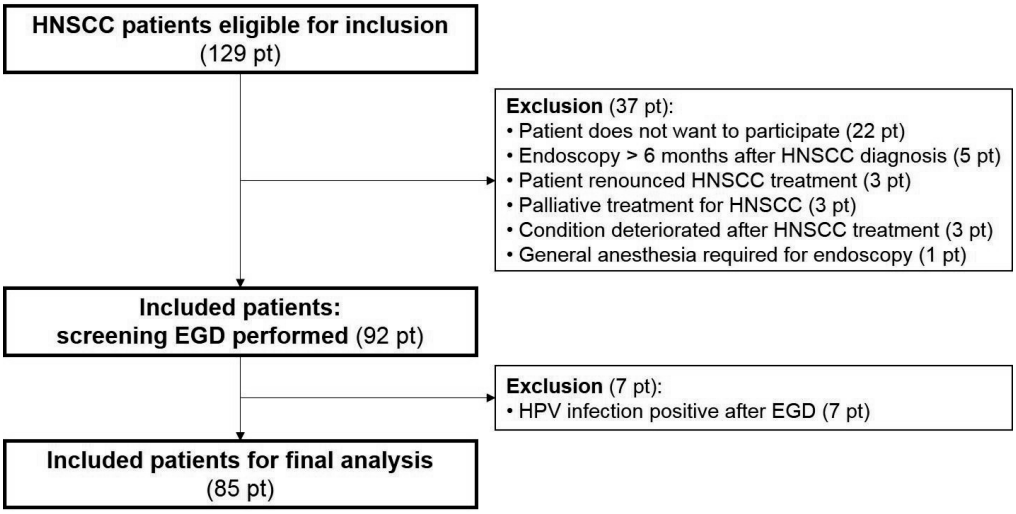


**Figure 1. Flow-chart in- and excluded patients**
HNSCC, head and neck squamous cell carcinoma; EGD, esophagogastroduodenoscopy; HPV, human papilloma virus; pt, patient(s)

**Table 1. Baseline characteristics of patients with HNSCC (n=85)**

| | |
|---|---|
| **Patient characteristics** | |
| **Male sex, n (%)** | 67 (79%) |
| **Median age, years (IQR)** | 65 (59-70) |
| **ASA classification, n (%)** | |
| I | 4 (5%) |
| II | 69 (81%) |
| III | 12 (14%) |
| **Present alcohol use, n (%)** | |
| **Yes** | **67 (79%)** |
| *Median units alcohol/week (IQR)* | 21 (19-42) |
| **No** | **18 (21%)** |
| *Alcohol use in the past, n* | 9 |
| *Median units alcohol/week (IQR)* | 35 (23-77) |
| **Current tobacco use, n (%)** | |
| **Yes** | **46 (54%)** |
| *Median pack years (IQR)* | 40 (29-55) |
| **No** | **39 (46%)** |
| *Smoking in the past, n* | 31 |
| *Median pack years (IQR)* | 40 (40-50) |
| **HNSCC characteristics** | |
| **Number of HNSCC** | |
| 1 | 79 (93%) |
| 2 | 6 (7%) |
| **Tumor location, n (%)** [a] | |
| Nasopharynx | 1 (1%) |
| Oral cavity | 15 (16%) |
| Oropharynx | 26 (29%) |
| Hypopharynx | 30 (33%) |
| Larynx | 19 (21%) |
| **Tumor stage, n (%)** [a] | |
| Tis | 7 (8%) |
| T1 | 15 (17%) |
| T2 | 29 (32%) |
| T3 | 24 (26%) |
| T4a / T4b | 14 (15%) / 2 (2%) |
| **N stage, n (%)** [a] | |
| N0 | 49 (55%) |
| N1 | 14 (15%) |
| N2 / N2a / N2b / N2c | 3 (3%) / 2 (2%) / 14 (15%) / 8 (9%) |
| N3b | 1 (1%) |
| **M stage, n (%)** | |
| M0 | 85 (100%) |
| **HNSCC treatment, n (%)** | |
| Chemotherapy | 1 (1%) |
| Chemoradiotherapy | 31 (37%) |
| Radiotherapy | 25 (30%) |
| Surgery | 11 (13%) |
| Surgery + radiotherapy | 8 (9%) |
| Surgery + chemoradiotherapy | 1 (1%) |
| Laser | 7 (8%) |
| No treatment | 1 (1%) |

[a] Calculated for the total number of head and neck tumors = 91
HNSCC, head and neck squamous cell carcinoma; IQR, interquartile range

**Esophageal second primary tumors**

The median time between HNSCC diagnosis and EGD was 9 days (IQR: 6-20). No adverse events occurred during EGD. A total of 15 suspected lesions were detected in 14 patients (16.5%).

**Confirmed ESPT**

ESPT was histopathologically confirmed in 5 out of 14 patients (Table 2 and 3; patients 1-5). This was an ESCC in one patient (patient 1) and HGD in four patients (patients 2-5). All ESPTs were ≥20 mm (range 20-80). The radiotherapy field for HNSCC was extended to the esophagus because of the presence HGD (T2 lesion on PET-scan) in one patient (patient 2) and the presence of LVI after ER for T1a ESCC in another patient (patient 1). The remaining three patients with HGD were treated with ER only (patients 3-5).



**Low grade dysplasia**

LGD was found in three patients (Table 2 and 3; patient 6-8). Two patients underwent ER and one patient died due to HNSCC before ER was performed.

**No dysplasia**

In 5 out of 14 patients, ESPT or LGD could not be confirmed on histopathological analysis. These patients are presented in Supplementary Table 2. The median size of these non-dysplastic lesions was 6 mm (IQR: 5-9). One out of 14 patients had a suspected lesion but histopathology was not obtained because of refusal of further treatment by the patient.

Overall, an ESPT was detected and histopathologically confirmed in 5 out of 85 patients (5.9%, 95% CI 1.9-13.2). LGD was detected in 3 out of 85 patients (3.5%, 95% CI 0.7-10.0). These (pre)malignant lesions were all found in an early stage and could be treated with curative intent. None of the ESPTs and LGD lesions were identified by MRI and/or CT-scan.

**Table 2. Patient and tumor characteristics of patients with esophageal second primary tumor or low-grade dysplasia**

| | Patient & HNSCC characteristics | | | | | | | | Screening esophagogastroduodenoscopy | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ID | Sex | Age | Alcohol (units/ week) | Smoking (PY) | HNSCC tumors | HNSCC sub-location | TN stage | Number of lesions, visible with WLE / NBI / LCE | Location esophagus (cm)[1] | Morphology[2] + diameter lesion (mm) | Pathology |
| ESPT | 1 | M | 67 | No | Yes (13) | 2 | Oropharynx + Hypopharynx | T2N2c + T2N2c | 1, WLE + NBI* | 20 | 0-IIa (20) | ESD: pT1a ESCC (m3, G1/2, LVI+, R0) |
| | 2 | M | 48 | Yes (42) | Yes (31) | 1 | Hypopharynx | T2N2b | 1, WLE + NBI* | 20 | 0-Is + 0-II (20) | Biopsy: HGD |
| | 3 | M | 62 | Yes (21) | Yes (20) | 2 | Oropharynx + Hypopharynx | T3N2c + T4aN2c | 1, NBI + LCE | 38 | 0-IIa (20) | Biopsy: LGD<br>EMR: HGD |
| | 4 | F | 62 | Yes (9) | Yes (30) | 1 | Hypopharynx | T4N2b | 1, WLE + NBI + LCE | 22-31 | 0-IIb + 0-IIa (80) | Biopsy: HGD<br>ESD: HGD |
| | 5 | M | 67 | No | No | 1 | Oropharynx | T2N0 | 1, WLE + NBI + LCE | 21-24 | 0-IIb (30) | ESD: HGD |
| LGD | 6 | M | 68 | Yes (28) | No (40) | 1 | Hypopharynx | T3N2b | 1, LCE | 28 | 0-IIb (6) | Biopsy: LGD<br>EMR: ND |
| | 7 | F | 67 | Yes (28) | No | 1 | Larynx | T2N0 | 1, LCE | 24 | 0-IIb (5) | EMR: LGD |
| | 8 | M | 77 | No | No | 1 | Hypopharynx | T3N2b | 1, WLE + NBI + LCE | 30 | 0-IIa (20) | Biopsy: LGD |

* LCE not performed, lesion was visible with WLE and NBI; [1] from the incisors; [2] according to the Paris classification[22]

EMR, endoscopic mucosal resection; ESCC, esophageal squamous cell carcinoma; ESD, endoscopic submucosal dissection; ESPT, esophageal second primary tumor; F, Female; HGD, high grade dysplasia; HNSCC, head and neck squamous cell carcinoma; LCE, Lugol chromoendoscopy; LGD, low grade dysplasia; M, Male; NBI, narrow band imaging; PY, pack years; TN, tumor node; WLE, white light high resolution endoscopy

**Table 3. Treatment and follow-up information of patients with second primary tumor or low-grade dysplasia**

| | ID | Treatment | Follow-up |
|---|---|---|---|
| **ESPT** | 1 | ESD + radiotherapy field HNSCC extended to the esophagus + chemotherapy | No recurrence |
| | 2 | Radiotherapy field HNSCC extended to the esophagus + chemotherapy | Recurrence ESCC after 9 months: laryngeal and pharyngeal extirpation + proximal esophagus resection |
| | 3 | EMR + endoscopic surveillance | No recurrence |
| | 4 | ESD + endoscopic surveillance | No recurrence |
| | 5 | ESD + endoscopic surveillance | No recurrence |
| **LGD** | 6 | EMR + endoscopic surveillance | No recurrence |
| | 7 | EMR + endoscopic surveillance | No recurrence |
| | 8 | EMR not performed: Patient died | Patient died |

EMR, endoscopic mucosal resection; ESCC, esophageal squamous cell carcinoma; ESD, endoscopic submucosal dissection; ESPT, esophageal second primary tumor; HNSCC, head and neck squamous cell carcinoma; LGD, low grade dysplasia.



### Endoscopic detection technique

In two out of five ESPTs, the lesion was detected with WLE and NBI. In both patients, LCE was not performed because this was not considered of additional value and would have only resulted in additional discomfort to the patient. Overall, ESPTs were detected with WLE, NBI, and LCE in four, five, and three patients, respectively. Of the three histopathological confirmed LGD lesions, all lesions were detected with LCE, whereas one was detected with NBI, and another one with WLE. Figure 2 shows two separate ESPTs, one detected by NBI and one by LCE. Figure 3 shows the number of ESPT, LGD and non-dysplastic lesions detected by WLE, NBI and LCE. The positive predictive value (PVV) for ESPT detection was highest with NBI (71.4%) and lowest with LCE (27.3%). The false positive detection rate was highest with LCE (45.5%).

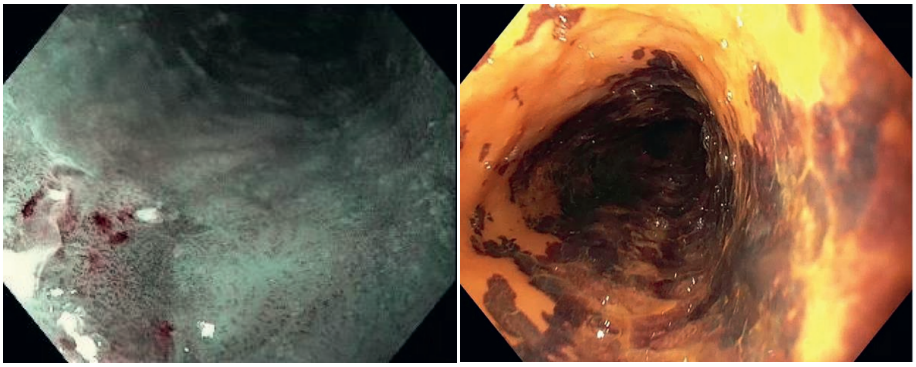

**Figure 2. Esophageal second primary tumor visible with narrow band imaging and Lugol chromoendoscopy** Left picture: high grade dysplasia visible with NBI (patient ID: 3), right picture: high grade dysplasia visible with Lugol chromoendoscopy (patient ID: 4).

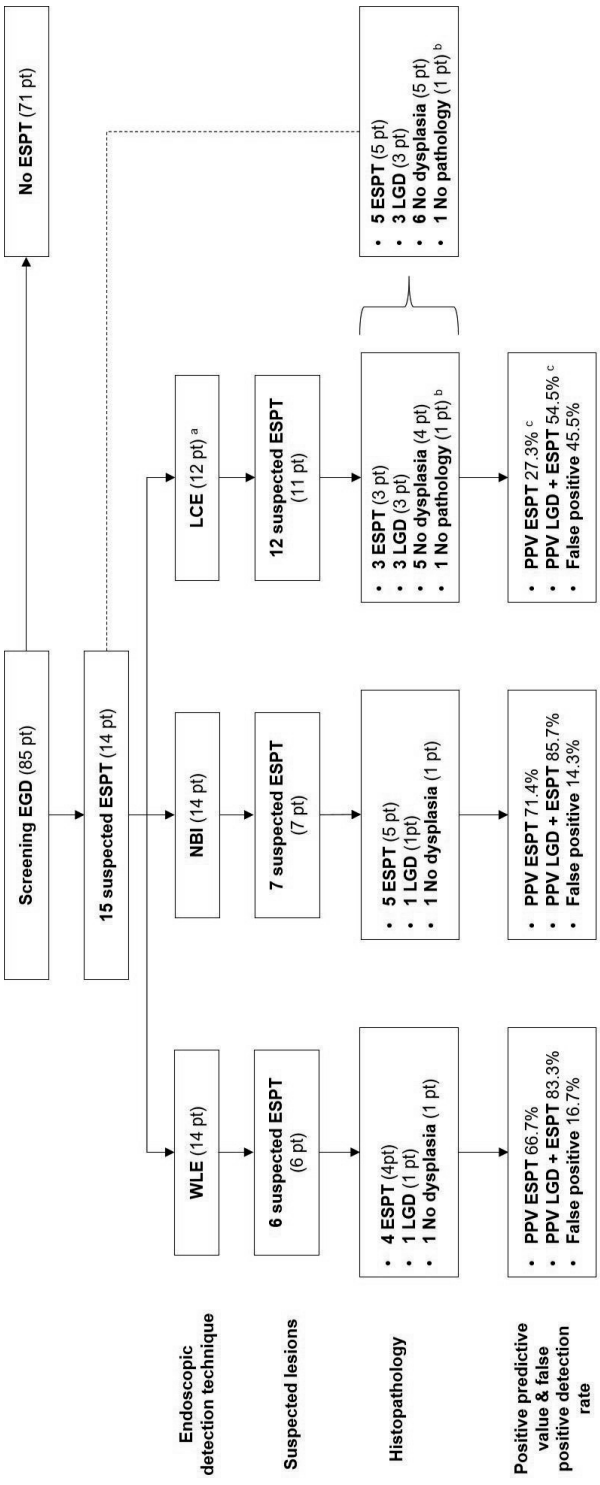


**Figure 3. Detection of esophageal second primary tumors and low-grade dysplasia by esophagogastroduodenoscopy**

[a] LCE not performed in two patients; [b] No pathology obtained in one patient; [c] calculated for all suspected ESPT of which pathology was obtained
EGD, esophagogastroduodenoscopy; ESPT, esophageal second primary tumor; LCE, Lugol chromoendoscopy; LGD, low-grade dysplasia; NBI, narrow band imaging; pt, patients; PPV, positive predictive value; WLE, white light high resolution endoscopy

## DISCUSSION

We performed a prospective endoscopic screening study in patients with HNSCC and found an ESPT incidence of 5.9%. ESPT or LGD was found in approximately one in 10 patients. All esophageal lesions were diagnosed at an early stage and could be treated with curative intent with either ER or radiotherapy. Since none of the ESPTs were identified by other imaging techniques, our findings suggest that screening for ESPT by EGD is of added value for a selected group of HNSCC patients.

Previous screening studies reported prevalences of ESPT between 4.1 and 40.9%.[8] A recent meta-analysis by our research group, which included more than 3,000 patients, found a pooled prevalence of 15.2% (95% CI 11.4-19.0).[8] This is much higher compared with our current findings, which may be explained by the fact that metachronous ESPTs were also included in the meta-analysis.[8] Another possible explanation is that the majority of previously published screening studies were performed in Asia. The prevalence of synchronous ESPTs is higher in the Asian population compared with the Western population.[8] This difference might be due to a higher exposure of risk factors (e.g. alcohol and tobacco) in the Asian population and a difference in genetic polymorphisms of alcohol metabolism between these two populations.[25] However, the majority of patients in our cohort were exposed to these risk factors. Western gastroenterologists might have a relative lack of experience in screening for early ESCC compared with Asian gastroenterologists, which might contribute to the difference in ESPT prevalence.



The only two screening studies in Western population reported incidences of 6.9% and 10.0%, which is more in line with our results.[12, 26] The French study by Dubuc *et al*., included 393 patients with a history of head and neck (*n*=384) or tracheobronchial squamous cell carcinoma (*n*=9). ESPT was detected in 27 of 393 patients (6.9%).[12] However, the time between HNSCC and ESPT diagnosis was not reported. The proportion of synchronous ESPTs is probably lower than 6.9%. Boller *et al*. included 40 patients with HNSCC, ESPT was detected in four patients (10.0%).[26] The mean time since HNSCC diagnosis was 5.0 years, it is therefore most likely that no synchronous ESPTs are detected in this study.[26]

All patients with an ESPT in our study had an oropharynx or hypopharynx carcinoma. Several studies have shown that patients with an HNSCC in these sub-locations have a higher risk of developing ESPT.[27] An endoscopic screening study by Gong *et al.* showed that the ESPT prevalence was highest in patients with hypopharynx carcinoma (21%).[27] Wang *et al*., reported an ESPT prevalence of 36% in patients with an oropharynx carcinoma and 29% in patients with a hypopharynx carcinoma, in contrast to an ESPT prevalence of only 9% in patients with laryngeal cancer.[28] According to a pooled analysis, the ESPT incidences are 14% and 28% for patients with an HNSCC in the oropharynx and hypopharynx, respectively.[8] This suggests that endoscopic screening for ESPT is most effective in these patients.

It is well established that esophageal lesion size is associated with malignancy with 20mm as the most common cut-off value.[26, 29] In an endoscopic screening study by Boller *et al*., none of the Lugol voiding lesions (LVL) <20mm showed dysplasia on histopathological assessment, whereas dysplasia was found in 80% of lesions ≥20mm.[26] In another endoscopic screening study, 37% of the LVL >10mm showed dysplasia or neoplasia compared with only 5% of the LVL between 5 and 10mm.[17] In our study, all ESPTs were ≥20mm, whereas the six non-

dysplastic lesions had a median diameter of only 6mm. Therefore, we would suggest follow-up with repeat EGD or biopsy instead of ER in esophageal lesions smaller than 20mm.

Although LCE is considered the gold standard for ESPT detection by many, its application is subject to debate because of its side effects and prolonged procedure time.[12] In addition, the specificity of LCE is low, since non-dysplastic lesions can also be unstained.[13] An endoscopic screening study by Shao *et al*. found that 74% of the LVL showed no dysplasia on histopathological assessment.[17] Another endoscopic screening study in patients with HNSCC showed that 82% of the LVL were non dysplastic.[26] A high false positive detection rate is also reflected by our results: 46% of lesions that were suspicious on LCE were false positive, compared with 14% in NBI.

Although our endoscopists have extensive experience in assessing esophageal lesions, the relatively high number of false positive lesions detected by LCE might indicate that LVL were easily misinterpreted by the endoscopists. However, our study was not designed to calculate the accuracy rates of endoscopic detection techniques. As reported in a systematic review and meta-analysis by Morita *et al.,* NBI was superior to LCE in differentiating ESPTs from other esophageal mucosa alterations, but the sensitivity rates of these techniques to detect ESPTs were comparable.[30] LCE is helpful to highlight suspected lesions but endoscopist' experience is still key in the characterization and detection of suspected ESPT.[31]

Our study is subject to certain limitations. First, we included relatively few patients. This made it impossible to perform risk factor analysis. Second, a large number of patients were excluded and these patients could potentially have had a synchronous ESPT. This might lead to a chance of bias skewing the incidence of ESPTs. Third, several patients had an incurable HNSCC, which came to light after they had underwent endoscopic screening. Since these patients would not have benefitted from endoscopic screening it would have been better if screening was performed after workup for HNSCC was completed. If endoscopic screening is implemented in daily practice, patients with incurable HNSCC will most likely not be included. Fourth, patient burden was not taken into account. Screening EGD is an invasive examination for patients. Patient burden is an important parameter for the decision whether screening should be performed.

The major strength of our study is its prospective design. All eligible patients were asked to participate, which prevented selection bias. This design also ensured that we had no missing data. Another strength is that screening EGD was performed in a systematic manner with three different endoscopic techniques. This presumably lead to a high detection rate with only minimal missed lesions.

We believe that screening for synchronous ESPTs in patients with HNSCC is promising. Screening should be first considered in high-risk patients (e.g. HNSCC located in the oropharynx and hypopharynx, patients with alcohol abuse). The combination of WLE and NBI is probably the most sensitive method. Although LCE can be performed, extra awareness is indicated in case of lesions <20mm because of the high rate of false positive lesions.

However, more research is necessary before screening for ESPT can be implemented. More studies with a larger patient cohort are necessary, preferably in a multicenter setting. This would enable a solid risk factor analysis and identify a specific subgroup of HNSCC patients

who would benefit most from screening. Future studies should also take patient burden, survival benefit and cost-effectiveness of screening into account.

## REFERENCES


1. Priante AVM, Castilho EC, Kowalski LP. Second primary tumors in patients with head and neck cancer. Curr Oncol Rep 2011;13(2):132-137.
2. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 1953; 6: 963-968
3. Atienza JA, Dasanu CA. Incidence of second primary malignancies in patients with treated head and neck cancer: a comprehensive review of literature. Curr Med Res Opin 2012; 28: 1899-1909
4. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med 2003; 349: 2241-2252
5. Linden PA, Towe CW, Watson TJ et al. Mortality After Esophagectomy: Analysis of Individual Complications and Their Association with Mortality. J Gastrointest Surg 2020 Sep;24(9):1948-1954.
6. Chung CS, Lo WC, Chen KC et al. Clinical benefits from endoscopy screening of esophageal second primary tumor for head and neck cancer patients: Analysis of a hospital-based registry. Oral Oncol 2019; 96: 27-33
7. Bradley PJ, Bradley PT. Searching for metachronous tumours in patients with head and neck cancer: the ideal protocol! Curr Opin Otolaryngol Head Neck Surg 2010; 18: 124-133
8. Bugter O, van de Ven SEM, Hardillo JA et al. Early detection of esophageal second primary tumors using Lugol chromoendoscopy in patients with head and neck cancer: A systematic review and meta-analysis. Head Neck 2019; 41: 1122-1130
9. Su HA, Hsiao SW, Hsu YC et al. Superiority of NBI endoscopy to PET/CT scan in detecting esophageal cancer among head and neck cancer patients: a retrospective cohort analysis. BMC Cancer 2020; 20: 69
10. Mandard AM, Hainaut P, Hollstein M. Genetic steps in the development of squamous cell carcinoma of the esophagus. Mutat Res 2000; 462: 335-342
11. Wang GQ, Abnet CC, Shen Q et al. Histological precursors of oesophageal squamous cell carcinoma: results from a 13 year prospective follow up study in a high risk population. Gut 2005; 54: 187-192
12. Dubuc J, Legoux J, Winnock M et al. Endoscopic screening for esophageal squamous-cell carcinoma in high-risk patients: a prospective study conducted in 62 French endoscopy centers. Endoscopy 2006; 38: 690-695
13. Goda K, Dobashi A, Yoshimura N et al. Narrow-Band Imaging Magnifying Endoscopy versus Lugol Chromoendoscopy with Pink-Color Sign Assessment in the Diagnosis of Superficial Esophageal Squamous Neoplasms: A Randomised Noninferiority Trial. Gastroenterol Res Pract 2015; 2015: 639462
14. Yoshida T, Inoue H, Usui S et al. Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. Gastrointest Endosc 2004; 59: 288-295
15. Inoue H, Rey JF, Lightdale C. Lugol chromoendoscopy for esophageal squamous cell cancer. Endoscopy 2001; 33: 75-79
16. Mori M, Adachi Y, Matsushima T et al. Lugol staining pattern and histology of esophageal lesions. Am J Gastroenterol 1993; 88: 701-705
17. Shao Y, Yu ZL, Ji M et al. Lugol chromoendoscopic screening for esophageal dysplasia/early squamous cell carcinoma in patients with esophageal symptoms in low-risk region in China. Oncol Lett 2015; 10: 45-50
18. Wang CH, Lee YC, Wang CP et al. Use of transnasal endoscopy for screening of esophageal squamous cell carcinoma in high-risk patients: yield rate, completion rate, and safety. Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society 2014; 26: 24-31
19. National Institute on Alcohol Abuse and Alcoholism. Helping patients who drink too much: A clinician's guide. NIH Publication no 05-3769, Bethesda 2005.

20. Morris LG, Sikora AG, Patel SG et al. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. J Clin Oncol 2011; 29: 739-746
21. Schlemper RJ, Riddell RH, Kato Y et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000; 47: 251-255
22. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003; 58: S3-43
23. Bosman FT CF, Hruban RH et al. WHO classification of tumours of the digestive system. Lyon: International Agency for Research on Cancer 2010; 3. 4th edition
24. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2015; 47: 829-854
25. Li H, Borinskaya S, Yoshimura K et al. Refined geographic distribution of the oriental ALDH2*504Lys (nee 487Lys) variant. Ann Hum Genet 2009; 73: 335-345
26. Boller D, Spieler P, Schoenegg R et al. Lugol chromoendoscopy combined with brush cytology in patients at risk for esophageal squamous cell carcinoma. Surg Endosc 2009; 23: 2748-2754
27. Gong EJ, Kim DH, Ahn JY 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: 752-759
28. Wang WL, Lee CT, Lee YC et al. Risk factors for developing synchronous esophageal neoplasia in patients with head and neck cancer. Head Neck 2011; 33: 77-81
29. Fukuzawa K, Noguchi Y, Yoshikawa T et al. High incidence of synchronous cancer of the oral cavity and the upper gastrointestinal tract. Cancer Lett 1999; 144: 145-151
30. Morita FH, Bernardo WM, Ide E 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
31. van de Ven SEM, Koch AD. When is Lugol still necessary in 2020? Endosc Int Open 2020; 8: E1478-E1480

# SUPPLEMENTARY

**Supplementary file 1**

Histopathologic evaluation of resected specimens for:

- Tumor depth invasion [1]
- Tumor differentiation (classified as good [G1], moderate [G2], poor/undifferentiated [G3/G4]) [2]
- The presence of lymphovascular invasion [2]
- Involvement of resection margins (R1) [2]

*[1] according to the Paris classification [20]*
*[2] according to the World Health Organization for tumor grading [21]*

## Supplementary file 2

**Table S2. Patient and tumor characteristics of patients with suspected esophageal second primary tumor without proven dysplasia or neoplasia**

| Patient & HNSCC characteristics | | | | | | | Screening esophagogastroduodenoscopy | | | | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ID | Sex | Age | Alcohol (units/week) | HNSCC tumors | HNSCC sub-location | TN stage* | Number of lesions, visible with WLE / NBI / LCE | Location esophagus (cm) [1] | Morphology [2] + diameter lesion (mm) | Pathology | Treatment and follow-up |
| 9 | M | 65 | Yes (21) | 1 | Larynx | T3N0 | 1, LCE | 29 | 0-IIb (5) | EMR: no abnormalities | EMR + endoscopic surveillance after 1 year |
| 10 | F | 68 | No | 1 | Hypopharynx | T2N0 | 1, LCE | 22 | 0-IIb (8) | Biopsy: no abnormalities | Endoscopic surveillance after 1 year |
| 11 | M | 68 | Yes (21) | 1 | Oropharynx | T1N2a | 1, LCE | 30 | 0-IIb (6) | EMR 2 lesions: inflammation | EMR + endoscopic surveillance after 1 year |
| 12 | M | 60 | Yes (49) | 1 | Hypopharynx | T4aN2 | 1, WLE + NBI | 30 | 0-IIb (10) | EMR: no abnormalities | EMR + endoscopic surveillance after 1 year |
| 13 | M | 61 | No | 2 | Oropharynx + hypopharynx | T1N0 + T4aN0 | 2, LCE | 26 + 32 | 0-IIb (6 + 5) | Biopsy 2 lesions: inflammation | Endoscopic surveillance after 1 year |

*M stage was M0 for all patients; [1] from the incisors; [2] according to the Paris classification
EMR, endoscopic mucosal resection; F, Female; HNSCC, head and neck squamous cell carcinoma; LCE, Lugol chromoendoscopy; M, Male; NBI, narrow band imaging; TN, tumor node; WLE, white light high resolution endoscopy

# CHAPTER 6

## When is Lugol still necessary in 2020? Referring to Costa-Santos et al.

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Detection of early esophageal squamous cell carcinoma (ESCC) is very important, because these cancers can be treated with minimally invasive endoscopic resection instead of surgery. Early ESCC is characterized by subtle flat lesions, which are easily overlooked during routine white light endoscopy.[1] To improve ESCC detection, the addition of Lugol iodine was introduced.[2] Today, Lugol dye chromoendoscopy (LCE) is considered by many the gold standard for the detection of early ESCC.[3, 4]

Lugol iodine was first used in the esophagus to screen for ESCC in 1966.[2] In the esophagus, Lugol iodine binds to glycogen.[5] Glycogen is diminished or absent in dysplastic or neoplastic tissue and abundant in normal squamous epithelium.[5] As a result, areas with dysplasia or neoplasia have reduced or even absent iodine staining, whereas normal squamous epithelium is intensely stained by Lugol iodine.[5] Although these unstained areas, so-called lugol voiding lesions, make it more easy to detect dysplasia or neoplasia, non-dysplastic lesions such as inflammation can also appear unstained.[1] As a consequence, LCE is highly sensitive but not very specific in the detection of ESCC.[1]



In addition, several side effects of LCE have been described such as chest discomfort, heartburn, nausea, pulmonary aspiration, and allergic reaction.[6, 7] Another disadvantage for both the patient and endoscopist is the extended procedure time.[7] Different concentrations of iodine solution (1% to 3%) have been used in studies, and patient discomfort seems to depend on the iodine concentration used.[8, 9] A recent randomized controlled trial showed that the use of 1% iodine solution resulted in less heartburn and retrosternal pain compared to 2% iodine solution ($p=0.02$).[8] In both groups, the color of the stained esophageal images were similar.[8] LCE with 1% iodine solution, therefore, is recommended.[8]

Early ESCC can also be identified by narrow-band imaging (NBI) as brown, well-demarcated lesions.[6] This is a real-time optical chromoendoscopy technique that was first described in 2004.[10] It visualizes the mucosa and intraepithelial papillary capillary loop (IPCL) patterns.[11] Although NBI is easy to use by pressing a button on the endoscope, the device is expensive and expertise is required.[6] For example, for inexperienced endoscopists, it might be difficult to distinguish inflammation from dysplastic lesions using NBI.

Because endoscopic imaging techniques have drastically improved over time and Lugol has several side effects, the questions arises whether and when Lugol is still necessary. Before we completely abandon the use of Lugol based on current knowledge and the evidence presented by Costa-Santos *et al.*, we have to consider different phases in the endoscopic treatment of ESCC. There are three important phases that finally lead to endoscopic treatment. First, lesions have to be detected. A second important step is characterization and if deemed amendable for endoscopic resection, the final important step is delineation. All three steps can be done using either Lugol or NBI. The question arises whether NBI is superior to Lugol in all these three steps or there are distinct advantages for each technique in the separate steps.

1. Lesion detection

Several studies have compared accuracy of LCE with NBI in the detection of early ESCC. Wang *et al*. reported that the combination of NBI and LCE in detection of ESCC showed the highest sensitivity (94.7%), compared to LCE (93.0%) and NBI (84.2%) alone.[9] A recent systematic review and meta-analysis, including 12 studies, showed that the sensitivity of NBI

and LCE were comparable (88% vs. 92%) and the specificity was superior with NBI (88% vs. 82%, *p<0.001*).[12] However, all endoscopies were performed by expert endoscopists.[9, 12] Therefore, accuracy rates may be lower when performed by a general endoscopist.

2. Lesion characterization

Esophageal lesions suspected of being dysplastic or neoplastic are highlighted by LCE as Lugol voiding lesions. Lugol voiding lesions are present or not, but no further characterization of these lesions can be made besides gross morphology. As a consequence, it might be difficult to distinguish inflammation from dysplasia or neoplasia or deeper invasion outside criteria for endoscopic treatment. In contrast to LCE, IPCLs visible with NBI can further characterize esophageal lesions. For example, variety in IPCL shapes, tortuous IPCL, presence of a demarcation line, lesions with brownish dots or brownish epithelium all were associated with mucosal high-grade neoplasia according to Ishihara *et al*.[13] Based on the presence of brownish dots or brownish epithelium, the sensitivity for detecting neoplasia was 100%.[13]

3. Lesion delineation

In the current issue of this journal, Costa-Santos *et al*. compared the effectiveness of NBI and LCE in defining lateral resection margins before endoscopic resection of ESCC and dysplasia.[14] Studies on this important step in endoscopic treatment have not been previously reported. In their study two groups of patients with ESCC or dysplasia who underwent en-bloc resection were defined: (1) inspection with NBI only; and (2) inspection with LCE (with or without NBI). Of 132 included lesions, 68 (52%) were inspected with LCE and 64 (48%) with NBI only. The complete lateral resection rate for invasive carcinoma did not differ between the two groups; the resection rate was 90% in the LCE group and 94% in the NBI group (*p=0.715*). Also, the lateral resection rate for dysplasia did not differ between the LCE (65%) and NBI (67%) groups (*p=0.813)*. Costa-Santos *et al*. concluded that mucosal inspection with LCE before endoscopic resection of ESCC and dysplasia was not associated with an increased complete lateral resection rate compared to inspection with NBI alone.[14]

The results of this study are very interesting and add to our knowledge about minimal invasive endoscopic treatment of early cancer. This study supports use of NBI for delineation but it does not show superiority of NBI versus Lugol. NBI was used in a recent cohort in which modern endoscopes were used, in contrast to the historical LCE cohort in which older endoscopes were used. NBI was combined with a white light imaging technique that has dramatically improved over the years, with improved magnification and image resolution. Results with the combination cannot be separated form use of NBI “alone”. In contrast, older endoscopes used in the LCE cohort did not display these superior features. Therefore, the technology in these two different cohorts with different endoscopes might have influenced the results of Costa-Santos *et al*. A fair comparison would be using both techniques with the same superior endoscopes. In addition, the authors did not clearly report on how many lesions in the LCE group were also inspected with NBI. Inspection with NBI before Lugol iodine staining may influence on the definition of lateral resection margins before endoscopic resection.

For both NBI and LCE, adequate expertise and experience on the part of the endoscopist is key in the detection, characterization, and delineation of esophageal lesions. Although NBI seems superior in terms of specificity and characterization of lesions, detection of lesions

depends on the experience of the endoscopist. Recognition of specific IPCL patterns is crucial in NBI, while detection of Lugol voiding lesion by LCE might be easier for an endoscopist with less experience. Future developments might very well include artificial intelligence. Computer algorithms can 'red flag' or even characterize suspicious areas. They are already part of video capsule endoscopy and their use is increasing in colonoscopy screening.[15, 16] In all likelihood, computer algorithms will make use of these superior imaging techniques and the role of Lugol will be pushed more to the background. Until that new era arrives, Lugol can still be very useful "red flag" in detection of early squamous neoplasia.

## REFERENCES


1. Goda K, Dobashi A, Yoshimura N et al. Narrow-Band Imaging Magnifying Endoscopy versus Lugol Chromoendoscopy with Pink-Color Sign Assessment in the Diagnosis of Superficial Esophageal Squamous Neoplasms: A Randomised Noninferiority Trial. Gastroenterol Res Pract 2015; 2015: 639462
2. Voegeli R. Schiller's iodine test in the diagnosis of esophageal diseases. Preliminary report. Pract Otorhinolaryngol (Basel) 1966; 28: 230-239
3. Bugter O, van de Ven SEM, Hardillo JA et al. Early detection of esophageal second primary tumors using Lugol chromoendoscopy in patients with head and neck cancer: A systematic review and meta-analysis. Head Neck 2019; 41: 1122-1130
4. Inoue H, Rey JF, Lightdale C. Lugol chromoendoscopy for esophageal squamous cell cancer. Endoscopy 2001; 33: 75-79
5. Mori M, Adachi Y, Matsushima T et al. Lugol staining pattern and histology of esophageal lesions. Am J Gastroenterol 1993; 88: 701-705
6. Lopes AB, Fagundes RB. Esophageal squamous cell carcinoma - precursor lesions and early diagnosis. World J Gastrointest Endosc 2012; 4: 9-16
7. Dubuc. Endoscopic screening for esophageal squamous-cell carcinoma in high-risk patients: a prospective study conducted in 62 french endoscopy centers. Endoscopy 2006
8. Gotoda T, Kanzaki H, Okamoto Y et al. Tolerability and efficacy of the concentration of iodine solution during esophageal chromoendoscopy: a double-blind randomized controlled trial. Gastrointest Endosc 2020; 91: 763-770
9. Wang CH, Lee YC, Wang CP et al. Use of transnasal endoscopy for screening of esophageal squamous cell carcinoma in high-risk patients: yield rate, completion rate, and safety. Digest Endosc 2014; 26: 24–31
10. Gono K, Obi T, Yamaguchi M et al. Appearance of enhanced tissue features in narrow-band endoscopic imaging. J Biomed Opt 2004; 9: 568-577
11. Yoshida T, Inoue H, Usui S et al. Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. Gastrointest Endosc 2004; 59: 288-295
12. Morita FH, Bernardo WM, Ide E 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
13. Ishihara R, Inoue T, Uedo N et al. Significance of each narrow-band imaging finding in diagnosing squamous mucosal high-grade neoplasia of the esophagus. J Gastroenterol Hepatol 2010; 25: 1410-1415
14. Costa-Santos MP, Ferreira AO, Mouradides C, et al. Is Lugol necessary for endoscopic resection of esophageal squamous cell neoplasia? Endosc Int Open. 2020; 8: E1471-E7.
15. Ahmad OF, Soares AS, Mazomenos E et al. Artificial intelligence and computer-aided diagnosis in colonoscopy: current evidence and future directions. Lancet Gastroenterol Hepatol 2019; 4: 71-80
16. Ding Z, Shi H, Zhang H et al. Gastroenterologist-Level Identification of Small-Bowel Diseases and Normal Variants by Capsule Endoscopy Using a Deep-Learning Model. Gastroenterology 2019; 157: 1044-1054 e1045

# PART III

## Endoscopic diagnosis and treatment of early esophageal cancer

# CHAPTER 7

## Favorable effect of endoscopic reassessment of clinically staged T2 esophageal adenocarcinoma: a multicenter prospective cohort study

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## ABSTRACT

**Background:** Clinical tumor stage of esophageal adenocarcinoma (EAC) is determined by endoscopic ultrasound and/or computed tomography scan, which have low accuracy for stages T1 and T2, potentially leading to overtreatment. We aimed to assess the proportion of cT2 EACs downstaged to cT1 after endoscopic reassessment (ERA) by an experienced interventional endoscopist.

**Methods:** We performed a prospective multicenter cohort study. Patients with cT2N0M0 EAC were included and underwent ERA. The primary outcome was proportion of cT2 EACs downstaged to cT1 after ERA.

**Results**: 15/25 included patients (60%) were downstaged from cT2 to cT1 EAC after ERA and underwent attempted endoscopic resection. Endoscopic resection was aborted in 3/15 patients because of tumor invasion into the muscle layer; all three underwent successful surgical resection. Endoscopic resection was successful in 12/15 patients (80%), all of whom had pT1 tumors. Overall, 10/25 (40%) were treated with endoscopic resection alone.

**Conclusion:** ERA downstaged about half of the cT2 tumors to cT1, rendering them suitable for endoscopic resection. ERA had substantial clinical impact on therapeutic management, preventing overtreatment in 40% of patients.

## INTRODUCTION

Patients with early stage (T1) esophageal adenocarcinoma (EAC) in the absence of poor prognostic criteria, have a good prognosis and can be treated with minimally invasive endoscopic resection.[1] Additional surgery is recommended when poor histological characteristics are present, such as those associated with increased risk of lymph node metastasis (LNM).[2]

Endoscopic ultrasound (EUS) is often used for clinical tumor staging because it is superior to computed tomography (CT) and positron emission tomography (PET).[3] Although EUS is accurate in staging T3 and T4 EAC, it is less accurate in differentiating between T2 and T1 EAC (sensitivity 43%–55%, specificity 80%–85%).[4, 5] This results in a substantial number of patients with pT1 stage who are overstaged as cT2 EAC. As a result, these patients unnecessarily undergo neoadjuvant chemoradiotherapy (nCRT) and surgery, which are associated with increased risks and morbidity.[6-8] Treatment strategies for cT2N0M0 (clinical Tumor-Node-Metastasis stage) EAC are therefore subject to debate, and accurate tumor staging is crucial.[6, 9]



It has been observed that endoscopic tumor staging, based on macroscopic tumor characteristics, is superior to tumor staging by EUS in cT2 EAC.[6, 10] Besides endoscopic staging, the endoscopist can also assess whether endoscopic resection is possible.[6] Ideally, this assessment should be performed by an endoscopist with experience in assessing the endoscopic resectability of tumors.[6, 10] The aim of this study was to assess the proportion of cT2 EACs downstaged to cT1 after endoscopic reassessment (ERA) by an experienced interventional endoscopist.

## METHODS

We conducted a multicenter, prospective observational cohort study in five hospitals specializing in endoscopic resection of early EAC (two academic, three nonacademic). The study was approved by the Medical Ethical Review Committee of the Erasmus Medical Centre in Rotterdam (MEC-2018–1061). All consecutive patients with cT2N0M0 EAC between April 2018 and April 2020 were asked to participate and informed consent was obtained. EAC diagnosis was established by routine clinical work-up, consisting of a standard endoscopy with EUS, CT scan, and/or PET scan. EUS was performed by an experienced endosonographer in the referral or expert center with high-resolution endosonography. EUS-guided fine-needle aspiration was performed in cases of suspected LNM. All staging examinations were systematically reviewed at multidisciplinary tumor board meetings by an expert gastrointestinal (GI) radiologist. If EAC staging had been performed at the referring center, cross-sectional imaging was reassessed by a GI radiologist in the expert center. Exclusion criteria were presence of metastasis, cytology-proven LNM, and esophageal stenosis.

### Endoscopic reassessment and endoscopic resection

All included patients underwent ERA using the latest series endoscopes, with white-light high-resolution endoscopy and narrow-band imaging, to determine clinical tumor stage. ERA for invasive features was performed by endoscopists with experience in endoscopic resection of

early EAC. Most endoscopists merely detect lesions and define upper and lower limits, whereas an endoscopist who actually carries out endoscopic resection looks for the precise borders and assesses the lesion for subtle signs of deep invasion that makes a lesion amenable to endoscopic resection or not. Invasive features included presence of a stricture, deep ulceration, nonprotruding depressed or excavated lesions, and a tumor that was not moving freely with peristalsis. If these features were absent, the tumor was staged cT1 and endoscopic resection was attempted. The type of resection technique was left to the discretion of the endoscopist. Endoscopic submucosal dissection (ESD) was recommended over endoscopic mucosal resection (EMR) for EACs >15mm, if the tumor was depressed, or when submucosal infiltration was suspected.[11]

**Histological evaluation**

All resection specimens were reviewed by a GI pathologist for tumor differentiation, presence of lymphovascular invasion, tumor depth infiltration (mucosal tumors m1–3; submucosal tumors sm1 [≤500 μm] and sm2/3 [>500 μm]), and tumor involvement of vertical resection margins (R0/R1).[12] All resection specimens were assessed for whether they fulfilled the criteria for a curative resection.[13] If endoscopic resection was outside curative criteria, additional treatment was discussed in a multidisciplinary tumor board meeting. When EAC tumor stage was estimated as cT2 after ERA, patients underwent subsequent nCRT followed by esophagectomy.[8] In these patients, tumor stage after nCRT based on residual disease (ypTN), and pre-treatment pathological tumor stage (prepTstage) and N-stage (prepN-stage) were assessed in surgical resection specimens.[14]

**Follow-up**

Patients were followed according to the European Society of Gastrointestinal Endoscopy guidelines if endoscopic resection had been performed [11], and according to the National Comprehensive Cancer Network guidelines if esophagectomy had been performed.[15] In general, this consisted of upper endoscopy every 3–6 months and then annually for curative endoscopic resection.[11] Follow-up was indicated every 3 months in the first year after esophagectomy.[15]

**Study end points**

The primary end point was the proportion of cT2 EACs downstaged to cT1 after ERA. Secondary end points were: 1) proportion of tumors that were successfully treated with endoscopic resection after ERA; 2) proportion of resected pT1 EACs that were within the accepted criteria for a curative endoscopic resection; 3) prepT-stage, prepN-stage, and ypTN-stage in patients treated with nCRT and esophagectomy, and final pathology TN-stage (pTN) in patients treated with esophagectomy only; and 4) sensitivity and specificity of the presence of invasive features during ERA in differentiating T1 from T2 EAC.

**Statistical analysis**

Baseline characteristics were presented using descriptive statistics. The 95% confidence intervals (CIs) were calculated for proportions, sensitivity, and specificity, and performed with the epiR package in R, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org). For sensitivity and specificity analyses, patients were only included when final pathologic tumor stage was known. Follow-up data were retrieved until October

2020. Analyses were carried out using IBM SPSS Statistics version 25 (IBM Corp., Armonk, New York, USA).

## RESULTS

### Baseline and tumor characteristics

A total of 25 patients with cT2N0M0 EAC were included; no patients were excluded. Baseline and tumor characteristics are presented in Table 1. Tumor stage was determined by EUS in 24/25 patients and by CT scan in 1/25 patients. The median follow-up time was 16.4 months (interquartile range [IQR] 11.0–23.5).

### Endoscopic reassessment

Information about ERA, subsequent management, and tumor stage is presented in Figure 1 and Table 2. The median time between cT2 EAC diagnosis and ERA was 26 days (IQR 0–35). ERA resulted in downstaging from cT2 to cT1 EAC in 15/25 patients (60%, 95%CI 39%–79%), who all underwent attempted endoscopic resection. The median time between ERA and endoscopic resection was 26 days (IQR 15–32). Successful endoscopic resection was performed in 12/15 patients (80%), all of whom had pT1 tumors. Five of these 12 patients (Table 2, patients 1–5) were within the accepted criteria for curative endoscopic resection, 5 patients (Table 2, patients 8–12) preferred a wait-and-see strategy, and 2 patients (Table 2, patients 6 and 7) received adjuvant treatment. ESD was aborted in 3/15 patients because of tumor invasion into the muscle layer (Table 2, patients 13–15). Figure 2 shows an example of a cT2 EAC that was downstaged to cT1 during ERA. In the remaining 10/25 patients (40%, 95% CI 21%–61%), ERA confirmed cT2 tumor stage based on the presence of invasive features (Table 2, patients 16–25). Seven of the 10 patients were treated with nCRT followed by surgery, without proven LNM in surgical resection specimens. Of the remaining three patients, one was treated with chemoradiotherapy followed by active surveillance within a research protocol, one received radiotherapy alone owing to poor condition, and the remaining patient renounced further treatment. Figure 3 shows a cT2 EAC that was confirmed as cT2 during ERA. Overall, 15/25 (60%, 95% CI 39%–79%) cT2 EACs turned out to be histologically proven pT1 or prepT1 EAC. A total of 12 of these 15 cT2 EACs were downstaged to cT1 EAC and therapeutic management changed for all 12 patients. Ten of 25 patients (40%, 95% CI 21%–61%) were treated with endoscopic resection only. In 13/25 patients (52%, 95% CI 31%–72%), the interventional endoscopist assessed EAC tumor stage as at least T2 during reassessment endoscopy (n=10) or attempted ESD (n=3). Ten of these 13 patients were treated with nCRT and surgery. PrepT-stage was at least T2 in 7/10 patients (70%).

**Table 1. Baseline and tumor characteristics**

| Parameter | Total cohort (n = 25) |
|---|---|
| **Patient characteristics** | |
| Sex, n (%) | |
| Male | 22 (88) |
| Female | 3 (12) |
| Age at diagnosis, median (IQR), years | 69 (57–74) |
| BMI, median (IQR), kg/m$^2$ | 29 (25–31) |
| ASA classification, n (%) | |
| I | 4 (16) |
| II | 14 (56) |
| III | 7 (28) |
| **Endoscopic tumor characteristics** | |
| Barrett's present, n (%) | 23 (92) |
| Tumor location, n (%) | |
| Lower limit of the esophagus | 23 (92) |
| Gastroesophageal junction | 2 (8) |
| Tumor diameter, median (IQR), mm | 30 (20–45) |
| **Morphology[1]** | |
| 0-I (protruded pedunculated) | 2 (8) |
| 0-Is (protruded sessile) | 6 (24) |
| 0-IIa (slightly elevated) | 2 (8) |
| 0-IIc (slightly depressed) | 1 (4) |
| 0-Is-IIa | 6 (24) |
| 0-Is-III | 1 (4) |
| 0-Is+IIa+IIc | 3 (12) |
| Not reported | 4 (16) |
| **Tumor differentiation grade (biopsy)** | |
| G1/2 | 10 (40) |
| G2/3 | 3 (12) |
| G3 | 1 (4) |
| Not reported in pathology report | 11 (44) |

[1]According to the Paris classification.[12]
IQR, interquartile range; BMI, body mass index; ASA, American Society of Anesthesiologists.

**Table 2. Tumor characteristics, treatment, and outcome of all included patients with cT2N0M0 esophageal adenocarcinoma**

| ID | Reason first diagnostic endoscopy | Invasive endoscopic features | ERA | Management after ERA | Pathologic tumor stage | Subsequent management and outcome (total follow-up period in months) |
|---|---|---|---|---|---|---|
| 1 | Barrett's surveillance | Not present | cT1 | ESD | T1a (M3,G2,LVI-,R0) | Curative ER → follow-up; no recurrence (16.4) |
| 2 | Barrett's surveillance | Not present | cT1 | EMR | T1a (M3,G2,LVI-,R0) | Curative ER → follow-up: synchronous EAC (pT1m1G1LVI-R0) treated with EMR (27.9) |
| 3 | Barrett's surveillance | Not present | cT1 | EMR | T1a (M2,G1,LVI-,R0) | Curative ER → follow-up: no recurrence (18.7) |
| 4 | Barrett's surveillance | Not present | cT1 | ESD | T1a (M3,G2,LVI-,R0) | Curative ER → follow-up: no recurrence (15.2) |
| 5 | Barrett's surveillance | Not present | cT1 | EMR | T1a (M2,G1,LVI-,R0) | Curative ER → follow-up: no recurrence (17.0) |
| 6 | Barrett's surveillance | Not present | cT1 | ESD | T1b (Sm2/3,G3,LVI+,R1) | dCRT → follow-up: no recurrence (10.9) |
| 7 | Barrett's surveillance | Not present | cT1 | EMR | T1b (Sm2/3,G2,LVI-,R1) | Esophagectomy (pT1aN0)[1] → follow-up: no recurrence (25.5) |
| 8 | Weight loss + fatigue | Not present | cT1 | EMR | T1b (Sm2/3,G3,LVI+,R0) | Endoscopic surveillance + EUS: no recurrence (26.0) |
| 9 | Barrett's surveillance | Not present | cT1 | ESD | T1b (Sm2/3,G1,LVI-,R0) | Endoscopic surveillance + EUS: no recurrence (18.5) |
| 10 | Accidental finding in the esophagus on PET-CT | Not present | cT1 | ESD | T1a (M3,G3,LVI-,R1) | Endoscopic surveillance + EUS: no recurrence (11.0) |
| 11 | Barrett's surveillance | Not present | cT1 | ESD | T1b (Sm2/3,G3,LVI+,R0)[2] | Palliative treatment due to the presence of metastases (bone and liver) after ESD: deceased due to metastases (5.6)[3] |
| 12 | Barrett's surveillance | Not present | cT1 | ESD | T1b (Sm2/3,G2,LVI+,R1) | Endoscopic surveillance + EUS: recurrence after 8.3 months → cT2N0M0 treated with CRT (13.1)[4] |

| | | | | | | |
|---|---|---|---|---|---|---|
| 13 | Vitamin B12 deficiency | Traction of the lesion to one point<br>Central ulcer in the tumor | cT1[5] | ESD aborted: tumor growth in muscle layer | ypT2N0 / prepT2N0 | nCRT + esophagectomy: no recurrence (25.8) |
| 14 | Barrett's surveillance | Traction of the lesion to one point | cT1[5] | ESD aborted: tumor growth in muscle layer | ypT3N3 / prepT3N3 | nCRT + esophagectomy: deceased due to peritoneal metastasis (14.0) |
| 15 | Barrett's surveillance | Not present | cT1 | ESD aborted: tumor growth in muscle layer | ypT0N0 / prepT2N1 | nCRT + by esophagectomy: no recurrence (29.0) |
| 16 | Melena | Fixed lesion<br>Not moving freely with peristalsis | cT2 | Radiotherapy | No pathology | Follow-up: deceased due to peritoneal metastasis (9.2) |
| 17 | Regurgitation and eructation | Circumference of the tumor: 100%<br>Tumor growth in the stomach | cT2 | nCRT + esophagectomy | ypT1bN0 / prepT1bN0 | Follow-up: deceased due to bone metastasis (14.5) |
| 18 | Dysphagia | Stenosis<br>Depressed center of the tumor<br>Not moving freely with peristalsis | cT2 | nCRT + esophagectomy | ypT2N0 / prepT3N0 | Follow-up: no recurrence (24.5) |
| 19 | Dysphagia | Stenosis<br>Ulcer | cT2 | nCRT + esophagectomy | ypT1aN0 / prepT2N0 | Follow-up: no recurrence (17.0) |
| 20 | Dysphagia | Stenosis<br>Not moving freely with peristalsis<br>Traction of the lesion to one point | cT2 | No treatment (patient preference) | No pathology | No follow-up (patient preference) (3.8) |
| 21 | Dysphagia | Stenosis<br>Ulcer | cT2 | nCRT + esophagectomy | ypT1bN0 / prepT1bN0 | Follow-up: lung metastasis after 22.6 months → palliative chemotherapy (22.6) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 22 | Anemia | Depressed lesion<br>Not moving freely with peristalsis<br>Ulcer | cT2 | nCRT + esophagectomy | ypT2N0 / prepT2N0 | Follow-up: no recurrence (17.7) |
| 23 | Barrett's surveillance | Depressed center of the tumor<br>Not moving freely with peristalsis | cT2 | nCRT + esophagectomy | ypT1bN0 / prepT1bN0 | Follow-up: no recurrence (15.0) |
| 24 | Dysphagia | Fixed lesion<br>Depressed center of the tumor | cT2 | CRT + active surveillance | No pathology | Follow-up: no recurrence (8.9) |
| 25 | Dysphagia | Stenosis<br>Depressed ulcer<br>Circumference of the tumor: 100% | cT2 | nCRT + esophagectomy | ypT3N0 / prepT3N3 | Follow-up: no recurrence (10.3) |

ERA, endoscopic reassessment; ESD, endoscopic submucosal dissection; LVI, lymphovascular invasion; ER, endoscopic resection; EMR, endoscopic mucosal resection; EAC, esophageal adenocarcinoma; EUS, endoscopic ultrasound; PET-CT, positron emission tomography-computed tomography; CRT, chemoradiotherapy; dCRT, definitive chemoradiotherapy; nCRT, neoadjuvant chemoradiotherapy.

[1] Lesion in esophagectomy specimen was probably a synchronous mucosal EAC, [2] Mixed adeno-neuroendocrine carcinoma confirmed after ESD, [3] First CT-scan did not show metastasis, [4] Active surveillance chosen based on patient preference, [5] Lesion moved freely with peristalsis, therefore EAC was assessed as cT1.

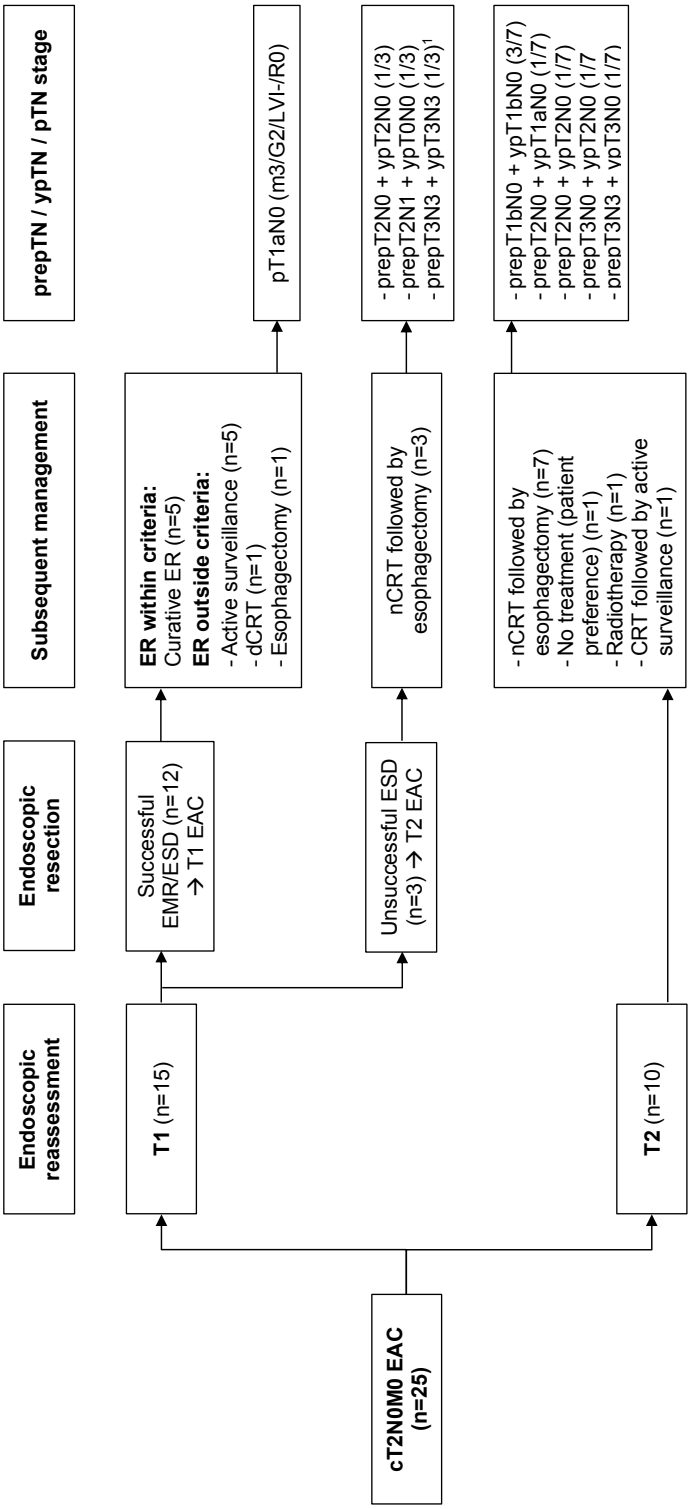


**Figure 1. Endoscopic reassessment and subsequent management**

EAC, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; ER, endoscopic resection; nCRT, neoadjuvant chemoradiotherapy; dCRT, definitive chemoradiotherapy; CRT, chemoradiotherapy. [1]15/29 resected lymph nodes were positive.

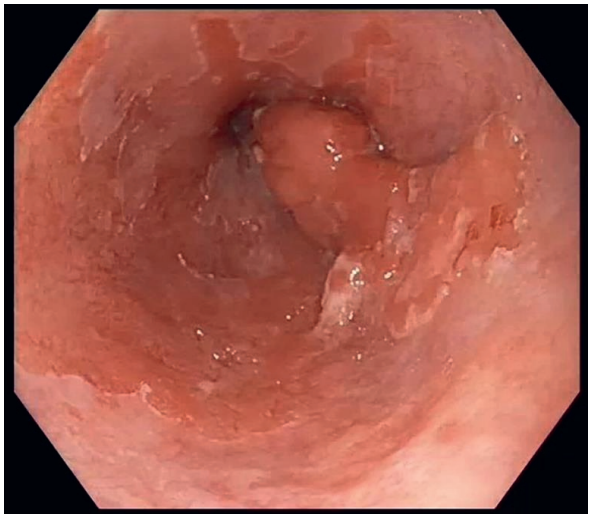

**Figure 2.** cT2N0M0 esophageal adenocarcinoma that was assessed as T1 during endoscopic reassessment and later successfully removed by endoscopic submucosal dissection. Pathology: pT1m3G2LVI-R0.



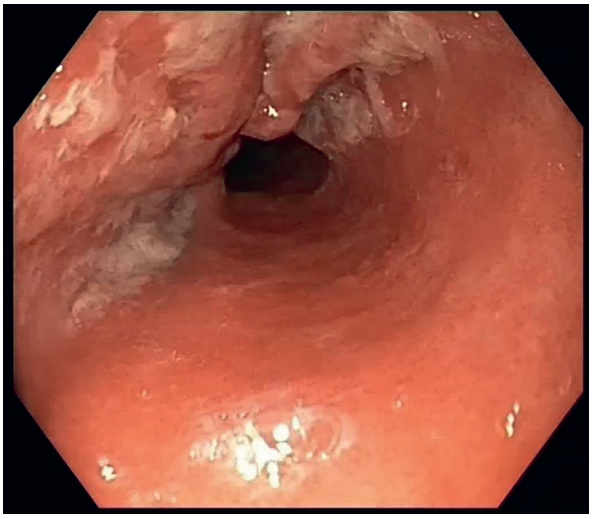

**Figure 3.** cT2N0M0 esophageal adenocarcinoma assessed as T2 during endoscopic reassessment. The tumor had a depressed center and did not move freely with the peristalsis. Pathology after neoadjuvant chemoradiotherapy and surgery: ypT2N0 (prepT3N0).

**Sensitivity and specificity of invasive features during ERA**

At least one invasive feature was present during ERA in 12/25 patients (Table 2). In 2/12 patients (Table 2, patients 13 and 14), the lesion moved freely with peristalsis and therefore the benefit of the doubt was given and these lesions were classified as cT1 EAC. The sensitivity of the presence of invasive features during endoscopy in detecting T2 EAC was 86% (95% CI 42%–100%) and the specificity was 80% (95% CI 52%–96%) (Table 3).

**Table 3. Presence and absence of invasive features during endoscopy and final pathologic tumor stage of esophageal adenocarcinoma**

| | ≥T2 EAC | T1 EAC | Total[1] |
|---|---|---|---|
| Invasive features present | 6 | 3 | 9 |
| Invasive features absent | 1[2] | 12 | 13 |
| Total | 7 | 15 | 22 |

EAC, esophageal adenocarcinoma; CI, confidence interval.

Diagnostic characteristics of the presence of invasive features in detecting T2 EAC: sensitivity 86% (95% CI 42–100), specificity 80% (95% CI 52–96), positive predictive value 67% (95% CI 30–93), and negative predictive value 92% (95% CI 64–100).

[1] Calculated for 22 patients; 3 patients were excluded from the analysis because no final pathologic tumor stage was known, [2] Corresponds with patient # 15 in Table 2.

## DISCUSSION

The results of our study showed that in patients with a cT2N0M0 EAC, ERA by an experienced interventional endoscopist downstaged about half of the cases to a cT1 EAC that was suitable for endoscopic resection. ERA prevented unnecessary adjuvant treatment in 40% of patients and therefore had a substantial clinical impact on the management of cT2 EAC. The presence of invasive tumor features during ERA for the detection of T2 EAC had a sensitivity of 86% (95 %CI 42%–100%) and a specificity of 80% (95%CI 52%–96%). We would suggest standardizing endoscopy reports for these invasive features. We advocate that all cT2-staged EACs should be considered for ERA by an endoscopist with experience in endoscopic resection of early EAC.

Retrospective studies have shown that up to 63% of pT1 EACs are overstaged as cT2 by EUS.[4–6, 9, 16] Tumor downstaging by ERA may avoid the substantial risk of treatment-related morbidity and mortality of esophagectomy, with or without nCRT, in patients with cT2N0M0 EAC, while maintaining equal curative outcomes when endoscopic resection is performed.[7, 17]

In accordance with this study, previous studies have demonstrated that a substantial number of cT2 EACs can be treated with endoscopic resection and are in fact pT1 EACs.[6, 18] Nelson *et al.* investigated whether patients with cT2N0 EAC benefit from attempted EMR to identify overstaged patients.[18] EMR effectively eradicated pT1 EAC in 56.7%.[18] However, only small tumors (< 2 cm) with mild fluorodeoxyglucose avidity were included in the study [18], and this may have resulted in an overestimation of the number of overstaged cT2 EACs. The median tumor size in our study was 30mm and ESD was performed in more than half of patients

treated with endoscopic resection. One might hypothesize that more cT2 EACs could be classified as pT1 EAC when ESD is performed. Our results reflect those of Gotink et al. who found that 85% of cT2N0 EACs were downstaged to cT1 EACs after ERA.[6] Although this percentage is higher than in our study, there was a selection bias in the former study; only patients with cT2 EAC that were considered "promising" underwent ERA.[6] This may have resulted in an overestimation of the number of downstaged cT2 EACs.

It could be argued that ERA should be the first step in determining clinical EAC tumor stage rather than EUS, especially when low EAC tumor stage is expected. May et al. compared the sensitivity and accuracy of endoscopic tumor staging by an experienced interventional endoscopist with tumor staging performed by EUS for early esophageal cancer.[10] Although not statistically significant, the sensitivity and accuracy of endoscopic tumor staging (82.9% and 83.4%) were slightly superior to those of EUS (79.8% and 79.6%).[10]

To our knowledge, this is the first prospective, multicenter, cohort study of ERA for cT2 EAC, which is a major strength of our study. Furthermore, there was no selection bias because no patients were excluded based on tumor characteristics. A major limitation of the present study is the small sample size, with only 25 patients included over 2 years. On the one hand, this might be explained by the relative low prevalence of cT2 EAC.[6] On the other hand, we may have only included the tip of the iceberg because many patients with cT2 EAC do not undergo ERA. The participating centers were all expert centers that usually treat patients who have been referred by other hospitals. Most endoscopists in nonexpert centers are not trained to assess whether cT2 EAC is suitable for endoscopic resection.[10] As a consequence, these patients are not referred to an expert center for an attempt at endoscopic resection. Although one could argue that the small sample size will limit the generalizability of our results, our results confirmed the low accuracy of EUS in staging early EAC and showed that ERA downstaged 60% of cT2 EACs, of which 80% were pT1 EACs.

We recommend ERA by an experienced interventional endoscopist for all cT2N0M0-staged EAC patients. ERA had a substantial clinical impact on therapeutic management, downstaging about half of the cases to T1 EAC in the current study. Although ERA prevented invasive adjuvant treatment in 40% of patients, the curative resection rate of downstaged tumors was 33%.

## REFERENCES


1. Bahin FF, Jayanna M, Hourigan LF et al. Long-term outcomes of a primary complete endoscopic resection strategy for short-segment Barrett's esophagus with high-grade dysplasia and/or early esophageal adenocarcinoma. Gastrointest Endosc 2016; 83: 68–77
2. Fitzgerald RC, di Pietro M, Ragunath K et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut 2014; 63: 7–42
3. Choi J, Kim SG, Kim JS et al. Comparison of endoscopic ultrasonography (EUS), positron emission tomography (PET), and computed tomography (CT) in the preoperative locoregional staging of resectable esophageal cancer. Surg Endosc 2010; 24: 1380–1386
4. O'Farrell NJ, Malik V, Donohoe CL et al. Appraisal of staging endoscopic ultrasonography in a modern high-volume esophageal program. World J Surg 2013; 37: 1666–1672
5. Pech O, Gunter E, Dusemund F et al. Accuracy of endoscopic ultrasound in preoperative staging of esophageal cancer: results from a referral center for early esophageal cancer. Endoscopy 2010; 42: 456–461
6. Gotink AW, Spaander MCW, Doukas M et al. Exploring diagnostic and therapeutic implications of endoscopic mucosal resection in EUS-staged T2 esophageal adenocarcinoma. Endoscopy 2017; 49: 941–948
7. Hamai Y, Hihara J, Taomoto J et al. Effects of neoadjuvant chemoradiotherapy on postoperative morbidity and mortality associated with esophageal cancer. Dis Esophagus 2015; 28: 358–364
8. van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012; 366: 2074–2084
9. Crabtree TD, Kosinski AS, Puri V et al. Evaluation of the reliability of clinical staging of T2 N0 esophageal cancer: a review of the Society of Thoracic Surgeons database. Ann Thorac Surg 2013; 96: 382–390
10. May A, Gunter E, Roth F et al. Accuracy of staging in early oesophageal cancer using high resolution endoscopy and high resolution endosonography: a comparative, prospective, and blinded trial. Gut 2004; 53: 634–640
11. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2015; 47: 829–854
12. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003; 58 Suppl: S3–43
13. Shaheen NJ, Falk GW, Iyer PG et al. ACG Clinical Guideline: Diagnosis and management of Barrett's esophagus. Am J Gastroenterol 2016; 111: 30–50
14. Brinkmann S, Noordman BJ, Holscher AH et al. External validation of pretreatment pathological tumor extent in patients with neoadjuvant chemoradiotherapy plus surgery for esophageal cancer. Ann Surg Oncol 2020; 27: 1250–1258
15. Ajani JA, D'Amico TA, Bentrem DJ et al. Esophageal and esophagogastric junction cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019; 17: 855–883
16. Rice TW, Mason DP, Murthy SC et al. T2N0M0 esophageal cancer. J Thorac Cardiovasc Surg 2007; 133: 317–324
17. Moss A, Bourke MJ, Hourigan LF et al. Endoscopic resection for Barrett's high-grade dysplasia and early esophageal adenocarcinoma: an essential staging procedure with long-term therapeutic benefit. Am J Gastroenterol 2010; 105: 1276–1283
18. Nelson DB, Mitchell KG, Weston BR et al. Should endoscopic mucosal resection be attempted for cT2N0 esophageal cancer? Dis Esophagus 2019; 32: 1–6

# CHAPTER 8

## Propofol sedation without endotracheal intubation is safe for endoscopic submucosal dissection in the esophagus and stomach

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## ABSTRACT

**Background:** Endoscopic submucosal dissection (ESD) for early esophageal and stomach cancer is usually performed under general anesthesia. However, propofol sedation without endotracheal intubation has been suggested as a viable alternative. The objective of this study was to evaluate the safety of propofol sedation without endotracheal intubation during ESD in the upper gastrointestinal tract.

**Methods:** We performed a retrospective cohort study of patients who underwent ESD for upper gastrointestinal tumors with propofol-remifentanil analgosedation in a tertiary referral center in the Netherlands between October 2013 and February 2018. Primary endpoints were the rates of intraprocedural endoscopy- and anesthesia-related complications. Secondary endpoints were the postprocedural complication rates within 30 days and endotracheal intubation conversion rates.

**Results:** Of 88 patients, intra-procedural ESD-related complications occurred in three patients (3.4%). Intra-procedural anesthesia-related complications occurred in two patients (2.3%), one of whom required conversion to endotracheal intubation. Post-procedural ESD-related complications occurred in 14 patients (15.9%), and minor postprocedural complications occurred in two patients (2.3%). Eighty-two (93.2%) patients were discharged within one day after ESD. No patient was readmitted for anesthesia-related complications.

**Conclusion:** Propofol-based sedation without endotracheal intubation is safe for ESD procedures in the esophagus and stomach with low anesthesia-related complication rates and short hospital stay.

## INTRODUCTION

Endoscopic submucosal dissection (ESD) is a widely used endoscopic resection method for early gastric and esophageal neoplasms that cannot be removed by endoscopic mucosal resection (EMR) or when submucosal invasion is suspected.[1, 2] ESD enables en bloc resection of the lesion and has a higher curative resection rate than EMR.[3-5] However, ESD is difficult and time-consuming and can result in pain and discomfort for the patient during the procedure.[3, 6] Minimal patient movement is preferred, as ESD involves complex and precise maneuvers.[7] Therefore, appropriate sedation and analgesia are required to limit complications, such as bleeding or perforation.[7-9]

Several types of (analgo) sedation have been used during ESD, ranging from conscious sedation using midazolam or propofol to general anesthesia.[10-12] The advantages of propofol over midazolam as a sedative agent are clearly established: fewer movements of the patient during ESD and faster recovery after the procedure because of the short half-life of propofol.[10, 13-17] Propofol provides stable sedation, and as a result, patients do not experience any restlessness.[8, 10, 13-15, 18] Combining remifentanil with propofol as analgosedation improves intraoperative hemodynamic control during painful procedures compared with fentanyl, which is mostly used in combination with midazolam.[19] Nowadays, most ESDs are performed under general anesthesia with endotracheal intubation.[12, 20-22] Aspiration in the course of long-lasting procedures or due to intraprocedural bleeding is a feared complication. The benefit of general anesthesia is continuous airway protection, which may lead to fewer respiratory problems and interruptions during the procedure and therefore fewer endoscopy- and anesthesia-related complications.[7, 12, 23] The downsides of general anesthesia are a prolonged post-procedural hospital stay, the need for an anesthesiologist, additional logistic challenges and higher procedural costs.[7, 12]



Currently, there are no guideline recommendations regarding the preferred sedation method during ESD in the esophagus and stomach. We have used propofol-remifentanil analgosedation without endotracheal intubation for ESD in our center since October 2013. In general, in the Netherlands, propofol sedation can be performed by a sedation practitioner (SP) specialized in procedural sedation without the need for an anesthesiologist.[24]

We hypothesize that ESD can be safely performed with analgosedation using propofol and remifentanil without endotracheal intubation with low endoscopy- and anesthesia-related complication rates. The aim of this study was to report on endoscopy- and anesthesia-related complications of ESDs in the upper gastrointestinal tract to determine the safety of propofol sedation without endotracheal intubation.

## MATERIALS AND METHODS

We retrospectively reviewed the medical records of all consecutive patients who were treated with ESD for upper gastro-intestinal tumors using propofol-remifentanil analgosedation in a tertiary referral center between October 2013 and February 2018. The study was approved by the Medical Ethical Review Committee (MEC-2018-1060).

**Anesthesia management**

Analgosedation was administered before and during ESD by an SP specialized in procedural sedation (L.L.). The SP is a registered anesthesia nurse having followed an additional theoretical and practical, specialist-supervised training. The SP is responsible for the sedation of the patient and is trained to manage potential medical complications of sedation such as airway and cardiovascular changes. The SP is competent in advanced life-support skills and airway management and understands the pharmacology of the drugs used. The SP is supervised by an anesthesiologist, who is not present in the endoscopy room but on call if necessary. Patients were continuously sedated with intravenous injection of 1%–2% propofol emulsion at a dose of 1–7 mg/kg/hour to achieve a Ramsay Sedation Scale (RSS) score 4 (Table 1). Analgesia was obtained with intravenous injection of remifentanil, starting at a dose of 2–9 mg/kg/minute. Additional medications that could be administered during the procedure were glycopyrronium (reduction of mucus secretion), scopolamine butyl (reduction of spasms of the gastrointestinal tract), esketamine (anesthetic), granisetron (antiemetic), dexamethasone (antiemetic and analgesic) and piritramide (analgesic). Supplemental oxygen was administered via nasal cannula with CO2 monitoring. Heart activity (including five- or six-lead electrocardiography), respiratory rate and RSS were continuously monitored. Blood pressure was monitored every five minutes. Ephedrine or low-dose norepinephrine was administered in case of low blood pressure and atropine in case of bradycardia. Oxygen flow was increased if desaturation occurred until saturation level >95% was achieved.

Sedation parameters were collected from the anesthesiology patient data management system, including anesthesia duration, medications used, and complications. Anesthesia duration was defined as the time between the start of propofol sedation until patient's awakening (RSS of 2).

**Table 1. Ramsey Sedation Scale**

| | |
|---|---|
| 1 | Patient is anxious and agitated or restless, or both |
| 2 | Patient is cooperative, oriented, and tranquil |
| 3 | Patient responds to command only |
| 4 | A brisk response to a light glabella tap or loud a auditory stimulus |
| 5 | A sluggish response to a light glabella tap or loud a auditory stimulus |
| 6 | No response to a light glabella tap or a loud auditory stimulus |

**Endoscopic submucosal dissection**

All ESDs were performed by a single endoscopist (A.K.), an interventional endoscopist specializing in ESDs. ESD involved marking of the lesion, circumferential mucosal incision and submucosal dissection with simultaneous hemostasis. After circumferential marking of the lesion, a saline solution containing epinephrine (0.01 mg/ml) and indigo carmine was injected into the submucosal layer underneath the lesion to elevate the lesion from the muscular layer. A circumferential incision was made in the mucosa using a HybridKnife® (ERBE Elektromedizin GmbH, Tuebingen, Germany) and the submucosal layer was dissected until the lesion was completely resected. All specimens were reviewed by an expert gastrointestinal pathologist and classified according to the Vienna classification of gastrointestinal neoplasia.[25]

**Data extraction**

Patient characteristics such as age, gender, use of anticoagulation, American Society of Anesthesiologists classification and clinical follow-up were collected from patient medical charts. Endoscopy characteristics such as location of the lesion, Paris classification, lesion size, accomplishment of en bloc resection (defined as a macroscopic complete resection of the lesion in a single specimen), intra-procedural ESD-related complications, and duration of the procedure (defined as the time between the introduction and removal of the endoscope) were collected from endoscopy reports.



**Complications**

Intra-procedural anesthesia-related complications were defined as oxygen desaturation (SpO2 <90%), hypotension (systolic blood pressure <80 mmHg), bradycardia (heart rate <50 bpm), apnea or coughing during the procedure that caused an interruption of the procedure or conversion to endotracheal intubation. Intra-procedural ESD-related complications were defined as adverse events (e.g. bleeding or perforation) that caused a change of procedure management, such as discontinuation of ESD. Post-procedural complications comprised of all adverse events that resulted in prolonged hospital stay, hospital readmission or additional medical interventions within 30 days.

**Statistical analysis**

Categorical data are presented with frequencies and percentages. Continuous data are presented with mean (range) and median (interquartile range (IQR)) for normally distributed and skewed data, respectively. Analysis was carried out using IBM SPSS version 24.

## RESULTS

A total of 97 ESDs were performed in 96 patients between October 2013 and February 2018 (Figure 1). Three patients received general anesthesia during ESD. In two patients, the procedure was combined with other surgical procedures. In the other patient, the lesion was located near the upper esophageal sphincter, necessitating endotracheal intubation. In three patients midazolam was used as a sedative because procedural time and anticipated technical challenges in relation to small lesion size were estimated to be minimal. Anesthesia reports

were missing in three patients. These nine patients were excluded from further analysis. A total of 88 ESDs in 87 patients were included in the final analysis.

ESD was performed in the esophagus (34/88; 38.6%), stomach (53/88; 60.2%) and duodenal bulb (1/88; 1.1%) (Figure 1). Baseline characteristics are outlined in Table 2. Median endoscopic procedure time was 100 minutes (IQR: 65–139) and median anesthesia sedation time was 125 minutes (IQR 97–166). Median dose given during the procedure was 403 mg (IQR 272–691) for propofol and 552 µg (IQR 351–552) for remifentanil.

**Tumor characteristics**

Tumor characteristics are outlined in Table 3. In seven patients (8.0%), the procedure was discontinued and no histology was obtained (muscular invasion: 5, bleeding: 2). The pathology report was missing for one patient, leaving 80 reports available for analysis. En bloc resection rate was 91% and piecemeal resection was performed in one patient (1.1%). Early cancer was found in 75/80 lesions (94%).

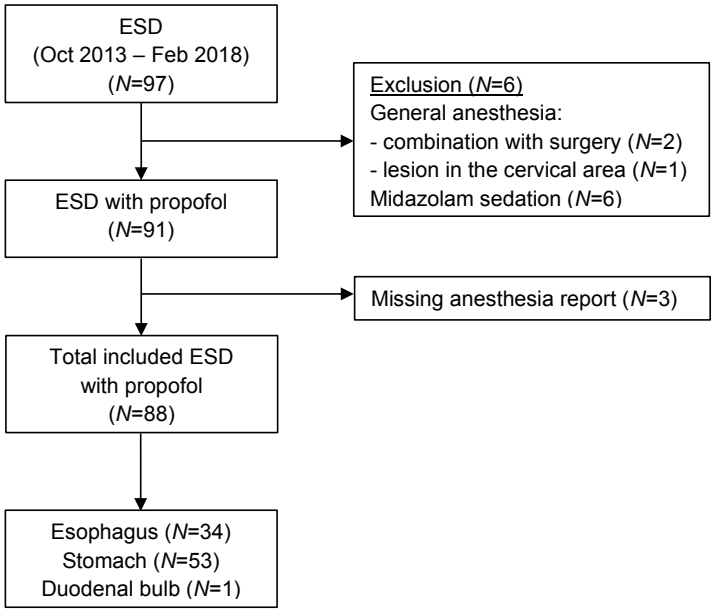


**Figure 1. flow chart of study inclusion**
ESD, endoscopic submucosal dissection

**Table 2. Baseline characteristics of 87 patients**

| | N (%) | Median (IQR) |
|---|---|---|
| **Age** | | 70 (60-76) |
| **Sex** | | |
| *Male* | 51 (58.6) | |
| *Female* | 36 (41.4) | |
| **BMI** (kg/m$^3$) | | 26.3 (22.9-28.7) |
| **ASA score** | | |
| I | 10 (11.5) | |
| II | 45 (51.7) | |
| II | 32 (36.8) | |
| **Anticoagulant therapy** | | |
| Yes | 34 (39.1) | |
| No | 53 (60.9) | |
| **Type of anticoagulant therapy** | | |
| Antiplatelet drugs | 16 (47.1) | |
| Vitamin K antagonist | 17 (50.0) | |
| Other [a] | 1 (2.9) | |

ASA, American Society of Anesthesiologists; BMI, body mass index; IQR, iterquartile range. [a] Dabigatran



**Table 3. Tumor characteristics (n=80)**

| | N (%) | Median (IQR) |
|---|---|---|
| **Histology** | | |
| Adenocarcinoma | 42 (52.5) | |
| Squamous cell carcinoma | 18 (22.5) | |
| Neuro endocrine tumor | 1 (1.3) | |
| Gastrointestinal stromacel tumor | 8 (10.0) | |
| High grade dysplasia | 6 (7.50) | |
| Low grade dysplasia | 1 (1.3) | |
| No malignancy | 4 (5.0) | |
| **R0 resection** | | |
| Yes | 56 (70.0) | |
| No | 17 (21.3) | |
| Unknown | 7 (8.7) | |
| **Tumor size, diameter (mm)** | | 30 (20-40) |

IQR, interquartile range

**ESD-related complications**

The complication rate was calculated for 88 ESD procedures (Table 4). Intra-procedural complications were reported in three procedures (3.4%; all bleeding). In one patient, ESD was converted to EMR and the bleeding was successfully treated with coagulation. In the other two patients, ESD was discontinued and no histology was obtained. One patient received surgical resection, the other patient received chemoradiotherapy as surgical resection was deemed not feasible because of extensive comorbidity. A postprocedural ESD-related complication occurred in 14 patients (15.9%). Six patients developed retrosternal pain for which three patients were given analgesic medication during prolonged hospitalization. One patient was hospitalized one extra day without requiring additional analgesics. A re-endoscopy was performed in two of six patients. In one patient, re-endoscopy after 24 days showed a normal healing ulcer that was treated with sucralfate. The other patient showed candidiasis on re-endoscopy after seven days that was treated with fluconazole. In both patients, no explanation for retrosternal pain was found. Five patients suffered from delayed bleeding. Re-endoscopy was performed in three of these five patients: two without any intervention and one with clip placement for a bleeding ulcer. In two patients, delayed bleeding resulted in prolonged hospitalization without requiring additional intervention. Three patients with delayed bleeding were on anticoagulation therapy, which was discontinued before the procedure. Bleeding occurred after anticoagulation therapy was restarted. Additional post-procedural ESD-related complications were dysphagia (two patients, re-endoscopy with esophageal dilatation) and gastric pain (one patient, prolonged hospitalization without intervention).

**Anesthesia-related complications**

An intraprocedural anesthesia-related complication occurred in two patients (2.3%). One patient coughed, causing a deep laceration in the muscular layer, which was treated with clip placement. The other patient suffered from hypotension and desaturation after a procedure of more than five hours. The anesthesia technique was converted to general anesthesia with endotracheal intubation, and the endoscopic procedure was completed successfully. No postprocedural anesthesia-related complication was observed.

Two postprocedural complications were not clearly anesthesia or ESD related. One patient experienced nausea directly after the procedure, which could be caused by intragastric blood or by sedation with propofol. Nausea disappeared shortly after antiemetic therapy was given. One patient showed atrial fibrillation several hours after the procedure. No clear connection could be established between atrial fibrillation and propofol sedation; the patient was known to have paroxysmal atrial fibrillation. Both patients were discharged the day after the procedure.

**Hospital stay**

Overall, the mean hospital stay after ESD was 0.9 days (± 2.6). Almost half of the patients were discharged on the same day as the procedure (43 patients, 48.9%). Thirty-nine patients (44.3%) were discharged the following day: 23 for logistic reasons and 16 for medical reasons. In six patients, hospital stay exceeded two days. No patient was readmitted for anesthesia-related complications.

**Table 4. Complications (n=88)**

| | N (%) |
|---|---|
| **Anesthesia-related complications** | |
| Intra-procedural | |
| Coughing | 1 (1.1) |
| Hypotension + desaturation | 1 (1.1) |
| *Total* | *2 (2.2)* |
| **ESD-related complications** | |
| Intra-procedural | |
| Bleeding | 3 (3.4) |
| Post-procedural | |
| Retrosternal pain | 6 (6.8) |
| Delayed bleeding | 5 (5.7) |
| Stomach pain | 1 (1.1) |
| Dysphagia | 2 (2.3) |
| *Total* | *14 (15.9)* |
| **Other postprocedural complications** | |
| Nausea | 1 (1.1) |
| Atrial fibrillation | 1 (1.1) |
| *Total* | *2 (2.2)* |

ESD, endoscopic submucosal dissection

## DISCUSSION



In this retrospective, observational cohort study, we found that ESD for gastrointestinal tumors in the esophagus and stomach could be safely performed with propofol-remifentanil analgosedation without endotracheal intubation. There was no mortality as a result of complications. Conversion to endotracheal intubation took place in one patient only. Coughing was observed in another patient, which brings the intraprocedural anesthesia-related complication rate to 2.3%. Two other minor postprocedural complications were observed that were not obviously anesthesia or ESD related, without additional consequences for the patient. No post-procedural anesthesia-related complications were observed. The intra-procedural ESD-related complication rate was 3.4% and post-procedural ESD-related complication rate was 15.9%. A total of 93.2% of the patients were discharged the same day or the day after the procedure.

Endoscopy-related complication rates in gastric ESDs range from 1.2% to 5.2% for perforation and 0% to 15.6% for delayed bleeding.[26] In ESDs performed in the esophagus, perforation ranges from 0% to 6.9% and delayed bleeding range from 0% to 5.2%.[27] Although no perforations occurred in our study, the overall postprocedural ESD-related complication rate was still 15.9%, which seems high compared with other studies. However, in our series pain was also considered a complication if this resulted in a longer hospital stay, even one day after the procedure. When taking only perforation and delayed bleeding into consideration, in line with what is reported in most studies, the ESD-related complication rate is 9.1% (8/88). This includes only bleeding in the stomach, which corresponds with the reported range of 0% to 15.6% in literature.[26] Studies in which the sedation method was taken into account reported low ESD-related complication rates during ESD when general anesthesia was used. Song et al. reported a lower perforation rate in esophageal ESDs in patients receiving general anesthesia compared with those who received propofol sedation (1.2% vs. 14.0%).[12] This

reported perforation rate of 14.0% when using propofol sedation seems exceedingly high. No perforations were reported in our study. Another study, using general anesthesia, reported no ESD-related complications during esophageal ESD and low complication rates in gastric ESD (bleeding: 1.6% and perforation: 1.7%).[7]

To judge the safety of ESD in relation to the sedation method used, it would be appropriate to focus on anesthesia-related complications. Several studies reported fewer anesthesia-related complications in patients receiving general anesthesia during ESD. In a study by Yurtlu et al., cough was observed more frequently during ESD in patients receiving propofol compared with general anesthesia (50% vs. 5.4%).[23] Likewise, desaturation occurred more often in the propofol sedation group (18.5% vs. 2.7%).[23] In contrast, we observed cough in only one patient (1.1%). This was likewise for desaturation (1.1%). Other studies in which general anesthesia was used during ESD in the esophagus and stomach reported no hypotension, desaturation or aspiration.[7, 28] We encountered no hypotension or aspiration either.

The published literature to date indicates that, compared with propofol sedation, the risk-benefit balance is in favor of general anesthesia. It is difficult, however, to discern to what extent the training and experience of the SP plays a decisive role in this equation. In our setting, propofol sedation is managed by an SP, a member of the anesthesiology department who is supervised by the anesthesiologist. Under these conditions, the results of propofol sedation were excellent and only one case required conversion to general anesthesia with endotracheal intubation. Moreover, our anesthesia-related complication rates are lower compared with other studies in which hemodynamic events and respiratory events during propofol sedation were reported to be 37.3% and 14.1%, respectively.[29]

Another reported advantage of general anesthesia is a shorter procedure time due to fewer interruptions during ESD.[28] In that particular study, however, the time between insertion and withdrawal of the endoscope was considered the ESD procedure time without including the time the patient was in operation room.[28] Therefore, the total procedure time including preparation for general anesthesia might be much longer. The median ESD procedure time in the study of Rong et al., in which general anesthesia was used was 42.5 minutes compared with 100 minutes in our study.[28] This is a huge difference. Rong and colleagues, however, excluded lesions >20 mm in contrast to a median lesion size of 30mm in our study, which explains this difference. In the same study less body movement and more comfort for the patient were reported as other advantages of general anesthesia.[28] In our anesthesia reports, interruptions and body movements were not reported, which precludes further quantitative analysis in our series. According to the SP (L.L.) and the endoscopist (A.K.) who performed all the procedures, no procedure was interrupted because of patient movements. In this retrospective study we could not report on patient satisfaction after the procedure.

This study demonstrates the feasibility and safety of propofol sedation for ESD. This was accomplished with limited hospital admission time with 48.9% of the patients being discharged the day of the procedure and another 44.3% being discharged the day after the procedure. In contrast, other studies in which general anesthesia was used for ESD reported a mean hospital stay of more than four days.[7, 12, 23]

Compared with propofol sedation, general anesthesia requires additional facilities, more expertise, and an anesthesiologist.[28] Furthermore, most patients cannot be discharged the same day when undergoing the procedure under general anesthesia, which results in a longer

hospital stay.[7, 12, 23] Therefore, general anesthesia in all likelihood results in higher costs, although formal cost-effectiveness studies are needed to quantify potential savings in a specific local setting.[28]

The main strength of this study is that all ESDs were performed by the same endoscopist (A.K.) and by the same SP (L.L.), both with extensive experience in this procedure. This limits confounding factors such as experience and technical skills. However, we are aware of the fact that such a dedicated team is quite unique in the clinical routine. In particular, an SP is not very common since an anesthesiologist is required in most countries when propofol sedation is used.[30] A second strength is that we included all consecutive ESDs in the upper digestive tract between October 2013 and February 2018 performed with propofol sedation regardless of location or size of the lesion.

Some limitations need to be discussed. This is a retrospective, observational, single center study, which potentially limits the generalizability of our results. There was no comparator group in our study, which could be seen as a limitation. A randomized controlled trial in which propofol sedation (performed by an SP) is compared with general anesthesia (performed by an anesthesiologist) during ESD is needed to definitively prove the safety of propofol sedation performed by an SP. Owing to the retrospective nature of this study, we did not know the exact number of interruptions during ESD caused by restlessness of the patient. Patient satisfaction could also not be assessed.



In conclusion, in this retrospective, observational proof-of-concept cohort study, propofol-remifentanil analgosedation without endotracheal intubation proved to be a feasible and safe sedation method for ESD in esophagus and stomach. Patients could be discharged shortly after the procedure without readmission for anesthesia-related complications. In line with these observations and logistical and financial ramifications, propofol-remifentanil analgosedation without endotracheal intubation for ESD should be considered over general anesthesia when a sedation practitioner is available.

## REFERENCES


1. Imagawa A, Okada H, Kawahara Y, et al. Endoscopic submucosal dissection for early gastric cancer: results and degrees of technical difficulty as well as success. *Endoscopy*. 2006; 38: 987-90
2. Weusten B, Bisschops R, Coron E, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. *Endoscopy*. 2017; 49: 191-8.
3. Maple JT, Abu Dayyeh BK, et al; ASGE Technology Committee. Endoscopic submucosal dissection. Gastrointest Endosc 2015; 81: 1311-1325
4. Oka S, Tanaka S, Kaneko I, et al. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc*. 2006; 64: 877-83
5. Takahashi H, Arimura Y, Masao H, et al. Endoscopic submucosal dissection is superior to conventional endoscopic resection as a curative treatment for early squamous cell carcinoma of the esophagus (with video). *Gastrointest Endosc*. 2010; 72: 255-64, 64 e1-2.
6. Shin S, Park CH, Kim HJ, Park SH, Lee SK and Yoo YC. Patient satisfaction after endoscopic submucosal dissection under propofol-based sedation: a small premedication makes all the difference. *Surg Endosc*. 2017; 31: 2636-44.
7. Yamashita K, Shiwaku H, Ohmiya T, et al. Efficacy and safety of endoscopic submucosal dissection under general anesthesia. *World J Gastrointest Endosc*. 2016; 8: 466-71
8. Wadhwa V, Issa D, Garg S, Lopez R, Sanaka MR and Vargo JJ. Similar Risk of Cardiopulmonary Adverse Events Between Propofol and Traditional Anesthesia for Gastrointestinal Endoscopy: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol*. 2017; 15: 194-206.
9. Lazzaroni M and Bianchi Porro G. Preparation, premedication, and surveillance. *Endoscopy*. 2005; 37: 101-9.
10. Kiriyama S, Gotoda T, Sano H, et al. Safe and effective sedation in endoscopic submucosal dissection for early gastric cancer: a randomized comparison between propofol continuous infusion and intermittent midazolam injection. *J Gastroenterol*. 2010; 45: 831-7.
11. Kikuchi H, Hikichi T, Watanabe K, et al. Efficacy and safety of sedation during endoscopic submucosal dissection of gastric cancers using a comparative trial of propofol versus midazolam. *Endosc Int Open*. 2018; 6: E51-E7.
12. Song BG, Min YW, Cha RR, et al. Endoscopic submucosal dissection under general anesthesia for superficial esophageal squamous cell carcinoma is associated with better clinical outcomes. *BMC Gastroenterol*. 2018; 18: 80.
13. Yamaguchi D, Yamaguchi N, Takeuchi Y, et al. Comparison of sedation between the endoscopy room and operation room during endoscopic submucosal dissection for neoplasms in the upper gastrointestinal tract. *BMC Gastroenterol*. 2017; 17: 127.
14. Nishizawa T, Suzuki H, Matsuzaki J, Kanai T and Yahagi N. Propofol versus traditional sedative agents for endoscopic submucosal dissection. *Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society*. 2014; 26: 701-6.
15. Nonaka S, Kawaguchi Y, Oda I, et al. Safety and effectiveness of propofol-based monitored anesthesia care without intubation during endoscopic submucosal dissection for early gastric and esophageal cancers. *Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society*. 2015; 27: 665-73.
16. Skues MA and Prys-Roberts C. The pharmacology of propofol. *J Clin Anesth*. 1989; 1: 387-400.
17. Wang D, Chen C, Chen J, et al. The use of propofol as a sedative agent in gastrointestinal endoscopy: a meta-analysis. *PLoS One*. 2013; 8: e53311.
18. Ominami M, Nagami Y, Shiba M, et al. Comparison of propofol with midazolam in endoscopic submucosal dissection for esophageal squamous cell carcinoma: a randomized controlled trial. *J Gastroenterol*. 2017.

19. Beers R and Camporesi E. Remifentanil update: clinical science and utility. *CNS Drugs*. 2004; 18: 1085-104.
20. Yang D, Coman RM, Kahaleh M, et al. Endoscopic submucosal dissection for Barrett's early neoplasia: a multicenter study in the United States. *Gastrointest Endosc*. 2017; 86: 600-7.
21. An W, Sun PB, Gao J, et al. Endoscopic submucosal dissection for gastric gastrointestinal stromal tumors: a retrospective cohort study. *Surg Endosc*. 2017; 31: 4522-31.
22. Hammad H, Kaltenbach T and Soetikno R. Endoscopic submucosal dissection for malignant esophageal lesions. *Curr Gastroenterol Rep*. 2014; 16: 386
23. Yurtlu DA, Aslan F, Ayvat P, et al. Propofol-Based Sedation Versus General Anesthesia for Endoscopic Submucosal Dissection. *Medicine (Baltimore)*. 2016; 95: e3680.
24. Richtlijn sedatie en/of analgesie (PSA) op locaties buiten de operatiekamer, Deel I: bij volwassen.http://mdl.nl/files/richtlijnen/Richtlijn_sedatie_of_analgesie_op_locaties_buiten_de_OK_definitief.pdf (2012, accessed 1 October 2018).
25. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut*. 2000; 47: 251-5.
26. Oda I, Suzuki H, Nonaka S and Yoshinaga S. Complications of gastric endoscopic submucosal dissection. *Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society*. 2013; 25 Suppl 1: 71-8
27. Isomoto H, Yamaguchi N, Minami H and Nakao K. Management of complications associated with endoscopic submucosal dissection/ endoscopic mucosal resection for esophageal cancer. *Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society*. 2013; 25 Suppl 1: 29-38.
28. Rong QH, Zhao GL, Xie JP and Wang LX. Feasibility and safety of endoscopic submucosal dissection of esophageal or gastric carcinomas under general anesthesia. *Med Princ Pract*. 2013; 22: 280-4.
29. Park CH, Shin S, Lee SK, et al. Assessing the stability and safety of procedure during endoscopic submucosal dissection according to sedation methods: a randomized trial. *PLoS One*. 2015; 10: e0120529
30. Statement on Safe Use of Propofol. *American Society of Anesthesiologists*. 2004. Available at: http://www.asah-q.org/standards-and-guidelines/statement-on-safe-use-of-propofol (2014, accessed 1 October 2018).

# CHAPTER 9

## Effectiveness of topical budesonide in preventing esophageal strictures after endoscopic resection of esophageal cancer

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## ABSTRACT

**Background and study aims:** A disadvantage of endoscopic resection (ER) of early esophageal cancer (EC) is the high stricture rate after resection. A risk factor for stricture development is a mucosal defect after ER of ≥75% of the esophageal circumference. Stricture rates up to 94% have been reported in these patients. The aim of this study was to investigate the effectiveness of oral treatment with topical budesonide for stricture prevention after ER of early EC. gastrointestinal tract.

**Patients and methods:** We performed a retrospective analysis of a prospective cohort study of patients who received topical budesonide after ER of EC between March 2015 and April 2020. The primary endpoint was the esophageal stricture rate after ER. Stricture rates of our cohort were compared with stricture rates of control groups in the literature.

**Results:** In total, 42 patients were treated with ER and topical budesonide. A total of 18 of 42 patients (44.9%) developed a stricture. The pooled stricture rate of control groups in the literature was 75.3% (95% CI 68.8%-81.9%). Control groups consisted of patients with esophageal squamous cell carcinoma with a mucosal defect after ER of ≥75% of the esophageal circumference. Comparable patients of our cohort had a lower stricture rate (47.8% vs. 75.3%, *p=0.007*).

**Conclusions:** Topical budesonide therapy after ER for EC seems to be a safe and effective method in preventing strictures. The stricture rate after budesonide treatment is lower compared to the stricture rate of patients who did not receive a preventive treatment after ER reported in the literature.

## INTRODUCTION

Over the past few decades, the incidence of esophageal cancer (EC) has increased.[1] The most common histological type of EC is esophageal squamous cell carcinoma (ESCC).[2] The overall survival of patients with EC has improved due to better treatment options such as neoadjuvant chemoradiotherapy, and the treatment shift from esophagectomy to endoscopic resection (ER) for early EC.[3-5]

Compared to surgery, ER has a lower morbidity and mortality for early EC while maintaining equal curative outcomes.[5] Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are established treatment options when EC is limited to the superficial layers.[6] ESD is recommended over EMR for a selected number of adenocarcinomas larger than 15mm with suspected submucosal invasion, and for all superficial ESCCs except if submucosal invasion is suspected.[7] Moreover, ESD provides en bloc resection and it reduces the number of recurrences compared to EMR.[8, 9]

A major disadvantage of ER of large esophageal tumors, however, is the high stricture rate after resection.[10, 11] Stricture formation after ER of early EC with a mucosal defect ≥75% of the esophageal circumference is reported up to 94.1% in the literature.[10] Esophageal strictures develop as a result of inflammation in the wound healing process of the mucosal defect following ER.[12] Previous studies have shown that a mucosal defect of ≥75% of the esophageal circumference was associated with esophageal stricture rates of 70% to 94% and it is reported as a significant risk factor for stricture development.[10, 13-15] Patients with strictures might suffer from dysphagia with the need for endoscopic dilations, and patients quality of life might substantially decrease.[16] In addition, endoscopic dilations are associated with an increased perforation risk.[17]



In an effort to reduce the stricture rate after ER of esophageal tumors, preventive strategies have been investigated.[18] For example, treatment with triamcinolone injections, the use of polyglycolic acid sheet (PGA) with fibrin glue, preventive endoscopic balloon dilation (EBD), and treatment with oral prednisolone.[16, 19-24] Although these studies have shown promising results in preventing strictures after ESD, limited patients were included and the optimal dose and duration of steroids has not yet defined.[16, 19-24] The use of triamcinolone injections in the esophagus has raised several concerns about the safety and effectiveness.[18] Moreover, systemic therapy with oral steroids is well-known to have several side effects.[25]

The question arises whether the use of topical steroids is effective in stricture prevention after ER of esophageal tumors, due to its effect in the suppression of the inflammatory process after ER.[12] Topical steroids have shown to be beneficial for eosinophilic esophagitis treatment and have resulted in stricture reduction after EMR of short Barrett's segment.[12, 26]

The aim of this study was to investigate the effectiveness of oral treatment with topical budesonide for the prevention of strictures after ER of EC (ESCC or esophageal adenocarcinoma (EAC)). We hypothesized a lower esophageal stricture rate when using topical budesonide compared to the stricture rate in patients who did not receive a preventive treatment after ER, reported in the literature. The secondary aim of this study was to investigate whether the use of topical budesonide after ER affects esophageal stricture treatment. We hypothesized that less dilations were required in patients treated with topical

budesonide who developed a stricture after ER compared to patients who did not receive preventive treatment after ER, reported in the literature.

## METHODS

### Study design

We performed a single-center, retrospective analysis of data that has been prospectively collected in our ongoing registry of ER of the esophagus at the Department of Gastroenterology and Hepatology at the Erasmus MC, University Medical Center. Patients treated with ER (EMR or ESD) for superficial ESCC or EAC between March 2015 and April 2020 were retrospectively included in this study. All patients that were deemed to have a high chance of stricture development (i.e. patients with a mucosal defect size after ER >50% of the esophageal circumference) were treated with topical budesonide after ER in order to prevent stricture development.[15] This was decided directly after ER by the treating endoscopist [A.K.]. Patients were excluded if they had known intolerance to budesonide, candida esophagitis, or immunocompromised conditions. Additionally, patients were excluded from final analysis if they were treated with prior ESD, EMR, radiotherapy, radiofrequency ablation, or endoscopic dilation in the area where the current ER was performed. These prior treatments could be of influence on stricture development. This study was approved by the Medical Ethical Review Committee of the Erasmus University MC in Rotterdam, the Netherlands [MEC-2019-0819].

### Data collection

Patient and tumor characteristics were collected from medical charts and endoscopy and pathology reports. An overview of collected characteristics can be found in Supplementary file 1. If a patient developed a second (metachronous) tumor, the first tumor was included for final analysis to avoid bias.

ER was performed with either EMR or ESD which was up to the discretion of the endoscopist or dictated by the tumor type. ESCC was always removed by ESD. EAC was only removed by ESD when submucosal invasion was expected. EMR was performed using the multiband mucosectomy method.[27] ESD was carried out with a HybridKnife® (ERBE Elektromedizin GmbH, Tuebingen, Germany), lifting fluid contained saline with indigo carmine and epinephrine.[28] All EMRs and ESDs were performed by a single endoscopist [A.K.].

### Treatment with budesonide after endoscopic resection

The standard dose for topical budesonide was 2.3 mg once a day, 2.3 mg twice a day or 1 mg twice a day, for a duration of 6 weeks from the first day after ER. In general, if adjuvant therapy (e.g. surgery or chemo-radiotherapy) was needed, budesonide was still given for 6 weeks because strictures can develop shortly after ER. For every patient, this was discussed in a multidisciplinary team. Only if adjuvant therapy started within this 6-week period, budesonide treatment discontinued earlier. The budesonide dose depended on the availability of topical budesonide in the pharmacy. In 2015, 2.3mg budesonide once a day was given, and 2.3mg budesonide twice a day was given beginning in 2016. In the last 6 months of inclusion, orodispersible topical budesonide tablets of 1mg became available for eosinophilic esophagitis (EoE) treatment wherefore this dose was chosen. Because no orodispersible budesonide tablets were available for most of the study, the dispersible tablet from a

budesonide enema was used for oral intake. Patients were instructed to let the tablet dissolve on the tongue and swallow the dispersed budesonide. This is a common off-label use of budesonide in the treatment of EoE. Recently, a budesonide orodispersible tablet has become available for the treatment of EoE.[29, 30]

**Endoscopic dilation**

Endoscopic dilation was only performed when the patient had dysphagia in combination with esophageal stenosis. Prophylactic dilation was not performed. The type and interval of endoscopic dilation was up to the discretion of the endoscopist. In general, two dilation techniques were used: bougie and balloon dilation.[31] Dilations were usually done with a weekly repetition if necessary.

**Study end points**

The primary end point was the esophageal stricture rate in patients who received topical budesonide therapy after ER of early EC. A stricture was defined as the inability to swallow solid food and/or the inability to pass a standard diagnostic endoscope (diameter: 9.9mm, GIF-H190 and GIF-H180J, Olympus) which resulted in the need for dilation. We only included strictures that developed before adjuvant treatment (e.g. radiotherapy, radiofrequency ablation, EMR, chemotherapy) started. Stricture development after adjuvant treatment could also be attributed to the adjuvant treatment. Therefore, the date of adjuvant therapy was considered as the last moment of follow-up in these patients and strictures after that date we not included. Stricture rates in our cohort were compared with stricture rates of comparable control groups in the literature. Secondary endpoints included identification of risk factors for stricture development, number of endoscopic dilations per patient, type of dilation (balloon/bougie), time to dilation after ER (days), number of patients with dysphagia, number of patients who experienced budesonide side effects, and the number of patients with adverse events (AEs) after dilation, including the type of AE. To investigate whether topical budesonide affects esophageal stricture treatment, the number of endoscopic dilations performed in patients who developed a stricture in our cohort was compared with the number of endoscopic dilations performed in patients who developed a stricture in control groups from the literature.



**Statistical analyses**

Continuous variables were presented with mean (range) and median (interquartile range (IQR)) for normally distributed and skewed data, respectively. Patients who developed a stricture were compared with patients who did not develop a stricture after ER to determine potential risk factors for stricture development. These two groups were compared with univariable analysis, performed by the independent Student's T-test for normally distributed continuous data and the Chi-square test for categorical data.

For the comparison of stricture rates and the number of dilations of patients in our cohort with patients who did not receive a preventive treatment after ER of EC, control groups of several studies were used in which other methods were investigated to prevent stricture development. For the selection of these control groups, a systematic literature search was performed in Pubmed and Medline by two independent reviewer (S.V. and M.S.). The search strategy and selection of relevant literature is outlined in Supplementary file 2. Stricture rates in the control groups were calculated for each study as the total number of patients who developed a stricture in the control group divided by the total number of patients in the control group. We

calculated the standard error (SE) for each study using the following formula: $SE = \sqrt{(s \cdot (1 - s) / n)}$; where, s = stricture rate and n = total number of patients in the control group. A fixed-effects meta-analysis was performed to estimate the stricture rate of the control studies. To evaluate the heterogeneity between the studies, the inconsistency index ($I^2$) was calculated.[32] The pooled stricture rate of the control studies was compared with the stricture rate of our cohort using the Z-test. We used descriptive statistics to compare the number of dilations of our study with the number of dilations in control studies; meta-analysis was not performed since all studies reported different values of the number of dilations (e.g. median in combination with range, mean in combination with 95% CI, and no standard deviations were reported). For all analyses, a two-sided p-value of <0.05 was considered significant. Statistical analyses were performed with the statistical software IBM SPSS Statistics (version 25) and Review Manager Software (version 5.3) was used for meta-analysis.

## RESULTS

A total of 64 patients were treated with ER for early EC. After exclusion of 22 patients (mucosal defect <50%; n=16, ESD performed in cardia; n=6), 42 patients received budesonide therapy after ER. One patient developed ESCC two times, only the first tumor was included for analysis to prevent bias. Baseline characteristics of all included patients are presented in Table 1. Most patients were male (n=25; 59.5%) and the median age was 67.0 years (IQR: 60.8-72.3).

**Table 1. Baseline characteristics of 42 patients and univariable analysis of the stricture group (n=18) versus the non-stricture group (n=24)**

| Characteristics | Total (n=42) | Stricture (n=18) | No stricture (n=24) | p-value |
|---|---|---|---|---|
| **Sex, n (%)** | | | | |
| Female | 17 (40.5%) | 7 (41.2%) | 10 (58.8%) | 0.86 |
| Male | 25 (59.5%) | 11 (44.0%) | 14 (56.0%) | |
| **Median age, years (IQR)** | 67.0 (60.8-72.3) | 66.0 (60.8-72.5) | 67.0 (60.5-72.3) | 0.96 |
| **ASA classification, n (%)** | | | | |
| I | 4 (9.5%) | 1 (25.0%) | 3 (75.0%) | 0.64 |
| II | 25 (59.5%) | 12 (48.0%) | 13 (52.0%) | |
| III | 13 (31.0%) | 5 (38.5%) | 8 (61.5%) | |
| **Smoking status, n (%)** | | | | |
| Current | 12 (31.6%) | 3 (25.0%) | 9 (75.0%) | 0.09 |
| Former | 18 (47.4%) | 8 (44.4%) | 10 (55.6%) | |
| Never | 8 (21.1%) | 6 (75.0%) | 2 (25.0%) | |
| *Missing* | *4* | *1* | *3* | |
| **Median Pack years (IQR)** | 42.5 (24.3-48.8) | 45.0 (25.5-49.5) | 40.0 (19.0-47.5) | 0.64 |
| *Missing* | *22* | *7* | *15* | |
| **Alcohol consumption, n (%)** | | | | |
| Current | 25 (64.1%) | 9 (36.0%) | 16 (64.0%) | 0.25 |
| Former | 7 (17.9%) | 3 (42.9%) | 4 (57.1%) | |
| Never | 7 (17.9%) | 5 (71.4%) | 2 (28.6%) | |
| *Missing* | *3* | *1* | *2* | |
| **Median units alcohol/week (IQR)** | 10.5 (4.5-21.0) | 17.0 (5.8-21.0) | 7 (3.3-31.5) | 0.57 |
| *Missing* | *12* | *6* | *6* | |

**Tumor and treatment characteristics**

Tumor and treatment characteristics are presented in Table 2 for 42 cases. Most tumors were located in the mid esophagus (14/42; 33.3%) and lower esophagus (15/42; 35.7%). The remaining tumors (13/42; 31.0%) were overlapping between two sub-locations or were located in the upper thoracic esophagus. The median circumferential range of the mucosal defect after ER was 80.0% (IQR: 75.0-100.0). A total of four patients had a mucosal defect less than 75% and the smallest reported circumferential range was 60%. The median surface of the resected specimen was 10.3 $cm^2$ (IQR: 6.8-16.7). In total, 25/42 (59.5%) tumors were ESCC and 17/42 (40.5%) tumors were EAC. There were four patients within the ESCC group with dysplasia; three with high grade dysplasia and one with low grade dysplasia. In total, 20 of 42 tumors showed submucosal invasion. In 16 cases, the absolute invasion depth was reported with a median of 975.0 µm (IQR: 562.5-1725.0).

ESD was performed in 37 (88.1%) cases, EMR was performed in five (11.9%) cases. The dose of oral budesonide was 2.3mg budesonide twice a day (31/42 [73.8%]), 2.3mg budesonide once a day (6/42 [14.3%]) or 1mg budesonide twice a day (5/42 [11.9%]). One patient discontinued budesonide treatment before the 6-week period was completed (reason unknown). This patient used budesonide for two weeks and developed a stricture two weeks thereafter. Overall, no side effects of topical budesonide were reported.

**Adjuvant treatment**

In total, 16 patients received adjuvant treatment after ER (Figure 1). The median time between ER and adjuvant treatment was 81 days (IQR: 48-147). In one patient, adjuvant treatment started 21 days after ER, before budesonide therapy was completed. In that patient, the ER specimen showed mucosal ESCC with LVI. This patient had two synchronous head and neck tumors, therefore, adjuvant radiotherapy was started for both esophageal and head and neck tumors.

**Table 2. Univariable analyses of tumor characteristics (42 tumors) and treatment characteristics between the stricture group (n=18) and non- stricture group (n=24)**

| Characteristics | Total (n=42) | Stricture (n=18) | No stricture (n=24) | p-value |
|---|---|---|---|---|
| **Tumor location, n (%)** | | | | |
| Upper thoracic esophagus | 4 | 1 (25.0%) | 3 (75.0%) | 0.50 |
| Mid thoracic esophagus | 14 | 7 (50.0%) | 7 (50.0%) | |
| Lower thoracic esophagus | 15 | 5 (33.3%) | 10 (66.7%) | |
| Overlapping | 9 | 5 (55.6%) | 4 (44.4%) | |
| **Median circumferential range of the mucosal defect after ER (%) (IQR)** | 80 (75-100) | 100 (75-100) | 75 (75-88) | **0.01** |
| **Circumferential range of mucosal defect after ER, n (%)** | | | | |
| 50-74% | 3 | 1 (33.3%) | 2 (66.6%) | 0.73 |
| 75-100% | 39 | 17 (43.6%) | 22 (56.4%) | |
| **Morphology (Paris classification), n (%)** | | | | |
| Protruded lesions | 3 | 2 (66.7%) | 1 (33.3%) | 0.25 |
| Overlapping protruded/flat elevated lesions | 8 | 4 (50.0%) | 4 (50.0%) | |
| Flat elevated lesions | 12 | 2 (22.2%) | 10 (83.3%) | |
| Overlapping flat elevated/flat lesions | 12 | 7 (58.3%) | 5 (41.7%) | |
| Flat lesions | 7 | 4 (57.1%) | 3 (42.9%) | |
| **Histology tumor, n (%)** | | | | |
| SCC [1] | 25 | 12 (48.0%) | 13 (52.0%) | 0.41 |
| Adenocarcinoma | 17 | 6 (35.3%) | 11 (64.7%) | |
| **Differentiation grade, n (%)** | | | | |
| Well/moderate [G1/G2] | 27 | 13 (48.1%) | 14 (51.9%) | 0.32 |
| Poor [G3] | 10 | 3 (30.0%) | 7 (70.0%) | |
| *Missing [2,3]* | *5* | *2* | *3* | |
| **Invasion depth, n (%)** | | | | |
| M2 | 1 | 0 (0.0%) | 1 (100.0%) | 0.26 |
| M3 | 16 | 7 (43.8%) | 9 (56.2%) | |
| SM1 | 1 | 1 (100.0%) | 0 (0.0%) | |
| SM2 | 8 | 4 (50.0%) | 4 (50.0%) | |
| SM3 | 9 | 2 (22.2%) | 7 (77.8%) | |
| SMx | 2 | 2 (100.0%) | 0 (0.0%) | |
| *Missing [2,3]* | *5* | *2* | *3* | |
| **Median surface resection specimen, $cm^2$ (IQR)** | 10.3 (6.8-16.7) | 11.1 (8.7-15.1) | 10.3 (5.7-18.1) | 0.63 |
| *Missing* | *6* | *1* | *5* | |
| **Median length of the resected specimen, cm (IQR)** | 4.5 (3.5-5.4) | 4.5 (3.8-5.3) | 4.4 (3.3-5.7) | 0.95 |
| **LVI present, n (%)** | | | | |
| Yes | 15 | 6 (40.0%) | 9 (60.0%) | 0.70 |
| *Missing [3]* | *1* | *0* | *1* | |
| **Vertical resection margin, n (%)** | | | | |
| Positive [R1] | 10 | 4 (40.0%) | 6 (60.0%) | 0.78 |
| Negative [R0] | 31 | 14 (45.2%) | 17 (54.8%) | |
| *Missing [3]* | *1* | *0* | *1* | |
| **Endoscopic resection method, n (%)** | | | | |
| ESD | 37 | 17 (45.9%) | 20 (54.1%) | 0.27 |
| EMR | 5 | 1 (20.0%) | 4 (80.0%) | |
| **Dose of budesonide, n (%)** | | | | |
| 2,3 mg 2dd budesonide | 31 | 13 (41.9%) | 18 (58.1%) | 0.93 |
| 2,3 mg 1dd budesonide | 6 | 3 (50.0%) | 3 (50.0%) | |
| 1,0 mg 2dd budesonide | 5 | 2 (40.0%) | 3 (60.0%) | |

ER, endoscopic resection; IQR, interquartile range; EC, esophageal carcinoma; SCC, squamous cell carcinoma; LVI, lymphovascular invasion; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection. [1] Including four patients with high grade dysplasia (n=3) or low grade dysplasia (n=1). [2] Not reported for patients with high grade dysplasia (n=3) or low grade dysplasia (n=1). [3] Resection specimen was lost for pathology review in one patient.

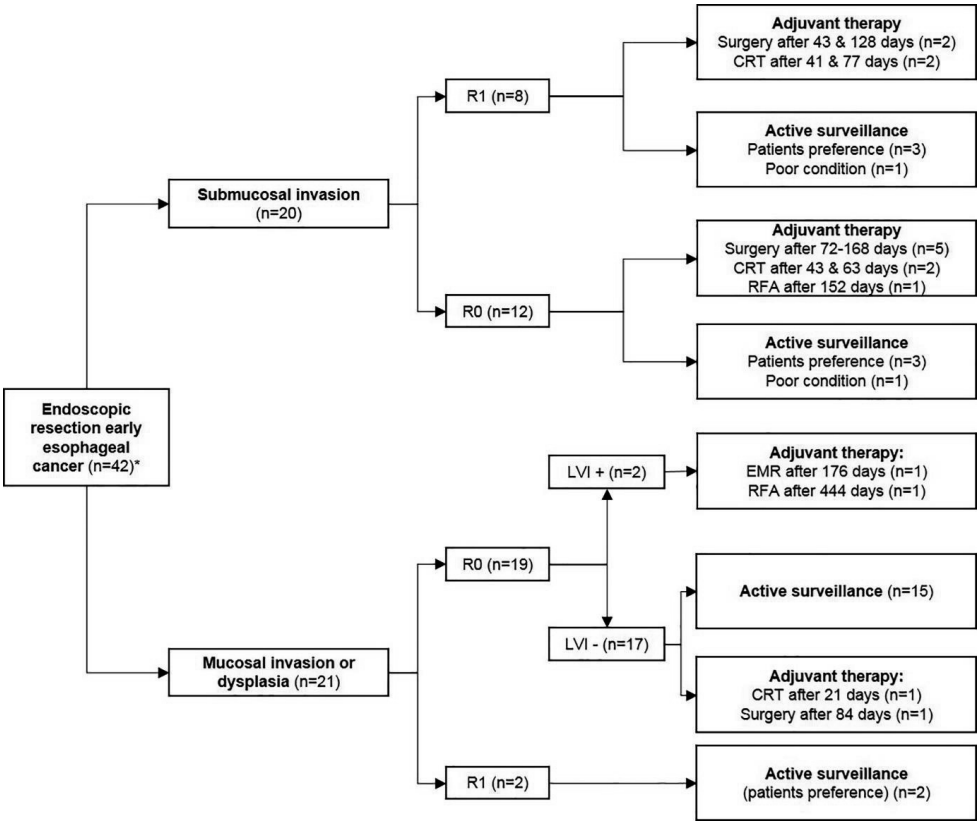



**Figure 1**. **Adjuvant treatment after endoscopic resection of early esophageal cancer**
CRT, chemoradiotherapy; EMR, endoscopic mucosal resection; LVI, lymphovascular invasion; RFA, radiofrequency ablation. *Resection specimen lost for pathology review in one patient; active surveillance was performed



### Stricture rate

Eighteen of 42 patients (44.9%) developed a stricture during follow-up. Patients with a mucosal defect of ≥75% of the esophageal circumference had a stricture rate of 43.6% (17/39) (Table 2). In this group (n=39) there were 16 cases of EAC and 23 cases of ESCC. The stricture rate for patients with EAC in this group was 37.5% (6/16) and for patients with ESCC 47.8% (11/23).

A total of nine studies were selected from the literature (Supplementary file 2).(7-15) Patients in control groups from these studies all had ESCC and a mucosal defect after ER with a circumference ≥75%. All studies were performed in Asia (five in Japan and three in China and one in Korea). In total, 104 of 147 patients who did not receive preventive treatment after ER developed a stricture. The stricture rate for these control groups ranged from 50.0% to 91.7%. Meta-analysis with fixed-effect model was used to calculate the pooled stricture rate since $I^2$

was 44% (low heterogeneity). The pooled stricture rate was 75.3% (95% CI 68.6%-81.9%) (Figure 2). The stricture rate in our cohort of patients with ESCC and a mucosal defect after ER with a circumference ≥75% was 47.8% and was significantly lower compared with the control groups (47.8% vs. 75.3%, *p=0.007*).

**Potential risk factors for stricture development**

Patients who developed a stricture were compared with patients who did not develop a stricture. The stricture group consisted of 18 of 42 patients (44.9%) whereas the non-stricture group consisted of 24 of 42 patients (57.1%). There was no significant difference in sex, age, smoking status, alcohol consumption or American Society of Anesthesiologists classification between the two groups (Table 1). The median circumferential range of the mucosal defect in the stricture group was 100.0% compared to 75.0% in the non-stricture group (*p=0.02*) (Table 2).

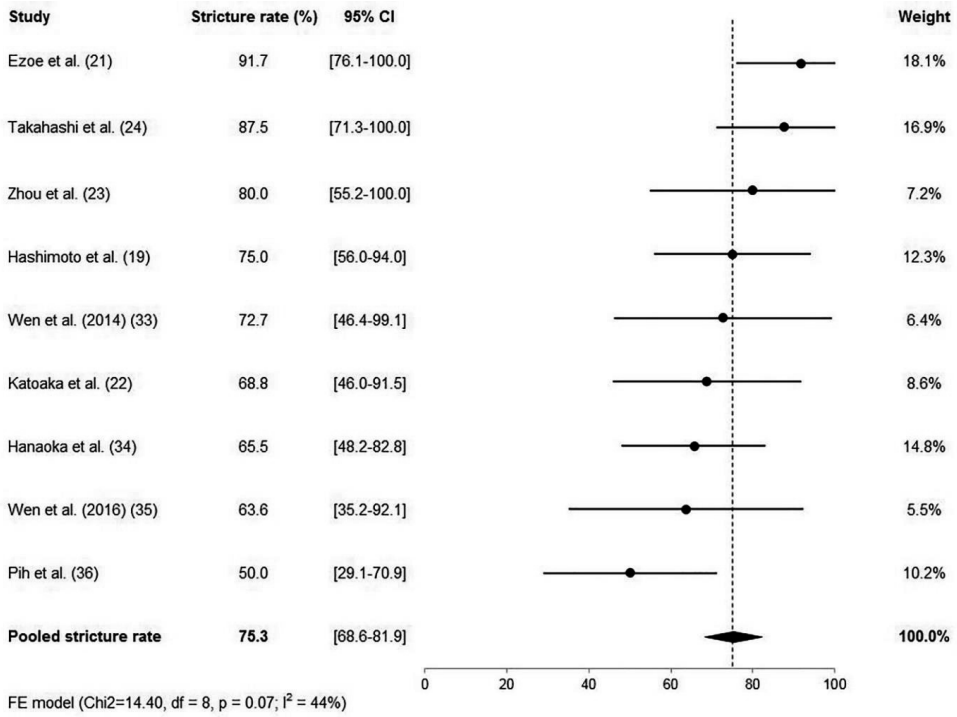



**Figure 2. Forest plot of the stricture rate of patients who did not receive a preventive treatment after endoscopic resection of esophageal carcinoma**

CI, confidence interval; df, degree of freedom; FE, fixed-effects; $I^2$, inconsistency index

**Stricture development and dilations**

The median follow up time of patients who developed a stricture (n=18) was 53.4 (IQR: 17.7-79.5) weeks. Dysphagia was reported in 17 of 18 patients (94.4%). In total, 147 dilations were performed. The median number of endoscopic dilations per patient was 6.0 (IQR: 4.0-14.0). The median number of dilations in patients with ESCC and a mucosal defect after ER with a circumference ≥75% was also 6.0 (IQR 2-16). In case of a stricture, bougie dilation (116/147; 78.9%) was more often used compared with EBD (31/147; 21.1%). The median time to dilation after ER was 29.0 (IQR: 20.0-44.5) days. Two patients developed an AE after dilation. One patient had a poor healing ulcer after dilation, which was successfully treated with pantoprazole. Another patient developed a perforation, which was treated with stent placement. The patient was hospitalized for two days for observation without further events. The stent was removed after four weeks and the perforation had healed.

The median number of dilations in patients who developed a stricture in control groups was reported in three studies; 8.1 (range 1-18), 4.5 (range 2-35) and 2 (range 0-15).[21, 22, 34] Other studies reported the mean number of dilations; 12.5 (95% CI 7.1-17.9) in Takahashi et al., 6.6 (range 0-20) in Hashimoto et al, 3.9 (range 0-17) in Wen et al. (2014) and 13.5 (range 0-28) in Zhou et al.[19, 23, 24, 33] No standard deviations were reported.

## DISCUSSION



ER of EC is an excellent minimally invasive treatment method to cure patients from early EC. A major disadvantage, however, is the development of esophageal strictures after the procedure.[10] Most strictures have been observed when the mucosal defect after the procedure extends beyond 75% of the esophageal circumference.[10, 13, 14] We performed a retrospective analysis of a prospectively collected cohort of patients who received topical budesonide after ER of early EC, to investigate whether the use of topical budesonide prevents esophageal strictures after ER.

We found an overall stricture rate of 44.9% in patients who received a 6-week treatment of topical budesonide after ER of early EC (both ESCC and EAC), compared with a pooled stricture rate of 75.3% when no preventive measures are taken as reported in the literature.[19, 21-24, 33-36] No side effects of budesonide were reported. All patients had an esophageal mucosal defect after ER with a circumference ≥60%. The median circumference of the mucosal defect was higher in patients who developed a stricture compared to patients who did not develop a stricture (100.0% versus 75.0%; *p=0.02*). All patients who developed a stricture were treated with endoscopic dilations, with a median time to dilation of 29.0 days (IQR 20.0-44.5) and the median number of dilation was 6.0 (IQR 4.0-14.0). There was only one perforation after dilation, successfully treated with stent placement.

The stricture rate of patients in our study with ESCC and a mucosal defect ≥75% of the esophageal circumference was 47.8%, which is lower than the pooled stricture rate in patients who did not receive preventive treatment after ER (75.3%; *p=0.007*). Topical budesonide therapy seems to be effective on stricture prevention after ER of early EC. The median number of dilations performed in patients who developed a stricture in our cohort (6.0) is in line with the median number of dilations, ranging from 2.0 to 8.1, performed in patients who did not receive preventive treatment after ER.[21, 22, 34] However, only three studies reported the median

number of dilations without a standard deviation or IQR. We could therefore not compare our results with control groups from the literature using meta-analysis. As a consequence, we could not investigate whether use of topical budesonide after ER affects esophageal stricture treatment.

Several studies have investigated different methods of preventing esophageal strictures after ER, such as preventive EBD, oral prednisolone, triamcinolone injections and treatment with viscous budesonide slurry.[12, 19, 21-24] Patients in these studies had an esophageal mucosal defect with a circumference ≥75%, comparable to our study. Although most of these studies reported a lower stricture rate in the treatment group compared to the stricture rate in our cohort, several limitations of these preventive methods are reported and all studies had small sample sizes with only 13 to 29 patients included in the treatment group.[12, 19, 21-24] The stricture rate in patients with ESCC who were treated with preventive EBD after ER was 59% compared to 92% in the control group *(p=0.04)*.[21] There was no significant difference in the number of dilations after stricture development in the treatment group compared to the control group (2.0 vs. 4.5; *p=0.05*).[21] Patients in the treatment group received preventive EBD every week until complete healing of the mucosal defect was observed, which could be associated with patient burden and additional costs.[21] Treatment with oral prednisolone in ESCC patients was reported in two studies and resulted in a significantly lower stricture rate of 17.7% to 23.1% compared to 68.8% to 80.0% in the control groups.[22, 23] In both studies, the number of required dilations was significantly higher in the control group compared to patients receiving oral prednisolone.[22, 23] A disadvantage of systematic therapy with oral steroids are several side effects that may occur such as; immune suppression, infections, optical damage and psychiatric disturbance.[25] Use of triamcinolone injections after ER in patients with ESCC resulted in a significantly lower stricture rate of 19.0% to 62.5% compared with 75.0% to 87.5% in control groups.[19, 24] In both studies, fewer dilations were required in the treatment groups. A limitation of this invasive method are the extra required endoscopic procedures, causing additional costs and potential patient burden. Moreover, there is a risk of developing perforations after these injections.[19] Bahin *et al*. reported the effect of an oral treatment with viscous budesonide slurry (a mix of budesonide with sucralose) in patients with an EAC and a significant stricture reduction after EMR was observed compared to a control group (13.8% vs 37.3%, *p<0.01*).[12] This treatment was only given to patients with an EAC, and patients with a Barrett segment larger than C3M5 were excluded.[12]

This is the first study to investigate the effect of topical budesonide on stricture prevention after ER of early esophageal neoplasia. Our study suggest that the use of topical budesonide is safe and effective for stricture prevention after ER. Topical budesonide is a noninvasive treatment, which is a major strength of this study, and no side effects were reported. However, our results have to be interpreted with caution due to several limitations. The first limitation is the retrospective design of our study, performed in a single center. We had several missing data, which may have influenced our results and could have resulted in information bias. The second limitation is the small sample size of 42 patients, of whom 18 patients developed a stricture. Therefore, we could not perform multivariable risk factor analysis to adjust for confounders. The third limitation is the non-randomized study design without the availability of a control group. Because there was no control group, it is impossible to know whether use of topical budesonide was the main reason for the lower stricture rate. Another limitation is the potential for selection bias. The endoscopist decided whether patients received budesonide after ER, based on the estimated risk of developing strictures. Further, although patients all

reported taking the medication correctly during follow-up, we did not have a formal procedure in place to confirm that. Because no topical budesonide tablets were available during the largest part of the study period, we prescribed the dispersible budesonide tablets from a budesonide enema. This off-label use could result in incorrect use of budesonide. Moreover, different doses of budesonide were used during the study period. It seems likely that an orodispersible tablet designed for this indication could yield an even higher effect in prevention of strictures. To address these limitations, a prospective, randomized controlled trial (RCT) is necessary to investigate the efficacy and tolerability of budesonide orodispersible tablets.

In conclusion, based on comparisons with historical published data, topical budesonide after ER for EC seems to be an effective method for preventing stricture development. The stricture rate was lower compared with the rates of patients who did not receive a preventive method after ER. However, a prospective RCT is required to investigate whether topical budesonide is safe and effective for prevention of strictures after ER in patients with early stage EC, and whether topical budesonide affects esophageal stricture treatment.

## REFERENCES


1. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424
2. Thun MJ, Linet MS, Cerhan JR. Cancer Epidemiology and Prevention 2018
3. Van Putten M, de Vos-Geelen J, Nieuwenhuijzen GAP et al. Long-term survival improvement in oesophageal cancer in the Netherlands. Eur J Cancer 2018; 94: 138-147
4. Shapiro J, van Lanschot JJB, Hulshof M et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015; 16: 1090-1098
5. Moss A, Bourke MJ, Hourigan LF et al. Endoscopic resection for Barrett's high-grade dysplasia and early esophageal adenocarcinoma: an essential staging procedure with long-term therapeutic benefit. Am J Gastroenterol 2010; 105: 1276–1283
6. Takahashi H, Arimura Y, Masao H et al. Endoscopic submucosal dissection is superior to conventional endoscopic resection as a curative treatment for early squamous cell carcinoma of the esophagus (with video). Gastrointest Endosc 2010; 72: 255–264, 264 e251-252
7. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2015; 47: 829–854
8. Fujishiro M, Yahagi N, Kakushima N et al. En bloc resection of a large semicircular esophageal cancer by endoscopic submucosal dissection. Surg Laparosc Endosc Percutan Tech 2006; 16: 237–241
9. Ono S, Fujishiro M, Niimi K et al. Long-term outcomes of endoscopic submucosal dissection for superficial esophageal squamous cell neoplasms. Gastrointest Endosc 2009; 70: 860–866
10. Shi Q, Ju H, Yao LQ et al. Risk factors for postoperative stricture after endoscopic submucosal dissection for superficial esophageal carcinoma. Endoscopy 2014; 46: 640–644
11. Tsujii Y, Nishida T, Nishiyama O et al. Clinical outcomes of endoscopic submucosal dissection for superficial esophageal neoplasms: a multicenter retrospective cohort study. Endoscopy 2015; 47: 775–783
12. Bahin FF, Jayanna M, Williams SJ et al. Efficacy of viscous budesonide slurry for prevention of esophageal stricture formation after complete endoscopic mucosal resection of short-segment Barrett's neoplasia. Endoscopy 2016; 48: 71–74
13. Katada C, Muto M, Manabe T et al. Esophageal stenosis after endoscopic mucosal resection of superficial esophageal lesions. Gastrointest Endosc 2003; 57: 165–169
14. Ono S, Fujishiro M, Niimi K et al. Predictors of postoperative stricture after esophageal endoscopic submucosal dissection for superficial squamous cell neoplasms. Endoscopy 2009; 41: 661–665
15. Lewis JJ, Rubenstein JH, Singal AG et al. Factors associated with esophageal stricture formation after endoscopic mucosal resection for neoplastic Barrett's esophagus. Gastrointest Endosc 2011; 74: 753–760
16. Iizuka T, Kikuchi D, Yamada A et al. Polyglycolic acid sheet application to prevent esophageal stricture after endoscopic submucosal dissection for esophageal squamous cell carcinoma. Endoscopy 2015; 47: 341–344
17. Takahashi H, Arimura Y, Okahara S et al. Risk of perforation during dilation for esophageal strictures after endoscopic resection in patients with early squamous cell carcinoma. Endoscopy 2011; 43: 184–189
18. Barret M, Beye B, Leblanc S et al. Systematic review: the prevention of oesophageal stricture after endoscopic resection. Aliment Pharmacol Ther 2015; 42: 20–39
19. Hashimoto S, Kobayashi M, Takeuchi M et al. The efficacy of endoscopic triamcinolone injection for the prevention of esophageal stricture after endoscopic submucosal dissection. Gastrointest Endosc 2011; 74: 1389–1393

20. Sakaguchi Y, Tsuji Y, Ono S et al. Polyglycolic acid sheets with fibrin glue can prevent esophageal stricture after endoscopic submucosal dissection. Endoscopy 2015; 47: 336–340
21. Ezoe Y, Muto M, Horimatsu T et al. Efficacy of preventive endoscopic balloon dilation for esophageal stricture after endoscopic resection. J Clin Gastroenterol 2011; 45: 222–227
22. Kataoka M, Anzai S, Shirasaki T et al. Efficacy of short period, low dose oral prednisolone for the prevention of stricture after circumferential endoscopic submucosal dissection (ESD) for esophageal cancer. Endosc Int Open 2015; 3: E113–117
23. Zhou G, Yuan F, Cai J et al. Efficacy of prednisone for prevention of esophageal stricture after endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. Thorac Cancer 2017; 8: 489–494
24. Takahashi H, Arimura Y, Okahara S et al. A randomized controlled trial of endoscopic steroid injection for prophylaxis of esophageal stenosis after extensive endoscopic submucosal dissection. BMC Gastroenterol 2015; 15: 1
25. Melillo N, Corrado A, Quarta L et al. Corticosteroids, a review. Panminerva Med 2007; 49: 29–33
26. Lucendo AJ, Miehlke S, Schlag C et al. Efficacy of Budesonide Orodispersible Tablets as Induction Therapy for Eosinophilic Esophagitis in a Randomized Placebo-Controlled Trial. Gastroenterology 2019; 157: 74–86 e15
27. Pouw RE, van Vilsteren FG, Peters FP et al. Randomized trial on endoscopic resection-cap versus multiband mucosectomy for piecemeal endoscopic resection of early Barrett's neoplasia. Gastrointest Endosc 2011; 74: 35–43
28. Park CH, Shin S, Lee SK et al. Assessing the stability and safety of procedure during endoscopic submucosal dissection according to sedation methods: a randomized trial. PLoS One 2015; 10: e0120529
29. Miehlke S, Hruz P, Vieth M et al. A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis. Gut 2016; 65: 390–399
30. Straumann A, Conus S, Degen L et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology 2010; 139: 1526–1537, 1537 e1521
31. Pasha SF, Acosta RD. ASGE Standards of Practice Committee. et al. The role of endoscopy in the evaluation and management of dysphagia. Gastrointest Endosc 2014; 79: 191–201
32. Higgins JP, Thompson SG, Deeks JJ et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557–560
33. Wen J, Lu Z, Yang Y et al. Preventing stricture formation by covered esophageal stent placement after endoscopic submucosal dissection for early esophageal cancer. Dig Dis Sci 2014; 59: 658–663
34. Hanaoka N, Ishihara R, Takeuchi Y et al. Intralesional steroid injection to prevent stricture after endoscopic submucosal dissection for esophageal cancer: a controlled prospective study. Endoscopy 2012; 44: 1007–1011
35. Wen J, Lu Z, Linghu E et al. Prevention of esophageal strictures after endoscopic submucosal dissection with the injection of botulinum toxin type A. Gastrointest Endosc 2016; 84: 606–613
36. Pih GY, Kim DH, Gong EJ et al. Preventing esophageal strictures with steroids after endoscopic submucosal dissection in superficial esophageal neoplasm. J Dig Dis 2019; 20: 609–616

## SUPPLEMENATRY

**Supplementary file 1.** Patient and tumor characteristics collected from medical charts, endoscopy reports and pathology reports.

Baseline characteristics: sex, age at time of endoscopic resection, smoking status (pack years), alcohol consumption (units per week) and ASA-classification.

Treatment characteristics: type of endoscopy resection (endoscopic mucosal resection or endoscopic submucosal dissection), dose of topical budesonide, treatment duration (weeks) and reported budesonide side effects.

Tumor characteristics: tumor location (upper esophagus; 18-24 cm from the incisors, mid esophagus; 24-32 cm from the incisors, lower esophagus; 32-40 cm from the incisors, and overlapping location between two parts of the esophagus), circumference of the mucosal defect after endoscopic resection estimated by the endoscopist, tumor morphology (Paris classification: protruded lesion [0-Ip, 0-Is, 0-Ips], overlapping protruded/flat elevated lesions [0-Is + 0-IIa], flat elevated lesions [0-IIa, 0-IIa + 0-IIc], overlapping flat elevated/flat lesion [0-IIa + 0-IIb], and flat lesions [0-IIb, 0-IIc, 0-IIc + 0-IIa]), histology (ESCC or EAC), invasion depth (mucosal [m1/m2/m3] or submucosal [sm1/sm2/sm3] invasion; according to the Paris classification), the presence of lymphovascular invasion, tumor differentiation (well/moderate [G1/G2]; and poor [G3]), lateral and vertical resection margins (positive [R1] or negative [R0]), and surface of the resected specimen (in $cm^2$). Surface of the resected specimen was calculated with measurements from pathology reports, since the diameter of the tumor and resected fragment were missing in a large number of endoscopy reports. In case of a piecemeal endoscopic mucosal resection, the surface of the resected fragment could not be reliably calculated.

Follow-up information: presence of a clinically important esophageal stricture resulting in dysphagia, and the total follow-up time (defined as the time from endoscopic resection to the last hospital visit in weeks). In case of stricture formation, the following information was collected; dilation performed (yes/no), number of dilations, type of dilation (balloon/bougie), time to dilation after endoscopic resection (days), dysphagia (yes/no) and the occurrence of adverse events after dilation.

**Supplementary file 2.** Systematic literature search strategy

A systematic literature search in Pubmed and Medline was performed on 21-07-2020, with no limit on publication date. Only English studies were selected. Title and abstract of the articles were reviewed by two reviewers (S.V. and M.S.). The full text of the selected articles was reviewed thereafter. Discrepancies were discussed mutually.

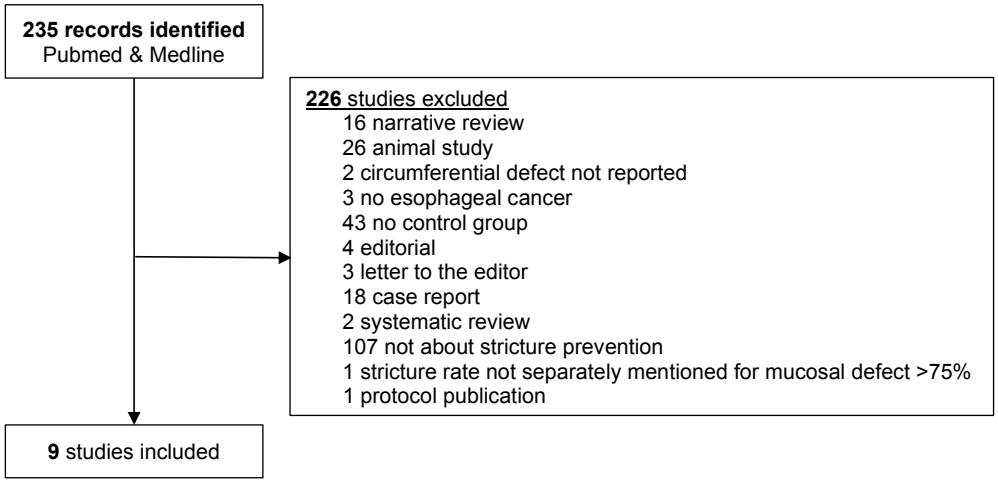
Literature search (Pubmed and Medline):

((Endoscopic Mucosal Resection [Mesh]) OR (Endoscopic Submucosal Dissection* [Title/Abstract]) OR (Dissection, Endoscopic Submucosal [Title/Abstract]) OR (Dissections, Endoscopic Submucosal [Title/Abstract]) OR (Submucosal Dissection, Endoscopic [Title/Abstract]) OR (Submucosal Dissections, Endoscopic)) AND ((Esophageal Neoplasm [Title/Abstract]) OR (Esophagus Neoplasm* [Title/Abstract]) OR (Cancer of Esophagus

[Title/Abstract]) OR (Cancer of the Esophagus [Title/Abstract]) OR (Esophagus Cancer* [Title/Abstract]) OR (Esophageal Cancer* [Title/Abstract]) OR (Esophagus Neoplasms [Mesh]) OR (Esophagus [Mesh]) OR (Adenocarcinoma [Mesh]) OR (Adenocarcinomas [Title/Abstract]) OR (Esophageal Squamous Cell Carcinoma [Mesh])) AND ((Esophageal Stenosis [Mesh]) OR (Esophageal Stenos* [Title/Abstract]) OR (Esophageal Stricture* [Title/Abstract]))

Selection criteria for included articles:

- The primary outcome of the study was the stricture rate after endoscopic resection
- The presence of a control group, including their stricture rate.
- Circumferential defect ≥75% after endoscopic resection of esophageal cancer
- Study performed in humans




**Supplementary Figure 1.** Study selection process

# CHAPTER 10.1

## Individual risk calculator to predict lymph node metastases in patients with submucosal (T1b) esophageal adenocarcinoma: a multicenter cohort study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## ABSTRACT

**Background:** Lymph node metastasis (LNM) is possible after endoscopic resection of early esophageal adenocarcinoma (EAC). This study aimed to develop and internally validate a prediction model that estimates the individual risk of metastasis in patients with pT1b EAC. early EC.

**Patients and methods:** A nationwide, retrospective, multicenter cohort study was conducted in patients with pT1b EAC treated with endoscopic resection and/or surgery between 1989 and 2016. The primary end point was presence of LNM in surgical resection specimens or detection of metastasis during follow-up. All resection specimens were histologically reassessed by specialist gastrointestinal pathologists. Subdistribution hazard regression analysis was used to develop the prediction model. The discriminative ability of this model was assessed using the c-statistic.

**Results:** 248 patients with pT1b EAC were included. Metastases were seen in 78 patients, and the 5-year cumulative incidence was 30.9% (95% confidence interval [CI] 25.1%–36.8%). The risk of metastasis increased with submucosal invasion depth (subdistribution hazard ratio [SHR] 1.08, 95%CI 1.02–1.14, for every increase of 500 µm), lymphovascular invasion (SHR 2.95, 95%CI 1.95–4.45), and for larger tumors (SHR 1.23, 95%CI 1.10–1.37, for every increase of 10 mm). The model demonstrated good discriminative ability (c-statistic 0.81, 95%CI 0.75–0.86).

**Conclusions:** A third of patients with pT1b EAC experienced metastasis within 5 years. The probability of developing post-resection metastasis was estimated with a personalized predicted risk score incorporating tumor invasion depth, tumor size, and lymphovascular invasion. This model requires external validation before implementation into clinical practice.

## INTRODUCTION

Esophageal adenocarcinoma (EAC) is an aggressive cancer, carrying a 5-year survival rate of 19%.[1] The most important prognostic factor for survival is the presence of lymph node metastasis (LNM).[2] Radical esophagectomy with lymphadenectomy has long been the standard treatment for EAC, including early cancer. Endoscopic resection is a safe and effective treatment and is indicated for the curative management of early EAC.[3] Additional surgery after endoscopic resection is advocated when the risk of LNM outweighs the risk of mortality associated with esophagectomy.[4]

Histopathological characteristics, such as lymphovascular invasion (LVI), poor tumor differentiation, and invasion into the submucosa of more than 500 µm, are associated with a risk of LNM.[5–7] When EAC is limited to the esophageal mucosa (T1a), the risk of LNM is only 1%–2% and radical endoscopic resection of the lesion suffices.[4, 8–11] When EAC invades the submucosa (T1b), guidelines recommend additional surgical resection of the esophagus and locoregional lymph nodes.[4, 9] The prevalence of LNM in esophagectomy specimens varies between 0 and 78% for T1b EACs and depends on the extent of invasion into the submucosa.[7, 12–15] Superficial submucosal invasion (sm1: ≤500 µm) was associated with variable LNM risk in previous studies (0–22%), while deep submucosal invasion was associated with higher LNM risk, ranging from 26%–36% (sm2: 501–1000 µm) to 50%–78% (sm3: >1000 µm).[12, 15–17]

In the challenging clinical scenario when LNM is not seen on imaging, management depends on metastasis risk assessment. Not every patient with pT1b EAC develops LNM, while surgery is associated with morbidity, mortality, and decreased quality of life.[18, 19] Endoscopic resection might be a good alternative for selected patients with pT1sm1 EAC in combination with “low risk” histopathological characteristics, such as well-to-moderate differentiation (G1/G2) and absent LVI.[20] Only 1.9% of these patients developed LNM.[20] Other studies also reported LNM risk of <2% in patients with pT1sm1 EAC with “low risk” histopathological characteristics.[21–23] In contrast, the LNM risk is reported to be higher (up to 9%) in patients with pT1sm1 EAC with at least one “high risk” histopathological characteristic, such as poor tumor differentiation or LVI.[24] The European Society of Gastrointestinal Endoscopy guidelines state that R0 resection of pT1bsm1,G1-2,LVI– is potentially curative and the decision about whether or not to perform additional treatment should be individualized in these patients in terms of morbidity and mortality risk vs LNM risk.[25]

Although many studies have described separate histopathological risk factors associated with LNM, no appropriate clinical tool is available that incorporates all accepted prognostic histopathological parameters to accurately predict the LNM risk on an individual basis. Little is known about how the individual risk increases with the accumulation of more than one histopathological feature. The aim of this study was to develop and internally validate a prediction model based on histopathological variables that estimates the risk of LNM or distant metastasis in individual patients with pT1b EAC.

## METHODS

### Study design

We performed a nationwide, retrospective, multicenter cohort study in collaboration with the Netherlands Cancer Registry (NCR). Since 1989, all patients diagnosed with pT1b EAC in the Netherlands have been included in the NCR. Patients diagnosed with pT1b EAC between 1989 and 2016 were selected for the current study. Eight hospitals participated in the study and were expert centers in EAC treatment. Patients with pT1b EAC were included if they were treated with primary surgery or endoscopic resection (with or without adjuvant surgery). Patients were excluded if they were treated with chemoradiotherapy prior to surgery, as we could not reliably assess whether LNM developed. We also excluded patients with no histopathology data available for review, when histological parameters could not be reassessed, or when no patient data were available in medical charts. The study was approved by the Medical Ethical Review Committee of the Erasmus Medical Center in Rotterdam, the Netherlands (MEC-2016-050) and by all local Medical Ethical Review Committees at the participating centers. Clinical data were collected from medical records, pathology reports, and endoscopy reports (Supplementary File 1).

### Histopathological reassessment

Owing to renewed pathology insights and different classification systems over the years, all resection specimens were histologically reassessed for the following parameters: submucosal invasion depth (μm), differentiation grade, and LVI. This was independently performed by three specialist gastrointestinal pathologists (F.tK., M.D., K.B.) for 84 patients, as explained in detail in our previous study.[26] The interobserver agreement was good for differentiation grade ($\kappa = 0.77$), excellent for LVI ($\kappa = 0.88$), and moderate for submucosal invasion depth ($\kappa = 0.60$).[26] For all other patients (n=164), histopathological reassessment for differentiation grade and LVI was performed by one pathologist (F.tK.) because the interobserver agreement was good and excellent, respectively, for these histopathological variables.[26] Submucosal invasion was assessed in a consensus meeting by two pathologists (K.B., M.D.) in the remaining 164 patients because the interobserver agreement was moderate for submucosal invasion depth.[26] The reassessment is explained in supplementary File 2.[27, 28]

After histopathological reassessment, patients were excluded if the tumor was located in the cardia or when tumor location was not known. Patients with vertical R1 or Rx endoscopic resection with residual tumor in biopsy or with residual EAC in surgical resection specimen were also excluded. In these cases, we could not reliably assess invasion depth or LVI. Patients with vertical R1 or Rx after endoscopic resection were included if no residual tumor was found during surgery.

### End points

The primary end point was the presence of LNM in surgically resected specimens (≥12 resected lymph nodes), or the development of metastasis during follow-up. Owing to the use of different surgical resection techniques over time, with less extensive lymphadenectomy in the past, the development of metastasis during follow-up was used as a surrogate end point for LNM in cases with fewer than 12 lymph nodes present. In cases of an endoscopic resection prior to surgical resection, the tumor was found in the endoscopic resection specimen and lymph node status in the surgical resection specimen. When no additional surgery was performed after endoscopic resection, the development of metastasis during follow-up was

used as a surrogate end point, and patients were excluded if biopsy-proven residual tumor was found after endoscopic resection.

**Follow-up**

Patient follow-up data were retrieved until November 2019. A minimum follow-up period of 2 years was required in cases with <12 lymph nodes resected during surgery or when no surgery was performed. Patients who died within 2 years after primary treatment with an unknown cause of death were excluded because it was not clear whether these patients died as a result of metastasis. Only when the cause of death was known in these patients they were included because it was clear whether metastasis had developed or not.

**Sample size calculation**

The prevalence of LNM in T1b EAC varies between 0 and 78% in previous studies.[5–7, 12–15] In these studies, LNM was found in 110/456 patients (24%, 95% confidence interval [CI] 20%–28%) who underwent esophagectomy. At least 10 events were needed per predictor in our model. We predefined that we would incorporate all four histopathological predictors: differentiation grade, submucosal invasion, LVI, and tumor size. A minimum of 40 patients with LNM were needed in our calculator. Using the lower CI for the prevalence of LNM in T1b EAC (20%), a sample size of at least 200 patients was needed for the study.

**Statistical analyses**

Baseline characteristics are described using standard descriptive statistics. Continuous data are presented as mean (range) for normally distributed data and median (interquartile range [IQR]) for skewed data. Categorical data are presented with frequencies and percentages.

**Univariable and multivariable analysis**



Different follow-up periods and the competing risk of all-cause/non-EAC mortality were taken into account using the Fine and Gray model. In the Fine and Gray model, subdistribution hazard ratios (SHRs) are estimated, describing the effect of covariates on the subdistribution hazard. SHRs and associated 95% CIs were calculated for candidate predictors. The 95% CIs were calculated through bootstrapping.

Based on previous literature about prediction model development, all variables with a *P* value of <0.2 at univariable analysis were incorporated into multivariable analysis.[29] The following variables were included in univariable analysis: sex, LVI, tumor differentiation grade, submucosal invasion depth, and tumor size. Microscopic or macroscopic tumor size was used for analysis.

Information about tumor size was missing in 38 of 248 patients (15.3%). We assumed these data were missing at random and used multiple imputation to impute the missing values 10 times. Separate analyses were performed on the 10 imputed datasets and results were subsequently pooled using Rubin rules.

Statistical analyses were performed in R version 3.6.3., the *mice* package was used for multiple imputation, and the *riskRegression* package was used to fit the Fine and Gray method.

**Prediction model and discriminative ability**

Only variables that were statistically significant ($p$ <0.05) after multivariable analysis were included in the final prediction model. For completeness, nonsignificant variables were also

incorporated into the prediction model to check whether they altered the predicted scores. Submucosal depth invasion was incorporated as a continuous variable (absolute depth invasion in µm) in the prediction model and later divided into different sm classifications in the score chart. Tumor size was also incorporated as a continuous variable in the prediction model and divided into <20 mm and ≥20 mm in the score chart; this cutoff value was chosen based on previous studies.[5, 24]

The discriminative ability of the model was assessed using the Harrell's concordance statistic (c-statistic), which varies between 0.5 (noninformative model) and 1.0 (perfect model). The model was internally validated using bootstrapping to calculate the Harrell's concordance statistic and to limit the risk of overfitting.[29] The coefficients from the subdistribution hazard regression were used to calculate the probability of developing LNM within 5 years (regression formula is presented in supplementary File 3).

Analyses were carried out using SPSS version 25 (IBM Corp., Armonk, New York, USA) for descriptive statistics and survival analysis using Kaplan–Meier, and R programming language, version 3.3.6 (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org) for univariable and multivariable analysis, cumulative incidence, and prediction model. All tests were two-sided. For final multivariable analysis, a two-sided test with a *p* value of <0.05 was considered statistically significant.

## RESULTS

A total of 524 patients with T1b EAC were selected from the NCR. After medical chart review, 90 patients were excluded (Figure 1). Histopathological reassessment was performed for 434 T1b EACs, and 115 patients were excluded because pathology did not reveal pT1b EAC (n = 76) or the tumor was not located in the esophagus (n=39). Medical charts of the 319 remaining patients with pT1b EAC were reviewed again and another 71 patients were excluded (Figure 1). A total of 248 patients were included in the final analysis.

**Patient and tumor characteristics**

Baseline characteristics are presented in Table 1. The median age of the cohort was 65.6 years (IQR 57.8–72.5) and 87.5% were male. Most patients were treated with primary surgery (166/248; 66.9%); additional surgery was performed in 49/82 (59.8%) patients who were treated with endoscopic resection. Of patients who were only treated by endoscopic resection (n=31), 30/31 (96.8%) did not develop metastasis during follow-up. Clinical N stage was cN0 in 180/248 patients (72.6%), cN1 in 42/248 patients (16.9%), and unknown before endoscopic resection in 17/248 patients (6.9%). The total number of patients with cN1 stage, including patients in whom imaging was performed after endoscopic resection, was 50. These patients were treated with surgery, and 27/50 (54.0%) were confirmed to have LNM after histopathological assessment.

Vertical resection margins were positive (R1) in pathology reports of 17/82 patients (20.7%) who underwent endoscopic resection. Additional surgical resection was performed in all patients and no residual tumor was found in surgical resection specimens.

Resection margins were reported as "unable to determine" (Rx) in 6/82 patients (7.3%). Additional surgery was performed in all patients and no residual tumor was found in surgical resection specimens.

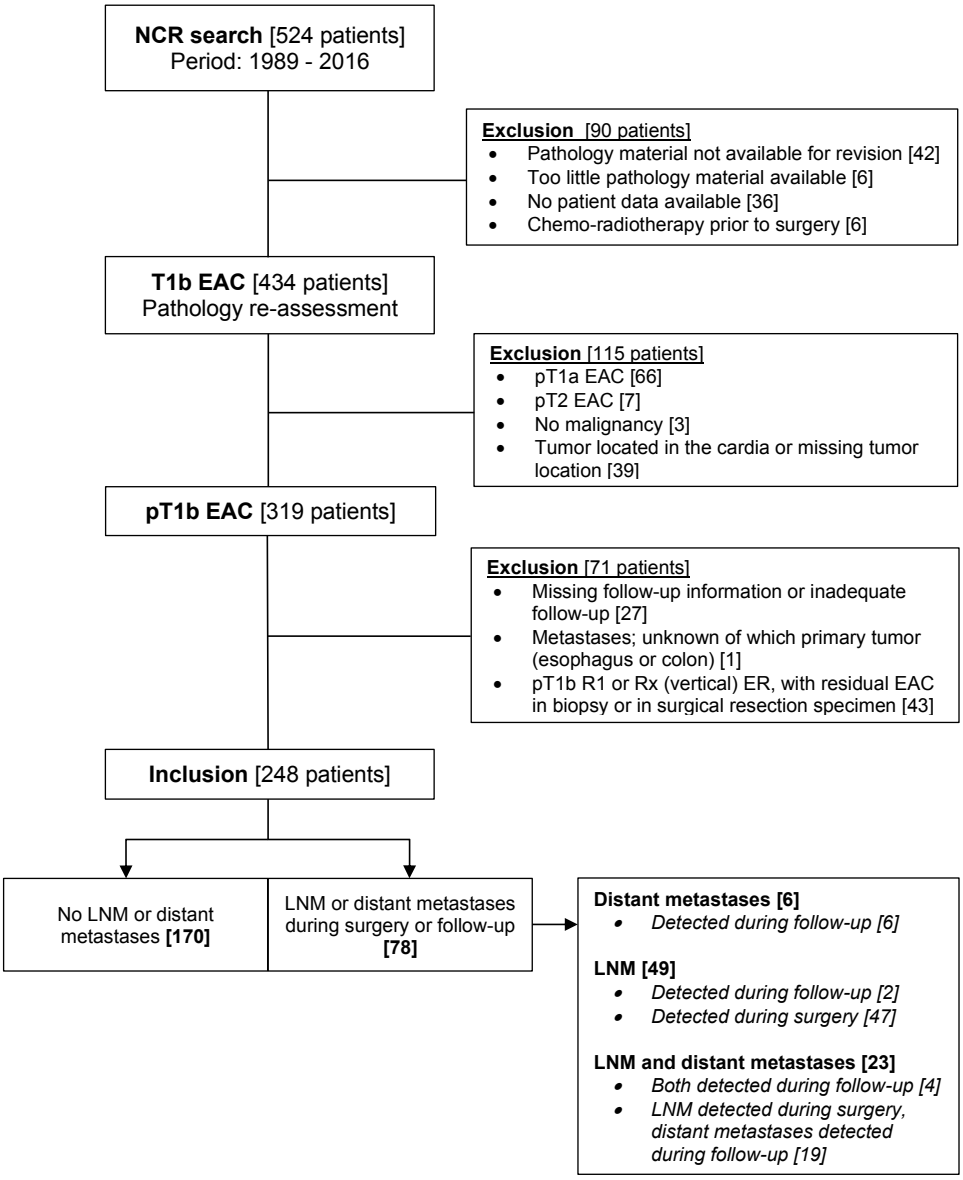



**Figure 1. Flow chart of patients**
NCR, Netherlands Cancer Registry; EAC, esophageal adenocarcinoma; LNM, lymph node metastasis

**Table 1. Clinicopathological features of the study cohort** (n = 248)

| | |
|---|---|
| Sex, n (%) | |
| Male | 217 (87.5) |
| Female | 31 (12.5) |
| Age, median (IQR), years | 65.6 (57.8–72.5) |
| Tumor location, n (%) | |
| Mid-esophagus | 7 (2.8) |
| Distal esophagus | 178 (71.8) |
| Gastroesophageal junction | 63 (25.4) |
| Primary management, n (%) | |
| Endoscopic resection | 82 (33.1) |
| EMR | 78 |
| ESD | 4 |
| Surgery | 166 (66.9) |
| Transhiatal | 114 |
| Laparoscopic transhiatal | 5 |
| Transthoracic | 38 |
| Thoraco laparoscopic | 4 |
| *Missing* | *5* |
| Vertical endoscopic resection margins, n (%)[1] | |
| R0 | 59 (72.0) |
| R1 | 17 (20.7 |
| Rx | 6 (7.3) |
| Barrett's, n (%) | |
| Yes | 173 (69.8) |
| No | 36 (14.5) |
| *Missing* | *39* |
| Tumor size | |
| Median (IQR), mm | 24.0 (15.0–32.0) |
| Missing, n | 29 |
| Differentiation grade, n (%) | |
| G1/2 | 162 (65.3) |
| G3/4 | 86 (34.7) |
| Sm invasion, n (%) | |
| Sm1 | 56 (22.6) |
| Sm2 | 51 (20.6) |
| Sm3 | 141 (56.9) |
| Submucosal invasion, median (IQR), µm | 1300 (590–2495) |
| Presence of LVI, n (%) | |
| No | 196 (79.0) |
| Yes | 52 (21.0) |
| Metastasis, n (%) | |
| No | 170 (68.5) |
| LNM | 49 (19.8) |
| Distant metastasis | 6 (2.4) |
| LNM + distant metastasis | 23 (9.3) |

IQR, interquartile range; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; sm, submucosal; LVI, lymphovascular invasion; LNM, lymph node metastasis. [1]Calculated for 82 patients in whom endoscopic resection was performed.

**Metastases**

The median follow-up time was 5.5 years (IQR 4.9–7.7) in patients treated with endoscopic resection only and when <12 lymph nodes were present in surgical resection specimens. The median follow-up time was 3.3 years (IQR 1.8–5.3) in patients treated with primary surgery with ≥12 lymph node dissections during surgery. The 5-year cumulative incidence of metastasis was 30.9% (95% CI 25.1%–36.8%) (Figure 2). In total, 78 patients developed metastasis. In 6/78 patients, only distant metastasis developed. All had undergone surgery (without LNM) for primary pT1b EAC. In only 2/6 patients were >12 lymph nodes (range 14–30) resected during surgery.

The majority of patients only developed LNM (49/78) and all these patients were treated with surgery; LNM was found during surgery in 47 patients. LNM was found during follow-up in only 2/49 patients; in one of these patients, adequate lymph nodes (n=18) had been resected during surgery.

Both LNM and distant metastasis were found in 23/78 patients. One patient was treated with endoscopic resection only (due to comorbidity), and both LNM and distant metastasis were detected during follow-up. A total of 22 patients were treated with surgery. LNM was found in the surgical resection specimen in 19/22 patients and during follow-up in 3/22 patients; in 2/3 patients, >12 lymph nodes had been resected during surgery. All distant metastasis were detected during follow-up.

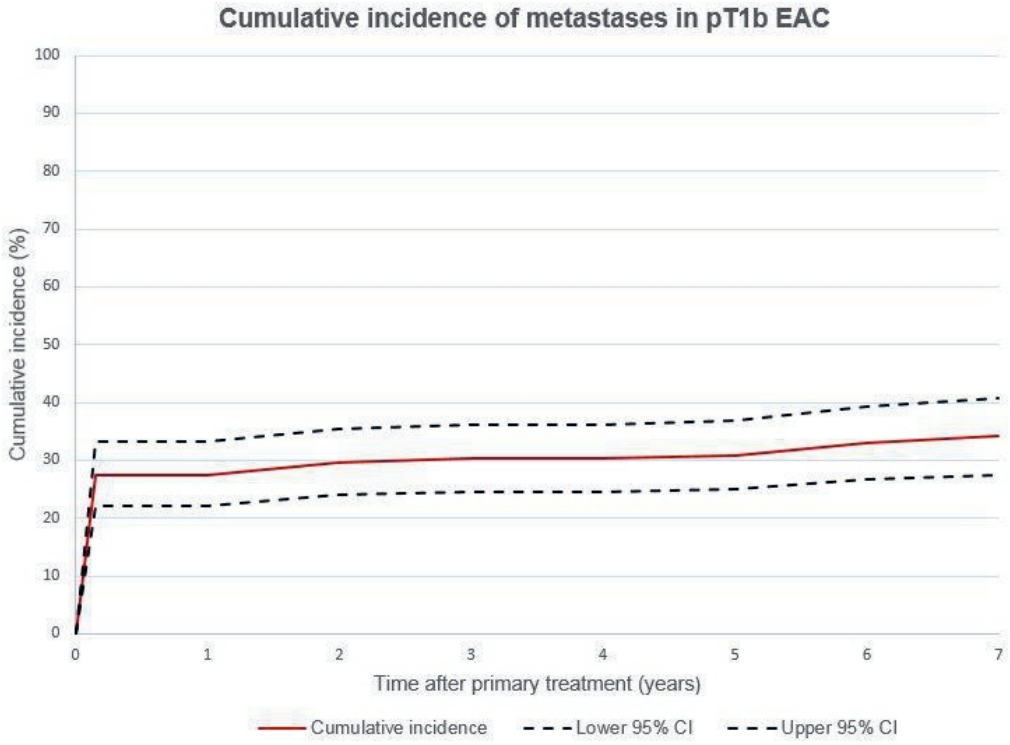
Of all detected LNMs (n=72), the majority were found in the surgical resection specimen (66/72; 91.7%). For all patients who developed metastasis (LNM or distant metastasis) during follow-up (n=31), the median time to detection was 1.9 years (IQR 1.2–4.9). The disease-specific 5-year survival rate after primary treatment was 87.5% (Supplementary file Figure 4).



**Prediction model**

In multivariable analysis, the risk of developing metastases was higher for LVI positive tumors (SHR 2.95, 95% CI 1.95–4.45), for tumors with deeper submucosal invasion (SHR 1.08, 95% CI 1.02–1.14), and for larger tumors (SHR 1.23, 95% CI 1.10–1.37) (Table 2). For every increase in invasion depth of 500 µm, the subdistribution hazard of developing metastases increased by 1.1. For every increase in tumor size of 10 mm, the subdistribution hazard of developing metastases increased by 1.2. These variables were all incorporated into the prediction model. Incorporating differentiation grade into the prediction model did not alter the outcomes and therefore this variable was not incorporated into the score chart (Table 3).

The risk of developing metastases for different combinations of histological variables is presented in the score chart (Table 3). The 5-year risk of developing metastases ranged from 5.9% (95% CI 2.3–11.2) for patients with pT1,sm1,LVI- tumors <20 mm to 70.1% (95% CI 60.5–78.7) for patients with pT1,sm3,LVI+ tumors ≥20 mm. After internal validation using bootstrapping, the prediction model demonstrated good discriminative ability with a c-statistic of 0.81 (95% CI 0.75–0.86).




| Interval | Begin total (n) | Metastases (n) | Death or lost to follow-up (censored cases) (n) | Cumulative Incidence (95% CI) |
|---|---|---|---|---|
| 0-1 year | 248 | 68 | 10 | 27.5% (22.1-33.2) |
| 1-2 year | 170 | 5 | 9 | 29.7% (24.1-35.5) |
| 2-3 year | 156 | 1 | 19 | 30.3% (24.6-36.1) |
| 3-4 year | 136 | 0 | 19 | 30.3% (24.6-36.1) |
| 4-5 year | 117 | 1 | 25 | 30.9% (25.1-36.8) |
| 5-6 year | 91 | 2 | 32 | 32.9% (26.6-39.2) |
| 6-7 year | 57 | 1 | 12 | 34.1% (27.5-40.7) |

**Figure 2. Cumulative incidence of developing metastases, with death (not related to esophageal adenocarcinoma or metastases) as competing risk.**

EAC, esophageal adenocarcinoma; CI, confidence interval.

**Table 2. Univariable and multivariable subdistributional hazard regression analysis of risk factors associated with metastases (no metastases n = 170, metastases n = 78)**

| Variable | Univariable subdistributional hazard regression analysis | | Multivariable subdistributional hazard regression analysis | |
|---|---|---|---|---|
| | SHR (95%CI) | *p* value | SHR (95%CI) | *p* value |
| Sex, n (%) | | | – | – |
| Female | Reference | | | |
| Male | 1.51 (0.74–3.10) | 0.26 | | |
| Differentiation grade | | | | |
| G1/2 (good/moderate) | Reference | | Reference | |
| G3/4 (poor/undifferentiated) | 1.78 (1.20–2.65) | <0.01 | 1.01 (0.66–1.55) | 0.96 |
| Submucosal invasion (per 500 µm) | 1.13 (1.08–1.18) | <0.01 | 1.08 (1.02–1.14)[1] | <0.01 |
| LVI | | | | |
| No | Reference | | Reference | |
| Yes | 3.58 (2.45–5.22) | <0.01 | 2.95 (1.95–4.45) | <0.01 |
| Tumor size (per 10 mm) | 1.39 (1.25–1.53) | <0.01 | 1.23 (1.10–1.37)[2] | <0.01 |

SHR, subdistribution hazard ratio; CI, confidence interval; LVI, lymphovascular invasion.
[1]For every 500 µm increase in submucosal invasion; [2]For every 10 mm increase in tumor size

**Table 3. Score chart for 5-year metastases risk (both lymph node metastases and distant metastases) for different combinations of histopathological variables in patients with pT1b esophageal adenocarcinoma**

| | LVI-, % (95%CI) | LVI+, % (95%CI) | Tumor size |
|---|---|---|---|
| sm1 | 5.9 (2.3–11.2) | 15.7 (6.0–29.3) | <20 mm |
| sm2 | 7.3 (2.6–13.8) | 19.3 (6.3–36.8) | |
| sm3 | 14.1 (7.9–21.9) | 34.7 (19.7–50.8) | |
| sm1 | 16.1 (6.2–29.2) | 38.8 (17.0–61.4) | ≥20 mm |
| sm2 | 19.4 (8.6–32.2) | 45.6 (20.8–67.9) | |
| sm3 | 35.2 (25.8–44.7) | 70.1 (60.5–78.7) | |

LVI, lymphovascular invasion; CI, confidence interval; sm, submucosa

## DISCUSSION

The selection of patients who need additional treatment due to the risk of LNM after endoscopic resection of pT1b EAC can be challenging. Not all T1b EACs are alike when it comes to metastasis risk; however, they are regarded as such in most guidelines when it comes to make rigorous treatment decisions. Although individual risk factors associated with metastases have been described, little is known about how these risk factors interrelate or whether combining them may improve estimation of LNM risk. A clinical tool that incorporates accepted prognostic parameters for LNM risk on an individual basis is not yet available.[5-7] We established a prediction model that includes histopathological tumor characteristics and estimates the individual risk of metastases in patients with pT1b EAC. This tool can be used in shared decision making about whether or not to undergo adjuvant treatment after minimally invasive endoscopic resection.

Patients treated with endoscopic resection or surgery for pT1b EAC were analyzed as one cohort to prevent possible selection bias. Endoscopic mucosal resection was introduced in 2001, and a selection bias would therefore have been created when separating patients included after 2001 based on treatment modality (endoscopic resection or surgery), because patients with relatively favorable tumor characteristics might have been treated more often with endoscopic resection instead of surgery. The median follow-up time was 5.5 years in patients treated with endoscopic resection or when <12 lymph nodes were present in surgical resection specimens. Because of this long follow-up period, we believe that analyzing both groups as a single cohort is acceptable.

In our cohort, approximately one third of patients had metastases. Risk factors for developing metastases were the presence of LVI and increased submucosal invasion depth and tumor size. After internal validation, the prediction model demonstrated good accuracy (c-statistic of 0.81). Based on our model, the estimated risk of developing metastases within 5 years of endoscopic resection or surgery ranged between 5.9% and 70.1%, depending on different combinations of histopathological variables. The high metastases risk for specific pT1b EACs is the direct result of the combination of all poor histopathological parameters. This risk can even exceed the risk of metastases for tumors with a higher T stage that do not present with LVI.[30]

The 5-year cumulative incidence of developing metastases was 30.9% (95% CI 25.1%–36.8%) in our cohort, which is in line with reported LNM rates (0–78%).[7, 12–15, 24, 31, 32] Previous studies have shown that LVI, poor tumor differentiation, progressive invasion depth, and larger tumor size are associated with LNM.[5, 7, 13, 32] We confirmed LVI, increasing invasion depth, and tumor size to be significant independent risk factors for metastases. In contrast, differentiation grade was only found to be significant in univariable analysis.

Studies have suggested a subgroup of patients with pT1b EAC in which conservative treatment after endoscopic resection may be safe.[5, 23, 24, 32] Graham et al. suggested that patients with pT1,G1/2,sm1,LVI-,R0 EAC can be treated with endoscopic resection alone because these patients (n=13) did not develop LNM during follow-up.[32] In addition, this study suggested conservative treatment after endoscopic resection of pT1bsm1 EACs with one high-risk pathological feature because 23% of the conservatively treated high-risk tumors developed LNM during follow-up.[32] However, the number of included patients in this study was too small to make recommendations.[32] Another study reported LNM in only 2% of “low-risk”

pT1b EAC patients; endoscopic resection was therefore suggested as an alternative treatment to esophagectomy.[24] A prediction model was lacking in these studies.

A study in which a prediction model was developed based on a weighted scoring system, showed that tumor size and LVI were predictors for LNM in patients with T1 EAC (both T1a and T1b), with a c-statistic of 0.82 (95% CI 0.75–0.89).[13] This study suggested that esophagectomy should be considered in patients with a high risk score (>5 points). However, patients with T1a tumors were also included and LNM was only predicted directly after surgery instead of taking follow-up into account. In addition, T1b tumors were not classified according to depth of infiltration (sm1-3).[13]

In the current large, nationwide, multicenter cohort study, histopathological reassessment and classification of all pT1b EACs was performed by consensus agreement between gastrointestinal pathologists with great expertise in EAC. The incorporated histopathological tumor characteristics were therefore valid, without missing data. Included patients were analyzed as a single cohort, regardless of primary treatment. An adequate follow-up period was guaranteed in patients treated with endoscopic resection and in patients with <12 resected lymph nodes during surgery. This is the first study with an adequate sample size that provides a good estimate for metastatic risk in patients with pT1b EAC.

However, the results of our model should be interpreted with caution due to limitations of the study. First, the retrospective study design could have resulted in selection and information bias. Several patients were excluded because of missing data. In addition, there was no standardized follow-up regimen. We are convinced, however, that it is not feasible to perform a study of this magnitude in a prospective design on T1b EAC. A second limitation and possible source of heterogeneity is the combined results of endoscopic and surgical resection specimens. Different specimen handling, sampling, and processing of endoscopic and surgical resection specimens (2 mm vs. 5 mm) may theoretically lead to an underestimation of the deepest invasion in surgical specimens and introduce bias in histological interpretation. We are aware that treatment methods have changed over time and different surgical resection techniques are used, with less extensive lymphadenectomy being performed in the past. This is, however, inevitable in retrospective studies. We therefore used the development of metastases during follow-up as a surrogate end point in these patients. A third limitation is that no additional immunohistochemical staining was performed for the assessment of LVI, because formalin-fixed paraffin-embedded tissue blocks were not readily available to us. Additional immunohistochemical staining in combination with hematoxylin and eosin staining may improve the detection of LVI.[33] The final limitation is that we did not perform external validation of the prediction model. We do not know whether our prediction model, which is mainly based on surgical data, can reliably be used to calculate LNM risk in patients treated with endoscopic resection. One can argue that the performance of the model cannot be simply transferred to patients treated with endoscopic resection. External validation of the prediction model, using histological outcomes diagnosed in endoscopic resection specimens of T1b EAC, is necessary to assess whether the model has adequate predictive value to be used in clinical practice, where the focus is on deciding whether or not patients treated with endoscopic resection for T1b EAC will benefit from additional surgery. This validation is desirable in order to test the model strength when implementing it into clinical practice. The current predicted individual metastases risk is an estimation based on a statistical model; these estimations do carry a degree of uncertainty.

In conclusion, one third of patients with pT1b EAC developed metastases. A personalized risk could be predicted based on the presence or absence of each histopathological characteristic, with good discriminative ability. Deep submucosal tumor invasion, the presence of LVI, and larger tumor size were poor prognostic factors for metastases.

## REFERENCES


1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69: 7–34
2. van der Schaaf M, Johar A, Wijnhoven B et al. Extent of lymph node removal during esophageal cancer surgery and survival. J Natl Cancer Inst 2015; 107: djv043
3. Chevaux JB, Piessevaux H, Jouret-Mourin A et al. Clinical outcome in patients treated with endoscopic submucosal dissection for superficial Barrett's neoplasia. Endoscopy 2015; 47: 103–112
4. Fitzgerald RC, di Pietro M, Ragunath K et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut 2014; 63: 7–42
5. Leers JM, DeMeester SR, Oezcelik A et al. The prevalence of lymph node metastases in patients with T1 esophageal adenocarcinoma a retrospective review of esophagectomy specimens. Ann Surg 2011; 253: 271–278
6. Liu L, Hofstetter WL, Rashid A et al. Significance of the depth of tumor invasion and lymph node metastasis in superficially invasive (T1) esophageal adenocarcinoma. Am J Surg Pathol 2005; 29: 1079–1085
7. Barbour AP, Jones M, Brown I et al. Risk stratification for early esophageal adenocarcinoma: analysis of lymphatic spread and prognostic factors. Ann Surg Oncol 2010; 17: 2494–2502
8. Dunbar KB, Spechler SJ. The risk of lymph-node metastases in patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systematic review. Am J Gastroenterol 2012; 107: 850–862
9. Spechler SJ, Sharma P, Souza RF et al. American Gastroenterological Association technical review on the management of Barrett's esophagus. Gastroenterology 2011; 140: e18–52
10. Pech O, May A, Manner H et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology 2014; 146: 652–660
11. Alvarez Herrero L, Pouw RE, van Vilsteren FG et al. Safety and efficacy of multiband mucosectomy in 1060 resections in Barrett's esophagus. Endoscopy 2011; 43: 177–183
12. Sepesi B, Watson TJ, Zhou D et al. Are endoscopic therapies appropriate for superficial submucosal esophageal adenocarcinoma? An analysis of esophagectomy specimens. J Am Coll Surg 2010; 210: 418–427
13. Lee L, Ronellenfitsch U, Hofstetter WL et al. Predicting lymph node metastases in early esophageal adenocarcinoma using a simple scoring system. J Am Coll Surg 2013; 217: 191–199
14. Stein HJ, Feith M, Bruecher BL et al. Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. Ann Surg 2005; 242: 566–575
15. Westerterp M, Koppert LB, Buskens CJ et al. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch 2005; 446: 497–504
16. Kaneshiro DK, Post JC, Rybicki L et al. Clinical significance of the duplicated muscularis mucosae in Barrett esophagus-related superficial adenocarcinoma. Am J Surg Pathol 2011; 35: 697–700
17. Bollschweiler E, Baldus SE, Schroder W et al. High rate of lymph-node metastasis in submucosal esophageal squamous-cell carcinomas and adenocarcinomas. Endoscopy 2006; 38: 149–156
18. Linden PA, Towe CW, Watson TJ et al. Mortality after esophagectomy: analysis of individual complications and their association with mortality. J Gastrointest Surg 2020 Sep;24(9):1948-1954.
19. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med 2011; 364: 2128–2137

20. Manner H, Pech O, Heldmann Y et al. Efficacy, safety, and long-term results of endoscopic treatment for early stage adenocarcinoma of the esophagus with low-risk sm1 invasion. Clin Gastroenterol Hepatol 2013; 11: 630–635
21. Manner H, May A, Pech O et al. Early Barrett's carcinoma with "low-risk" submucosal invasion: long-term results of endoscopic resection with a curative intent. Am J Gastroenterol 2008; 103: 2589–2597
22. Scholvinck D, Kunzli H, Meijer S et al. Management of patients with T1b esophageal adenocarcinoma: a retrospective cohort study on patient management and risk of metastatic disease. Surg Endosc 2016; 30: 4102–4113
23. Alvarez Herrero L, Pouw RE, van Vilsteren FG et al. Risk of lymph node metastasis associated with deeper invasion by early adenocarcinoma of the esophagus and cardia: study based on endoscopic resection specimens. Endoscopy 2010; 42: 1030–1036
24. Manner H, Pech O, Heldmann Y et al. The frequency of lymph node metastasis in early-stage adenocarcinoma of the esophagus with incipient submucosal invasion (pT1b sm1) depending on histological risk patterns. Surg Endosc 2015; 29: 1888–1896
25. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2015; 47: 829–854
26. Gotink AW, ten Kate FJ, Doukas M et al. Do pathologists agree with each other on the histological assessment of pT1b oesophageal adenocarcinoma? United European Gastroenterol J 2019; 7: 261–269
27. Bosman FT, Carneiro F, Hruban RH, Theise ND, eds. WHO classification of tumours of the digestive system. 4th edn. Volume 3. Lyon: International Agency for Research on Cancer 2010
28. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003; 58: S3–43
29. Steyerberg EW. Clinical prediction models – a practical approach to development, validation, and updating. 2nd edn. New York: Springer-Verlag; 2009
30. Siewert JR, Stein HJ, Feith M et al. Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons from more than 1,000 consecutive resections at a single center in the Western world. Ann Surg 2001; 234: 360–367
31. Buskens CJ, Westerterp M, Lagarde SM et al. Prediction of appropriateness of local endoscopic treatment for high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. Gastrointest Endosc 2004; 60: 703–710
32. Graham D, Sever N, Magee C et al. Risk of lymph node metastases in patients with T1b oesophageal adenocarcinoma: a retrospective single centre experience. World J Gastroenterol 2018; 24: 4698–4707
33. Hosono I, Miyahara R, Furukawa K et al. Use of immunostaining for the diagnosis of lymphovascular invasion in superficial Barrett's esophageal adenocarcinoma. BMC Gastroenterol 2020; 20: 175

## SUPPLEMENTARY

**Supplementary file 1.** Patient and tumor characteristics collected from medical charts, endoscopy reports and pathology reports.

Patient characteristics: sex and age.

Tumor characteristics: tumor location (mid esophagus; 24-32cm from the incisors, distal esophagus; 32-40cm from the incisors, gastro-esophageal junction; junction between the esophagus and the stomach approximated by the most proximal extent of the gastric folds), tumor size (mm), differentiation grade, submucosal invasion depth (µm), the presence of lymphovascular invasion (LVI), radicality of vertical resection margins after endoscopic resection, and the presence of Barrett's esophagus after endoscopic resection.

Treatment characteristics: primary treatment (endoscopic resection or surgery) and resection method (endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), transhiatal, laparoscopic transhiatal, transthoracic, thoraco-laparoscopic esophagus resection, or gastric resection).

Follow-up data: the presence and date of LNM or distant metastases (metastases) during follow-up, last date of follow-up, vital outcome, and date and cause of death in case of mortality.

**Supplementary file 2.** Histopathological reassessment.

Formalin-fixed paraffin-embedded (FFPE) tissue blocks and hematoxylin and eosin stained (H&E) slides were obtained from pathology departments. For differentiation grade and LVI, whole case H&E slide sets were reassessed. Tumor differentiation grade was classified as G1: well differentiated, G2: moderately differentiated, G3: poorly differentiated and G4: undifferentiated, according to the World Health Organization classification for tumor grading.[27] For final analysis, G1 and G2, and G3 and G4 were combined. LVI was defined as either present or absent. The histopathological reassessment of submucosal invasion depth is explained in detail in Gotink et al.[26] All H&E slides were reassessed by one pathologist [F.tK.] to confirm submucosal invasion. The H&E slide and corresponding FFPE block with the deepest submucosal tumor invasion were identified and additional sections of 4 µm thick were cut. The slides were deparaffinized and incubated with pankeratin, Protease and desmin. Subsequently, slides were counterstained with hematoxylin and digitalized to measure the submucosal invasion depth (µm). Absolute submucosal invasion depth was assessed in a consensus meeting by two pathologists [M.D., K.B.]. Additionally, tumors with maximum invasion depth ≤500µm were defined as sm1; invasion depth of 501µm-1000µm as sm2, and invasion depth >1000µm as sm3 according to the Paris classification.[28] In patients who underwent additional surgery after endoscopic resection, both resection specimens (endoscopy and surgery) were reassessed when residual tumor was found in the surgical resection specimen to determine the deepest submucosal invasion.

**Supplementary file 3.**

Regression formula to calculate the predicted 5-year metastases risk: lp <- 0.21 * Tumor length/10 + 0.08 * submucosal invasion/500 + 1.09 * LVI positive P(LNM free survival after 5 years) = 1 – exp(-exp(lp) * 0.095)

**Supplementary file 4.** Disease specific survival after primary treatment of esophageal adenocarcinoma.

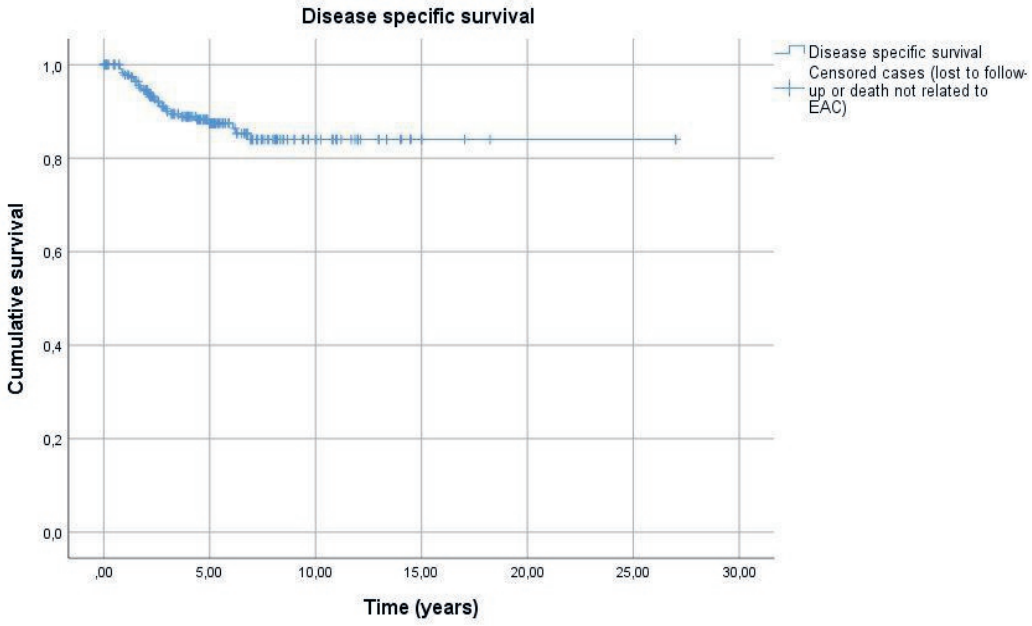



**Figure S4:** Disease specific survival after primary treatment of esophageal adenocarcinoma

| Interval (years) | Number at risk* (n) | EAC related death (n) | Non EAC related death or lost to follow-up (censored cases) (n) |
|---|---|---|---|
| 0 – 1 | 248 | 5 | 22 |
| 1 – 2 | 221 | 7 | 13 |
| 2 – 3 | 201 | 9 | 25 |
| 3 – 4 | 167 | 2 | 21 |
| 4 – 5 | 144 | 2 | 27 |
| 5 – 6 | 115 | 0 | 36 |
| 6 – 7 | 79 | 3 | 13 |
| 7 – 8 | 63 | 0 | 15 |
| 8 – 9 | 48 | 0 | 11 |
| 9 – 10 | 37 | 0 | 6 |
| 10 – 15 | 31 | 0 | 25 |
| 15 – 20 | 6 | 0 | 4 |

**at start interval*

# CHAPTER 10.2

## Quantification of lymphovascular invasion is useful to predict lymph node metastases in patients with submucosal (T1b) esophageal adenocarcinoma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## ABSTRACT

**Aim:** To quantify lymphovascular invasion (LVI) and to assess the prognostic value in patients with pT1b esophageal adenocarcinoma (EAC).

**Methods:** In this nationwide, retrospective cohort study, patients were included if they were treated with surgery or endoscopic resection for pT1b EAC. Primary endpoint was the presence of metastases (lymph node metastases or distant metastases) in surgical resection specimens or during follow-up. A prediction model to identify risk factors for metastases was developed and internally validated.

**Results:** 248 patients were included. LVI was distributed as follows: no LVI (n=196; 79.0%), 1 LVI focus (n=16; 6.5%), 2-3 LVI foci (n=21; 8.5%), and ≥4 LVI foci (n=15; 6.0%). Seventy-eight patients had metastases. The risk of metastases was increased for tumors with 2-3 LVI foci (Subdistribution hazard ratio [SHR] 3.39, 95% CI 2.10-5.47) and ≥4 LVI foci (SHR 3.81, 95% CI 2.37-6.10). The prediction model demonstrated a good discriminative ability (c-statistic 0.81).

**Conclusion:** The risk of metastases is higher when more LVI foci are present. Quantification of LVI could be useful for a more precise risk estimation of metastases. This model needs to be externally validated before implementation into clinical practice.

## INTRODUCTION

The presence of lymph node metastases (LNM) is an important prognostic factor in submucosal esophageal adenocarcinoma (pT1b EAC).[1] Various risk factors for LNM have been identified including depth of infiltration, grade of differentiation and lymphovascular invasion (LVI ).[2-6]

We recently developed a prediction model based on histopathological risk factors to estimate the risk for metastases in patients with pT1b EAC.[6] We showed that LVI was the strongest predictor for metastases with an estimated 5-year risk of developing metastases ranging between 15.7%-70.1% for pT1b EAC with LVI as compared to 5.9%-35.2% for those without LVI.[6] Other studies reported a worse 5-year survival in patients with pT1b EAC with LVI compared to pT1b EAC without LVI (27% vs. 77%, *p<0.01*).[7, 8]

LVI is often reported as a dichotomous parameter; either absent or present.[6-14] Intuitively, there may be a differential metastatic risk in case of only a single LVI focus versus a case with extensive LVI. This is supported by a study on gastric cancer in which a higher number of lymphatic tumor emboli was an independent predictor for LNM.[15] We hypothesized that the number of LVI foci in pT1b EAC is of influence on patient outcome. Quantification of LVI may possibly further classify these patients into low- and high-risk for the development of metastases.

The aim of this study was to quantify LVI and to assess the prognostic value in patients with pT1b EAC.



## MATERIALS AND METHODS

This was a nationwide retrospective cohort study. Patients diagnosed with pT1b EAC between 1989 and 2016 were included. This study was approved by all Medical Ethical Review Committees in the participating centers [MEC-2016-050]. A detailed description of in- and exclusion criteria, data collection, patient selection, reassessment of histopathological variables and the statistical analyses can be found in our previous study, as the present study is an extension to our previous study.[6] Histopathology reassessment was performed by three gastrointestinal pathologist for 84 patients to calculate the inter-observer agreement as explained in our previous study.[16] For the other 164 patients, histopathological reassessment was performed by one pathologist for LVI ($\kappa = 0.88$) and differentiation grade ($\kappa = 0.77$) because of the good and excellent interobserver agreement.[16]

A model was developed to predict the risk of metastases in patients with pT1b EAC.[6] In the prediction model of the present study, quantification of LVI on a four tier assessment scale is incorporated instead of interpreting LVI as a dichotomous parameter. The same patient cohort is used and the same statistical analyses are performed as in our previous study.[6] The added value of LVI quantification to the model was assessed using the likelihood ratio test and quantified by the increase in Harrell's concordance index (c-statistic).

### Histopathological reassessment of LVI and LVI quantification

Whole case hematoxylin and eosin stained (H&E) slide sets were used for LVI reassessment. Immunohistochemical staining was not performed because formalin-fixed paraffin embedded tissue blocks were not available. Initially, LVI was defined as being present or absent as in standard clinical practice. All slides were assessed with high power up to and including the submucosa. When LVI was present, all LVI foci were counted in every H&E slide that was available. In general, resection specimens of 2mm thickness were assessed when endoscopic resection was performed in contrast to 5mm thickness when surgical resection was performed. Figure 1 shows an example of an H&E slide with three LVI foci. The LVI focus number was the sum of all counted LVI foci in all H&E slides from one patient. In patients in whom LVI was analyzed by three pathologists, the highest LVI focus number was included for analysis. Patients were categorized into four groups based on the number of LVI foci; no-LVI, 1 LVI focus, 2-3 LVI foci or ≥4 LVI foci. This 4-tier assessment scale was used to create different LVI foci groups with less LVI (1 LVI focus), moderate LVI (2-3 LVI foci), or extensive LVI (≥4 LVI foci).

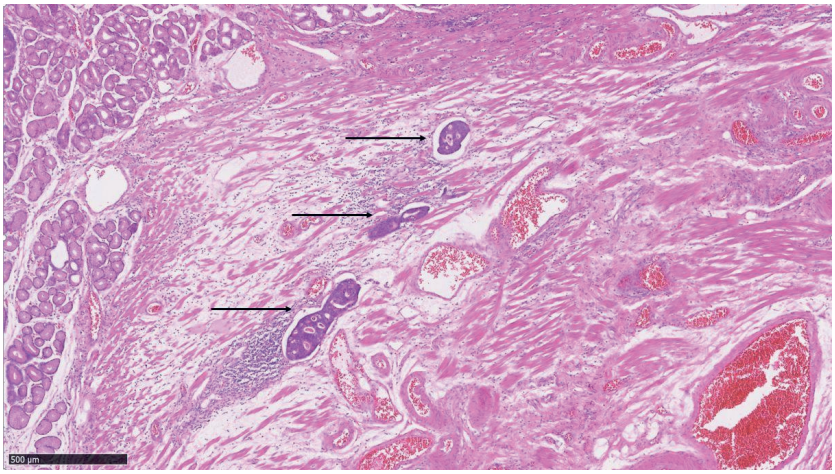


**Figure 1**. Quantification of LVI; three LVI foci, indicated by an arrow. This case nicely illustrated an example of three foci of LVI which may very well all be located in the same lymph vessel.

### Endpoints

The primary endpoint was the presence metastases defined as LNM in surgical resection specimens or the development of metastases (LNM or distant metastases) during follow-up. In case surgical resection was performed, at least 12 lymph nodes were required for adequate assessment of LNM.[16] The development of metastases during follow-up was used as a surrogate endpoint in case no surgery was performed after endoscopic resection (ER), or if surgical resection specimen contained <12 lymph nodes without LNM. In these cases, a minimum follow-up period of two years was required. If patients died within these two years, they were only included if cause of death was known.

## RESULTS

In total, 248 patients with pT1b EAC were included. Patient characteristics are presented in Table 1. Primary endoscopic resection was performed in 82 of 248 (33.1%) patients and primary surgery was performed in 166 of 248 (66.9%) patients. Of patients who were treated with endoscopic resection, additional surgery was performed in 49/82 (59.8%) patients. Local recurrence was detected during follow-up in 12 of 248 (4.8%) patients, of whom 11 also developed metastasis.

**Table 1. Patient characteristics and number of LVI foci** (n=248)

| Parameter | Total cohort (n=248) |
|---|---|
| **Gender, n (%)** | |
| Male | 217 (87.5%) |
| Female | 31 (12.5%) |
| **Median age, years (IQR)** | 65.6 (57.8-72.5) |
| **Presence of LVI, n (%)** | 52 (21.0%) |
| **LVI foci** | |
| *1* | *16* |
| *2* | *10* |
| *3* | *11* |
| *4* | *6* |
| *5-10* | *9* |
| **Metastasis, n (%)** | |
| LNM | 49 (19.8%) |
| Distant metastasis | 6 (2.4%) |
| LNM + Distant metastasis | 23 (9.3%) |

IQR, interquartile range; LVI, lymphovascular invasion; LNM, lymph node metastases;

### Quantification of LVI

There were 52 patients with LVI positive tumors. The LVI focus number was distributed from 1 to 10 foci (Table 1). LVI quantification was determined by three gastrointestinal pathologist in 17/52 patients [F.tK., M.D., K.B.]. In the remaining 35 patients, LVI quantification was determined by one pathologist [F.tK.] because the inter-observer variability was excellent for LVI (κ=0.88).(17) The median LVI focus number was 2.5 (IQR 1-4). One, two or three LVI foci were most often present (37/52; 71.2%). LVI was categorized as follows: no LVI (n=196; 79.0%), 1 LVI focus (n=16; 6.5%), 2-3 LVI foci (n=21; 8.5%), and ≥4 LVI foci (n=15, 6.0%).

### Metastases

Some 78 of 248 patients had metastases (Table 1), with a 5-year cumulative incidence of 30.9% (95% CI 25.1%-36.8%) (Figure 2, Chapter 10.1). In patients treated with primary surgery (≥12 lymph node dissections) the median follow-up time was 3.3 years (IQR 1.8-5.3). In patients treated with surgery (<12 lymp node dissections) or endoscopic resection only, the median follow-up period was 5.5 years (IQR 4.9-7.7) The majority of patients developed LNM only (49/78). These patients were all treated with surgery: LNM were detected during surgery

in 47 patients and during follow-up in two patients. Six patients developed distant metastases only, all were treated with surgery for EAC (without LNM). Adequate lymph nodes (>12) were resected in only two of these six patients. Twenty-three patients developed both LNM and distant metastases. Surgery was performed in 22/23 patients, LNM was found in surgical resection specimen in 19 patients and during follow-up in three patients. One patient was treated with endoscopic resection only due to comorbidity, metastases were detected during follow-up. Of all patients who developed metastases during follow-up, the median interval between EAC diagnosis and detection of metastases was 1.9 years (IQR: 1.2-4.9).

**Risk factor analysis**

*Univariable analysis*

The number of LVI foci was associated with presence of metastases. Tumors with 1 LVI focus had metastases in 37.5%, tumors with 2-3 LVI foci had metastases in 71.4% and tumors with ≥4 LVI foci had metastases in 93.3% (Table 2). In contrast, 22% of patients without LVI developed metastases.

*Multivariable analysis*

For every increase of tumor invasion with 500µm, the subdistribution hazard of developing metastases increased with 1.08 (95% CI 1.02-1.14) (Table 2). The presence of 2-3 LVI foci (SHR 3.39, 95% CI 2.10-5.47) and the presence of ≥4 LVI foci (SHR 3.81, 95% CI 2.37-6.10) were independent predictors for metastases compared to patients without LVI. In contrast, the presence of only one LVI focus was not significantly correlated with metastases after multivariable analysis. For every increase of tumor size with 10mm, the subdistribution hazard of developing metastases increased with 1.23 (95% CI 1.09-1.38). Poor differentiation grade was not an independent risk factor for metastases (SHR 0.98, 95% CI 0.65-1.50), this variable was therefore not incorporated into the prediction model.

**Prediction model development and validation**

The 5-year risk of developing metastases for different combinations of histopathological tumor characteristics is illustrated in Table 3B. The prediction model with LVI incorporated as a dichotomous variable is presented in Table 3A.[6] In Table 3B, the predicted score was 16.1% (95% CI 6.2-29.2) for patients with pT1b EAC ≥20mm, sm1 invasion depth without LVI, compared to 22.2% (95% CI 6.2-45.3) when one LVI focus is present, 37.0% (95% CI 16.0-62.3) when 2-3 LVI foci are present and 47.1% (95% CI 21.1-72.9) ) when ≥4 LVI foci are present. Internal validation of the prediction model showed a good discriminative ability with a c-statistic of 0.81 (95% CI 0.74-0.87), which did not increase compared to the c-statistic of the previous model (p=0.71).

**Table 2. Univariable and multivariable subdistributional hazard regression analysis of risk factors associated with metastases**

| Variable | No metastases (n=170) | Metastases (n=78) | Univariable subdistributional hazard regression | | Multivariable subdistributional hazard regression | |
|---|---|---|---|---|---|---|
| | | | SHR (95% CI) | p-value | SHR (95% CI) | p-value |
| **Sex, n (%)** | | | | | | |
| Female | 24 (77%) | 7 (23%) | Reference | | - | - |
| Male | 146 (67%) | 71 (33%) | 1.51 (0.74-3.10) | 0.26 | | |
| **Differentiation grade, n (%)** | | | | | | |
| G1/G2 (good/moderate) | 121 (75%) | 41 (25%) | Reference | | Reference | |
| G3/4 (poor/undifferentiated) | 49 (57%) | 37 (43%) | 1.78 (1.20-2.65) | **<0.01** | 0.98 (0.65-1.50) | 0.94 |
| **Median tumor length (mm) (IQR)** | 20 (13-29) | 30 (25-44) | 1.39 (1.25-1.53)* | **<0.01** | 1.23 (1.09-1.38)* | **<0.01** |
| **Median submucosal invasion (µm) (IQR)** | 958 (409-2100) | 2165 (1173-3500) | 1.13 (1.08-1.18)** | **<0.01** | 1.08 (1.02-1.14)** | **<0.01** |
| **LVI, n (%)** | | | | | | |
| No LVI | 153 (78%) | 43 (22%) | Reference | **-** | Reference | |
| LVI 1 | 10 (62.5%) | 6 (37.5%) | 1.81 (0.84-3.90) | 0.13 | 1.72 (0.89-3.32) | 0.11 |
| LVI 2-3 | 6 (28.6%) | 15 (71.4%) | 3.90 (2.47-6.15) | **<0.01** | 3.39 (2.10-5.47) | **<0.01** |
| LVI ≥4 | 1 (6.7%) | 14 (93.3% | 5.54 (3.82-8.04) | **<0.01** | 3.81 (2.37-6.10) | **<0.01** |

* for every increase of 10mm; ** for every 500µm increase of sm invasion; LVI, lymphovascular invasion; IQR, interquartile range; SHR, Subdistribution Hazard Ratio; CI, Confidence Interval

**Table 3A. Score chart; 5-year risk (%) of developing metastases for different combinations of histopathological characteristics in pT1b esophageal adenocarcinoma; LVI incorporated as present or absent.**

| Tumor size | Submucosal invasion | LVI - | LVI + |
|---|---|---|---|
| | | % (95% CI) | % (95% CI) |
| <20mm | sm1 | 5.9 (2.3-11.2) | 15.7 (6.0-29.3) |
| | sm2 | 7.3 (2.6-13.8) | 19.3 (6.3-36.8) |
| | sm3 | 14.1 (7.9-21.9) | 34.7 (19.7-50.8) |
| ≥20mm | sm1 | 16.1 (6.2-29.2) | 38.8 (17.0-61.4) |
| | sm2 | 19.4 (8.6-32.2) | 45.6 (20.8-67.9) |
| | sm3 | 35.2 (25.8-44.7) | 70.1 (60.5-78.7) |

CI, confidence interval; LVI, lymphovascular invasion; sm, submucosal

**Table 3B. Score chart; 5-year risk (%) of developing metastases for different combinations of histopathological characteristics in pT1b esophageal adenocarcinoma; LVI incorporated as absent, 1 LVI focus, 2-3 LVI foci or ≥4 LVI foci.**

| Tumor size | Submucosal invasion | LVI - | LVI 1x | LVI 2-3 | LVI ≥4 |
|---|---|---|---|---|---|
| | | % (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) |
| <20mm | sm1 | 5.9 (2.3-11.2) | 10.9 (3.0-24.4) | 19.5 (7.4-37.7) | 25.7 (9.7-48.3) |
| | sm2 | 7.3 (2.6-13.8) | 13.4 (3.8-30.1) | 24.1 (8.6-44.2) | 31.6 (11.0-55.5) |
| | sm3 | 14.1 (7.9-21.9) | 26.3 (10.6-45.3) | 43.5 (26.6-61.5) | 54.4 (33.7-72.8) |
| ≥20mm | sm1 | 16.1 (6.2-29.2) | 22.2 (6.2-45.3) | 37.0 (16.0-62.3) | 47.1 (21.1-72.9) |
| | sm2 | 19.4 (8.6-32.2) | 26.3 (8.4-51.0) | 44.4 (20.2-66.2) | 55.2 (26.4-77.9) |
| | sm3 | 35.2 (25.8-44.7) | 48.4 (21.5-69.3) | 70.2 (56.6-81.4) | 80.6 (72.3-88.5) |

CI, confidence interval; LVI, lymphovascular invasion; sm, submucosal

## DISCUSSION

LVI has so far only been evaluated as a dichotomous parameter: either absent or present.[6-9] In this study, we aimed to determine whether quantification of LVI provides additional prognostic information in patients with pT1b EAC. The results of our study show that the presence of more LVI foci was correlated with a higher risk for metastases. We believe that quantification of LVI may further classify pT1b EAC for a more accurate risk estimation of metastases.

Accurate risk estimation is important for shared decision making, whether or not to undergo adjuvant therapy after ER of pT1b EAC. Compared to the risk in LVI+ patients in the previous model, the metastases risk in the current model is lower in case of 1 LVI focus and higher in case of 2-3 LVI foci and ≥4 LVI foci.[6] As a consequence, a lower metastases risk can result in the decision to perform endoscopic surveillance instead of esophagectomy and a high metastases risk may result in an advice to offer neo-adjuvant therapy before esophagectomy.

The more accurate this prediction is, the better a patient can be informed and the better the decision about (neo-)adjuvant therapy can be made.

Remarkable is that the presence of only 1 LVI focus was not an independent predictor for metastases. The predicted 5-year metastases risk in patients with only 1 LVI focus is more in line with the risk in patients without LVI. One could argue that the presence of 1 LVI focus is negligible.

To our knowledge, this is the first study that evaluates quantification of LVI in pT1b EAC. We could therefore not compare our results with previous studies. LVI has also been identified as a strong predictor for LNM in other cancer types.[15, 18] The number of lymphatic tumor emboli was an independent predictor for LNM in early gastric cancer with LVI.[15] The more lymphatic tumor emboli were present, the higher the LNM risk.[15]

Despite the promising results of our study, it is unlikely that the application of the current model will change clinical practice soon. The difference in predicted metastasis risk between the LVI foci groups is relatively small and still high in all scenarios. Although the metastases risk in patients with only 1 LVI focus is much lower than the risk in patients with 2-3 or ≥4 LVI foci, the advice for adjuvant treatment or active surveillance after ER will probably not change based on the number of LVI foci. We are looking for a better risk assessment for metastasis to make active surveillance possible on the one hand. On the other hand, the presence of extensive LVI could be a reason to combine surgery with neo-adjuvant therapy. The better this risk assessment, the better we can apply tailored therapy for patients with pT1b EAC. Therefore, further research on LVI quantification is necessary to assess whether it is possible to identify a subgroup of patients with LVI positive tumors with a low or high risk of metastases.



Our study is subject to certain limitation First, the retrospective design of our study could result in information and selection bias. There was no standard follow-up regime, which could have resulted in a different number of reported and actual number of metastases. Second, although the inter-observer agreement for LVI was excellent as presented in our previous study, differences in LVI foci between pathologists were not discussed in a consensus meeting.[17] Moreover, when multiple LVI foci were detected, it was uncertain whether these foci represented LVI in different vascular structures. It is very well possible that multiple foci in the H&E section actually represented tumor localization in the same vascular structure. Third, additional immunohistochemical staining was not performed in the assessment of LVI and this may improve LVI detection.[19] Moreover, retraction artifacts related to tissue specimen preparation are difficult to distinguish from LVI in H&E slides.[20] Fourth, endoscopic and surgical resection specimens were combined in the results of our study, which introduces heterogeneity. Sampling and processing of endoscopic and surgical resection specimens are different (2mm vs. 5mm) and this might introduce bias in histological interpretation. In addition, the number of LVI foci were counted in every available H&E slide. It might be that the number of LVI foci is higher when more slides are available in one patient. However, studies about this subject are lacking. The last limitation is that external validation of our prediction model was not performed. Although our sample size was large, it was still not large enough to perform external validation. As a consequence, we do not know whether our model has adequate predictive value to be used in clinical practice. External validation is desirable when implementing it into daily clinical practice.

A major strength of our study is that all histopathological slides and tumor characteristics were reassessed by gastrointestinal pathologists. The incorporated tumor characteristics were valid without missing data. Another strength of the study is the cooperation with the Netherlands Cancer Registration, which enabled us to incorporate all eligible patients.

To conclude, this prediction model suggests that quantification of LVI may further refine risk estimation in pT1b EAC. External validation of the model and more research regarding LVI quantification are required to confirm our findings.

## REFERENCES


1. Van der Schaaf M, Johar A, Wijnhoven B et al. Extent of lymph node removal during esophageal cancer surgery and survival. J Natl Cancer Inst 2015; 107:
2. Barbour AP, Jones M, Brown I et al. Risk stratification for early esophageal adenocarcinoma: analysis of lymphatic spread and prognostic factors. Ann Surg Oncol 2010; 17: 2494-2502
3. Liu L, Hofstetter WL, Rashid A et al. Significance of the depth of tumor invasion and lymph node metastasis in superficially invasive (T1) esophageal adenocarcinoma. Am J Surg Pathol 2005; 29: 1079-1085
4. Leers JM, DeMeester SR, Oezcelik A et al. The prevalence of lymph node metastases in patients with T1 esophageal adenocarcinoma a retrospective review of esophagectomy specimens. Ann Surg 2011; 253: 271-278
5. Shimada H, Nabeya Y, Matsubara H et al. Prediction of lymph node status in patients with superficial esophageal carcinoma: analysis of 160 surgically resected cancers. Am J Surg 2006; 191: 250-254
6. Gotink AW and van de Ven SEM et al. Individual risk calculator to predict lymph node metastases in patients with submucosal (T1b) esophageal adenocarcinoma: a multicenter cohort study. Endoscopy 2021
7. Watanabe M, Kuwano H, Araki K et al. Prognostic factors in patients with submucosal carcinoma of the oesophagus. Br J Cancer 2000; 83: 609-613
8. Cen P, Hofstetter WL, Correa AM et al. Lymphovascular invasion as a tool to further subclassify T1b esophageal adenocarcinoma. Cancer 2008; 112: 1020-1027
9. Manner H, Wetzka J, May A et al. Early-stage adenocarcinoma of the esophagus with mid to deep submucosal invasion (pT1b sm2-3): the frequency of lymph-node metastasis depends on macroscopic and histological risk patterns. Dis Esophagus 2017; 30: 1-11
10. Torres CM, Wang HH, Turner JR et al. Pathologic prognostic factors in esophageal squamous cell carcinoma: a follow-up study of 74 patients with or without preoperative chemoradiation therapy. Mod Pathol 1999; 12: 961-968
11. Tomita N, Matsumoto T, Hayashi T et al. Lymphatic invasion according to D2-40 immunostaining is a strong predictor of nodal metastasis in superficial squamous cell carcinoma of the esophagus: algorithm for risk of nodal metastasis based on lymphatic invasion. Pathol Int 2008; 58: 282-287
12. Amano T, Matsumoto T, Hayashi T et al. Subepithelial extension of squamous cell carcinoma in the esophagus: histopathological study using D2-40 immunostaining for 108 superficial carcinomas. Pathol Int 2007; 57: 759-764
13. Mori D, Yamasaki F, Shibaki M et al. Lateral peritumoral lymphatic vessel invasion can predict lymph node metastasis in esophageal squamous cell carcinoma. Mod Pathol 2007; 20: 694-700
14. Inoue A, Moriya H, Katada N et al. Intratumoral lymphangiogenesis of esophageal squamous cell carcinoma and relationship with regulatory factors and prognosis. Pathol Int 2008; 58: 611-619
15. Park JW, Ahn S, Lee H et al. Predictive factors for lymph node metastasis in early gastric cancer with lymphatic invasion after endoscopic resection. Surg Endosc 2017; 31: 4419-4424
16. Dutkowski P, Hommel G, Bottger T et al. How many lymph nodes are needed for an accurate pN classification in esophageal cancer? Evidence for a new threshold value. Hepatogastroenterology 2002; 49: 176-180
17. Gotink AW, Ten Kate FJ, Doukas M et al. Do pathologists agree with each other on the histological assessment of pT1b oesophageal adenocarcinoma? United European Gastroenterol J 2019; 7: 261-269
18. Blok JM, Pluim I, Daugaard G et al. Lymphovascular invasion and presence of embryonal carcinoma as risk factors for occult metastatic disease in clinical stage I nonseminomatous germ cell tumour: a systematic review and meta-analysis. BJU Int 2020; 125: 355-368

19. Hosono I, Miyahara R, Furukawa K et al. Use of Immunostaining for the diagnosis of Lymphovascular invasion in superficial Barrett's esophageal adenocarcinoma. BMC Gastroenterol 2020; 20: 175
20. Kojima M, Shimazaki H, Iwaya K et al. Pathological diagnostic criterion of blood and lymphatic vessel invasion in colorectal cancer: a framework for developing an objective pathological diagnostic system using the Delphi method, from the Pathology Working Group of the Japanese Society for Cancer of the Colon and Rectum. J Clin Pathol 2013; 66: 551-558

# PART IV

## Summary, discussion and conclusion

# CHAPTER 11.1

## Summary

## Summary

This thesis aims to provide insights in the incidence and risk of second and multiple primary tumors (MPTs) in the upper aerodigestive tract (UADT) in patients with esophageal squamous cell carcinoma (ESCC) and in patients with head and neck squamous cell carcinoma (HNSCC). The second aim of this thesis is to investigate whether screening for these MPTs should be recommended. The third aim of this thesis is to optimize clinical staging and endoscopic resection (ER) of early esophageal cancer (EC) and to develop a prediction model that estimates the risk of lymph node metastases (LNM) in individual patients with submucosal (pT1b) esophageal adenocarcinoma (EAC).

Several aspects of EC are introduced in **Part I** of this thesis. **Chapter 1.1** provides an overview of the epidemiology, clinical presentation, diagnosis and treatment of early EC, risk factors for LNM, the risk for second primary tumors (SPTs) in the UADT, endoscopic detection and ER techniques, and the prevention of esophageal strictures after ER. **Chapter 1.2** describing the aims and outline of this thesis.

### Screening and diagnosis of second and multiple primary tumors in the upper aerodigestive tract

**Part II** discusses the screening for and diagnosis of MPTs in the UADT in patients with ESCC and in patients with HNSCC.

#### Esophageal squamous cell carcinoma and the risk of multiple primary tumors in the upper aerodigestive tract

**Chapter 2** describes a nationwide, retrospective cohort study in which the risk of synchronous and metachronous MPTs in the UADT in patients with primary ESCC is compared with the general population. Most studies about this topic are performed in the Asian population. Out of 9,058 included patients who were diagnosed with ESCC between 2000 and 2016, 476 patients (5.3%) developed an SPT or MPTs in the UADT. Most MPTs were located in the head and neck region (49.5%) and were diagnosed synchronously with the primary tumor (60.4%). Compared with the general population, patients with ESCC had a significantly increased risk of developing both synchronous (SIR 10.95, 99% CI 9.40-12.53) and metachronous (SIR 4.36, 99% CI 3.56-5.10) MPTs, with the highest risk of developing MPTs in the head and neck region. Approximately one in five patients with ESCC who survive longer than six months will develop an SPT within 15 years. The high cumulative incidence suggests that screening for MPTs is of additional value. However, patients with high-stage ESCC have a poor prognosis and these patients might not benefit from screening programs since their prognosis is predominantly determined by ESCC. Diagnosing MPTs in these patients probably does not lead to any survival benefit. We therefore conclude that prospective screening studies are necessary to determine the true MPT incidence and to investigate the yield and benefit of screening for MPTs, taking the probability of ESCC survival into account.

**Chapter 3** describes a systematic review and meta-analysis of studies that performed screening for head and neck second primary tumors (HNSPT) in patients with ESCC. The purpose of the study was to investigate the yield of endoscopic screening for HNSPTs in patients with primary ESCC. The primary outcome of this study was the pooled prevalence of

HNSPT. A total of 12 studies were included in this systematic review and the total number of included patients was 6,483. The pooled prevalence of HNSPTs was 6.7% (95% CI: 4.9-8.4, range: 3.0-29.6%). Most HNSPTs were located in the hypopharynx (60.3%) and had a low tumor stage (85.3%). We conclude that the concept of endoscopic screening for HNSPTs in patients with ESCC is promising.

All included screening studies were performed in Japan. It is unknown whether the results of those studies are also applicable to the Western population. Therefore, more research is necessary to assess the HNSPT prevalence in the Western population. Additional research should also focus on the question which type of ESCC increases the risk of HNSPTs and the risk factors associated with HNSPT.

In **Chapter 4** we describe a systematic review and meta-analysis concerning screening for esophageal second primary tumors (ESPTs) in patients with HNSCC. Studies were included when screening of the esophagus was performed with Lugol chromoendoscopy (LCE). A total 3,386 patients in 15 studies were included. The pooled prevalence of ESPTs was 15.2% (95% CI 11.4-19.0, range: 4.1-40.9%). Only three Western studies were included, in which the prevalence was 6.0% (95% CI: 2.3-9.7). In contrast, the prevalence in the 12 Asian studies was 17.7% (95% CI: 12.7-22.7). Patients with HNSCC located in the hypopharynx had the highest ESPT prevalence. The pooled prevalence in our review is higher than what has been reported in retrospective non-screening studies (1-6%). We conclude that there is strong evidence to perform esophageal screening with LCE in an Asian patient population. It is unknown whether this also applies to the Western population, since only three Western screening studies met our inclusion criteria.

Based on the conclusions drawn from **Chapter 4**, we performed a prospective screening study to determine the incidence of synchronous ESPTs in patients with HNSCC in a Western country. This study is described in **Chapter 5**. Patients diagnosed with HNSCC in the oropharynx, hypopharynx, any other sub-location of the head and neck region in combination with active alcohol abuse, or patients with two HNSCCs regardless of sub-location, were eligible for inclusion. All patients underwent screening esophagogastroduodenoscopy (EGD) with white light high resolution endoscopy (WLE), narrow-band imaging (NBI), and LCE by an experienced interventional endoscopist during the work-up for HNSCC. An ESPT was defined as ESCC or high grade dysplasia (HGD). During an inclusion period of 12 months, 85 patients were included and underwent screening EGD. An ESPT was pathologically confirmed in 5/85 (5.9%) of patients. The detection rate of all (pre)malignant lesions, including LGD (n=3), was 9.4%. All ESPTs were detected in an early stage and could be treated with curative intent. In case of ESCC diagnosis, combined treatment with radiotherapy for both HNSCC and ESCC was performed. Esophageal lesions larger than 20 mm were predominantly seen in patients with ESPT. None of the ESPTs were detected with imaging techniques before EGD was performed. Therefore, we believe that screening for synchronous ESPTs in patients with HNSCC is promising. Screening should be first considered in high-risk patients (*i.e.* HNSCC located in the oropharynx and hypopharynx and patients with alcohol abuse). The combination of WLE and NBI is probably the most sensitive screening method. Although LCE can be performed, extra awareness is indicated in case of lesions smaller than 20mm because of the high rate of false positive lesions.

**Endoscopic detection techniques**

**Chapter 6** discusses the added value of LCE by describing three important phases of endoscopic treatment of early ESCC. This chapter has been published as an editioral referring to an article by Costa-Santos et al. which concluded that mucosal inspection with LCE before endoscopic resection is not associated with an increased complete lateral resection rate compared to inspection with NBI alone.[1]

The first phase of endoscopic treatment of early ESCC is the detection of the lesion. It has been suggested that the accuracy in the detection of early ESCC is highest when NBI and LCE are combined. However, the specificity of NBI is superior to the other techniques.

The second phase is the characterization of the lesion. LCE is able to highlight suspected lesions in the esophagus as Lugol voiding lesions (LVLs). These LVLs are present or not, but no further characterization of these lesions can be made besides gross morphology. In contrast, intraepithelial papillary capillary loop (IPCL) patterns visible with NBI can further characterize esophageal lesions.

The third phase is lesion delineation. Costa-Santos et al. concluded that mucosal inspection with LCE before ER of ESCC or dysplasia was not associated with an increased complete lateral resection rate compared to inspection with NBI alone.

Based on previous literature and the results of Costa-Santos et al., we conclude that for both NBI and LCE adequate expertise and experience on the part of the endoscopist is key in the detection, characterization, and delineation of esophageal lesions. Although NBI seems superior in terms of specificity and characterization of lesions, detection of lesions depends on the experience of the endoscopist. Recognition of specific IPCL patterns is crucial in NBI, while detection of LVL by LCE might be easier for an endoscopist with less experience.

## Endoscopic diagnosis and treatment of early esophageal cancer



**Part III** discusses endoscopic diagnosis and treatment of early esophageal cancer and mainly focusses on esophageal adenocarcinoma (EAC).

**Endoscopic reassessment of cT2 esophageal adenocarcinoma**

**Chapter 7** describes a multicenter prospective cohort study of patients with clinical T2 EAC. Clinical tumor stage of EAC is most often determined by endoscopic ultrasound (EUS), but the accuracy of EUS is low for tumor stages T1 and T2. This may result in overtreatment of T1 tumors which are overstaged as cT2.These patients unnecessarily undergo invasive treatment. The aim of this study was to assess the proportion of cT2 EAC downstaged to cT1 after endoscopic reassessment (ERA) by an experienced interventional endoscopist.

Patients with cT2N0M0 EAC were included in this study and underwent ERA. Fifteen out of 25 (60%) included patients were downstaged from cT2 to cT1 EAC, whom all underwent ER. Twelve out of 15 patients underwent successful ER and all tumors proved to be stage pT1. Ten out of these 12 patients were treated with ER only, five within the curative criteria for ER. ER was unsuccessful in 3/15 patients due to tumor invasion in the muscle layer. In the remaining 10 out of 25 (40%) patients, ERA confirmed cT2 tumor stage. Overall, 15 out of 25 cT2 EAC turned out to be pT1 EAC or prepT1 EAC. The sensitivity of the presence of invasive

features during ERA in detecting T2 EAC was 86% (95% CI 42-100) and the specificity was 80% (95% CI 52-96). Based on **Chapter 7**, we concluded that in patients with cT2N0M0 EAC according to CT/EUS assessment, ERA by an experienced interventional endoscopist downstages about half of the cases to a cT1 EAC suitable for ER. ERA prevents unnecessary invasive adjuvant treatment in 40% of patients and has therefore a substantial clinical impact on the management of clinically diagnosed T2 EAC. We advocate that all cT2 staged EACs should be considered for ERA by an endoscopist with experience in ER of early EAC.

**Chapter 8** describes a retrospective, observational, cohort study of patients who underwent ESD for early esophageal and stomach cancer performed with propofol-remifentanil analgosedation without endotracheal intubation. We evaluated the safety of propofol sedation without endotracheal intubation and reported on endoscopy- and anesthesia-related complications. Out of 88 included patients, only three intra-procedural ESD-related complications occurred (3.4%). Intra-procedural anesthesia-related complications only occurred in two patients (2.3%), one of whom required conversion to endotracheal intubation. Based on **Chapter 8**, we concluded that propofol-based sedation without endotracheal intubation is safe for ESD procedures in the esophagus and stomach with low anesthesia-related complication rates. In line with these observations and logistical and financial ramifications, propofol-remifentanil analgosedation without endotracheal intubation for ESD should be considered over general anesthesia.

A disadvantage of ER of early EC is the high rate of post-resection strictures. A risk factor for stricture development is a large mucosal defect after ER (≥75% of the esophageal circumference). **Chapter 9** describes the effectiveness of a treatment with topical Budesonide for the prevention of esophageal strictures after ER for esophageal cancer. This is a retrospective analysis of a prospective cohort study of patients who received topical budesonide after ER of EC. Forty-two patients who were treated with ER and topical budesonide were included in this study. A total of 18/42 (44.9%) patients developed a stricture. The pooled stricture rate was calculated for control groups in the literature, which was 75.3% (95% CI 68.8-81.9%). Comparable patients of our cohort had a lower stricture rate (47.8% vs. 75.3%, $p<0.01$). We conclude that topical budesonide therapy after ER for early EC seems to be a safe and effective method in preventing strictures. The stricture rate after budesonide treatment is lower compared to the stricture rate of patients who did not receive a preventive treatment as reported in the literature.

Once ER is performed, the decision to perform adjuvant treatment depends on histopathologic features in ER specimen and the risk of LNM. No clinical tool is available that combines the risk of different histopathologic features to predict the LNM risk on an individual basis. **Chapter 10.1** describes a multicenter retrospective cohort study of patients with submucosal (pT1b) EAC that underwent ER or primary surgery. We developed a prediction model that incorporates all accepted prognostic parameters to accurately predict the LNM risk on an individual basis. A total of 248 patients with pT1b EAC were included. We show that the cumulative incidence of developing metastases within 5 year after primary EAC treatment is 30.9% (95% CI 25.1-36.8). The probability of developing post resection metastases can be estimated with a personalized prediction risk score incorporating tumor invasion depth, tumor size and lymphovascular invasion. For example, the predicted 5-year metastases risk in patients with T1b EAC <20mm, without LVI and submucosal invasion ≤500µm (sm1) is 5.9% (95% CI 2.3-11.2), compared to 70.1% (95% CI 60.5-78.7) in patients with T1b EAC ≥20mm,

with LVI and sm3. The prediction model demonstrated a good discriminative ability with a c-statistic of 0.81 (95% CI 0.75-0.86).

**Chapter 10.2** describes whether quantification of LVI provides additional prognostic information for the development of metastasis in patients with pT1b EAC. LVI is classified in four categories based on LVI foci in resection specimens: no LVI, 1 LVI focus, 2-3 LVI foci, and ≥4 LVI foci. We show that more LVI foci was correlated with a higher risk of developing metastasis. The presence of only 1 LVI focus was not an independent predictor for metastases. For example, the predicted 5-year metastasis risk in patients with T1b EAC <20mm, sm1, LVI negative was 14.1% (95% CI 7.9-21.9), compared to 26.3% (95% CI 10.6-45.3) when 1 LVI focus was present, 43.5% (95% CI 26.6-61.5) when 2-3 LVI foci were present, and 54.4% (95% CI 33.7-72.8) when ≥4 LVI foci were present. These results suggest that quantification of LVI may further refine risk estimation in pT1b EAC.

In **Part IV** we summarize the main findings of this thesis in **Chapter 11.1**. **Chapter 11.2** includes the general discussion and recommendations for further research. The conclusion of this thesis is described in **Chapter 11.3**.

# CHAPTER 11.2

## General discussion and future perspectives

# General discussion and future perspectives

## Screening and diagnosis of second and multiple primary tumors in the upper aerodigestive tract

The first aim of this thesis was to provide insights in the incidence and risk of second and multiple primary tumors (MPTs) in the upper aerodigestive tract (UADT) in patients with esophageal squamous cell carcinoma (ESCC), and in patients with head and neck squamous cell carcinoma (HNSCC). The second aim of this thesis was to investigate whether screening for these MPTs is recommended.

### Esophageal squamous cell carcinoma and the risk of multiple primary tumors in the upper aerodigestive tract

Most retrospective studies about MPT incidence in the UADT in patients with ESCC have been performed in the Asian population. These studies reported MPT incidence rates up to 19%.[2-5] Comparable studies performed in a Western population reported MPT incidence rates up to 6%.[6-8]

In **Chapter 2**, we assessed the incidence and risk of developing MPTs in the UADT and stomach in patients with ESCC in the Netherlands. Our cohort consisted of patients with ESCC registered in the National Cancer Registry of the Netherlands. In this study, the 15-year cumulative incidence of metachronous second primary tumors (SPTs) was 19.7%. The risk of developing both synchronous and metachronous MPTs in patients with primary ESCC was increased compared to the general population. Like in other studies, the head and neck region had the highest risk of developing MPTs.[7, 9-11] This study is the largest study about MPT development in ESCC patients in Europe, with more than 9,000 patients included over a period of 16 years. Because this is a registry study, there is a possible underestimation of the true MPT incidence. Due to the retrospective design of the study, there was a substantial amount of missing data. In addition, we did not know whether MPTs were diagnosed during regular follow-up or as a result of patients symptoms. Because of these limitations, we could not report on specific risk factors for MPT development (*e.g.* smoking and alcohol) and no specific advice for time-interval for screening could be drawn from this study. Further research on this topic should consist of a prospective screening study.



Because **Chapter 2** showed that the MPT prevalence was highest in the head and neck region, the first step for further research should be a screening study for head and neck second primary tumors (HNSPTs) in patients with primary ESCC. The advantage of a prospective screening study is that several potential risk factors for HNSPT development can be recorded and screening can be performed systematically and homogeneous. One of the most important questions to answer is whether screening will result in the detection of early stage HNSPTs and whether screening will result in survival benefit. To achieve survival benefit, screening should be performed in patients that can be treated with curative intent for their ESCC. In addition, the follow-up time after screening should be long enough to investigate the effect of screening on patient survival.

**Screening for head and neck second primary tumors in patients with esophageal squamous cell carcinoma**

In **Chapter 3**, we conducted a systematic literature search and meta-analysis of studies that performed endoscopic screening for HNSPTs in patients with ESCC. A total of 12 studies were included.[12-23] The prevalence of HNSPTs in these studies ranged between 3.0% and 29.6%. Meta-analysis showed that the pooled prevalence of HNSPTs was 6.7% (95% CI 4.9-8.4). Most HNSPTs were located in the hypopharynx (60.3%). However, screening of the entire head and neck region was performed in only four of twelve included studies. We could therefore not determine which head and neck sub-location had the highest risk of developing SPTs. Most HNSPTs had a low tumor stage (85.3%). These low stage HNSPTs can be curatively treated and have an excellent prognosis.

Although this systematic review suggests that screening for HNSPTs is promising, all screening studies were performed in Japan. Screening studies performed in a Western population are necessary to investigate the incidence of HNSPTs and to investigate whether screening is justified in only ESCC patients that can be treated with curative intent.

**Screening for esophageal second primary tumors in patients with head and neck squamous cell carcinoma**

In patients with HNSCC, the esophagus in particular is at increased risk of developing MPTs.[24] Early diagnosis and treatment of an esophageal second primary tumor (ESPT) may improve the overall outcome of patients with HNSCC.[25, 26] In **Chapter 4**, we conducted a systematic literature search and meta-analysis of studies that performed endoscopic screening of the esophagus with Lugol chromoendoscopy (LCE) to detect ESPTs in patients with HNSCC. A total of 15 studies were included, of which 12 were performed in the Asian population and three in the non-Asian population.[27-42] The pooled prevalence of ESPT was 15.2% (95% CI 11.4-19.0). The ESPT prevalence was highest in patients with HNSCC located in the hypopharynx. More than 50% of ESPTs were low-stage and could be treated with curative intent.

Based on **Chapter 4**, we recommend screening for ESPTs in an Asian patient population with HNSCC. A major limitation of this systematic review is that only three non-Asian studies were included, of which two studies were performed in Europe. It is therefore important to perform a prospective screening study in a Western population with HNSCC.

This prospective screening study is described in **Chapter 5**. Eighty-five patients with an increased risk of ESPT development were included and underwent screening esophagogastroduodenoscopy (EGD), within two weeks after HNSCC diagnosis. EGD was performed with white light high resolution endoscopy (WLE), narrow-band imaging (NBI), and LCE.

In **Chapter 5**, we found an ESPT incidence of 5.9% (95% CI 1.9-13.2). ESPT or low-grade dysplasia was found in one in ten patients. All esophageal lesions were diagnosed at an early stage and could be treated with curative intent with either endoscopic resection (ER) or radiotherapy. Since none of the ESPTs were identified by other imaging techniques (*i.e.*, MRI and/or CT-scan), we suggest that screening for ESPT by EGD is of added value for a selected group of patients with HNSCC. The combination of WLE and NBI is probably the most sensitive screening method. Although LCE can be performed, extra awareness is indicated in case of lesions <20mm because of the high rate of false positive lesions.

However, before screening for ESPT can be implemented in daily clinical practice, further research on this topic should be conducted focusing on the following aspects:

1. More studies with a larger patient cohort are necessary, preferably in a multicenter setting. This would enable a solid risk factor analysis and identify a subgroup of patients who are at high risk of developing ESPTs and would benefit most from endoscopic screening.
2. Patient burden should be taken into account. This is an important parameter for the decision whether screening should be performed. Screening EGD is an invasive examination for patients. Although eight patients were treated for ESPT or low-grade dysplasia in **Chapter 5**, three patients received an unnecessary endoscopic mucosal resection (EMR) and no lesions were found in the other 74 patients.
3. Survival benefit should be taken into account. It is important to take HNSCC prognosis into account since patients with poor prognosis will probably not benefit from screening, and screening will not lead to survival benefit in these patients.
4. Screening for metachronous ESPTs should be performed to determine the optimal timing of screening.
5. It is necessary to determine the cost-effectiveness of screening EGD.

**Endoscopic detection techniques**

To continue the discussion whether LCE is still necessary to date as pointed in **Chapter 5**, the added value of LCE is discussed further in **Chapter 6**. The added value of LCE is discussed by describing three different phases of endoscopic ESCC treatment. The first phase is the detection of ESCC. Based on previous literature, we conclude that accuracy rates of ESCC detection are highest when NBI and LCE are combined.[43, 44] The second phase is the characterization of ESCC. Although LCE can easily highlight suspected dysplastic or neoplastic lesions in the esophagus, further characterization of the lesion cannot be made. In contrast, characterization of esophageal lesions with intraepithelial papillary capillary loop patterns is possible with NBI.[45] The third phase is the delineation of ESCC before ER. According to Costa-Santos et al., defining lateral resection margins before ER of ESCC by LCE does not result in an increased complete lateral resection rate compared to NBI.[1]



Based on previous literature, NBI seems superior to LCE in several aspects. However, key in the detection and treatment of ESCC is adequate expertise and experience of the endoscopist. In the near future, the role of LCE will probably be pushed more to the background, in particular when artificial intelligence will be implemented.

## Endoscopic diagnosis and treatment of early esophageal cancer

The third aim of this thesis was to optimize clinical staging and ER of early esophageal cancer and to develop a prediction model that estimates the risk of lymph node metastasis (LNM) in individual patients with submucosal (pT1b) esophageal adenocarcinoma (EAC).

**Endoscopic reassessment of cT2 esophageal adenocarcinoma**

Clinical tumor stage of EAC is determined by endoscopic ultrasound (EUS) and/or CT-scan. The accuracy of these tools is low for stages T1 and T2.[46, 47] This may result in overtreatment of patients who are overstaged as cT2 EAC, and therefore unnecessarily underwent invasive treatment, associated with increased risks and morbidity.[48-51] **Chapter 7** describes a

multicenter prospective cohort study of patients with cT2N0M0 EAC who underwent endoscopic reassessment (ERA) by an endoscopist with experience in ER of early EAC. In this study, we aimed to assess the proportion of cT2 EAC downstaged to cT1 after ERA.

ERA downstaged about half of the cases to a T1 EAC, suitable for ER. In 40% of patients, unnecessary invasive adjuvant treatment was prevented. We conclude that ERA has a substantial clinical impact on the management of cT2 EAC. All cT2 EAC should be considered for ERA by an experienced endoscopist. The results of **Chapter 7** are in line with previous studies reporting that a substantial number of cT2 EAC are in fact pT1 EAC and can be treated with ER.[48, 52]

A limitation of our study is the small sample size of only 25 patients included over two years. However, we may have only included the tip of the iceberg because many patients with cT2 EAC remain unnoticed. Participating study centers included patients who were referred by other non-expert hospitals. Endoscopists in non-expert hospitals are most often not trained to assess whether cT2 EAC is suitable for ER, and these patients are therefore not referred to an expert center for an attempt at ER. Although the small sample size could limit the generalizability of our results, our results confirm the low accuracy of EUS in staging early EAC and show that ERA downstaged 60% of cT2 EAC, of which 80% were pT1 EAC. There are substantial implications of ERA for this patient group and we are therefore convinced that ERA by an experienced endoscopist can be implemented in daily clinical practice.

**Sedation during endoscopic resection**

In **Chapter 8** we retrospectively evaluated the safety of propofol sedation without endotracheal intubation during endoscopic submucosal dissection (ESD) of esophageal and gastric tumors. We conclude that ESD can be safely performed with propofol-remifentanil analgosedation without endotracheal intubation. Intra-procedural anesthesia-related complications occurred in only 2.3% of patients and no post-procedural anesthesia-related complications were observed. Conversion to endotracheal intubation took place in only one patient and 93.2% of the patients were discharged the same day or the day after ESD.

General anesthesia will probably result in higher costs compared to propofol sedation. It requires additional facilities and an anesthesiologist.[53] Patients cannot be discharged the same day as the ESD procedure and this will result in longer hospital stay and additional costs.[54-56] However, formal cost-effectiveness studies are needed to quantify potential savings.[53]

A major advantage of our study is that all procedures were managed by a sedation practitioner who was present during the procedures. This sedation practitioner is a member of the anesthesiology department and is supervised by the anesthesiologist. Previous literature indicates that, compared to propofol sedation, the risk-benefit balance is in favor of general anesthesia.[56] However, in these studies, no sedation practitioner was available during procedures with propofol sedation. It is therefore difficult to discern to what extent the training and experience of the sedation practitioner plays a decisive role in this equation. We conclude that propofol-remifentanil analgosedation without endotracheal intubation for ESD should be considered over general anesthesia when a sedation practitioner is available.

A suggestion for further research is a randomized controlled trial in which general anesthesia (performed by an anesthesiologist) is compared with propofol sedation (performed by a

sedation practitioner). This randomized controlled trial should preferably be performed in a multicenter setting. In addition, patient satisfaction and cost-effectiveness analysis should be taken into account.

**Esophageal strictures after endoscopic resection**

A disadvantage of ER in the esophagus is the risk of developing esophageal strictures. This risk is especially high when the mucosal defect of the esophageal circumference after ER is more than 75%.[57] Although several methods to prevent these strictures have been investigated, the optimal preventive method is currently not known.

In **Chapter 9** we investigated the effectiveness of oral treatment with topical budesonide for the prevention of strictures after ER of esophageal cancer (both ESCC and EAC). We conclude that the use of topical budesonide is safe and effective in stricture prevention after ER. No side effects of budesonide are reported. The stricture rate of patients in our cohort (44.9%) was lower compared to the pooled stricture rate (75.3%) of patients who did not receive a preventive treatment as reported in the literature.[58-66] Several studies, that investigated other methods to prevent strictures, reported a lower stricture rate compared to our study.[58, 60-62] However, these methods include oral prednisolone and triamcinolone injections in the esophagus which are associated with many side effects.[58, 67]

Limitations of our study include its retrospective design and the non-randomized study design without the availability of a control group. Prospective confirmation is needed, preferably through a randomized controlled trial. In addition, topical budesonide was used off-label because it was not developed to prevent esophageal strictures. It seems likely that an orodispersible tablet designed for this indication could yield an even higher effect in the prevention of strictures.

**Lymph node metastasis in esophageal adenocarcinoma**



The prevalence of LNM in T1b EAC varies between 0-78%.[68-72] Guidelines recommend additional surgical resection of the esophagus and loco-regional lymph node dissection when EAC invades the submucosa.[73, 74] However, not every patient with pT1b EAC develops LNM and surgery is associated with morbidity, mortality, and decreased quality of life.[49, 75] Individual risk factors associated with LNM have been described.[68, 76, 77] However, little is known about how these risk factors interrelate and whether combining them may improve estimation of LNM risk.

**Chapter 10.1** presents a nationwide, retrospective cohort study of patients treated with ER or surgery for pT1b EAC. In this chapter, we established a prediction model that includes histopathological tumor characteristics and estimates the individual risk of metastases in patients with pT1b EAC.

The 5-year cumulative incidence of metastasis in our cohort was 30.9% (95% CI 25.1-36.8%). After internal validation of the prediction model, the estimated risk of developing metastasis within five years after ER or primary surgery for pT1b EAC ranged between 5.9-70.1%, depending on different combinations of histopathological parameters. The prediction model demonstrated a good discriminative ability, with a c-statistic of 0.81 (95% CI 0.75-0.86).

Although such prediction model has not been previously reported, further research is necessary before this model can be implemented in daily clinical practice. Future studies should perform external validation of the prediction model because we could not perform this due to the lack of a validation cohort. Moreover, the current prediction model is mainly based on surgical data and we do not know whether this model can reliably be used to calculate LNM risk in patients treated with ER. Therefore, external validation should be performed on a cohort consisting of patients with pT1b EAC treated with ER.

Since this was a retrospective study with possible selection and information bias, prospective confirmation is needed. To date, the decision to perform adjuvant therapy after ER of pT1b EAC, as stated in the ESGE guidelines, is based on less patient data than the current study. Moreover, no prediction model including different combinations of histopathological parameters is published to date.

Another limitation of our study that needs to be tackled in future studies is that we did not perform additional immunohistochemical staining for the assessment of lymphovascular invasion (LVI) which may improve the detection of LVI.[78]

**In Chapter 10.2** we aimed to determine whether quantification of LVI provides additional prognostic information in patients with pT1b EAC. LVI was incorporated in the prediction model as no-LVI, 1 LVI focus, 2-3 LVI foci, or ≥4 LVI foci. We showed that the presence of more LVI foci in resection specimen of pT1b EAC was correlated with a higher risk of metastasis. Compared to the risk in LVI+ patients in the previous model, as described in **Chapter 10.1**, the metastasis risk in the current model is lower in case of 1 LVI focus and higher in case of 2-3 LVI foci and ≥4 LVI foci.

Despite the promising results of the prediction model, it is unlikely that the application of the this model will change clinical practice soon. The difference in predicted metastasis risk between the LVI foci groups is relatively small and the absolute risk is high in all scenarios. Although the metastasis risk in patients with only 1 LVI focus is much lower than the risk in patients with 2-3 or ≥4 LVI foci, the advice for adjuvant treatment or active surveillance after ER will probably not change based on the number of LVI foci. On one hand, we are looking for a better risk assessment for metastasis to make active surveillance possible. On the other hand, the presence of extensive LVI could be a reason to combine surgery with neo-adjuvant therapy. The better this risk assessment, the better we can apply tailored therapy for patients with pT1b EAC.

The same patient cohort was used for **Chapter 10.1** and **Chapter 10.2**. Therefore, limitations of **Chapter 10.2** also include its retrospective design, the lack of a validation cohort, and the fact that immunohistochemical staining for LVI assessment was not performed. Especially the last limitation is important for a study focusing on LVI. Moreover, quantification of LVI in pT1b EAC has not been previously reported in the literature. More research regarding LVI quantification is therefore necessary to investigate its added value in patients with pT1b EAC.

# CHAPTER 11.3

## Conclusion

## Conclusion

Patients with ESCC have an increased risk of developing MPTs compared to the general Dutch population. The MPT prevalence is highest in the head and neck region. For synchronous MPTS, the risk is approximately ten times higher. For metachronous MPTS, the risk is approximately four times higher.

Based on a systematic review and meta-analysis, we conclude that the pooled prevalence of HNSPTs in ESCC patients is 6.7% (95% CI 4.9-8.4). Based on a second systematic review and meta-analysis, we conclude that screening for esophageal second primary tumors (ESPTs) in Asian patients with head and neck squamous cell carcinoma (HNSCC) is justified. The pooled ESPT prevalence in patients with HNSCC is 15.2% (95% CI 11.4-19.0).

In a prospective screening study, we show that the ESPT incidence is 5.9% (95% CI 1.9-13.2) in patients with HNSCC in the Netherlands. All detected esophageal lesions could be treated with curative intent. These lesions were not detected by other imaging techniques. We conclude that screening for ESPT by esophagogastroduodenoscopy is of added value for a selected group of patients with HNSCC. Narrow-band imaging seems superior to LCE in the detection and characterization of early ESCC. Adequate expertise and experience of the endoscopist is key in the detection and treatment of early ESCC.

This thesis shows that endoscopic reassessment (ERA) of cT2N0M0 esophageal adenocarcinoma (EAC) downstages about half of the cases to a T1 EAC, suitable for endoscopic resection (ER). We conclude that ERA has a substantial clinical impact on the management of cT2 EAC, preventing overtreatment in 40% of patients. ERA of cT2N0M0 EAC should be implemented in daily clinical practice.

In a retrospective study on the safety of propofol sedation without endotracheal intubation during endoscopic submucosal dissection (ESD) of esophageal and gastric tumors, we conclude that ESD can be safely performed with propofol sedation without endotracheal intubation.



Based on comparisons with historical published data, oral treatment with topical budesonide after ER of esophageal cancer seems to be an effective method for preventing strictures. However, before topical budesonide can be implemented in daily clinical practice, a randomized controlled trial on the effectivity of topical budesonide in stricture prevention is necessary.

We established a prediction model that includes histopathological tumor characteristics and estimated the individual risk of metastasis in patients with pT1b EAC. We show that the 5 year cumulative incidence of metastasis after primary treatment of pT1b EAC is 30.9% (95% CI 25.1-36.8). The estimated risk of developing metastasis within 5 years after ER or primary surgery of pT1b EAC ranges between 5.9% and 70.1%, depending on different combinations of histopathological parameters (tumor size, submucosal invasion depth and lymphovascular invasion [LVI]). In order to improve the prediction model, we quantified LVI as the total number of LVI foci and show that more LVI foci in pT1b EAC is correlated with higher rates of metastasis. We suggest that quantification of LVI could be useful for a more precise risk estimation of metastasis.

## REFERENCES:


1. Costa-Santos MP, Ferreira AO, Mouradides C, et al. Is Lugol necessary for endoscopic resection of esophageal squamous cell neoplasia? Endosc Int Open. 2020; 8: E1471-E7.
2. Natsugoe S, Matsumoto M, Okumura H, et al. Multiple primary carcinomas with esophageal squamous cell cancer: clinicopathologic outcome. World J Surg. 2005; 29: 46-9.
3. Lee GD, Kim YH, Kim JB, et al. Esophageal Cancer Associated with Multiple Primary Cancers: Surgical Approaches and Long-term Survival. Ann Surg Oncol. 2013; 20: 4260-6.
4. Nagasawa S, Onda M, Sasajima K, Takubo K and Miyashita M. Multiple primary malignant neoplasms in patients with esophageal cancer. Dis Esophagus. 2000; 13: 226-30.
5. Kumagai Y, Kawano T, Nakajima Y, et al. Multiple primary cancers associated with esophageal carcinoma. Surg Today. 2001; 31: 872-6
6. Levi F, Randimbison L, Maspoli M, Te VC and La Vecchia C. Second neoplasms after oesophageal cancer. Int J Cancer. 2007; 121: 694-7.
7. Zhu G, Chen Y, Zhu Z, et al. Risk of second primary cancer after treatment for esophageal cancer: a pooled analysis of nine cancer registries. Dis Esophagus. 2012; 25: 505-11.
8. Ribeiro Júnior U, Cecconello I, Safatle-Ribeiro AV, Zilberstein B and Pinotti HW. Squamous cell carcinoma of the esophagus and multiple primary tumors of the upper aerodigestive tract. Arq Gastroenterol. 1999; 36: 195-200.
9. Chuang SC, Hashibe M, Scelo G, et al. Risk of second primary cancer among esophageal cancer patients: a pooled analysis of 13 cancer registries. Cancer Epidemiol Biomarkers Prev. 2008; 17: 1543-9.
10. Chen SC, Teng CJ, Hu YW, et al. Secondary primary malignancy risk among patients with esophageal cancer in Taiwan: a nationwide population-based study. PLoS One. 2015; 10: e0116384.
11. Matsubara T, Yamada K and Nakagawa A. Risk of second primary malignancy after esophagectomy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol. 2003; 21: 4336-41.
12. Lo OS, Law S, Wei WI, et al. Esophageal cancers with synchronous or antecedent head and neck cancers: a more formidable challenge? Ann Surg Oncol. 2008; 15: 1750-6.
13. Nonaka S, Saito Y, Oda I, Kozu T and Saito D. Narrow-band imaging endoscopy with magnification is useful for detecting metachronous superficial pharyngeal cancer in patients with esophageal squamous cell carcinoma. J Gastroenterol Hepatol. 2010; 25: 264-9.
14. Morimoto H, Yano T, Yoda Y, et al. Clinical impact of surveillance for head and neck cancer in patients with esophageal squamous cell carcinoma. World J Gastroenterol. 2017; 23: 1051-8.
15. Shimizu Y, sukagoshi H, Fujita M, et al. Head and neck cancer arising after endoscopic mucosal resection for squamous cell carcinoma of the esophagus. Endoscopy. 2003; 35: 322-6.
16. Motoyama S, Saito R, Kitamura M and Ogawa J. Outcomes of active operation during intensive followup for second primary malignancy after esophagectomy for thoracic squamous cell esophageal carcinoma. J Am Coll Surg. 2003; 197: 914-20.
17. Kaneko K, Yano T, Minashi K, et al. Treatment strategy for superficial pharyngeal squamous cell carcinoma synchronously combined with esophageal cancer. Oncology. 2013; 84: 57-64.
18. Kagei K, Hosokawa M, Shirato H, et al. Efficacy of intense screening and treatment for synchronous second primary cancers in patients with esophageal cancer. Jpn J Clin Oncol. 2002; 32: 120-7.
19. Onochi K, Shiga H, Takahashi S, et al. Risk Factors Linking Esophageal Squamous Cell Carcinoma With Head and Neck Cancer or Gastric Cancer. J Clin Gastroenterol. 2019; 53: e164-e70.
20. Watanabe A, Hosokawa M, Taniguchi M, Tsujie H and Sasaki S. Head and neck cancer associated with esophageal cancer. Auris Nasus Larynx. 2007; 34: 207-11.

21. Muto M, Minashi K, Yano T, Saito Y and Oda I. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. J Clin Oncol. 2010 Mar 20;28(9):1566-72.
22. Abiko S, Shimizu Y, Miyamoto S, et al. Risk assessment of metachronous squamous cell carcinoma after endoscopic resection for esophageal carcinoma based on the genetic polymorphisms of alcoholdehydrogense-1B aldehyde dehydrogenase-2: temperance reduces the risk. J Gastroenterol. 2018; 53: 1120-30.
23. Katada C, Muto M, Nakayama M, 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: 1291-6.
24. Atienza JA and Dasanu CA. Incidence of second primary malignancies in patients with treated head and neck cancer: a comprehensive review of literature. Curr Med Res Opin. 2012; 28: 1899-909.
25. Chung CS, Lo WC, Lee YC, Wu MS, Wang HP and Liao LJ. Image-enhanced endoscopy for detection of second primary neoplasm in patients with esophageal and head and neck cancer: A systematic review and meta-analysis. Head Neck. 2016; 38 Suppl 1: E2343-9.
26. Bradley PJ and Bradley PT. Searching for metachronous tumours in patients with head and neck cancer: the ideal protocol! Curr Opin Otolaryngol Head Neck Surg. 2010; 18: 124-33.
27. Boller D, Spieler P, Schoenegg R, et al. Lugol chromoendoscopy combined with brush cytology in patients at risk for esophageal squamous cell carcinoma. Surg Endosc. 2009; 23: 2748-54.
28. Dubuc J, Legoux J, Winnock M, et al. Endoscopic screening for esophageal squamous-cell carcinoma in high-risk patients: a prospective study conducted in 62 French endoscopy centers. Endoscopy. 2006; 38: 690-5.
29. Fukuhara T, Hiyama T, Tanaka S, et al. Characteristics of esophageal squamous cell carcinomas and lugol-voiding lesions in patients with head and neck squamous cell carcinoma. J Clin Gastroenterol. 2010; 44: e27-33.
30. Gong EJ, Kim DH, Ahn JY, 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.
31. Fukuzawa K, Noguchi Y, Yoshikawa T, et al. High incidence of synchronous cancer of the oral cavity and the upper gastrointestinal tract. Cancer Lett. 1999; 144: 145-51.
32. Hashimoto CL, Iriya K, Baba ER, et al. Lugol's dye spray chromoendoscopy establishes early diagnosis of esophageal cancer in patients with primary head and neck cancer. Am J Gastroenterol. 2005; 100: 275-82.
33. Ikawa H, Tonogi M, Yamane GY, et al. Upper gastrointestinal tract cancers as double-cancers in elderly patients with oral squamous cell carcinoma. Bull Tokyo Dent Coll. 2012; 53: 9-16.
34. Lee YC, Wang CP, Chen CC, et al. Transnasal endoscopy with narrow-band imaging and Lugol staining to screen patients with head and neck cancer whose condition limits oral intubation with standard endoscope (with video). Gastrointest Endosc. 2009; 69: 408-17.
35. Morimoto M, Nishiyama K, Nakamura S, et al. Significance of endoscopic screening and endoscopic resection for esophageal cancer in patients with hypopharyngeal cancer. Jpn J Clin Oncol. 2010; 40: 938-43.
36. Muto M, Hironaka S, Nakane M, Boku N, Ohtsu A and Yoshida S. Association of multiple Lugol-voiding lesions with synchronous and metachronous esophageal squamous cell carcinoma in patients with head and neck cancer. Gastrointest Endosc. 2002; 56: 517-21.
37. Tanabe H, Yokota K, Shibata N, Satoh T, Watari J and Kohgo Y. Alcohol consumption as a major risk factor in the development of early esophageal cancer in patients with head and neck cancer. Intern Med. 2001; 40: 692-6.
38. An W, Sun PB, Gao J, et al. Endoscopic submucosal dissection for gastric gastrointestinal stromal tumors: a retrospective cohort study. Surg Endosc. 2017; 31: 4522-31.
39. Wang CH, Lee YC, Wang CP, et al. Use of transnasal endoscopy for screening of esophageal squamous cell carcinoma in high-risk patients: yield rate, completion rate, and safety. Digestive

endoscopy: official journal of the Japan Gastroenterological Endoscopy Society. 2014; 26: 24-31.
40. Wang WL, Lee CT, Lee YC, et al. Risk factors for developing synchronous esophageal neoplasia in patients with head and neck cancer. Head Neck. 2011; 33: 77-81.
41. Wang WL, Wang CP, Wang HP, et al. The benefit of pretreatment esophageal screening with image-enhanced endoscopy on the survival of patients with hypopharyngeal cancer. Oral Oncol. 2013; 49: 808-13.
42. Horiuchi M, Makuuchi H, Machimura T, Tamura Y, Sakai M. Survival benefit of screening for early esophageal carcinoma in head and neck cancer patients. Dig Endosc 1998;10(2):110-115.
43. Gotoda T, Kanzaki H, Okamoto Y, et al. Tolerability and efficacy of the concentration of iodine solution during esophageal chromoendoscopy: a double-blind randomized controlled trial. Gastrointest Endosc. 2020; 91: 763-70.
44. Yoshida T, Inoue H, Usui S, Satodate H, Fukami N and Kudo SE. Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. Gastrointest Endosc. 2004; 59: 288-95.
45. Ishihara R, Inoue T, Uedo N, et al. Significance of each narrow-band imaging finding in diagnosing squamous mucosal high-grade neoplasia of the esophagus. J Gastroenterol Hepatol. 2010; 25: 1410-5.
46. O'Farrell NJ, Malik V, Donohoe CL, et al. Appraisal of staging endoscopic ultrasonography in a modern high-volume esophageal program. World J Surg. 2013; 37: 1666-72.
47. Pech O, Gunter E, Dusemund F, Origer J, Lorenz D and Ell C. Accuracy of endoscopic ultrasound in preoperative staging of esophageal cancer: results from a referral center for early esophageal cancer. Endoscopy. 2010; 42: 456-61.
48. Gotink AW, Spaander MCW, Doukas M, et al. Exploring diagnostic and therapeutic implications of endoscopic mucosal resection in EUS-staged T2 esophageal adenocarcinoma. Endoscopy. 2017; 49: 941-8.
49. Linden PA, Towe CW, Watson TJ, et al. Mortality After Esophagectomy: Analysis of Individual Complications and Their Association with Mortality. J Gastrointest Surg 2020 Sep;24(9):1948-1954.
50. Hamai Y, Hihara J, Taomoto J, Yamakita I, Ibuki Y and Okada M. Effects of neoadjuvant chemoradiotherapy on postoperative morbidity and mortality associated with esophageal cancer. Dis Esophagus. 2015; 28: 358-64.
51. Low DE, Kuppusamy MK, Alderson D, et al. Benchmarking Complications Associated with Esophagectomy. Ann Surg. 2019; 269: 291-8.
52. Nelson DB, Mitchell KG, Weston BR, et al. Should endoscopic mucosal resection be attempted for cT2N0 esophageal cancer? Dis Esophagus. 2019; 32: 1-6.
53. Rong QH, Zhao GL, Xie JP and Wang LX. Feasibility and safety of endoscopic submucosal dissection of esophageal or gastric carcinomas under general anesthesia. Med Princ Pract. 2013; 22: 280-4.
54. Yamashita K, Shiwaku H, Ohmiya T, et al. Efficacy and safety of endoscopic submucosal dissection under general anesthesia. World J Gastrointest Endosc. 2016; 8: 466-71.
55. Song BG, Min YW, Cha RR, et al. Endoscopic submucosal dissection under general anesthesia for superficial esophageal squamous cell carcinoma is associated with better clinical outcomes. BMC Gastroenterol. 2018; 18: 80.
56. Yurtlu DA, Aslan F, Ayvat P, et al. Propofol-Based Sedation Versus General Anesthesia for Endoscopic Submucosal Dissection. Medicine (Baltimore). 2016; 95: e3680.
57. Shi Q, Ju H, Yao LQ, et al. Risk factors for postoperative stricture after endoscopic submucosal dissection for superficial esophageal carcinoma. Endoscopy. 2014; 46: 640-4.
58. Hashimoto S, Kobayashi M, Takeuchi M, Sato Y, Narisawa R and Aoyagi Y. The efficacy of endoscopic triamcinolone injection for the prevention of esophageal stricture after endoscopic submucosal dissection. Gastrointest Endosc. 2011; 74: 1389-93.

59. Ezoe Y, Muto M, Horimatsu T, et al. Efficacy of preventive endoscopic balloon dilation for esophageal stricture after endoscopic resection. J Clin Gastroenterol. 2011; 45: 222-7.
60. Takahashi H, Arimura Y, Okahara S, et al. A randomized controlled trial of endoscopic steroid injection for prophylaxis of esophageal stenoses after extensive endoscopic submucosal dissection. BMC Gastroenterol. 2015; 15: 1.
61. Kataoka M, Anzai S, Shirasaki T, et al. Efficacy of short period, low dose oral prednisolone for the prevention of stricture after circumferential endoscopic submucosal dissection (ESD) for esophageal cancer. Endosc Int Open. 2015; 3: E113-7.
62. Zhou G, Yuan F, Cai J, et al. Efficacy of prednisone for prevention of esophageal stricture after endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. Thorac Cancer. 2017; 8: 489-94.
63. Wen J, Lu Z, Yang Y, et al. Preventing stricture formation by covered esophageal stent placement after endoscopic submucosal dissection for early esophageal cancer. Dig Dis Sci. 2014; 59: 658-63.
64. Hanaoka N, Ishihara R, Takeuchi Y, et al. Intralesional steroid injection to prevent stricture after endoscopic submucosal dissection for esophageal cancer: a controlled prospective study. Endoscopy. 2012; 44: 1007-11.
65. Wen J, Lu Z, Linghu E, et al. Prevention of esophageal strictures after endoscopic submucosal dissection with the injection of botulinum toxin type A. Gastrointest Endosc. 2016; 84: 606-13.
66. Pih GY, Kim DH, Gong EJ, et al. Preventing esophageal strictures with steroids after endoscopic submucosal dissection in superficial esophageal neoplasm. J Dig Dis. 2019; 20: 609-16.
67. Melillo N, Corrado A, Quarta L and Cantatore FP. Corticosteroids, a review. Panminerva Med. 2007; 49: 29-33.
68. Barbour AP, Jones M, Brown I, et al. Risk stratification for early esophageal adenocarcinoma: analysis of lymphatic spread and prognostic factors. Ann Surg Oncol. 2010; 17: 2494-502.
69. Sepesi B, Watson TJ, Zhou D, et al. Are endoscopic therapies appropriate for superficial submucosal esophageal adenocarcinoma? An analysis of esophagectomy specimens. J Am Coll Surg. 2010; 210: 418-27.
70. Lee L, Ronellenfitsch U, Hofstetter WL, et al. Predicting lymph node metastases in early esophageal adenocarcinoma using a simple scoring system. J Am Coll Surg. 2013; 217: 191-9.
71. Stein HJ, Feith M, Bruecher BL, Naehrig J, Sarbia M and Siewert JR. Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. Ann Surg. 2005; 242: 566-73; discussion 73-5.
72. Westerterp M, Koppert LB, Buskens CJ, et al. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch. 2005; 446: 497-504.
73. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ and American Gastroenterological A. American Gastroenterological Association technical review on the management of Barrett's esophagus. Gastroenterology. 2011; 140: e18-52; quiz e13.
74. Fitzgerald RC, di Pietro M, Ragunath K, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut. 2014; 63: 7-42.
75. Finks JF, Osborne NH and Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med. 2011; 364: 2128-37.
76. Leers JM, DeMeester SR, Oezcelik A, et al. The prevalence of lymph node metastases in patients with T1 esophageal adenocarcinoma a retrospective review of esophagectomy specimens. Ann Surg. 2011; 253: 271-8.
77. Liu L, Hofstetter WL, Rashid A, et al. Significance of the depth of tumor invasion and lymph node metastasis in superficially invasive (T1) esophageal adenocarcinoma. Am J Surg Pathol. 2005; 29: 1079-85.

78. Hosono I, Miyahara R, Furukawa K, et al. Use of Immunostaining for the diagnosis of Lymphovascular invasion in superficial Barrett's esophageal adenocarcinoma. BMC Gastroenterol. 2020; 20: 175.

# PART V

## Appendices

# CHAPTER 12

## Nederlandse samenvatting

## Nederlandse samenvatting

Dit proefschrift heeft tot doel om inzicht te verschaffen in de incidentie en het risico op tweede en meerdere primaire tumoren (MPT's) in de luchtwegen en het bovenste deel van het spijsverteringskanaal in patiënten met een plaveiselcelcarcinoom (PCC) in de slokdarm en in patiënten met een PCC in de hoofd-hals regio. Het tweede doel van dit proefschrift is om te onderzoeken of screening op deze MPT's nodig is. Het derde doel van dit proefschrift is om de klinische stadiëring en endoscopische resectie (ER) van vroegcarcinomen in de slokdarm te optimaliseren en om een predictie model te ontwikkelen dat het risico op metastasen kan voorspellen in individuele patiënten met een submucosaal (pT1b) adenocarcinoom van de slokdarm.
Slokdarmkanker wordt geïntroduceerd in **Deel I** van dit proefschrift. **Hoofdstuk 1.1** geeft een overzicht van de epidemiologie, klinische presentatie, diagnose en behandeling van vroegcarcinomen in de slokdarm, risico factoren op lymfekliermetastasen, het risico op tweede primaire tumoren in de luchtwegen en het bovenste deel van het spijsverteringskanaal in patiënten met een PCC van de slokdarm en in patiënten met een PCC in de hoofd-hals regio, endoscopische detectietechnieken, ER technieken, en de preventie van slokdarmstricturen na ER. Dit hoofdstuk wordt gevolgd door **Hoofdstuk 1.2** waarin de doelen en de opzet van dit proefschrift worden beschreven.

**Screening en diagnose van tweede en meerdere primaire tumoren in de luchtwegen en het bovenste deel van het spijsverteringskanaal**

**Deel II** beschrijft de screening en diagnose van MPT's in de luchtwegen en het bovenste deel van het spijsverteringskanaal in patiënten met een PCC van de slokdarm en in patiënten met een PCC in de hoofd-hals regio.

**Plaveiselcelcarcinoom van de slokdarm en het risico op meerdere primaire tumoren in de luchtwegen en het bovenste deel van het spijsverteringskanaal**



**Hoofdstuk 2** beschrijft een landelijke, retrospectieve, cohort studie waarin het risico op synchrone en metachrone MPT's in de luchtwegen en het bovenste deel van het spijsverteringskanaal in patiënten met een primaire PCC van de slokdarm wordt vergeleken met de algemene populatie. De meeste onderzoeken over dit onderwerp zijn uitgevoerd in een Aziatische patiënten populatie. De studie beschreven in dit hoofdstuk werd uitgevoerd in samenwerking met de Nederlandse Kanker Registratie (IKNL). Van de 9058 geïncludeerde patiënten die gediagnosticeerd werden met een PCC van de slokdarm tussen 2000 en 2016 ontwikkelde 476 patiënten (5,3%) een tweede primaire tumor of MPT's in de luchtwegen en het bovenste deel van het spijsverteringskanaal. De meeste MPT's waren gelokaliseerd in de hoofd-hals regio (49,5%) en werden synchroon gediagnosticeerd (60,4%). In vergelijking met de algemene populatie hadden patiënten met een PCC van de slokdarm een significant hoger risico op het ontwikkelen van zowel synchrone (SIR 10,95, 99% CI 9,40-12,53) als metachrone (SIR 4,36, 99% CI 3,56-5,10) MPT's. De hoofd-hals regio had het hoogste risico op het ontwikkelen van MPT's. De 15-jaar cumulatieve incidentie op het ontwikkelen van metachrone tweede primaire tumoren was 19,7% in de groep patiënten die langer leefden dan 6 maanden na diagnose van een PCC van de slokdarm. Dit betekent dat ongeveer 1 op de 5 patiënten met een PCC van de slokdarm die langer leeft dan 6 maanden een tweede primaire tumor ontwikkelt binnen 15 jaar. Deze hoge cumulatieve incidentie zou kunnen suggereren dat

screening op MPT's nuttig kan zijn. Echter, patiënten met een hoog stadium PCC van de slokdarm hebben een slechte prognose en deze patiënten hebben waarschijnlijk geen voordeel van een screening programma omdat hun prognose al bepaald wordt door de slokdarmtumor. Het diagnosticeren van MPT's in deze patiënten is waarschijnlijk niet klinisch relevant. We concluderen daarom dat prospectieve screeningstudies nodig zijn om de werkelijke incidentie van MPT's te bepalen en om de opbrengst en het voordeel van screening op MPT's te onderzoeken. Daarnaast dient rekening te worden gehouden met de overleving van patiënten met een PCC van de slokdarm.

Zoals in **Hoofdstuk 2** beschreven is het risico op MPT ontwikkeling het hoogst in de hoofd-hals regio. **Hoofdstuk 3** beschrijft een systematische review en meta-analyse van studies die screening hebben uitgevoerd op tweede primaire tumoren in de hoofd-hals regio in patiënten met een PCC van de slokdarm. Het doel van dit systematische review was om te onderzoeken wat de opbrengst van endoscopische screening op hoofd-hals tweede primaire tumoren is in patiënten met een PCC van de slokdarm. De primaire uitkomstmaat van deze studie was de gepoolde prevalentie van hoofd-hals tweede primaire tumoren. In totaal werden er 12 studies geïncludeerd in dit systematische review met in totaal 6483 geïncludeerde patiënten. Alle studies waren uitgevoerd in Japan. De gepoolde prevalentie van hoofd-hals tweede primaire tumoren was 6,7% (95% CI: 4,9-8,4, bereik: 3,0-29,6%). De meeste hoofd-hals tweede primaire tumoren waren gelokaliseerd in de hypopharynx (60,3%) en werden geclassificeerd met een laag tumor stadium (85,3%). Patiënten met een laag stadium hoofd-hals tumor kunnen curatief behandeld worden en deze patiënten hebben vaak een uitstekende prognose. We concluderen dat het concept van endoscopische screening op hoofd-hals tweede primaire tumoren bij patiënten met een PCC van de slokdarm veelbelovend is. Omdat alle geïncludeerde studies werden uitgevoerd in Japan, zou deze screening in Japan moeten worden gestandaardiseerd. Deze hoofd-hals screening zou dan moeten worden uitgevoerd tijdens de work-up en follow-up van een PCC van de slokdarm. Omdat alle geïncludeerde studies uitgevoerd werden in Japan is het noodzakelijk om Westerse screening studies uit te voeren, om te beoordelen wat de prevalentie is van hoofd-hals tweede primaire tumoren in een Westerse populatie. Daarnaast zijn er meer screeningstudies nodig om te onderzoeken welk type PCC van de slokdarm het risico op hoofd-hals tweede primaire tumoren verhoogt en om te onderzoeken welke risicofactoren verband houden met het ontstaan van hoofd-hals tweede primaire tumoren.

In **Hoofdstuk 4** beschrijven we een systematische review en meta-analyse over screening op slokdarm tweede primaire tumoren in patiënten met een PCC in de hoofd-hals regio. Studies werden alleen geïncludeerd als slokdarm screening werd uitgevoerd met Lugol chromoendoscopy (LCE). Er werden 15 studies geïncludeerd met in totaal 3386 geïncludeerde patiënten. De gepoolde prevalentie van slokdarm tweede primaire tumoren, van alle geïncludeerde studies, was 15.2% (95% CI 11.4-19.0, bereik: 4.1-40.9%). Er waren maar 3 Westerse studies geïncludeerd, de gepoolde prevalentie van deze studies was 6.0% (95% CI: 2.3-9.7). Dit in tegenstelling tot de gepoolde prevalentie van slokdarm tweede primaire tumoren in de 12 Aziatische studies, wat 17.7% (95% CI: 12.7-22.7) was. De prevalentie van tweede primaire tumoren was het hoogst in patiënten met een hoofd-hals PCC in de hypofarynx. De gepoolde prevalentie, zoals gerapporteerd in dit systematisch review is hoger dan de prevalentie die gerapporteerd is in retrospectieve, niet-screening studies (1-6%). We concluderen dat er een sterk bewijs is om slokdarmscreening uit te voeren met LCE in een Aziatische patiëntenpopulatie. We kunnen echter niet hetzelfde bevestigen voor een

Westerse patiëntenpopulatie omdat er maar drie Westerse studies werden uitgevoerd. Er zijn daarom meer Westerse screening studies nodig.

Na de conclusies die we getrokken hebben uit **Hoofdstuk 4**, hebben we een prospectieve screening studie uitgevoerd om de incidentie van synchrone tweede primaire tumoren in de slokdarm te bepalen in patiënten met een hoofd-hals PCC in Nederland. Deze studie wordt beschreven in **Hoofdstuk 5**. Patiënten die gediagnosticeerd zijn met een hoofd-hals PCC in de orofarynx, hypofarynx, een andere hoofd-hals sub-locatie in combinatie met actief alcohol gebruik, of patiënten met twee PCC's in de hoofd-hals regio ongeacht de sub-locatie, werden geïncludeerd in deze studie. Screening gastro duodenoscopie werd uitgevoerd met wit licht hoge resolutie endoscopie (WLE), 'narrow-band imaging' (NBI), en LCE door een ervaren interventie endoscopist tijdens de work-up voor een PCC in de hoofd-hals regio. Een tweede primaire tumor in de slokdarm werd gedefinieerd als een PCC of hooggradige dysplasie (HGD). Gedurende één jaar werden er in totaal 85 patiënten geïncludeerd die allen een screening gastro duodenoscopie ondergingen. Een tweede primaire tumor was pathologisch bewezen in 5/85 (5.9%) patiënten. Het detectie percentage van alle (pre)maligne laesies, inclusief laaggradige dysplasie (LGD) (n=3), was 9.4%. Alle tweede primaire tumoren werden gedetecteerd in een vroeg stadium en konden curatief behandeld worden met ER of radiotherapie. In de patiënt waarbij er een slokdarm PCC werd gediagnosticeerd kon gecombineerde behandeling met radiotherapie voor zowel hoofd-hals als slokdarm PCC worden uitgevoerd. Slokdarmlaesies groter dan 20 mm werden hoofzakelijk gezien in patiënten met een slokdarm tweede primaire tumor. Geen van deze tweede primaire tumoren werden gedetecteerd door beeldvormende technieken vóór gastro duodenoscopie was uitgevoerd. De studie suggereert daarom dat endoscopische screening van deze geselecteerde patiëntengroep van toegevoegde waarde was. Screening zou eerst moeten worden overwogen in hoog-risico patiënten (dat wil zeggen: een hoofd-hals PCC gelokaliseerd in de orofarynx of hypofarynx en patiënten met een hoofd-hals PCC die alcohol gebruiken). The combinatie van WLE en NBI is waarschijnlijk de meest sensitieve screening methode. Hoewel LCE ook kan worden uitgevoerd, is extra alertheid geïndiceerd in het geval van laesies kleiner dan 20 mm vanwege het hoge percentage vals-positieve laesies.



**Endoscopische detectietechnieken**

**Hoofdstuk 6** beschrijft een "editorial" verwijzend naar Costa-Santos et al. In dit hoofdstuk wordt de toegevoegde waarde van LCE bediscussieerd door drie belangrijke fases te beschrijven in de behandeling van vroeg PCC's in de slokdarm.

De eerste fase is de detectie van de laesie. In de literatuur wordt vermeld dat de accuratesse van de detectie van vroeg PCC's in de slokdarm het hoogst is als NBI en LCE gecombineerd worden. De specificiteit is echter superieur met NBI.

De tweede fase is de karakterisering van de laesie. LCE kan verdachte laesies in de slokdarm markeren als "Lugol voiding laesies" (LVL's). Deze LVL's zijn aanwezig of niet, maar er kan geen verdere karakterisering van deze laesies worden gemaakt op grove morfologie na. Daarentegen kunnen intra-epitheliale papillaire capillaire lus (IPCL) patronen die zichtbaar zijn met NBI slokdarmlaesies verder karakteriseren.

De derde fase is de afbakening van de laesie. Costa-Santos et al. concludeerde dat inspectie van de mucosa met LCE vóór ER van een PCC of dysplasie van de slokdarm niet

geassocieerd was met een verhoogde mate van volledige laterale resectie vergeleken met inspectie met alleen NBI. Gebaseerd op eerdere literatuur en de studie van Costa-Santos et al., concluderen we dat voor zowel NBI als LCE adequate expertise en ervaring van de endoscopist cruciaal is voor de detectie, karakterisering, en afbakening van slokdarm laesies. Alhoewel NBI superieur lijkt op het gebied van specificiteit en karakterisering van laesies, hangt de detectie van laesies af van de ervaring van de endoscopist. Herkenning van specifieke IPCL-patronen is cruciaal bij NBI, terwijl de detectie van LVL's door LCE gemakkelijker lijkt voor een endoscopist met weinig ervaring.

## Endoscopische diagnose en behandeling van een vroeg carcinoom in de slokdarm

**Deel III** beschrijft de endoscopische diagnose en behandeling van vroeg carcinomen in de slokdarm, de focus ligt hierbij op adenocarcinomen van de slokdarm.

### Endoscopische herbeoordeling van cT2 adenocarcinomen van de slokdarm

**Hoofdstuk 7** beschrijft een multicentrische, prospectieve cohort studie van patiënten met een klinisch T2 adenocarcinoom van de slokdarm. Het klinisch tumor stadium van een adenocarcinoom van de slokdarm wordt meestal bepaald door een endoscopische echo. De accuratesse van een endoscopische echo is echter laag voor tumor stadium T1 en T2. Dit zou kunnen resulteren in een overbehandeling van patiënten waarbij de tumor "overgestadieerd" is als T2 en deze patiënten ondergaan onnodige aanvullende invasieve behandeling. Het doel van deze studie was om de proportie van T2 adenocarcinomen van de slokdarm te bepalen die na endoscopische herbeoordeling door een ervaren interventie endoscopist beoordeeld worden als een T1 tumor.

Patiënten met een T2N0M0 adenocarcinoom van de slokdarm werden geïncludeerd in deze studie en ondergingen een endoscopische herbeoordeling van de tumor. In 15 van de 25 (60%) geïncludeerde patiënten werd de T2 tumor gedownstaged naar een T1 tumor, zij ondergingen allemaal een poging tot ER. Twaalf van de 15 patiënten ondergingen een succesvolle ER en zij hadden allemaal een bewezen pT1 tumor. Tien van deze 12 patiënten werden alleen behandeld met ER, waarvan de ER curatief was in 5 patiënten. Een poging tot ER werd onderbroken in 3 van de 15 patiënten doordat de tumor ingroeide in de spierlaag. Endoscopische herbeoordeling bevestigde het T2 tumor stadium in de overige 10 van de 25 (40%) patiënten. In totaal bleken 15 van de 25 cT2 adenocarcinomen van de slokdarm pT1 stadium of prepT1 stadium te zijn. De sensitiviteit van de aanwezigheid van invasieve kenmerken van de tumor tijdens endoscopische herbeoordeling in het detecteren van een T2 tumor was 86% (95% CI 42-100) en de specificiteit was 80% (95% CI 52-96).

Gebaseerd op **Hoofdstuk 7** concluderen we dat in patiënten met een cT2N0M0 adenocarcinoom van de slokdarm (gebaseerd op een beoordeling met CT-scan of endoscopische echo), endoscopische herbeoordeling door een ervaren interventie endoscopist resulteert in het "downstagen" naar een T1 slokdarmtumor geschikt voor ER, in ongeveer de helft van de patiënten.

Endoscopische herbeoordeling voorkomt onnodige invasieve aanvullende behandeling in 40% van de patiënten en heeft daarom een substantiële klinische impact op de behandeling van T2 adenocarcinomen van de slokdarm. We pleiten ervoor dat alle T2 gestadieerde

adenocarcinomen van de slokdarm in aanmerking moeten komen voor een endoscopische herbeoordeling door een endoscopist met ervaring in ER van vroegcarcinomen in de slokdarm.

**Hoofdstuk 8** beschrijft een retrospectieve, observationele, cohort studie van patiënten die een endoscopische submucosal dissectie (ESD) hebben ondergaan voor vroegcarcinomen in de slokdarm of maag, uitgevoerd met propofol sedatie zonder endotracheale intubatie. We evalueren de veiligheid van propofol sedatie zonder endotracheale intubatie en rapporteren over endoscopie- en anesthesie gerelateerde complicaties. In drie van de 88 geïncludeerde patiënten heeft er een intra-procedurele ESD-gerelateerde complicatie plaatsgevonden. Intra-procedurele anesthesie-gerelateerde complicaties vonden plaats in twee patiënten (2.3%), waarvan in één patiënt er een conversie naar endotracheale intubatie heeft plaatsgevonden. Gebaseerd op **Hoofdstuk 8**, concluderen we dat sedatie met propofol zonder endotracheale intubatie veilig is voor ESD procedures in de slokdarm en maag, met een laag aantal anesthesie-gerelateerde complicaties. In lijn met deze resultaten en logistieke en financiële consequenties, dient propofol sedatie zonder endotracheale intubatie voor ESD te worden overwogen in plaats van algemene anesthesie.

Een nadeel van ER van vroeg carcinomen in de slokdarm is de hoge strictuur kans na de resectie. Een risicofactor voor strictuur ontwikkeling is een mucosaal defect van ≥75% van de circumferentie van de slokdarm na ER. **Hoofdstuk 9** beschrijft de effectiviteit van een behandeling met topicale Budesonide op de preventie van slokdarmstricturen na een ER van een vroeg carcinoom in de slokdarm. Het betreft een retrospectieve analyse van een prospectieve cohort studie van patiënten die topicale budesonide hebben gekregen na ER van slokdarmkanker. Tweeënveertig patiënten die behandeld werden met ER en topicale budesonide werden geïncludeerd in deze studie. In totaal ontwikkelden 18/42 (44.9%) patiënten een strictuur. Het gepoolde strictuur percentage was berekend voor controle groepen (zonder Budesonide behandeling) uit de literatuur, wat 75.3% (95% CI 68.8-81.9%) was. Vergelijkbare patiënten uit ons cohort hadden een lager strictuur percentage (47.8% vs. 75.3%, *p=0.007*). We concluderen dat een behandeling met topicale budesonide na ER van slokdarmkanker een veilige en effectieve methode lijkt te zijn in het voorkomen van slokdarmstricturen. Het strictuur percentage na behandeling met Budesonide is lager in vergelijking met het strictuur percentage van patiënten die géén preventieve behandeling hebben gekregen na ER, gerapporteerd in de literatuur.



Zodra ER is uitgevoerd, hangt de beslissing om aanvullende behandeling uit te voeren af van de histologische kenmerking van het ER-preparaat en het risico op lymfekliermetastasen. Er is geen klinische “tool” beschikbaar die het risico van verschillende histologische kenmerken combineert om het risico op lymfekliermetastasen te voorspellen in individuele patiënten. **Hoofdstuk 10.1** beschrijft een multicentrische, retrospectieve cohort studie van patiënten met een submucosaal (pT1b) adenocarcinoom van de slokdarm die ER of primaire chirurgie hebben ondergaan. We hebben een voorspellingsmodel ontwikkeld dat alle geaccepteerde prognostische parameters bevat om het risico op metastasen op individuele basis nauwkeurig te voorspellen. In totaal werden er 248 patiënten met een pT1b adenocarcinoom van de slokdarm geïncludeerd. We laten zien dat de cumulatieve incidentie op het ontwikkelen van metastasen binnen 5 jaar na de primaire behandeling van een adenocarcinoom van de slokdarm 30,9% (95% CI 25,1-36,8) is. De kans op het ontwikkelen van metastasen na resectie kan worden geschat met een gepersonaliseerde voorspellingsrisico score die de diepte van de tumorinvasie, tumorgrootte en lymfovasculaire invasie (LVI) omvat. Het

voorspelde risico op metastasen binnen 5 jaar na primaire behandeling is bijvoorbeeld 5,9% (95% CI 2,3-11,2) in patiënten met een T1b adenocarcinoom van de slokdarm <20mm, zonder LVI en sm1 diepte invasie, vergeleken met een risico van 70,1% (95% CI 60,5-78,7) in patiënten met een T1b adenocarcinoom van de slokdarm ≥20mm, met LVI en sm3 diepte invasie. Het voorspellingsmodel had een goede accuratesse met een c-statistic van 0,81 (95% CI 0,75-0,86).

**Hoofdstuk 10.2** beschrijft of kwantificatie van LVI aanvullende prognostische informatie geeft op het ontwikkelen van metastasen in patiënten met een pT1b adenocarcinoom van de slokdarm. LVI is geclassificeerd in 4 categorieën gebaseerd op het aantal LVI foci in het resectie preparaat: geen LVI, 1 LVI focus, 2-3 LVI foci, en ≥4 LVI foci. We laten zien dat de aanwezigheid van meer LVI foci gecorreleerd is met een hoger metastasen risico. De aanwezigheid van slechts één LVI focus was geen onafhankelijke voorspeller voor metastasen. Het voorspelde 5-jaars metastasen risico is bijvoorbeeld 14,1% (95% CI 7,9-21,9) in patiënten met een T1b adenocarcinoom van de slokdarm <20mm, sm1 diepte invasie en geen LVI, in vergelijking met 26,3% (95% CI 10,6-45,3) als één LVI focus aanwezig is, 43,5% (95% CI 26,6-61,5) als 2-3 LVI foci aanwezig zijn, en 54,4% (95% CI 33,7-72,8) als ≥4 LVI foci aanwezig zijn. Deze resultaten suggereren dat kwantificatie van LVI de risicoschatting in pT1b EAC verder kan verfijnen.

In **Deel IV** vatten we de belangrijkste bevindingen van dit proefschrift samen in **Hoofdstuk 11.1. Hoofdstuk 11.2** omvat de algemene discussie gevolgd door de aanbevelingen voor toekomstig onderzoek. De conclusie van dit proefschrift wordt beschreven in **Hoofdstuk 11.3.**

# CHAPTER 13

## Abbreviations

## Abbreviations

| | |
|---|---|
| AE | adverse event |
| ASA | American Society of Anesthesiologists |
| BE | Barrett's esophagus |
| BMI | body mass index |
| CI | confidence interval |
| CRT | chemoradiotherapy |
| CT | computed tomography |
| dCRT | definitive chemoradiotherapy |
| df | degree of freedom |
| EAC | esophageal adenocarcinoma |
| EBD | endoscopic balloon diltion |
| EC | esophageal cancer |
| EGD | esophagogastroduodenoscopy |
| EGJ | esophagogastric junction |
| EMR | endoscopic mucosal resection |
| EoE | eosinophilic esophagitis |
| ER | endoscopic resection |
| ERA | endoscopic reassessment |
| ESCC | esophageal squamous cell carcinoma |
| ESD | endoscopic submucosal dissection |
| ESGE | European Society of Gastrointestinal Endoscopy |
| ESPT | esophageal second primary tumors |
| EUS | endoscopic ultrasound |
| F | female |
| FFPE | formalix-fixed paraffin-embedded |
| FE | fixed-effects |
| FNA | fine needle aspiration |
| GEJ | gastroesophageal junction |
| GI | gastro-intestinal |
| H&E | hematoxylin and eosin stained |
| HGD | high grade dysplasia |
| HGIN | high grade neoplasia |
| HN | head and neck |
| HNSCC | head and neck squamous cell carcinoma |
| HNSPT | head and neck second primary tumor |
| HR | hazard ratio |
| HPV | human papilloma virus |
| $I^2$ | inconsistency index |
| IQR | interquartile range |
| IPCL | intraepithelial papillary capillary loop |

| | |
|---|---|
| LCE | lugol chromoendoscopy |
| LGD | low grade dysplasia |
| LGIN | low grade neoplasia |
| LNM | lymph node metastasis |
| LVI | lymphovascular invasion |
| LVL | lugol voiding lesions |
| M | male |
| MBM | multiband mucosectomy |
| MINORS | Methodological Index for Non Randomized Studies |
| MPT | multiple primary tumor |
| MRI | magnetic resonance imaging |
| NBI | narrow band imaging |
| NCR | Netherlands Cancer Registry |
| nCRT | neo-adjuvant chemoradiotherapy |
| PET | positron emission tomography |
| PGA | polygycolic acid sheet |
| prepTstage | pre-treatment pathological tumor stage |
| prepNstage | pre-treatment pathological node stage |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| Pro | prospective |
| pt | patient |
| pTN-stage | pathological tumor and node stage |
| PVV | positive predictive value |
| PY | pack years |
| RCT | randomized controlled trial |
| Rel | relevance |
| Retro | retrospective |
| RFA | radiofrequency ablation |
| RSS | Ramsay Sedation Scale |
| SCC | squamous cell carcinoma |
| SHR | subdistribution hazard ratio |
| SIR | standardized incidence ratio |
| SE | standard error |
| SP | sedation practitioner |
| SPT | second primary tumor |
| Tis | carcinoma in situ |
| TNM | Tumor Node Metastasis |
| UADT | upper aerodigestive tract |
| WLE | white light (high resolution) endoscopy |
| ypTN-stage | residual tumor and node stage after radiotherapy |

# CHAPTER 14

## Contribution Authors

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# CHAPTER 15

## Bibliography

## Bibliography

*Described in this thesis*


1. Van de Ven SEM, L Suzuki, Gotink AW, ten Kate FJC, Nieboer D, Weusten BLAM, Brosens LAA, Van Hillegersberg R, Alvarez Herrero L, Seldenrijk CA, Alkhalaf A, Moll FCP, Curvers W, Van Lijnschoten G, Tang T, Van der Valk H, Nagengast WB, Kats-Ugurlu G, Plukker JTM, Houben MHMG, Van der Laan J, Pouw RE, Bergman JJGHM, Meijer SL, Van Berge Henegouwen MI, Wijnhoven PBL, De Jonge PJF, Doukas M, Bruno MJ, Biermann K, Koch AD. **Quantification of lymphovascular invasion is useful to predict lymph node metastases in patients with submucosal (T1b) esophageal adenocarcinoma**.
*Accepted United European Journal of Gastroenterology; 2021*

2. Van de Ven SEM, de Graaf W, Bugter O, Spaander MCW, Nikkessen S, de Jonge PJF, Hardillo JA, Sewnaik A, Monserez DA, Mast H, Keereweer S, Bruno MJ, Baatenburg de Jong RJ, Koch AD. **Screening for synchronous esophageal second primary tumors in patients with head and neck cancer**.
*Diseases of the Esophagus; 2021, PMID 34075402*

3. Van de Ven SEM, Spaander MCW, Pouw RE, Tang TJ, Houben MHMG, Schoon EJ, de Jonge PJF, Bruno MJ, Koch AD. **Favorable effect of endoscopic reassessment of clinically staged T2 esophageal adenocarcinoma: a multicenter prospective cohort study**. *Endoscopy; 2021, PMID 33530109*

4. Van de Ven SEM*, Gotink AW*, ten Kate FJC, Nieboer D, Suzuki L, Weusten BLAM, Brosens LAA, Van Hillegersberg R, Alvarez Herrero L, Seldenrijk CA, Alkhalaf A, Moll FCP, Schoon EJ, Van Lijnschoten G, Tang T, Van der Valk H, Nagengast WB, Kats-Ugurlu G, Plukker JTM, Houben MHMG, Van der Laan JS, Pouw RE, Bergman JJGHM, Meijer SL, Van Berge Henegouwen MI, Wijnhoven PBL, De Jonge PJF, Doukas M, Bruno MJ, Biermann K**, Koch AD**. **Individual risk calculator to predict lymph node metastases in patients with submucosal (T1b) esophageal adenocarcinoma: a multicenter cohort study**. **/** both authors contributed equally Endoscopy; 2021, PMID 33626582*

5. Van de Ven SEM, Falger JM, Verhoeven RHA, Baatenburg de Jong RJ, Spaander MCW, Bruno MJ, Koch AD. **Increased risk of second primary tumors in patients with esophageal squamous cell carcinoma: a nationwide study in a Western population**. *United European Gastroenterology Journal; 2021, PMID 33270530*

6. Van de Ven, SEM, Snijders MJBL, Bruno MJ, Koch AD. **Effectiveness of topical budesonide in preventing esophageal strictures after endoscopic resection of esophageal cancer**. *Endoscopy Internation Open; 2020, PMID 33269312*

7. Van de Ven SEM, Koch AD. **When is Lugol still necessary in 2020?** *Endoscopy International Open; 2020, PMID 33049006*

8. Van de Ven SEM, Bugter O, Hardillo JA, Bruno MJ, Baatenburg de Jong RJ, Koch AD. **Screening for head and neck second primary tumors in patients with esophageal squamous cell cancer: a systematic review and meta-analysis**. *United European Journal of Gastroenterology; 2019, PMID 31839955*

9. Van de Ven SEM, Leliveld L, Klimek M, Hilkemeijer TRH, Bruno MJ, Koch AD. **Propofol sedation without endotracheal intubation is safe for endoscopic submucosal dissection in the esophagus and stomach**. *United European Journal of Gastroenterology; 2019, PMID 31019709*

10. Bugter O, Van de Ven SEM**,** Hardillo JA, Bruno MJ, Koch AD, Baatenburg de Jong RJ. **Early detection of esophageal second primary tumors using Lugol chromoendoscopy in patients with head and neck cancer: a systematic review and meta-analysis**. *Head and Neck; 2019, PMID 30593712*

*Other publications*

1. van Munster SN, Frederiks C, Nieuwenhuis E, Alvarez Herrero L, Bogte A. Alkhalaf A, Schenk BE, Schoon EJ, Curvers WL, Koch AD, van de Ven SEM, de Jonge PJF, Tang TJ, Nagengast WB, Peters FT, Westerhof J, Houben MHMG, Bergman JJGHM, Pouw RE, Weusten BLAM. **Incidence and outcomes of poor healing and poor squamous regeneration after radiofrequency ablation therapy for early Barrett's neoplasia**. *Endoscopy; 2021, PMID 34062597*

2. van Munster SN, Nieuwenhuis E, Weusten BLAM, Alvarez Herrero L, Bogte A, Alkhalaf A, Schenk BE, Schoon EJ, Curvers W, Koch AD, van de Ven SEM, de Jonge PJF, Tang TJ, Nagengast WB, Peters FTM, Westerhof J, Houben MHMG, Bergman JJGHM, Pouw RE, Dutch Barrett Expert Centers. **Long-term outcomes after endoscopic treatment for Barrett's neoplasia with radiofrequency ablation +/- endoscopic resection: results from the national Dutch database in a 10-year period**. *Gut; 2021, PMID 33753417*

3. Van Munster SN, Nieuwenhuis EA, Weusten BLAM, Alvarez Herrero L, Bogte A, Alkhalaf A, Schenk BE, Schoon EJ, Curvers W, Koch AD, van de Ven SEM, de Jonge PJF, Tang T, Nagengast WB, Peters FTM, Westerhof J, Houben MHMG, Bergman JJGHM, Pouw RE. **Endoscopic resection without subsequent ablation therapy for early barrett's neoplasia: endoscopic finding and long-term mortality**. *J Gastrointest Surg; 2021, PMID: 33140322*

4. Van de Ven SEM, Backes Y, Hilbink M, Seerden TCJ, Kessels K, de Vos tot Nederveen Cappel WH, Groen JN, Wolfhagen FHJ, Geesing JMJ, ter Borg F, van Bergeijk J, Spanier BWM, Mundt MW, Pullens HJM, Boonstra JJ, Opsteeg B, van Lent AUG, Schrauwen RWM, Laclé MM, Moons LMG, Terhaar sive Droste JS. **Periprocedural adverse events after endoscopic resection of T1 colorectal carcinomas**. *GIE; 2020, PMID: 31525362*

5. Van de Ven SEM, Derikx LAAP, Nagtegaal ID, van Herpen CM, Takes RP, Melchers WJG, Pierik M, van den Heuvel T, Verhoeven RHA, Hoentjen F, Nissen LHC. **Laryngeal carcinoma in patients with inflammatory bowel disease: clinical outcomes and risk factors**. *Inflamm Bowel Dis; 2020, PMID: 31559415*

6. Van de Ven SEM, Pavlov KV, Beutler JJ, Scheffer RCH. **Bile cast nephropathy caused by obstructive pancreatic carcinoma and failed ERCP**. *ACG Case Report Journal; 2018, PMID: 30775391*

7. Haeren RH, Van de Ven SEM**,** van Zandvoort MA, Vink H, van Overbeeke JJ, Hoogland G, Rijkers K. **Assessment and Imaging of the Cerebrovascular Glycocalyx**. *Curr Neurovascular Research. 2016, PMID 27142381*

# CHAPTER 16

## PhD portfolio

## PhD Portfolio

| | |
|---|---|
| Name PhD student: | Steffi Elisabeth Maria van de Ven |
| PhD period: | December 2017 – December 2020 |
| Promotor: | Prof. dr. M.J. Bruno |
| Co-promotor: | Dr. A.D. Koch |
| Department Erasmus MC: | Gastroenterology and Hepatology |

**Courses and workshops**

| | Year | Workload |
|---|---|---|
| Basic course OpenClinica | 2018 | 6 hours |
| Biomedical English Writing Course, Erasmus Postgraduate School for Molecular Medicine (MolMed), Erasmus MC, Rotterdam | 2018 | 24 hours |
| Biostatistical Methods I: Basic Principles Part A (CC02a), Netherlands institute for Health Sciences (NIHES), Rotterdam | 2018 | 40 hours |
| BROK course, Consultatiecentrum Patiëntgebonden onderzoek (CPO), Erasmus MC, Rotterdam | 2018 | 24 hours |
| EndNote workshop, Erasmus MC library, Rotterdam | 2018 | 6 hours |
| Photoshop & Illustrator workshop, Erasmus Postgraduate School for Molecular Medicine (MolMed), Erasmus MC, Rotterdam | 2018 | 8 hours |
| Presenting skills for junior researchers, Erasmus Postgraduate School for Molecular Medicine (MolMed), Erasmus MC, Rotterdam | 2018 | 24 hours |
| Systematic Literature Retrieval in PubMed, Erasmus MC library, Rotterdam | 2018 | 6 hours |
| Systematic Literature Retrieval in other databases, Erasmus MC library, Rotterdam | 2018 | 6 hours |
| Workshop “Coachen van toekomstige Erasmus artsen basis”, Erasmus MC, Rotterdam | 2018 | 6 hours |
| Integrity in scientific research, Dept. of Medical ethics and Philosophy, Erasmus MC, Rotterdam | 2019 | 16 hours |
| Workshop on Microsoft Excel 2010: Basic, Erasmus Postgraduate School for Molecular Medicine (MolMed), Erasmus MC, Rotterdam | 2019 | 6 hours |
| Hands-on-training: Get your PhD done – with Outlook and OneNote, Erasmus Postgraduate School for Molecular Medicine (MolMed), Erasmus MC, Rotterdam | 2019 | 6 hours |

**Oral presentations**

| | Year | Workload |
|---|---|---|
| Elevator pitch subsidie ronde spijsverteringskankers 2018 – SCOPE studie: "*Screening for synchronous second primary esophageal tumors in patients with head and neck cancer",* MLDS patiëntenvereniging, Amersfoort, the Netherlands | 2018 | 12 hours |
| *Increased risk of second primary tumors in patients with esophageal squamous cell carcinoma: a nationwide study in a Western population.* Digestive Disease Days, Veldhoven, the Netherlands | 2019 | 12 hours |
| Protocol presentation "*Double-blind, randomized, placebo-controlled, phase IIa trial on the efficacy and tolerability of an 8-week treatment with two different doses of budesonide orodispersible tablets vs. plcebo for prevention of esophageal strictures in adult patients after endoscopic submucosal dissection for squamous cell carcinoma – PEGASUS-1 trial"* Investigator meeting, Zürich, Switzerland | 2019 | 12 hours |
| *Individual risk calculator to predict lymph node metastases in patients with submucosal (T1b) esophageal adenocarcinoma: multicenter cohort study*. Webinar Digestive Disease Days, the Netherlands | 2020 | 12 hours |
| *Endoscopic reassessment of cT2N0M0 esophageal adenocarcinoma leads to downstaging to T1 tumors and prevents unnecessary adjuvant treatment: a multicenter prospective cohort study.* E-poster presentation in moderated poster session. United European Gastroenterology Week, Amsterdam, The Netherlands | 2020 | 12 hours |
| *Screening for synchronous second primary esophageal tumors in patients with head and neck cancer.* Virtual Digestive Diseases Days, the Netherlands | 2021 | 12 hours |
| *Quantification of lymphovascular invasion is useful to predict lymph node metastases in patients with submucosal (T1b) esophageal adenocarcinoma.* Virtual European Society for Gastrointestinal Endoscopy Days | 2021 | 12 hours |
| ***Canceled due to COVID-19*** | | |
| *Individual risk calculator to predict lymph node metastases in patients with submucosal (T1b) esophageal adenocarcinoma: multicenter cohort study*. European Society for Gastrointestinal Endoscopy, Dublin, Ireland **Awarded with a travel grant** | 2020 | X |
| *Quantification of lymphovascular invasion is useful to predict lymph node metastases in patients with submucosal (T1b) esophageal adenocarcinoma.* European Society for Gastrointestinal Endoscopy, Dublin, Ireland | 2020 | X |

**Poster presentations**

| | Year | Workload |
|---|---|---|
| *Propofol sedation without endotracheal intubation is safe for endoscopic submucosal dissection in the esophagus and stomach*. United European Gastroenterology Week, Vienna, Austria | 2018 | 12 hours |
| *Screening for head and neck second primary tumors in patients with esophageal squamous cell cancer: a systematic review and meta-analysis*. European Society for Gastrointestinal Endoscopy Days, Prague, Czech Republic | 2019 | 12 hours |
| *Screening for head and neck second primary tumors in patients with esophageal squamous cell cancer: a systematic review and meta-analysis*. Digestive Disease Week 2019, San Diego, United States of America | 2019 | 12 hours |
| *Risk of second primary tumors in patients with esophageal squamous cell carcinoma in a Western population.* United European Gastroenterology Week, Barcelona, Spain. **Awarded with a travel grant.** | 2019 | 12 hours |
| *Screening for head and neck second primary tumors in patients with esophageal squamous cell cancer: a systematic review and meta-analysis.* United European Gastroenterology Week, Barcelona, Spain | 2019 | 12 hours |
| *Individual risk calculator to predict lymph node metastases in patients with submucosal (T1b) esophageal adenocarcinoma: multicenter cohort study.* E-poster (due to COVID-19). Virtual Digestive Disease Week 2020, Chicago, United States of America | 2020 | 8 hours |
| *Screening for synchronous second primary tumor in patients with head and neck cancer.* E-poster presentation (due to COVID-19). Virtual United European Gastroenterology Week, Amsterdam, The Netherlands | 2020 | 8 hours |
| *Endoscopic reassessment of cT2N0M0 esophageal adenocarcinoma leads to downstaging to T1 tumors and prevents unnecessary adjuvant treatment: a multicenter prospective cohort study.* E-poster presentation (due to COVID-19). Virtual United European Gastroenterology Week, Amsterdam, The Netherlands | 2020 | 8 hours |
| *Screening for synchronous esophageal second primary tumors in patients with head and neck cancer.* E-poster presentation (due to COVID-19). Virtual European Society for Gastrointestinal Endoscopy Days. | 2021 | 8 hours |

### Attended (inter)national conferences

| | Year | Workload |
|---|---|---|
| Digestive Disease Days, Veldhoven, the Netherlands (2x) | 2018 | 32 hours |
| European Gastroenterology Week, Vienna, Austria | 2018 | 28 hours |
| European Society for Gastrointestinal Endoscopy Days, Prague, Czech Republic | 2019 | 28 hours |
| Digestive Disease Days, Veldhoven, the Netherlands | 2019 | 16 hours |
| European Gastroenterology Week, Barcelona, Spain | 2019 | 28 hours |
| Webinar Digestive Disease Days, the Netherlands | 2020 | 8 hours |
| Virtual United European Gastroenterology Week | 2020 | 8 hours |
| Virtual Digestive Disease Days, the Netherlands | 2021 | 16 hours |
| Virtual European Society for Gastrointestinal Endoscopy Days | 2021 | 20 hours |

### Attended seminars

| | Year | Workload |
|---|---|---|
| Journal clubs, department of Gastroenterology and Hepatology, Erasmus MC, Rotterdam | ’17 - ‘20 | 60 hours |
| Barrett and Esophagus research meeting, Department of Gastroenterology and Hepatology, Pathology, and Surgery, Erasmus MC, Rotterdam | ’17 - ‘20 | 52 hours |
| Barret Expert Center meeting, Barrett Expert Centers in the Netherlands (two times a year, in 2020 canceled due to COVID-19) | ’17 - ‘19 | 30 hours |
| Casuïstische patiënten bespreking, NVGE (3x) | ’19 – ‘20 | 9 hours |
| Medical Business Masterclass | 2019 | 12 hours |
| Investigator meeting “*Double-blind, randomized, placebo-controlled, phase IIa trial on the efficacy and tolerability of an 8-week treatment with two different doses of budesonide orodispersible tablets vs. plcebo for prevention of esophageal strictures in adult patients after endoscopic submucosal dissection for squamous cell carcinoma – PEGASUS-1 trial”* - Zürich, Switzerland | 2019 | 24 hours |

### Supervision

| | Year | Workload |
|---|---|---|
| Supervising graduation project Janne Falger, medical student MUMC: “Risk of second primary tumors in patients with esophageal squamous cell carcinoma in a Western population” | 2019 | 160 hours |
| Supervising graduation project Manon Snijders, medical student EUR: “The effectiveness of topical budesonide in preventing esophageal strictures after endoscopic resection of esophageal cancer" | 2020 | 160 hours |
| Coach professional Bachelor medicine students, Erasmus University Rotterdam, Rotterdam, The Netherlands | ’18 – ‘20 | 72 hours |

**Extracurricular**

| | Year |
|---|---|
| Secretary Promeras, representing board of all PhD students, Erasmus MC, Rotterdam | ’18 - ‘19 |
| Chair of Promeras, representing board of all PhD students, Erasmus MC, Rotterdam | ’19 - ‘20 |
| PhD committee, Erasmus MC, Rotterdam | 2019 |
| Chair “Commissie ANIOS/arts-onderzoekers”, De Jonge Specialist, representing board of all medical doctors in training, the Netherlands | ’18 - ‘20 |

**Grant allocation**

| | Year |
|---|---|
| Dutch Digestive Foundation (MLDS), project: “Screening for synchronous second primary esophageal tumors in patients with head and neck cancer (SCOPE study)” | 2018 |

**Peer review activities**

Diseases of the Esophagus, Endoscopy, Endoscopy International Open, Gastroenterology Research and Practice, World Journal of Surgical Oncology, Translational Cancer Research

# CHAPTER 18

## About the author

## About the author

Steffi Elisabeth Maria van de Ven was born on January 23, 1991 in Beek en Donk, the Netherlands. She attended pre-university education at the Dr. Knippenbergcollege in Helmond, from which she graduated in 2009. She started studying Medicine at Maastricht University in September 2009. During medical school, she worked as a triagist at the after hours General Practitioners Center. After obtaining her bachelor degree, Steffi started her internships in 2012.

In testament to her eagerness to travel, she went abroad for her internships three times. She completed her internship in Ophthalmology at the Aarhus University Hospital in Denmark. Then, she participated in an ellective internship in Community Medicine at the B.P. Koirala Institute in Dharan, Nepal. Finally, she took her internship in Pediatrics at the Tygerberg Hospital in Cape Town, South Africa.

She obtained her medical degree in June 2015 and started working as a resident not in training (ANIOS) in September 2015 at the department of Internal Medicine and Gastroenterology of Zuyderland Medical Center in Heerlen. It was there that her interest in the field of Gastroenterology was born. In August 2016, she started working as ANIOS at the Department of Gastroenterology and Hepatology of Jeroen Bosch Hospital in ‘s-Hertogenbosch.

In December 2017, she started her PhD trajectory as described in this thesis under supervision of prof. dr. M.J. Bruno and dr. A.D. Koch at the Department of Gastroenterology and Hepatology of the Erasmus Medical Center in Rotterdam.

During her PhD trajectory, she served as chairwoman and secretary of Promeras, the representing body of all PhD students in the Erasmus Medical Center. She was an active member of *De Jonge Specialist* for which she served as chairwoman of the ANIOS and PhD-Student Committee. She was also a mentor of a refugee doctor from Afghanistan as part of the Stichting voor Vluchteling Studenten UAF program.

In May 2021, she started with her Internal Medicine residency at the Franciscus Gasthuis & Vlietland Hospital (program director Dr. Y.C. Schrama) as part of the training in Gastroenterology and Hepatology at the Erasmus MC University Medical Center (program director prof. dr. C.J. van der Woude). Steffi lives in Rotterdam together with Joost.