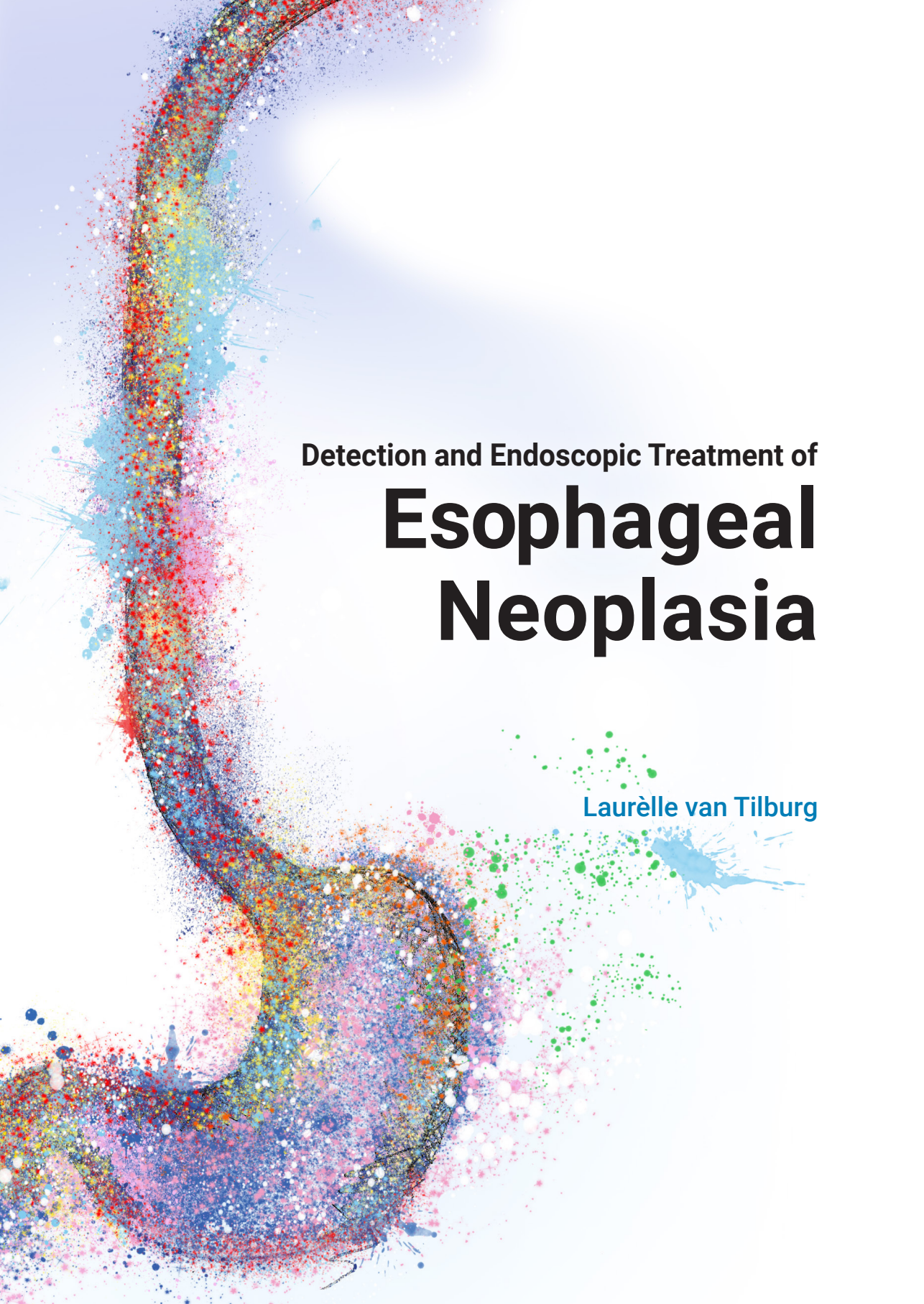


Detection and Endoscopic Treatment of

Esophageal Neoplasia

Laurèlle van Tilburg

Detection and Endoscopic Treatment of Esophageal Neoplasia

Laurèlle van Tilburg

Detection and Endoscopic Treatment of Esophageal Neoplasia

ISBN: 978-94-6469-832-9

Cover design: Wendy Schoneveld
Lay-out: Laurèlle van Tilburg and ProefschriftMaken
Printing: ProefschriftMaken | proefschriftmaken.nl

The printing of this thesis has been financially supported by the department of Gastroenterology and Hepatology of the Erasmus MC, Erasmus Universiteit Rotterdam, Nederlandse Vereniging voor Gastroenterologie, Research Manager, ChipSoft, dr. Falk Pharma B.V. Benelux and ABN AMRO.

Detection and Endoscopic Treatment of Esophageal Neoplasia

Detectie en endoscopische behandeling van vroegcarcinomen in de slokdarm

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof. dr. A.L. van Bredenoord

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 29 mei 2024 om 13:00 uur

door

Laurèlle van Tilburg

geboren te Tilburg

ERASMUS UNIVERSITY ROTTERDAM

Promotiecommissie

Promotor	Prof. dr. M.J. Bruno
Overige leden	Prof. dr. K.K. Krishnadath
	Prof. dr. J.B. van Lanschot
	Dr. J. Honing
Copromotor	Dr. A.D. Koch

S.M. Brakenhoff

Paranimfen L.A. van Kleef

Table of contents

Part I

Introduction

Chapter 1

General introduction

Aims and outline of this thesis

GENERAL INTRODUCTION

Incidence and risk factors

The incidence of esophageal cancer is rapidly rising with more than 600.000 new cases worldwide in 2020.[1] In the Netherlands, the incidence of esophageal cancer increased by 400% during recent decades.[2] This is predominantly caused by an increased incidence of esophageal adenocarcinoma (EAC) in Western countries, while the incidence of esophageal squamous cell carcinoma (ESCC) remained constant and still accounts for approximately 85% of esophageal cancers worldwide.[1] The differences in the epidemiology between these two histopathological types of esophageal cancer (i.e. EAC and ESCC) can be partly explained by their different risk profiles.[1, 3] Well-known risk factors for EAC include obesity, smoking, and the presence of a Barrett's esophagus (BE), while the major risk factors of ESCC include smoking and alcohol consumption (Figure 1).[3]

Figure 1. Common risk factors for the development of esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) in Western countries.

Clinical presentation and survival

Patients with esophageal cancer frequently present with clinical symptoms such as progressive dysphagia and weight loss.[4] Some patients may present with retrosternal discomfort, regurgitation of food or salvia, or an iron deficiency anemia. Unfortunately, most esophageal cancers remain asymptomatic and undetected until the cancer has reached an advanced stage.[4] Only 3% of esophageal cancers are diagnosed at an early stage (i.e. T1a/b) and 59% of the patients with esophageal cancer can potentially be treated with curative intent.[2, 4] Consequently, esophageal cancer is one of the most lethal cancers with 554.100 deaths in 2020 and 5-year survival rates of 10 to 30%.[1, 5] The detection of early-stage esophageal cancer is associated with significantly better 5-year survival rates of 85 to 100%, as it potentially can be treated curatively with endoscopic resection.[6]

Endoscopic detection

Most early esophageal cancers are diagnosed during upper gastrointestinal endoscopy.[7] Guidelines advocate that endoscopic assessment should be performed by an expert endoscopist using high definition white light endoscopy and optical chromoendoscopy, such as narrow band imaging (NBI).[7, 8] NBI uses a blue light filter (i.e. light with a wavelength of 400-430 nm) to highlight the capillaries in the superficial mucosa through peak absorption of hemoglobin (415 nm).[9] For squamous neoplasia, changes in the intrapapillary capillary loop patterns – the microvasculature of the esophageal epithelium – can be classified according to the Japanese Esophageal Society (JES) classification to predict the invasion depth.[8] All visible lesions are assessed for their size, location, and morphology according to the Paris classification.[10] Recent years, artificial intelligence systems are being developed to assist the endoscopist with the detection and delineation of esophageal neoplasia and identify patients eligible for endoscopic resection (ER).[11-13]

Dysplasia, the histopathological precursor of esophageal squamous cell carcinoma

Esophageal cancer is thought to develop via a cascade from regular esophageal tissue via increasing grades of dysplasia.[14] Dysplasia is characterized by neoplastic alterations of the epithelium and is considered the most important histopathological precursor of esophageal cancer.[14-16] Dysplastic lesions can be subtle and are easily missed during endoscopic screening (Figure 2). Dye-based chromoendoscopy (i.e. lugol's staining) may assist in the endoscopic detection and delineation of squamous dysplasia.[8] Lugol's staining binds to the glycogen in the squamous epithelium, which is diminished in dysplastic cells.[17]

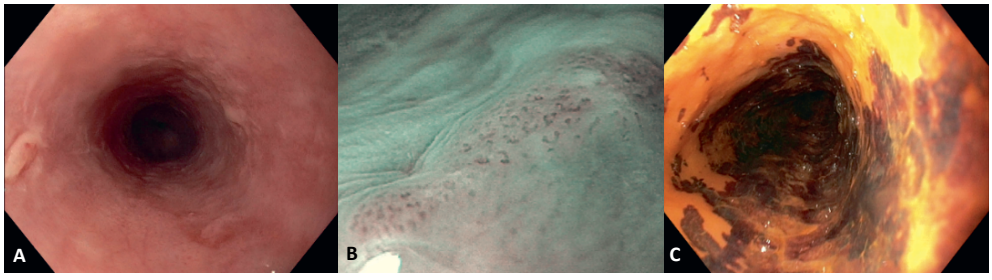


Figure 2. Squamous dysplasia during endoscopy. A) shows an irregular mucosal epithelium with white light imaging. B) shows changes in the microvasculature of the esophageal mucosa with narrow band imaging; intrapapillary capillary loops type B1 according to the Japanse Esophageal Society classification.[8] C) shows a lugol voiding lesion; a yellowish unstained area with sharp demarcation after the application of lugol's staining (1.2% iodine solution). All three patients were treated with endoscopic resection and histopathological assessment showed high grade dysplasia.

The grade of squamous dysplasia is used to predict the risk of neoplastic progression and determine the most appropriate treatment or follow up strategy.[14, 16] In an Asian study with a median of 13.5 years of endoscopic surveillance, the risk of neoplastic progression was up to 24% for patients with mild dysplasia, 50% for moderate dysplasia, and 74% for severe dysplasia.[14] However, as the ESCC incidence and guidelines for treatment and surveillance for squamous dysplasia differ between Eastern and Western countries, these data should not be generalized to patients with squamous dysplasia in Western countries.

Published studies investigating squamous dysplasia remain scarce, especially in Western countries. Unfortunately, the optimal management for the distinct grades of squamous dysplasia remains unclear, because the corresponding risk of developing ESCC is unknown in Western countries. The World Health Organization advises to use a two-tiered classification with low grade and high grade dysplasia to increase the level of inter-observer agreement among Western pathologists.[16] The guideline of the European Society of Gastrointestinal Endoscopy (ESGE) advocates that endoscopic treatment should be performed for high grade dysplasia and ESCC limited to the mucosa, but it remains controversial whether endoscopic treatment or surveillance is indicated for low grade dysplasia.[8]

Second primary tumors in the upper aerodigestive tract

Patients with ESCC have an increased risk to develop second primary tumors (SPTs).[18] These SPTs are often located in the upper aerodigestive tract, consisting of the head and neck region, esophagus, stomach, and lungs (Figure 3).[18] Similarly, patients with primary lung cancer or head and neck squamous cell carcinoma (HNSCC) also have an increased risk of SPTs in the esophagus.[19, 20] This is often explained by the theory of field cancerization, which was introduced by Slaughter *et al.* in 1953.[21] This theory states that long-term exposure to common carcinogens such as tobacco smoking and alcohol consumption, can result in premalignant changes of the epithelium surrounding the primary tumor.[21]

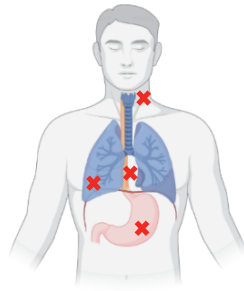


Figure 3. Second primary tumor locations in the upper aerodigestive tract; the head and neck region, esophagus, lungs, and stomach.

Endoscopic screening in patients with HNSCC holds the potential to detect esophageal SPTs in early and curable stages.[22, 23] Early-stage SPTs can be treated with ER, potentially improving the survival of patients with HNSCC.[24] The detection of SPTs can be divided in synchronous (within 6 months) and metachronous (after more than 6 months), according to the time interval between HNSCC diagnosis and endoscopic screening. In Eastern countries with a higher incidence of head and neck cancer and esophageal cancer, screening for SPTs in the esophagus is routinely implemented in patients with HNSCC.[25-27] In Western countries, the yield of screening is less established and routine screening for SPTs has not been implemented in most countries.

Endoscopic resection techniques

In recent decades, the treatment for early esophageal neoplasia shifted from esophagectomy towards ER.[28] Whereas esophagectomy was the gold standard treatment for all patients with dysplasia and T1 cancers two decades ago, currently ER is the treatment of choice for dysplasia and cancers invading the mucosa (i.e. T1a). Two mainly used techniques of ER exist; endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). EMR can be performed using a cap (cap-assisted) or a band ligation device (multi-band mucosectomy, MBM). A limitation of EMR is that larger lesions (>20mm) must be removed using multiple adjacent resections (i.e. piecemeal resection), which is associated with higher local recurrence rates than en bloc resection.[29, 30]

Therefore, ESD was developed in the 2000s in Japan to assist in en bloc resection of larger lesions in the gastrointestinal tract.[31] During ESD, coagulation markings are placed at 2mm margin from the border of the neoplastic area with the tip of the knife. Subsequently, submucosal lifting is performed to expand the submucosal space. Mucosal incision and then submucosal dissection are performed. An ESD is a technically challenging procedure, as it is associated with a longer learning curve and longer procedure times, compared to EMR.[30]

Endoscopic resection of esophageal squamous cell carcinoma and risk of strictures

For squamous dysplasia and most early ESCC (i.e. with T1a or superficial submucosal invasion, T1sm1), ESD is the indicated treatment as it is associated with higher en bloc and radical resection rates (i.e. resection in one piece with tumor-negative resection margins, R0). Thereby ESD potentially allows for curative resection and precise histopathological assessment.[8] Theoretically, ESD enables en bloc resection independently of the size of the lesion. However, mucosal defects involving $\geq$75% of the circumference after ESD are associated with a major risk of stricture development (Figure 4).[32] This risk increases up to

100% for ESDs involving the entire circumference (cESDs) and therefore stricture prophylaxis is often provided to these patients.[32, 33] Unfortunately, even with applied stricture prophylaxis, the vast majority of the patients treated with cESD develop an esophageal stricture requiring endoscopic dilation.[33] It remains up to debate if the benefits of a potentially curative cESD outweigh the risks in terms of stricture development and adverse events (i.e. perforation and delayed bleeding), compared to esophagectomy, which is also accompanied by mortality, considerable morbidity and decreased quality of life.[8, 33]

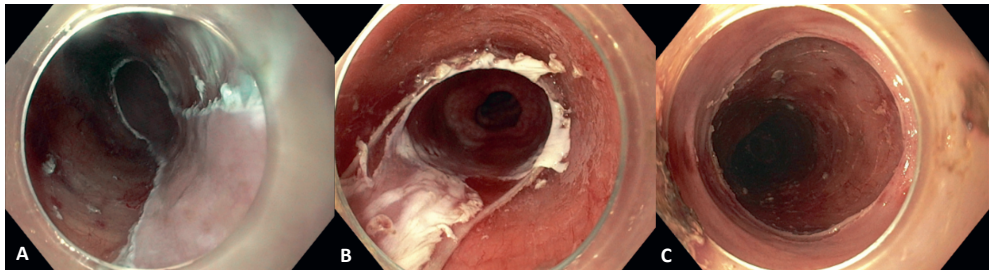


Figure 4. Circumferential size of the mucosal defect after endoscopic submucosal dissection; 80% in image A, 90% in image B, and 100% in image C.

Endoscopic resection of esophageal adenocarcinoma

For Barrett's dysplasia and EAC sized ≤20mm with a low suspicion of submucosal invasion (i.e. Paris type 0-IIa and 0-IIb), EMR is recommended.[8] Treatment with ESD can be considered in case of suspected submucosal invasion, EAC with lesion size >20mm and lesions located in a fibrotic area.[8] Subsequently, the histopathological characteristics of the ER specimen are used to assess the risk of lymph node metastasis and residual cancer. High risk features for lymph node metastasis include deeper submucosal invasion (i.e. sm2/3), poor tumor differentiation and the presence of lymphovascular invasion.[6] Based on these risks, advice regarding the further appropriate treatment strategy is discussed, ranging from endoscopic follow up to additional treatment with surgery or chemoradiotherapy.[34]

Tumor-positive vertical resection margin

Most physicians consider a tumor-positive vertical resection margin (R1v) after ER of Barrett's neoplasia equal to the presence of residual cancer. Consequently, additional surgery is advocated after an R1v resection, but residual neoplasia is not always present in the surgical resection specimen (Figure 5).[30, 35] Moreover, esophagectomy is, even when performed in high volume centers, associated with a substantial mortality (2-5%), morbidity (20-50%), and persisting decreased quality of life.[36, 37]

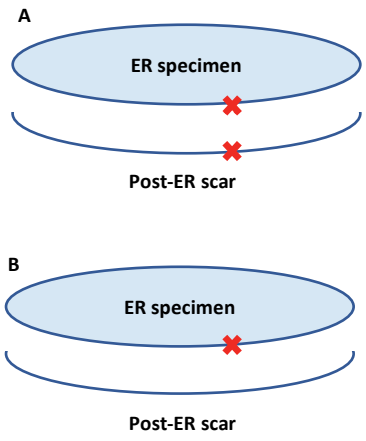


Figure 5. Presence (image A) and absence (image B) of residual neoplasia after endoscopic resection of Barrett's neoplasia with tumor-positive vertical resection margin. ER, endoscopic resedction.

Published studies on residual cancer after R1v resections are relatively scarce and of limited quality.[38-41] These studies use various definitions of R1 and accurate histopathological assessment of the vertical resection margin of ER specimen can be challenging.[42] In these studies, the risk of residual cancer may be lower than generally assumed (range: 0% to 57%).[38-41] Studies with a systematic assessment and histopathological confirmation of R1v margins by experienced pathologists are currently lacking and, consequently, the risk of residual cancer is still unclear.

AIMS

In this thesis, different aspects of the detection and endoscopic treatment of patients with esophageal neoplasia are discussed. The first aim of this thesis is to improve the diagnosis of early esophageal cancer among patients at high risk, including patients with current or previous head and neck squamous cell carcinoma (HNSCC) and patients with esophageal squamous dysplasia. The second aim is to report on outcomes of endoscopic resection (ER) for esophageal neoplasia in Western countries.

OUTLINE OF THIS THESIS

Part I contains the general introduction and outline of this thesis.

In **Part II**, endoscopic detection of abnormalities during upper gastrointestinal endoscopy and patients at increased risk of esophageal cancer are assessed. **Chapter 2** provides an overview of the current state of artificial intelligence for the detection, characterization, and delineation of cancers in the upper gastrointestinal tract and their premalignant stages. **Chapter 3** reports on the risk of esophageal squamous cell carcinoma in patients with distinct grades of squamous dysplasia in a Western country.

Part III focuses on second primary tumors (SPTs) in the upper aerodigestive tract. In **Chapter 4**, the prevalence of lung SPTs in patients with esophageal cancer and vice versa is discussed. **Chapter 5** reports on the knowledge and awareness of SPTs among gastroenterologists and head and neck surgeons in the Netherlands. In **Chapter 6**, endoscopic screening for SPTs in the upper gastrointestinal tract patients with current or previous HNSCC is investigated. This chapter also contains a response letter, discussing the yield of endoscopic screening for esophageal SPTs.

Part IV describes endoscopic treatment of early esophageal cancers. **Chapter 7** reports on the yield and safety of circumferential endoscopic submucosal dissection (cESD) for esophageal squamous cell carcinoma in Western countries. In this study, curative resection rates in terms of en bloc and radical resections and the risk of esophageal strictures and adverse events related to the cESD are described. In **Chapter 8**, the risk of local residual cancer after endoscopic resection of Barrett's neoplasia with confirmed tumor-positive vertical resection margin is explored.

A summary and general discussion of this thesis is presented in **Chapter 9**. The conclusions are presented in **Chapter 10**.

REFERENCES

1. Morgan E, Soerjomataram I, Rumgay H, et al. The global landscape of esophageal squamous cell carcinoma and esophageal adenocarcinoma incidence and mortality in 2020 and projections to 2040: New estimates from GLOBOCAN 2020. Gastroenterology. 2022.
2. Incidence of esophageal and gastric cancer (In Dutch: *Incidentie slokdarm- en maagkanker*): Netherlands Cancer Registry; 2023 [Accessed 01/10/2023; Available from: https://iknl.nl/kankersoorten/slokdarm-en-maagkanker/registratie/incidentie].
3. Engel LS, Chow WH, Vaughan TL, et al. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst. 2003;95(18):1404-13.
4. Saltzman JR, Gibson MK, Goldberg RM. Clinical manifestations, diagnosis, and staging of esophageal cancer. UpToDate Waltham, MA: UpToDate. 2020.
5. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. The Lancet. 2018;391(10125):1023-75.
6. Van Munster S, Nieuwenhuis E, Weusten BLAM, et al. 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. 2022;71(2):265-76.
7. Committee ASoP, Evans JA, Early DS, et al. The role of endoscopy in the assessment and treatment of esophageal cancer. Gastrointest Endosc. 2013;77(3):328-34.
8. Pimentel-Nunes P, Libânio D, Bastiaansen BAJ, et al. Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline–Update 2022. Endoscopy. 2022.
9. Barbeiro S, Libanio D, Castro R, et al. Narrow-Band Imaging: Clinical Application in Gastrointestinal Endoscopy. GE Port J Gastroenterol. 2018;26(1):40-53.
10. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc. 2003;58(6 Suppl):S3-43.
11. Frazzoni L, Arribas J, Antonelli G, et al. Endoscopists' diagnostic accuracy in detecting upper gastrointestinal neoplasia in the framework of artificial intelligence studies. Endoscopy. 2022;54(4):403-11.
12. Yu H, Singh R, Shin SH, et al. Artificial intelligence in upper GI endoscopy - current status, challenges and future promise. J Gastroenterol Hepatol. 2021;36(1):20-4.
13. van der Sommen F, de Groof J, Struyvenberg M, et al. Machine learning in GI endoscopy: practical guidance in how to interpret a novel field. Gut. 2020;69(11):2035-45.
14. 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(2):187-92.
15. Li H, Zhang S, Zhou J, et al. Endoscopic surveillance for premalignant esophageal lesions: A community-based multicenter, prospective cohort study. Clinical Gastroenterology and Hepatology. 2022.
16. World Health O. WHO classification of tumours: digestive system tumours: World Health Organization (WHO); 2019.
17. van de Ven SEM, Koch AD. When is Lugol still necessary in 2020? Endosc Int Open. 2020;8(10):E1478-E80.
18. van de Ven SE, Falger JM, Verhoeven RH, et al. Increased risk of second primary tumours in patients with oesophageal squamous cell carcinoma: A nationwide study in a Western population. United European Gastroenterol J. 2020:2050640620977129.
19. 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(6):1648-55.
20. Abdel-Rahman O, Cheung WY. Subsequent thoracic cancers among patients diagnosed with lung cancer: a SEER database analysis. Curr Med Res Opin. 2017;33(11):2009-17.
21. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer. 1953;6(5):963-8.
22. van de Ven SEM, de Graaf W, Bugter O, et al. Screening for synchronous esophageal second primary tumors in patients with head and neck cancer. Dis Esophagus. 2021.
23. 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(4):1122-30.

24. Zhang N, Li Y, Chang X, et al. Long-term effectiveness of one-time endoscopic screening for esophageal cancer: A community-based study in rural China. Cancer. 2020;126(20):4511-20.
25. 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):752-9.
26. Thakur K, Singh CA, Thakar A, et al. Prevalence of Synchronous ESCN in Head and Neck Cancer: A Single-Institution Perspective. Laryngoscope. 2021;131(3):E807-E14.
27. Arnold M, Ferlay J, van Berge Henegouwen MI, et al. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. Gut. 2020;69(9):1564-71.
28. Semenkovich TR, Hudson JL, Subramanian M, et al. Trends in Treatment of T1N0 Esophageal Cancer. Ann Surg. 2019;270(3):434-43.
29. Pech O, Behrens A, May A, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut. 2008;57(9):1200-6.
30. van Munster S, Verheij E, Nieuwenhuis E, et al. Extending treatment criteria for Barrett's neoplasia: results of a nationwide cohort of 138 ESDs. Endoscopy. 2021.
31. Ohkuwa M, Hosokawa K, Boku N, et al. New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. Endoscopy. 2001;33(3):221-6.
32. van de Ven SEM, Snijders M, Bruno MJ, et al. Effectiveness of topical budesonide in preventing esophageal strictures after endoscopic resection of esophageal cancer. Endosc Int Open. 2020;8(12):E1795-E803.
33. Minamide T, Kawata N, Maeda Y, et al. Clinical outcomes of endoscopic submucosal dissection for superficial circumferential esophageal squamous cell carcinoma. Gastrointest Endosc. 2023;97(2):232-40 e4.
34. Gotink AW, van de Ven SEM, Ten Kate FJ, et al. Individual risk calculator to predict lymph node metastases in patients with submucosal (T1b) esophageal adenocarcinoma: a multicenter cohort study. Endoscopy. 2021.
35. Weusten B, Bisschops R, Coron E, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. 2017.
36. Low DE, Kuppusamy MK, Alderson D, et al. Benchmarking complications associated with esophagectomy. Annals of surgery. 2019;269(2):291-8.
37. Pech O, Bollschweiler E, Manner H, et al. Comparison between endoscopic and surgical resection of mucosal esophageal adenocarcinoma in Barrett's esophagus at two high-volume centers. Annals of surgery. 2011;254(1):67-72.
38. Kunzli HT, Belghazi K, Pouw RE, et al. Endoscopic management and follow-up of patients with a submucosal esophageal adenocarcinoma. United European Gastroenterol J. 2018;6(5):669-77.
39. Subramaniam S, Chedgy F, Longcroft-Wheaton G, et al. Complex early Barrett's neoplasia at 3 Western centers: European Barrett's Endoscopic Submucosal Dissection Trial (E-BEST). Gastrointest Endosc. 2017;86(4):608-18.
40. 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(4):600-7.
41. Prasad GA, Buttar NS, Wongkeesong LM, et al. Significance of neoplastic involvement of margins obtained by endoscopic mucosal resection in Barrett's esophagus. Am J Gastroenterol. 2007;102(11):2380-6.
42. Krause J, Rösch T, Steurer S, et al. Quantitative analysis of submucosal excision depth in endoscopic resection for early Barrett’s cancer. Endoscopy. 2021.

Part II

Endoscopic detection
and risk for esophageal cancer

Chapter 2

Artificial intelligence in upper gastrointestinal endoscopy

Laurelle van Tilburg*, Meltem Tokat*, Arjun D. Koch, Manon C.W. Spaander

*Shared first authorship

Digestive diseases. 2022

ABSTRACT

Background: Over the past decade, several artificial intelligence (AI) systems are developed to assist in endoscopic assessment of (pre)cancerous lesions of the gastrointestinal (GI) tract. In this review, we aimed to provide an overview of the possible indications of AI technology in upper GI endoscopy, and hypothesize about potential challenges for its use in clinical practice.

Summary: Application of AI in upper GI endoscopy has been investigated for several indications: (1) detection, characterization, and delineation of esophageal and gastric cancer (GC) and their premalignant conditions, (2) prediction of tumor invasion, and (3) detection of *Helicobacter pylori.* AI systems show promising results with an accuracy up to 99% for the detection of superficial and advanced upper GI cancers. AI outperformed trainee and experienced endoscopists for the detection of esophageal lesions and atrophic gastritis. For GC, AI outperformed mid-level and trainee but not expert endoscopists.

Key Messages: Application of artificial intelligence (AI) in upper gastrointestinal endoscopy may improve early diagnosis of esophageal and gastric cancer and may enable endoscopists to better identify patients eligible for endoscopic resection. The benefit of AI on the quality of upper endoscopy still needs to be demonstrated, while prospective trials are needed to confirm accuracy and feasibility during real-time daily endoscopy.

INTRODUCTION

Accurate endoscopic detection of esophageal and gastric cancers and their premalignant conditions, such as Barrett neoplasia, gastric atrophy, and intestinal metaplasia, is essential for the detection of these cancers at an early stage.[1-4] The challenge of endoscopic procedures lies in the real-time interpretation of endoscopic imagery, which is complex and sensitive to human error. Current endoscopic cancer screening and surveillance strategies encounter several pitfalls, including inter-observer variability in the detection of lesions, time consuming biopsy protocols, and biopsy sampling error.[1, 5, 6] Especially subtle and early (pre)malignant lesions in the esophagus and stomach can easily be missed by endoscopists (Figure 1). Artificial intelligence (AI) technology has the potential to overcome these obstacles. AI models have been introduced as a tool to aid in endoscopic detection, characterization, and delineation of premalignant and malignant lesions of the upper gastrointestinal (GI) tract.[7-11] Over the past decade, several AI systems have been developed to assist endoscopists in the detection and staging of lesions in the upper GI tract. In this review, we aimed to provide an overview of the possible indications of AI systems in upper GI endoscopy (Figure 2) and hypothesize about potential challenges for its use in clinical practice.

Principles of AI

AI refers to a machine-based intelligence which mimics human cognitive functions, such as learning and decision-making. Machine learning (ML) is a form of AI consisting of a teaching algorithm to recognize data patterns and utilize data to predict new data. In order to predict outcomes, a ML algorithm needs to be exposed to different example data sets. Deep learning (DL) is an advanced ML method, which uses layers of artificial neural networks to hierarchically structure data and extract features without human aid. Similar to the human brain, DL methods approach tasks by analyzing information from different concepts before assigning them to a specific class. Different from conventional ML algorithms that need human intervention to correct errors, DL has the ability to learn from its mistakes. This self-learning ability of DL technology makes it possible to increase its performance as exposure to data increases.

The most widely known DL method in endoscopy is based on convolutional neural network (CNN) and consists of a neural network architecture which is mainly used for image recognition and classification. To achieve sufficient diagnostic accuracy, a DL system needs to be trained and validated with large amounts of labelled data during different steps. First, the algorithm is subjected to a large dataset of mostly non-endoscopic labelled images. These labelled images are often obtained from open access databases, such as ImageNet.[12]

Second, the algorithm needs to be trained and validated with a dataset of labelled endoscopic images. Last, when performance is sufficient, the algorithm needs to be tested. Computer-aided detection (CAD) systems in GI endoscopy are ML methods specifically developed to assist endoscopists to improve accurate detection and staging of pathology, including early stages of disease and selection of optimal biopsy sites.

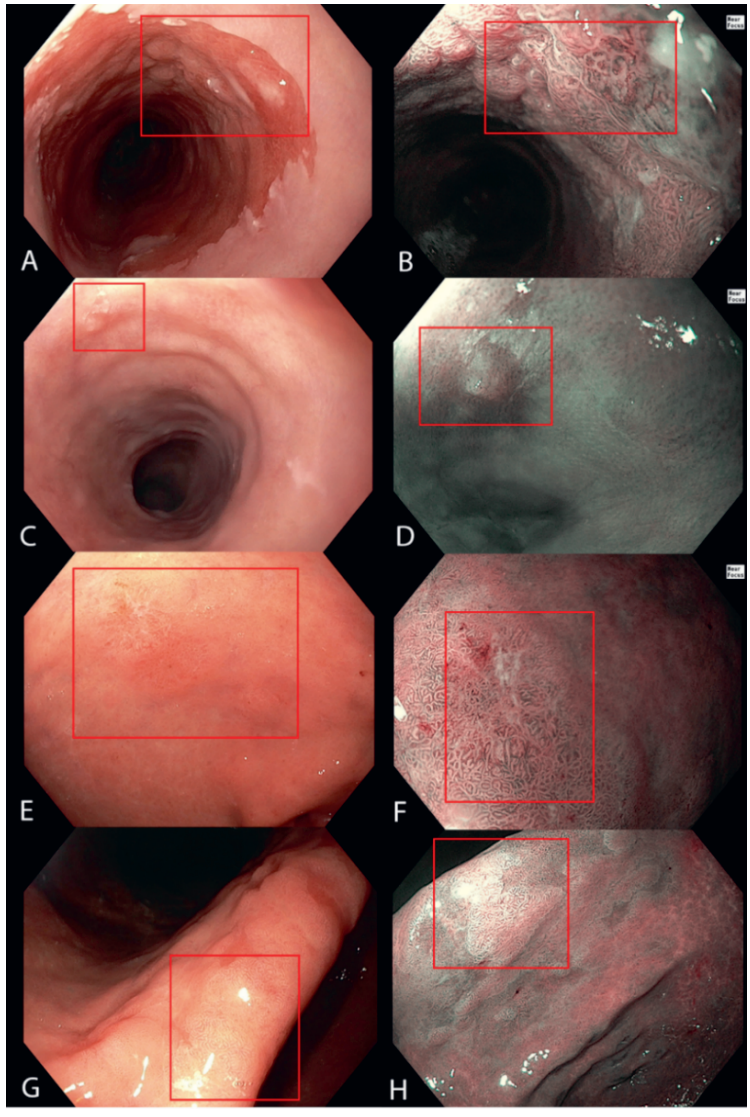


Figure 1. Endoscopic images of subtle early esophageal and gastric (pre)malignant lesions of which detection rates can be increased with assistance of artificial intelligence. Endoscopy images of Barrett's neoplasia (images A and B), esophageal squamous cell carcinoma (images C and D), early gastric cancer (E and F) and gastric intestinal metaplasia located at the angulus (images G and H).

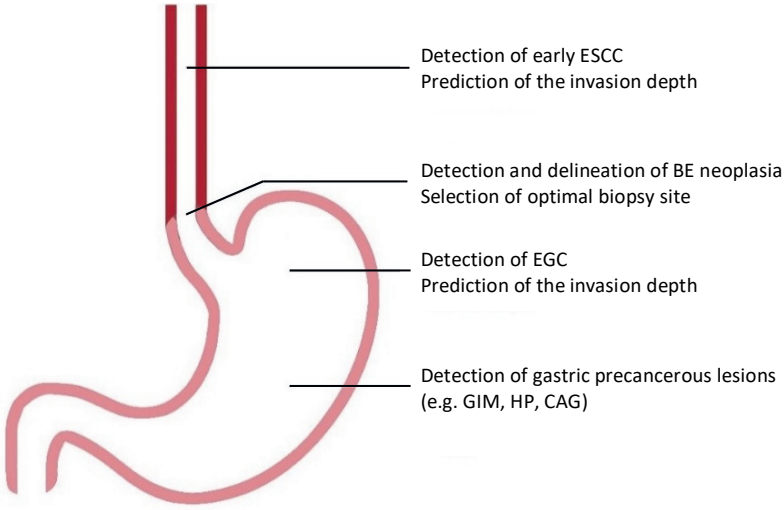


Figure 2. Application of artificial intelligence in upper gastrointestinal endoscopy - topics addressed in this review. BE, Barrett's esophagus; CAG, chronic atrophic gastritis; EGC, early gastric cancer; ESCC, esophageal squamous cell carcinoma; GIM, gastric intestinal metaplasia; HP, *Helicobacter Pylori*.

Neoplasia in Barrett's esophagus

The incidence of esophageal adenocarcinoma (EAC) is rapidly increasing in Western society.[13, 14] Barrett's esophagus (BE) is a precancerous condition, which may progress to EAC.[15] Therefore, guidelines recommend endoscopic surveillance of BE in order to diagnose neoplastic progression in early stages. Endoscopic assessment of the esophagus with high definition (HD) white light endoscopy (WLE) is advised to optimize the detection of dysplastic Barrett mucosa.[1, 2] Chromoendoscopy can be utilized to aid in detection of lesions, however, additional value to WLE has not been proven.[16] Given the low progression rate among BE patients, which is estimated at 0.5% per year, the majority of gastroenterologists never encounter dysplasia and therefore may be less familiar with the mucosal changes associated with presence of neoplasia.[17] Visible neoplastic lesions, including early EAC, may remain undetected, especially when endoscopic surveillance is performed by endoscopists with limited experience in the recognition of early neoplastic lesions.[18, 19] Low grade dysplasia may present itself with very subtle mucosal changes and is therefore easily missed.[6] To increase the diagnostic yield of dysplasia, guidelines recommend to take four-quadrant biopsies at each 2 cm interval of the Barrett segment, known as the Seattle protocol.[20] Combined with WLE, it is estimated that up to 90% of high grade dysplasia (HGD) and EAC cases are detected.[21] Nevertheless, adherence to this protocol is poor as it is a time-consuming procedure, especially in patients with a long-segment BE.[22]

AI in the detection of Barrett's neoplasia

Several ML methods were developed to aid in diagnosis of BE neoplasia (Table 1). The majority of papers evaluated diagnostic performance of CNN algorithms in WLE images.[7, 10, 23-27] Hashimoto *et al.*[23] developed an algorithm based on CNN technology to aid in the detection of Barrett neoplasia by image annotation of areas suspect for neoplasia. The pretrained algorithm was trained with 916 images of BE patients with HGD and early EAC. The CNN then analyzed 225 images of dysplastic BE and 233 of nondysplastic Barrett's esophagus (NDBE) images with 95% accuracy. The ARGOS consortium performed several studies with AI algorithms to aid in the detection, characterization and delineation of BE neoplasia and to improve the selection of biopsy sites.[7, 24, 26, 28] De Groof *et al.*[7] developed an AI model based on prospectively collected WLE images for the detection and delineation of BE neoplasia with a sensitivity, specificity and accuracy of 95%, 85% and 92%, respectively. Application of CAD in detection of Barrett neoplasia is also being explored in NBI images and videos.[23, 27, 28] Struyvenberg *et al.*[28] developed a CAD system using 30,021 NBI video frames (average video consisted of 250 fragments obtained during 10 seconds of video) and detected BE neoplasia with accuracy of 83%.

Recently, the first prospective studies during live endoscopic procedures were performed by de Groof *et al.*[25] and Ebigbo *et al.*[10] De Groof *et al.*[26] trained their CAD model with 1,704 high resolution images of 669 patients with histologically confirmed Barrett neoplasia or NDBE. Algorithm performance was externally validated with separate datasets, each containing 80 images which were also scored for the presence of dysplasia by 53 general endoscopists. The CAD system classified images as dysplastic or nondysplastic with 90% sensitivity, 88% specificity and 89% accuracy. The AI model outperformed the endoscopists in detection of early Barrett neoplasia in another dataset containing 80 images, as the sensitivity, specificity and accuracy of the CAD system and endoscopists was respectively 93% vs 72%, 83% vs 74% and 88% vs 73%.[26] The CAD model was tested during real-time endoscopy with an accuracy of 90%.[25] Ebigbo *et al.*[27] developed a CAD-DL system based on 148 HD-WLE and NBI images of 33 early EAC and 41 NDBE areas in one database and 100 HD-WLE images of 17 early EAC and 22 NDBE areas in a second database. Based on the images in these two datasets, the AI model reached a 92-97% sensitivity and 88-100% specificity for WLE images and 94% sensitivity and 80% specificity for NBI images. Afterwards, the developed CNN-CAD algorithm was tested during real-time daily endoscopy in 14 patients with BE neoplasia with an accuracy of 89.9%.[10] The majority of previous mentioned studies showed high accuracy of AI models in the detection of BE neoplasia. Main limitations of these studies were the retrospective design and small sample size.

Table 1. Application of artificial intelligence in the detection of Barrett's neoplasia.

Authors	Country	Study design	Aim	Modality	AI model			Endoscopists			
					Sens %	Spec %	Accuracy %	Experience (years)	Sens %	Spec %	Accuracy %
Ebigbo *et al*. (2020)[10]	Germany	Pro	Detection of BE neoplasia during live endoscopy	WLE	84	100	90	NR	NR	NR	NR
de Groof *et al*. (2020)[26]	Netherlands	Retro	Detection of BE neoplasia	WLE	93	83	88	Seniors >5 Juniors <3 Fellows Novices	77 79 71 60	73 76 76 72	75 78 73 66
de Groof *et al*. (2020)[25]	Netherlands	Pro	Detection and delineation of BE neoplasia, selection of optimal biopsy site	WLE	91	89	90	NR	NR	NR	NR
Hashimoto *et al*. (2020)[23]	USA	Retro	Detection and image annotation of BE neoplasia	WLE/ME-NBI	96	94	95	NR	NR	NR	NR
Ebigbo *et al*. (2019)[27]	Germany	Retro	Detection of BE neoplasia	WLE NBI	92-97 94	88-100 80	NR	NR	76 99	80 78	NR
de Groof *et al*. (2019)[7]	Netherlands	Pro data collection	Detection and delineation of BE neoplasia	WLE	95	85	92	NR	NR	NR	NR
van der Sommen *et al*. (2016)[24]	Netherlands	Retro	Detection and delineation of BE neoplasia	WLE	86	87	NR	Experts[1]	95-100	73-93	NR

AI, Artificial Intelligence; BE, Barrett's esophagus; ME, magnified endoscopy; NBI, narrow band imaging; NDBE, nondysplastic Barrett's esophagus; Pro, prospective; Retro, retrospective; Sens, sensitivity; Spec, specificity; USA, United States of America; WLE, white light endoscopy; NR, not reported. [1]Years of experience (of subgroups) of endoscopists unknown.

Esophageal squamous cell carcinoma

Squamous cell carcinoma remains the predominant histologic type of esophageal cancer, which accounts for 80% of the cases worldwide.[29, 30] The incidence rates of esophageal squamous cell carcinoma (ESCC) vary strongly among geographic regions, with highest rates in Eastern Asia.[29] Most ESCC are detected in advanced stages and therefore associated with a poor 5-year survival rate of merely 20%.[31] The prognosis of early ESCC is considerably better, since the risk of lymph node and distant metastasis is associated with the tumor invasion depth.[32] Additional lugol's iodine staining or WLE and NBI can be used to increase the detection of subtle esophageal lesions.[33, 34] The combination of magnification and NBI during endoscopy allows visualization of the microvasculature of the esophageal epithelium, which can be classified according to the intraepithelial papillary capillary loop (IPCL) classification.[35] This classification can help to differentiate dysplasia from nondysplastic lesions in daily clinical practice.[36]

AI in the detection of ESCC

Most studies that investigated AI for the early detection of ESCC derive from Asian countries.[29, 37-43] AI models based on CNN during WLE are mostly investigated to detect squamous dysplasia and early ESCC (shown in Table 2).[37-41] Horie *et al.* [9] developed a CNN-CAD system for the detection of esophageal cancers (both ESCC and EAC; 8,428 images for system development and 1,118 images for validation). This study showed that CNN-CAD can correctly detect esophageal cancers, including both superficial and advanced cancers with a sensitivity of 98%. Furthermore, the CNN-CAD system was accurately able to detect small cancerous lesions <10mm that can be easily missed, even by experienced endoscopists. Shimamoto *et al.* (2020) compared the use of DL during WLE and during NBI for the accurate detection of the invasion depth in ESCC. The accuracy was higher in WLE than in magnification with NBI (98.7% vs 89.2%).[41] Ohmori *et al.*[37] showed that their AI system had a high sensitivity for the detection of ESCC using non-ME NBI and high accuracy for the differentiation of ESCC from noncancerous lesions.

Endoscopic screening and detection of ESCC remains challenging, partly because it is liable to the inter-observer variability between endoscopists.[35] Early stage ESCC are difficult to detect, especially for trainee endoscopists (sensitivity of NBI for ESCC detection in trainee versus expert endoscopists: 53% vs 100%).[44] Several studies compared diagnostic parameters of developed AI models to endoscopists.[37-42, 45] Cai *et al.*[38] developed a DNN-CAD system based on WLE (2,428 images from 746 patients for training, 187 images from 52 patients for validation) which was compared to three groups of endoscopists (seniors with >15 years of experience, mid-levels with 5-15 years of experience and juniors with

<5years of experience). Sensitivity of AI for detection of ESCC appeared to be higher, even for the experienced endoscopists. AI system versus senior, mid-level and junior endoscopists was 97.8% vs 86.3%, 78.6% and 61.9%, respectively. Zhao *et al.*[42] developed a CAD model based on magnification with NBI to investigate automated classification of IPCLs. The mean diagnostic accuracy of the CAD system was higher than that of mid-level and junior endoscopists for the detection of malignant esophageal lesions ($P < 0.001$). Fukuda and colleagues[45] divided the diagnostic process into two parts: detection (identify suspicious lesions) and characterization (differentiate cancer from no cancer). The developed CNN-DL system had a better diagnostic performance than the expert endoscopists. Major limitations of these studies included the small sample size of images used for both training[38, 42] and validation.[37, 38, 42, 45] Furthermore, the samples of participating endoscopists with different levels of endoscopic experience were relatively small, ranging from 4 to 15 endoscopists per subgroup.

AI in prediction of invasion depth of ESCC

The tumor invasion depth is an important prognostic factor in ESCC.[46] Accurate endoscopic detection of the invasion depth is essential for decision making between endoscopic resection or proceeding to esophagectomy with lymphadectomy.[47] To optimize endoscopic prediction of invasion depth, the role of AI was studied.[39-41] Shimamoto *et al.*[41] developed an AI system on WLE and NBI images from endoscopic videos to estimate the invasion depth, which was compared to experienced endoscopists (7-25 years of experience). The AI model outperformed the endoscopists in both non-ME and magnification with NBI with a sensitivity, specificity and accuracy of AI versus endoscopists using magnification and NBI of 71%, 95% and 89% versus 42%, 97% and 84%, respectively. Tokai and colleagues[40] developed an AI model to predict the ESCC invasion depth on 1,751 images, which was validated on 291 images. The diagnostic accuracy of the AI model outperformed 12 out of 13 endoscopists.

Table 2. Application of artificial intelligence in the detection of esophageal squamous cell carcinoma and prediction of the invasion depth.

Authors	Country	Study design	Aim	Modality	AI model			Endoscopists			
					Sens %	Spec %	Accuracy %	Experience (years)	Sens %	Spec %	Accuracy %
Guo *et al.* (2020)[43]	India	Retro	Detection of ESCC	NBI images NBI videos	98 100	95 91	NR	NR	NR	NR	NR
Ohmori *et al.* (2020)[37]	Japan	Retro	Detection of ESCC and Differentiation ESCC vs no cancer	WLE ME-NBI/BLI	90 98	76 56	81 77	8-24	87 83	67 70	75 76
Fukuda *et al.* (2020)[45]	Japan	Retro	Detection of ESCC and differentiation ESCC vs no cancer	NBI/BLI	91	51	63	8-23	74-79	72-76	75
Tokai *et al.* (2020)[40]	Japan	Retro	Detection of ESCC and prediction of invasion depth	WLE	84	73	81	NR	79	62	74
Shimamoto *et al.* (2020)[41]	Japan	Retro	Prediction of invasion depth of ESCC	WLE ME-NBI/BLI	87 71	50 95	99 89	7-25	45 42	97 97	85 84
Cai *et al.* (2019)[38]	China	Retro	Detection of ESCC	WLE	98	85	91	>15 5-15 <5	86 79 62	91 84 92	89 82 77
Zhao *et al.* (2019)[42]	China	Retro	Feasibility of automated IPCLs classification	ME-NBI	87	84	89	>15 10-15 5-10	91 79 68	84 71 76	92 82 73
Nakagawa *et al.* (2019)[39]	Japan	Retro	Prediction of the invasion depth of ESCC	WLE	90	96	90	9-23	89	88	90

AI, Artificial Intelligence; BLI, blue light imaging; ESCC, esophageal squamous cell carcinoma; IPCL, intrapapillary capillary loop; Retro, retrospective; ME, magnified endoscopy; NBI, narrow band imaging; Sens, sensitivity; Spec, specificity; WLE, white light endoscopy; NR, not reported.

Gastric precancerous lesions and early gastric cancer

Helicobacter pylori (HP) infection can cause chronic atrophic gastritis (CAG) and gastric intestinal metaplasia (GIM), which are both precancerous conditions associated with increased risk of gastric cancer (GC) development.[3, 48] GC is often diagnosed in an advanced stage with an estimated 5-year survival rate of 20%.[30] Endoscopic surveillance is offered to patients with CAG and GIM to detect GC in an early stage, as detection of early gastric cancer (EGC) improves survival.[3] Current surveillance strategies consist of adequate inspection of the gastric mucosa and standardized random biopsy sampling according to the Sydney protocol for topographic mapping.[3] Guidelines recommend use of HD-chromoendoscopy in GC surveillance as it improves optical diagnosis of precancerous lesions and EGC.[3, 49-51] The treatment strategy is determined by the invasion depth, which is an important prognostic factor in EGC.[3, 30] In early cases, diagnosis of EGC can be difficult as features can be subtle and EGC is easily missed in presence of other pathology such as gastritis. AI models may improve the diagnostic accuracy by locating areas suspect for cancer and aid the endoscopist in detection and staging of gastric pathology.

AI in the detection of EGC

The application of AI for the detection of EGC has been investigated in WLE images[52-57] and optical chromoendoscopy images (Table 3).[8, 58-63] Li *et al.*[8] developed a CNN model on 386 images of benign lesions and 1,702 images of EGC for model development and 171 images of noncancerous lesions and 170 EGC images to test the models' performance. The AI model had a diagnostic accuracy of 91% versus 87% when used by experts and 70 to 74% for non-expert endoscopists. Horiuchi *et al.*[58] tested a CAD system to detect EGC using 174 NBI videos that contained 87 cancerous lesions. The CAD system was trained with 2,570 images containing cancerous and noncancerous gastric lesions. The performance of the CAD system was benchmarked against 11 endoscopists with experience in NBI and showed varying results. Only 2 endoscopists were outperformed by the CAD system. Similar results were found in the study of Ikenoyama *et al.*[55] that assessed the application of AI in detecting gastric cancer with both WLE and NBI.

Table 3. Application of artificial intelligence in the detection of early gastric cancer and prediction of the invasion depth.

Authors	Country	Study design	Aim	Modality	AI model			Endoscopists			
					Sens %	Spec %	Accuracy %	Experience (EGDs/years)	Sens %	Spec %	Accuracy %
Ikenoyama *et al.* (2021)[55]	Japan	Retro	Detection of EGC	WLE/NBI	58	87	NR	Mean 18.6	37	97	NR
								Mean 8.2	27	97	
Ueyama *et al.* (2021)[60]	Japan	Retro	Detection of EGC	ME-NBI	98	100	99	NR	NR	NR	NR
Horiuchi *et al.*(2020)[58]	Japan	Retro	Detection of EGC	ME-NBI	87	83	85	>10	54-94	62-95	58-92
			Differentiation EGC vs gastritis		95	71	85	5-10	68-85	89-99	78-88
Nagao *et al.* (2020)[61]	Japan	Retro	Prediction of invasion depth of EGC	WLE	84	99	94	NR	NR	NR	NR
				NBI	75	100	94				
Li *et al.* (2020)[8]	China	Retro	Detection of EGC	ME-NBI	91	91	91	>10	78-81	94-95	87
								3	74-78	62-73	70-74
Cho *et al.* (2019)[54]	China	Retro	Detection of EGC	WLE	28	88	75				
			Differentiation EGC vs precancerous lesions		50	91	76	Mean 6.7	69-93	87-100	82-98
Wu *et al.* (2019)[53]	Japan	Retro	Detection of EGC	WLE	94	91	93	Expert[1]	94	87	90
								Senior	90	85	87
								Trainee	75	89	81
Yoon *et al.* (2019)[52]	Korea	Retro	Detection of EGC	WLE	91	98	AUC:0.98	NR	NR	NR	NR
			Prediction of invasion depth		79	78	AUC:0.85				
Zhu *et al.* (2019)[56]	USA	Retro	Prediction of invasion depth of EGC	WLE	76	96	89	>5.000	87	70	77
								2.000-5.000	63	62	66
Hirasawa *et al.* (2018)[57]	Japan	Retro	Detection of EGC	WLE	92	NR	92	NR	NR	NR	NR
Kanesaka *et al.* (2018)[59]	Taiwan	Retro	Detection and delineation of EGC	ME-NBI	97	95	96	NR	NR	NR	NR

Table 3. Application of artificial intelligence in the detection of early gastric cancer and prediction of the invasion depth. (continued)

Authors	Country	Study design	Aim	Modality	AI model			Endoscopists			
					Sens %	Spec %	Accuracy %	Experience (EGDs/years)	Sens %	Spec %	Accuracy %
Miyaki *et al.* (2013, 2015)[62,63]	Japan	Retro	Detection of EGC Differentiation EGC vs no cancer	FICE	85	87	86	NR	NR	NR	NR

AI, Artificial Intelligence; AUC, area under the curve; BLI, blue light imaging; EC, esophageal cancer; EGC, early gastric cancer; FICE, flexible spectral imaging color enhancement; ME, magnified endoscopy; NBI, narrow band imaging; USA, United States of America; Retro, retrospective; Sens, sensitivity; Spec, specificity; WLE, white light endoscopy; NR, not reported. [1]Years of experience of subgroups of endoscopists unknown.

AI in prediction of invasion depth of EGC

Few research groups have developed CAD systems to assess the invasion depth of EGC.[52, 56, 61] Nagao *et al.*[61] developed a CNN-CAD system using 16,557 images of 1,084 GC cases that underwent endoscopic resection or surgery, to study if invasion depth of EGC can be determined. Prediction of invasion depth was analyzed in both WLE and NBI modality. The CAD system predicted the invasion depth with sensitivity of 84% and 75%, specificity of 99% and 100% and accuracy of 94% and 94% during WLE and NBI images, respectively. Yoon *et al.*[52] analyzed 11,539 images of both GC (T1a and T1b) and non-EGC and predicted the invasion depth with an AUC of 0.85. However, in case of undifferentiated histology, the accuracy of the AI model was significantly lower. Despite the high performance of the CAD systems, only images were used to train and calculate performance of the algorithm, video analysis has yet to be tested.

AI in detection of gastric precancerous lesions and HP infection

Recent AI systems developed to enhance endoscopic detection of gastric precancerous lesions and HP are shown in Table 4.[11, 64-71] In 2 studies, AI models were compared to endoscopists with different levels of experience in detection of CAG.[11, 64] Zhang *et al.*[64] designed a CNN model to detect CAG by using 5,470 antrum images of 1,699 patients. Images were classified as mild, moderate, and severe CAG. CAG was histologically confirmed in 3,042 images. The performance of the CNN model was compared to 3 expert endoscopists. The model outperformed the endoscopists with a sensitivity, specificity and accuracy of 95%, 94% and 94%, respectively. Highest detection rate was seen in severe CAG, with an accuracy of 99%. Guimarães *et al.*[11] showed similar results and reported a 93% accuracy for the detection of CAG in WLE images of the proximal stomach. Yan and colleagues[71] developed a CNN-CAD model for the detection of GIM with magnification and NBI. The AI model reported a diagnostic accuracy of 89% with an accuracy of 84% for expert endoscopists with 10 years of endoscopic experience (p = 0.42).

Zheng *et al.*[66] developed a CAD system to determine HP infection status, based on endoscopic images. In total, 15,484 gastric images of 1,959 patients of which 1,157 with a HP infection were used. This study aimed to investigate whether the AI model could accurately diagnose HP infection during endoscopy without the need for biopsies. The CNN system showed a high performance with an accuracy of 92%. Nakashima *et al.*[68] used a DL model to diagnose HP infection with the use of WLE and blue light imaging. The research group conducted a single-center prospective study with 222 participants of which 105 had a confirmed HP infection. The DL model had an AUC of 0.96 with blue light imaging. However, with WLE images, the AUC of the AI model decreased to 0.66.

Table 4. Application of artificial intelligence in the detection of gastric precancerous lesions and Helicobacter Pylori infection.

Authors	Country	Study design	Aim	Modality	AI model			Endoscopists			
					Sens %	Spec %	Accuracy %	Experience (EGDs/years)	Sens %	Spec %	Accuracy %
Zhang *et al.* (2020)[64]	China	Retro	Detection of CAG	WLE	95	94	94	Experts[1]	88-92	90-91	89-92
								Trainee	60-62	58-60	59-61
Guimarães *et al.* (2020)[10]	Germany	Retro	Detection of CAG	WLE	100	88	93	>1,500 EGDs	64	89	79
								<1,500 EGDs	96	71	81
Yan *et al.* (2020)[71]	China	Retro	Detection of GIM	ME-NBI	92	86	89	10	87	81	84
Yasuda *et al.* (2020)[70]	Japan	Retro	Detection of HP infection	NBI	90	86	88	Expert[1]	93	89	91
								Endoscopist	90	92	90
								Senior resident	93	83	87
Zheng *et al.* (2019)[66]	China	Retro	Detection of HP infection	WLE	92	99	94	NR	NR	NR	NR
Shichijo *et al.* (2019)[67]	Japan	Retro	Detection of HP infection	WLE	NR	NR	80	NR	NR	NR	NR
Nakashima *et al.* (2018)[68]	Japan	Pro data collection	Detection of HP infection	WLE	67	60	AUC 0.66	NR	NR	NR	NR
				NBI	97	83-87	AUC 0.96				
Itoh *et al.* (2018)[69]	Japan	Retro	Detection of HP infection	WLE	87	87	AUC 0.96	NR	NR	NR	NR
Huang *et al.* (2004)[65]	Taiwan	Retro	Detection precancerous lesions and HP infection	WLE	85	91	85	Experts[1]	NR	NR	74-81
								Trainee			65-73

AI, Artificial Intelligence; AUC, area under the curve; CAG, chronic atrophic gastritis; EGD, esophagogastroduodenoscopy; GIM = gastric intestinal metaplasia; HP, Helicobacter Pylori; NBI, narrow band imaging; Pro, prospective; Retro, retrospective; Sens, sensitivity; Spec, specificity; WLE, white light endoscopy; NR, not reported.
[1]Years of experience of subgroups of endoscopists unknown.

Conclusion and potential challenges of implementing AI upper endoscopy into clinical practice

In this review, we have shown that AI systems have been applied in upper GI endoscopy for several indications: (1) detection, characterization, and delineation of esophageal and GC and their premalignant conditions, (2) prediction of tumor invasion, and (3) diagnosis of a HP infection. The current status of AI models for each indication in upper GI endoscopy is shown in Table 5. So far, all AI studies in upper GI endoscopy have shown promising results with high performance for accurate detection and staging of (pre)malignant lesions in both the esophagus and stomach. The benefit, especially on the quality of endoscopy by the use of AI in upper GI however, still needs to be demonstrated and may differ between endoscopists based on their skills and experience.

The use of AI in upper GI endoscopy may be of additional value for clinical practice for different reasons. AI has the potential to provide real-time assistance by red flagging cancers that remained undetected by endoscopists and may improve the yield of biopsies by indicating the optimal biopsy sites during live endoscopic procedures. More accurate prediction of tumor invasion of early-stage cancers may improve the selection of patients eligible for endoscopic resection and may prevent unnecessary invasive surgery. And more accurate endoscopic diagnosis of HP infection and gastric precancerous lesions by AI models may replace gastric biopsies.

To date, most AI models in upper GI endoscopy are developed in an ideal setting with high quality imagery. This setting does not always reflect real-life endoscopy, where good visualization of the mucosa depends on the experience and skills of the endoscopists, which is essential for optimal performance of AI. Although several studies compared AI models to endoscopists, studies reporting on the diagnostic performance of AI models for each experience level of endoscopists are scarce. The outcome of these studies will better illuminate for which indication AI may be of additional value in relation to endoscopists' own experience and skills. For example, in GC, AI outperformed mid-level and trainee but not expert endoscopists. Besides studies linking the performance of AI models to endoscopists with different levels of experience, studies that investigate AI during real-time upper GI endoscopy are still very scarce. To date, no AI systems have been validated in large groups of patients during live endoscopic procedures. Large prospective trials are awaited for to validate the additional value and confirm the clinical significance of AI models during real-life endoscopy.

In conclusion, AI models in upper GI endoscopy showed high diagnostic performance for the detection, characterization and delineation of upper GI lesions. In addition, AI shows promising results in the prediction of the tumor invasion depth and diagnosis of HP. The benefit of AI correlated to endoscopist skills and experience need to be further addressed, while prospective studies are needed to confirm its accuracy and feasibility during real-time daily endoscopy.

Table 5. Current status of AI systems for each indication in upper gastrointestinal endoscopy.

Indications	Current status of AI systems	Next step
Barrett's neoplasia		
• Detection, characterization, and delineation • Selection of optimal biopsy site	• Algorithms are trained and validated with datasets of labeled endoscopic images • Prospective studies during live endoscopic procedures in small groups of patients	• Validation of AI algorithms in large groups of patients during live endoscopic procedures • Assess AI performance when used by endoscopists with different levels of experience
Squamous dysplasia and esophageal squamous cell carcinoma		
• Detection • Prediction of the invasion depth	• Algorithms are trained and validated with datasets of labeled endoscopic images • Retrospective studies with high quality images or videos	Prospective data collection of images and videos
Early gastric cancer		
• Detection • Prediction of the invasion depth	• Algorithms are trained and validated with a dataset of labeled endoscopic images • Retrospective studies with high quality images or videos	Prospective data collection of images and videos
Gastric precancerous lesions		
• Detection	• Trained and validated algorithms with datasets of labeled endoscopic images • Prospective data collection with high quality images	Prospective studies during live endoscopic procedures

AI, artificial intelligence; BE, Barrett's esophagus; CAG, chronic atrophic gastritis; EGC, early gastric cancer; ESCC, esophageal squamous cell carcinoma; GIM, gastric intestinal metaplasia; HP, Helicobacter pylori.

REFERENCES

1. Weusten B, Bisschops R, Coron E, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. 2017.
2. Qumseya B, Sultan S, Bain P, et al. ASGE guideline on screening and surveillance of Barrett's esophagus. Gastrointestinal endoscopy. 2019;90(3):335-59. e2.
3. Pimentel-Nunes P, Libanio D, Marcos-Pinto R, et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy. 2019;51(4):365-88.
4. Lordick F, Mariette C, Haustermans K, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v50-v7.
5. Kerkhof M, Van Dekken H, Steyerberg EW, et al. Grading of dysplasia in Barrett's oesophagus: substantial interobserver variation between general and gastrointestinal pathologists. Histopathology. 2007;50(7):920-7.
6. Curvers WL, ten Kate FJ, Krishnadath KK, et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. Am J Gastroenterol. 2010;105(7):1523-30.
7. de Groof J, van der Sommen F, van der Putten J, et al. The Argos project: The development of a computer-aided detection system to improve detection of Barrett's neoplasia on white light endoscopy. United European Gastroenterol J. 2019;7(4):538-47.
8. Li L, Chen Y, Shen Z, et al. Convolutional neural network for the diagnosis of early gastric cancer based on magnifying narrow band imaging. Gastric Cancer. 2020;23(1):126-32.
9. Horie Y, Yoshio T, Aoyama K, et al. Diagnostic outcomes of esophageal cancer by artificial intelligence using convolutional neural networks. Gastrointest Endosc. 2019;89(1):25-32.
10. Ebigbo A, Mendel R, Probst A, et al. Real-time use of artificial intelligence in the evaluation of cancer in Barrett's oesophagus. Gut. 2020;69(4):615-6.
11. Guimaraes P, Keller A, Fehlmann T, et al. Deep-learning based detection of gastric precancerous conditions. Gut. 2020;69(1):4-6.
12. Deng J, Dong W, Socher R, et al., editors. Imagenet: A large-scale hierarchical image database. 2009 IEEE conference on computer vision and pattern recognition; 2009: Ieee.
13. Steevens J, Botterweck AA, Dirx MJ, et al. Trends in incidence of oesophageal and stomach cancer subtypes in Europe. Eur J Gastroenterol Hepatol. 2010;22(6):669-78.
14. Cook MB, Chow WH, Devesa SS. Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977-2005. Br J Cancer. 2009;101(5):855-9.
15. Duits LC, van der Wel MJ, Cotton CC, et al. Patients With Barrett's Esophagus and Confirmed Persistent Low-Grade Dysplasia Are at Increased Risk for Progression to Neoplasia. Gastroenterology. 2017;152(5):993-1001 e1.
16. Ngamruengphong S, Sharma VK, Das A. Diagnostic yield of methylene blue chromoendoscopy for detecting specialized intestinal metaplasia and dysplasia in Barrett's esophagus: a meta-analysis. Gastrointestinal endoscopy. 2009;69(6):1021-8.
17. Yousef F, Cardwell C, Cantwell MM, et al. The incidence of esophageal cancer and high-grade dysplasia in Barrett's esophagus: a systematic review and meta-analysis. American journal of epidemiology. 2008;168(3):237-49.
18. Noordzij IC, van de Ende MCMVL, Curvers WL, et al. Dysplasia in Random Biopsies from Barrett's Surveillance Is an Important Marker for More Severe Pathology. Digestive Diseases and Sciences. 2020:1-8.
19. Schölvinck DW, Van Der Meulen K, Bergman JJ, et al. Detection of lesions in dysplastic Barrett's esophagus by community and expert endoscopists. Endoscopy. 2017;49(02):113-20.
20. Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association technical review on the management of Barrett's esophagus. Gastroenterology. 2011;140(3):e18-52; quiz e13.
21. Konda VJA, Ross AS, Ferguson MK, et al. Is the risk of concomitant invasive esophageal cancer in high-grade dysplasia in Barrett's esophagus overestimated? Clinical Gastroenterology and Hepatology. 2008;6(2):159-64.
22. Roumans CAM, van der Bogt RD, Steyerberg EW, et al. Adherence to recommendations of Barrett's esophagus surveillance guidelines: a systematic review and meta-analysis. Endoscopy. 2020;52(1):17-28.

23. Hashimoto R, Requa J, Dao T, et al. Artificial intelligence using convolutional neural networks for real-time detection of early esophageal neoplasia in Barrett's esophagus (with video). Gastrointest Endosc. 2020;91(6):1264-71 e1.
24. van der Sommen F, Zinger S, Curvers WL, et al. Computer-aided detection of early neoplastic lesions in Barrett's esophagus. Endoscopy. 2016;48(7):617-24.
25. de Groof AJ, Struyvenberg MR, Fockens KN, et al. Deep learning algorithm detection of Barrett's neoplasia with high accuracy during live endoscopic procedures: a pilot study (with video). Gastrointest Endosc. 2020;91(6):1242-50.
26. de Groof AJ, Struyvenberg MR, van der Putten J, et al. Deep-Learning System Detects Neoplasia in Patients With Barrett's Esophagus With Higher Accuracy Than Endoscopists in a Multistep Training and Validation Study With Benchmarking. Gastroenterology. 2020;158(4):915-29 e4.
27. Ebigbo A, Mendel R, Probst A, et al. Computer-aided diagnosis using deep learning in the evaluation of early oesophageal adenocarcinoma. Gut. 2019;68(7):1143-5.
28. Struyvenberg MR, de Groof AJ, van der Putten J, et al. A computer-assisted algorithm for narrow-band imaging-based tissue characterization in Barrett's esophagus. Gastrointest Endosc. 2020.
29. Arnold M, Ferlay J, van Berge Henegouwen MI, et al. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. Gut. 2020;69(9):1564-71.
30. 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(6):394-424.
31. 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;94:138-47.
32. Henry MA, Lerco MM, Naresse LE, et al. Outcome of superficial squamous cell carcinoma of the esophagus: a clinicopathological study. Acta Cir Bras. 2013;28(5):373-8.
33. Lu P, Gu J, Zhang N, et al. Risk factors for precancerous lesions of esophageal squamous cell carcinoma in high-risk areas of rural China: A population-based screening study. Medicine (Baltimore). 2020;99(31):e21426.
34. Gruner M, Denis A, Masliah C, et al. Narrow-band imaging versus Lugol chromoendoscopy for esophageal squamous cell cancer screening in normal endoscopic practice: Randomized controlled trial. Endoscopy. 2020.
35. Inoue H, Honda T, Nagai K, et al. Ultra-high magnification endoscopic observation of carcinoma in situ of the esophagus. Digestive Endoscopy. 1997;9(1):16-8.
36. 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(1):41-8.
37. Ohmori M, Ishihara R, Aoyama K, et al. Endoscopic detection and differentiation of esophageal lesions using a deep neural network. Gastrointest Endosc. 2020;91(2):301-9 e1.
38. Cai SL, Li B, Tan WM, et al. Using a deep learning system in endoscopy for screening of early esophageal squamous cell carcinoma (with video). Gastrointest Endosc. 2019;90(5):745-53 e2.
39. Nakagawa K, Ishihara R, Aoyama K, et al. Classification for invasion depth of esophageal squamous cell carcinoma using a deep neural network compared with experienced endoscopists. Gastrointest Endosc. 2019;90(3):407-14.
40. Tokai Y, Yoshio T, Aoyama K, et al. Application of artificial intelligence using convolutional neural networks in determining the invasion depth of esophageal squamous cell carcinoma. Esophagus. 2020;17(3):250-6.
41. Shimamoto Y, Ishihara R, Kato Y, et al. Real-time assessment of video images for esophageal squamous cell carcinoma invasion depth using artificial intelligence. J Gastroenterol. 2020;55(11):1037-45.
42. Zhao YY, Xue DX, Wang YL, et al. Computer-assisted diagnosis of early esophageal squamous cell carcinoma using narrow-band imaging magnifying endoscopy. Endoscopy. 2019;51(4):333-41.
43. Guo L, Xiao X, Wu C, et al. Real-time automated diagnosis of precancerous lesions and early esophageal squamous cell carcinoma using a deep learning model (with videos). Gastrointest Endosc. 2020;91(1):41-51.
44. Ishihara R, Takeuchi Y, Chatani R, et al. Prospective evaluation of narrow-band imaging endoscopy for screening of esophageal squamous mucosal high-grade neoplasia in experienced and less experienced endoscopists. Dis Esophagus. 2010;23(6):480-6.
45. Fukuda H, Ishihara R, Kato Y, et al. Comparison of performances of artificial intelligence versus expert endoscopists for real-time assisted diagnosis of esophageal squamous cell carcinoma (with video). Gastrointest Endosc. 2020;92(4):848-55.
46. Goda K, Irisawa A. Japan Esophageal Society classification for predicting the invasion depth of superficial esophageal squamous cell carcinoma: Should it be modified now? Dig Endosc. 2020;32(1):37-8.

47. Domper Arnal MJ, Ferrandez Arenas A, Lanas Arbeloa A. Esophageal cancer: Risk factors, screening and endoscopic treatment in Western and Eastern countries. World J Gastroenterol. 2015;21(26):7933-43.
48. Correa P, Piazuelo MB. The gastric precancerous cascade. Journal of digestive diseases. 2012;13(1):2-9.
49. Pimentel-Nunes P, Libânio D, Lage J, et al. A multicenter prospective study of the real-time use of narrow-band imaging in the diagnosis of premalignant gastric conditions and lesions. Endoscopy. 2016;48(08):723-30.
50. Banks M, Graham D, Jansen M, et al. British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. Gut. 2019;68(9):1545-75.
51. Kikuste I, Marques-Pereira R, Monteiro-Soares M, et al. Systematic review of the diagnosis of gastric premalignant conditions and neoplasia with high-resolution endoscopic technologies. Scandinavian journal of gastroenterology. 2013;48(10):1108-17.
52. Yoon HJ, Kim S, Kim JH, et al. A Lesion-Based Convolutional Neural Network Improves Endoscopic Detection and Depth Prediction of Early Gastric Cancer. J Clin Med. 2019;8(9).
53. Wu L, Zhou W, Wan X, et al. A deep neural network improves endoscopic detection of early gastric cancer without blind spots. Endoscopy. 2019;51(6):522-31.
54. Cho BJ, Bang CS, Park SW, et al. Automated classification of gastric neoplasms in endoscopic images using a convolutional neural network. Endoscopy. 2019;51(12):1121-9.
55. Ikenoyama Y, Hirasawa T, Ishioka M, et al. Detecting early gastric cancer: comparison between the diagnostic ability of convolutional neural networks and endoscopists. Digestive Endoscopy. 2021;33(1):141-50.
56. Zhu Y, Wang Q-C, Xu M-D, et al. Application of convolutional neural network in the diagnosis of the invasion depth of gastric cancer based on conventional endoscopy. Gastrointestinal endoscopy. 2019;89(4):806-15. e1.
57. Hirasawa T, Aoyama K, Tanimoto T, et al. Application of artificial intelligence using a convolutional neural network for detecting gastric cancer in endoscopic images. Gastric Cancer. 2018;21(4):653-60.
58. Horiuchi Y, Hirasawa T, Ishizuka N, et al. Performance of a computer-aided diagnosis system in diagnosing early gastric cancer using magnifying endoscopy videos with narrow-band imaging (with videos). Gastrointest Endosc. 2020;92(4):856-65 e1.
59. Kanesaka T, Lee TC, Uedo N, et al. Computer-aided diagnosis for identifying and delineating early gastric cancers in magnifying narrow-band imaging. Gastrointest Endosc. 2018;87(5):1339-44.
60. Ueyama H, Kato Y, Akazawa Y, et al. Application of artificial intelligence using a convolutional neural network for diagnosis of early gastric cancer based on magnifying endoscopy with narrow-band imaging. Journal of Gastroenterology and Hepatology. 2021;36(2):482-9.
61. Nagao S, Tsuji Y, Sakaguchi Y, et al. Highly accurate artificial intelligence systems to predict the invasion depth of gastric cancer: efficacy of conventional white-light imaging, nonmagnifying narrow-band imaging, and indigo-carmine dye contrast imaging. Gastrointestinal Endoscopy. 2020;92(4):866-73. e1.
62. Miyaki R, Yoshida S, Tanaka S, et al. Quantitative identification of mucosal gastric cancer under magnifying endoscopy with flexible spectral imaging color enhancement. Journal of gastroenterology and hepatology. 2013;28(5):841-7.
63. Miyaki R, Yoshida S, Tanaka S, et al. A computer system to be used with laser-based endoscopy for quantitative diagnosis of early gastric cancer. Journal of Clinical Gastroenterology. 2015;49(2):108-15.
64. Zhang Y, Li F, Yuan F, et al. Diagnosing chronic atrophic gastritis by gastroscopy using artificial intelligence. Dig Liver Dis. 2020;52(5):566-72.
65. Huang CR, Sheu BS, Chung PC, et al. Computerized diagnosis of Helicobacter pylori infection and associated gastric inflammation from endoscopic images by refined feature selection using a neural network. Endoscopy. 2004;36(07):601-8.
66. Zheng W, Zhang X, Kim JJ, et al. High Accuracy of Convolutional Neural Network for Evaluation of Helicobacter pylori Infection Based on Endoscopic Images: Preliminary Experience. Clin Transl Gastroenterol. 2019;10(12):e00109.
67. Shichijo S, Endo Y, Aoyama K, et al. Application of convolutional neural networks for evaluating Helicobacter pylori infection status on the basis of endoscopic images. Scand J Gastroenterol. 2019;54(2):158-63.
68. Nakashima H, Kawahira H, Kawachi H, et al. Artificial intelligence diagnosis of Helicobacter pylori infection using blue laser imaging-bright and linked color imaging: a single-center prospective study. Ann Gastroenterol. 2018;31(4):462-8.
69. Itoh T, Kawahira H, Nakashima H, et al. Deep learning analyzes Helicobacter pylori infection by upper gastrointestinal endoscopy images. Endosc Int Open. 2018;6(2):E139-E44.

70. Yasuda T, Hiroyasu T, Hiwa S, et al. Potential of automatic diagnosis system with linked color imaging for diagnosis of Helicobacter pylori infection. Dig Endosc. 2020;32(3):373-81.
71. Yan T, Wong PK, Choi IC, et al. Intelligent diagnosis of gastric intestinal metaplasia based on convolutional neural network and limited number of endoscopic images. Computers in Biology and Medicine. 2020;126:104026.

Chapter 3

Increased risk of esophageal squamous cell carcinoma in patients with squamous dysplasia: a nationwide cohort study in the Netherlands

Laurelle van Tilburg, Manon C.W. Spaander, Marco J. Bruno, Lindsey Oudijk, Lara R. Heij, Michail Doukas, Arjun D. Koch

Diseases of the esophagus. 2023

ABSTRACT

Background: Squamous dysplasia is the histological precursor of esophageal squamous cell carcinoma (ESCC). The optimal management for distinct squamous dysplasia grades remains unclear because the corresponding risk of developing ESCC is unknown. We aimed to assess the ESCC risk in patients with esophageal squamous dysplasia in a Western country.

Methods: This nationwide cohort study included all patients with esophageal squamous dysplasia, diagnosed between 1991 and 2020 in the Dutch nationwide pathology databank (Palga). Squamous dysplasia was divided in mild-to-moderate dysplasia (mild, low grade, and moderate dysplasia) and higher-grade dysplasia (high grade dysplasia, severe dysplasia, carcinoma in situ). ESCC were identified in Palga and the Netherlands Cancer Registry. The primary end point was diagnosis of prevalent (≤6 months) and incident (>6 months after squamous dysplasia) ESCC.

Results: In total, 873 patients (55% male, aged 68 years SD±13.2) were diagnosed with esophageal squamous dysplasia, comprising mild-to-moderate dysplasia (n=456), higher-grade dysplasia (n=393) and dysplasia not otherwise specified (n=24). ESCC was diagnosed in 77 (17%) patients with mild-to-moderate dysplasia (49 prevalent, 28 incident ESCC) and in 162 (41%) patients with higher-grade dysplasia (128 prevalent, 34 incident ESCC). After excluding prevalent ESCC, the annual risk of ESCC was 4.0% (95%CI: 2.7-5.7%) in patients with mild-to-moderate dysplasia and 8.5% (95%CI: 5.9-11.7%) in patients with higher-grade dysplasia.

Conclusions: All patients with squamous dysplasia, including those with mild-to-moderate dysplasia, have a substantial risk of developing ESCC. Consequently, endoscopic surveillance of the esophageal mucosa or endoscopic resection of dysplasia should be considered for patients with mild-to-moderate dysplasia in Western countries.

INTRODUCTION

Over 85% of the esophageal cancers are esophageal squamous cell carcinoma (ESCC) worldwide.[1] In Western countries, the age-standardized incidence rate of ESCC ranged between 1.0 and 2.5 per 100.000 persons in 2018.[1] As most ESCC are detected in advanced and incurable stages, the 5-year survival rate of patients with ESCC is merely 22%.[2, 3] The detection of ESCC at early stages is associated with a considerably better 5-year survival of 85 to 100%, as early-stage ESCC can potentially be treated curatively with endoscopic resection (ER).[2, 3]

The cornerstone in detecting ESCC at early stages consists of the identification of high risk patients for ESCC. An important group of high risk patients are patients with esophageal squamous dysplasia, a histological precursor lesion of ESCC. Squamous dysplasia is defined as neoplastic alterations of the esophageal squamous epithelium, without invasion.[4] ESCC is thought to develop via the dysplasia-carcinoma cascade: from normal squamous epithelium via increasing grades of dysplasia to ESCC.[5, 6] Adequate endoscopic detection and treatment of patients with squamous dysplasia allows for early detection of ESCC or can even prevent ESCC development.[7, 8]

The pathological assessment of squamous dysplasia can be challenging and currently two classification systems are used worldwide: a three-tiered and two-tiered classification.[4, 9] Both classifications are based on the proportion of the squamous epithelium with histopathological abnormalities.[4, 9] The three-tier system is predominantly used in Asian countries and classifies squamous dysplasia in mild, moderate, and severe dysplasia.[9] In an Asian study with 13.5 years of endoscopic surveillance, the risk of neoplastic progression was up to 24% for mild dysplasia, 50% for moderate dysplasia, and 74% for severe dysplasia.[9-14] However, it is unknown whether this risk of ESCC can be generalized to patients with squamous dysplasia in Western countries, as the incidence of ESCC differs strongly between Western and Asian countries.[1]

In Western countries, the World Health Organization advises to use the two-tiered classification with low grade and high grade dysplasia to increase the level of inter-observer agreement among pathologists.[4, 15] Current guidelines in Western countries advocate that ER should be performed for high grade dysplasia and ESCC limited to the mucosa, but it remains controversial whether endoscopic surveillance or treatment is indicated for low grade dysplasia.[16] The optimal management for distinct squamous dysplasia grades remains unclear because the corresponding risk of developing ESCC for each distinct grade of squamous dysplasia is unknown. We, therefore, aimed to assess the ESCC risk in patients with squamous dysplasia in a Western country.

METHODS

Study design and patients

We performed a nationwide, retrospective study including all patients diagnosed with esophageal squamous dysplasia between January 1991 and December 2020 in the Netherlands. Patients were identified via the Dutch nationwide pathology databank (Palga).[17] The development of ESCC in included patients was identified from Palga and the Netherlands Cancer Registry (NCR; nationwide registry of all cancers). All patient data were coded and anonymized by a third trust party and, therefore, no informed consent was needed. This study was approved by the Medical Ethical Review Committee of the Erasmus Medical Centre (MEC-2022-0274). 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.

Palga search

The Palga database contains all Dutch pathology reports with nationwide coverage since 1991, linked to an encrypted individual patient identification number and diagnostic code.[17] The diagnostic code reflects the location, type, and histopathological diagnosis of the tissue sample (e.g. esophagus x biopsy x grade dysplasia). The Palga database was searched for the diagnostic codes for dysplasia and atypia in the esophagus (search details are described in Table S1). Inclusion criteria were all diagnostic codes for squamous dysplasia in the esophagus. Exclusion criteria were dysplasia in a Barrett's esophagus or columnar epithelium, dysplasia located in the stomach and patients with previous or simultaneous (i.e. in the pathology specimen of the same date) esophageal cancer, and patients developing esophageal adenocarcinoma.

Histopathological definitions

Squamous dysplasia is characterized by the presence of both cytological and architectural atypia.[4] Characteristics of cytological atypia include cell enlargement, pleomorphism, hyperchromasia, loss of polarity, and overlapping. Architectural atypia is defined as abnormal maturation of the epithelium. The grade of dysplasia is based on the proportion of the squamous epithelium with pathological abnormalities.[4, 9] Mild, moderate and severe dysplasia are limited to the lower third, middle third and three thirds of the squamous epithelium (Figure 1).[9] Low grade dysplasia is defined as mild cytological atypia confined to the lower half of the squamous epithelium.[4] High grade dysplasia is characterized by severe cytological atypia or the presence of mild cytological atypia in more than half of the squamous epithelium.[4] Carcinoma in situ (CIS) is defined as the presence of dysplastic cells

throughout the full thickness of the squamous epithelium, without invasion.[9] If squamous dysplasia could not be graded, because of biopsy size or orientation, this is referred to as dysplasia not otherwise specified (NOS).[9]

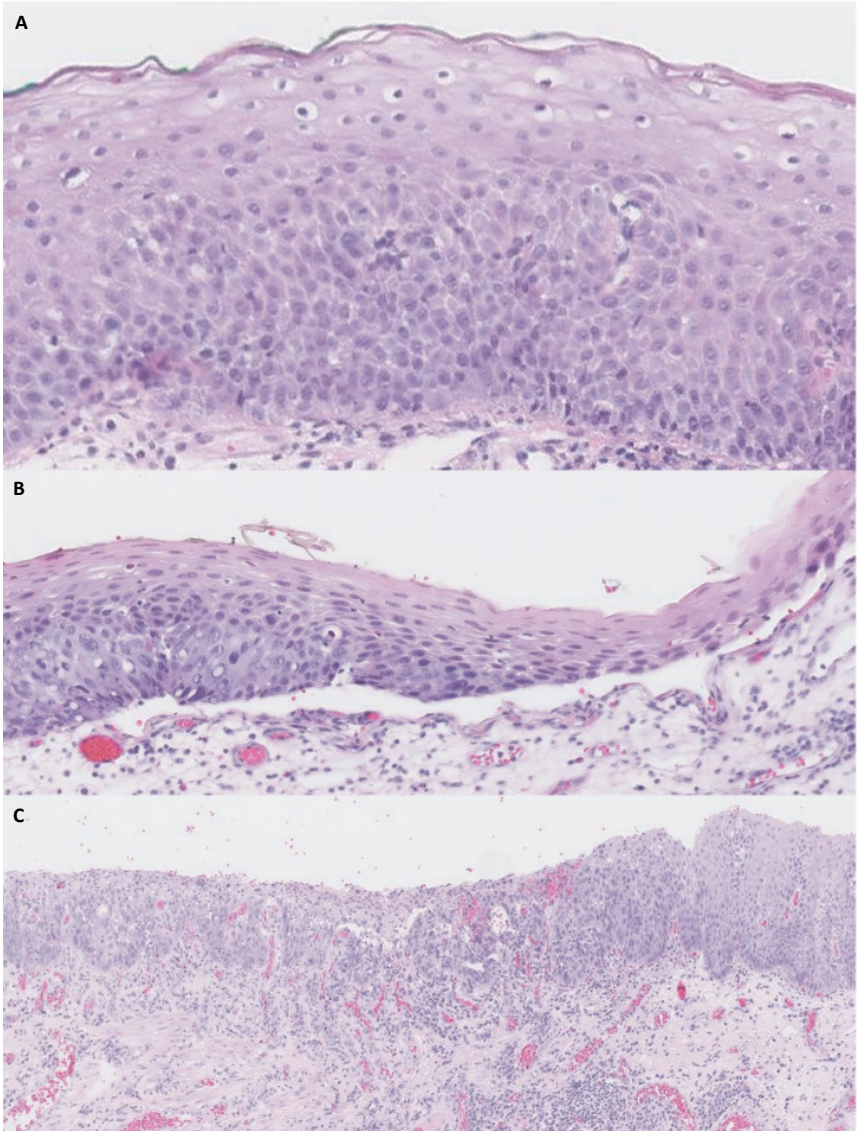


Figure 1. Distinct grades of squamous dysplasia in the esophagus. A) shows mild dysplasia with dysplastic cells limited to the lower third of the squamous epithelium. B) shows moderate dysplasia with dysplastic cells limited to the middle third of the squamous epithelium. Both image A and B are referred to as low grade dysplasia in the two-tiered classification. C) shows severe dysplasia with dysplastic cells extending to the full thickness of the squamous epithelium (hematoxylin-eosin staining, original magnification x100 in A and B and x50 in C).

Data collection

From Palga, anonymized pathology reports with conclusions and microscopic assessment were collected from 5 years before the diagnosis squamous dysplasia and all follow up reports till July 2022. We extracted the following characteristics for all included patients: sex, age, year of squamous dysplasia, number of endoscopies with biopsies and time intervals, and date of last follow up or the diagnosis of ESCC. The time interval between squamous dysplasia and ESCC diagnosis was divided in *prevalent* (within 6 months) and *incident* (> 6 months). For patients with ESCC, the following characteristics were collected from the NCR; age at ESCC diagnosis, histopathological characteristics, and location of ESCC (cervical; <18 cm from the incisors, upper third; 18-24 cm from the incisors, middle third; 24-32 cm from the incisors, lower third; 32-40 cm from the incisors, and overlap; between two parts of the esophagus). The TNM stage of ESCC and treatment strategy (on 31-01-2021) were also assessed.

Study end points

The primary end point of this study was the proportion of patients with squamous dysplasia that were subsequently diagnosed with ESCC. Secondary end points included (1) the risk of ESCC for distinct grades of squamous dysplasia, (2) the time between first squamous dysplasia diagnosis and the detection of ESCC, and (3) characteristics and outcomes of patients with squamous dysplasia and subsequent ESCC.

Statistics

Descriptive statistics are presented as means with standard deviations (SD), medians with inter-quartile ranges (IQR) and counts with percentages, according to the nature of the data. For sub-group analyses, patients with mild, low grade, and moderate dysplasia were combined in the group mild-to-moderate dysplasia and patients with high grade dysplasia, severe dysplasia, and CIS were combined in the group higher-grade dysplasia. Sub-groups were compared using the X^2 test. The percentage annual risk of ESCC was calculated with number of events divided by number of patient years at risk, multiplied by 100. Cox proportional hazards analyses were performed to identify and quantify potential risk factors for the detection of ESCC and were presented as hazard ratios (HR) with 95% confidence intervals (CI). The statistical package (survminer) in R was used for the cumulative incidence plot. Two-side *P*-values <0.05 were considered significant. Analyses were performed in IBM SPSS for Windows version 28 (SPSS Inc) and R version 4.2.2 (The R Foundation Statistical Computing, Vienna, Austria).

RESULTS

Patients

The Palga search identified 9,687 patients with dysplasia in esophageal pathology specimen between January 1991 and December 2020 in the Netherlands (Figure S1). After review of pathology reports, 873 patients with a confirmed first diagnosis of squamous dysplasia in the esophagus were included. The mean age of included patients was 68.0 years (SD ±13.2) and 55.1% was male.

Baseline characteristics of squamous dysplasia

The baseline grade of dysplasia of included patients was mild (n=179), low grade (n=80), moderate (n=197), high grade (n=77), and severe (n=244) dysplasia, and CIS (n=72) (Table 1). In 79/197 patients with moderate dysplasia, the grade of dysplasia could be divided into low grade (69.6%) and high grade dysplasia (30.4%), based on complete pathology reports. Squamous dysplasia was diagnosed between 2020 to 2010 (38.9%), 2000 to 2010 (33.9%), and 1991 to 2000 (27.2%). Most cases of low grade (75.0%) and high grade dysplasia (71.4%) were diagnosed between 2011 and 2020 (Figure 2) (*P*<0.001).

Table 1. Baseline characteristics of included patients with esophageal squamous dysplasia.

Characteristic	Total cohort	Mild-to-moderate dysplasia	Higher-grade dysplasia
No. of patients	**873**	**456**	**393**
Sex, male	481 (55.1%)	255 (55.9%)	213 (54.2%)
Age, years	68 (SD±13.2)	66 (SD±13.6)	71 (SD±12.2)
Year of diagnosis			
1991-2000	237 (27.2%)	139 (30.5%)	92 (23.4%)
2000-2010	296 (33.9%)	146 (32.0%)	142 (36.1%)
2010-2020	340 (38.9%)	171 (37.5%)	159 (40.5%)

Data presented as n with (%) or mean with standard deviation (SD). Patients with mild (n=179), low grade (n=80), and moderate dysplasia (n=197) were combined in the group mild-to-moderate dysplasia. Patients with high grade dysplasia (n=77), severe dysplasia (n=244), and carcinoma in situ (n=72) were combined in the group higher-grade dysplasia. In the total cohort (n=873), patients with baseline squamous dysplasia not otherwise specified (n=24), are also included.

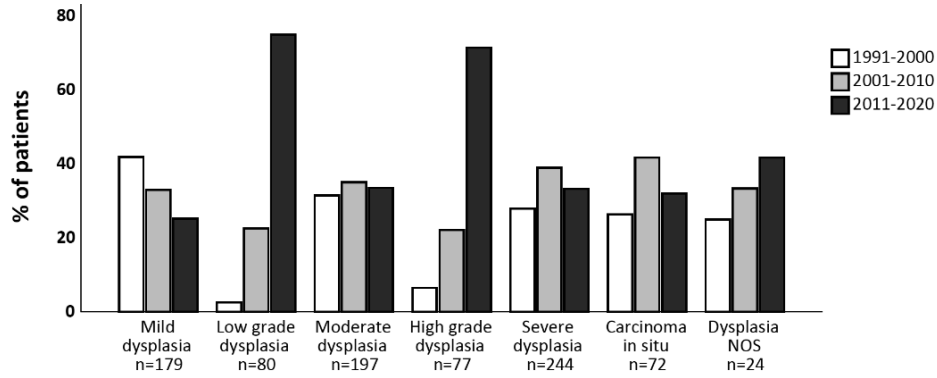


Figure 2. The proportion of patients with distinct grades of squamous dysplasia during recent decades. Most cases of low grade (75.0%) and high grade dysplasia (71.4%) were diagnosed from 2011 to 2020 (*P*<0.001). NOS, not otherwise specified, due to biopsy size or orientation.

Treatment strategies for baseline mild, low grade and moderate dysplasia

The cohort included 456 patients with mild-to-moderate dysplasia of which 57.0% of the patients underwent endoscopic re-assessment with histopathology or treatment. This was performed after a median of 12 weeks (IQR 6-29). During the first endoscopic-reassessment, ESCC was detected in 5.1%, 1.8%, and 12.8% of patients with baseline mild, low grade, and moderate dysplasia, respectively (Figure 3). The median histopathological follow up time was 10 months (IQR 3-42) and patients received a median of 2 (IQR 1-4) endoscopies. Thirteen (2.8%) patients with mild-to-moderate dysplasia were treated with primary ER (n=12; 2.6%) or surgery (n=1; 0.2%). The ER and surgery specimens showed mild-to-moderate dysplasia (n=6), higher-grade dysplasia (n=5), and ESCC (n=2). The remaining patients (43.0%) had no histopathological follow up.

Treatment strategy for baseline high grade dysplasia, severe dysplasia and CIS

A total of 71.5% of 393 included patients with higher-grade dysplasia underwent endoscopic re-assessment with histopathology or treatment. Endoscopic re-assessment was performed after a median of 5 weeks (IQR 2-10) and revealed mild-to-moderate dysplasia (5.0%), higher-grade dysplasia (39.6%), and ESCC (32.7%). Patients underwent a median of 2 endoscopies (IQR 1-4) during follow up till diagnosis of ESCC or last follow up. 71 (18.1%) patients with higher-grade dysplasia underwent treatment with ER (9.7%), surgery (4.3%), or chemotherapy and/or radiotherapy (4.1%). Pathological assessment of ER and surgery specimens showed no dysplasia (n=1), mild-to-moderate dysplasia (n=1), higher-grade dysplasia (n=25), and ESCC (n=28). In the remaining patients (28.5%), no histopathological follow up was available.

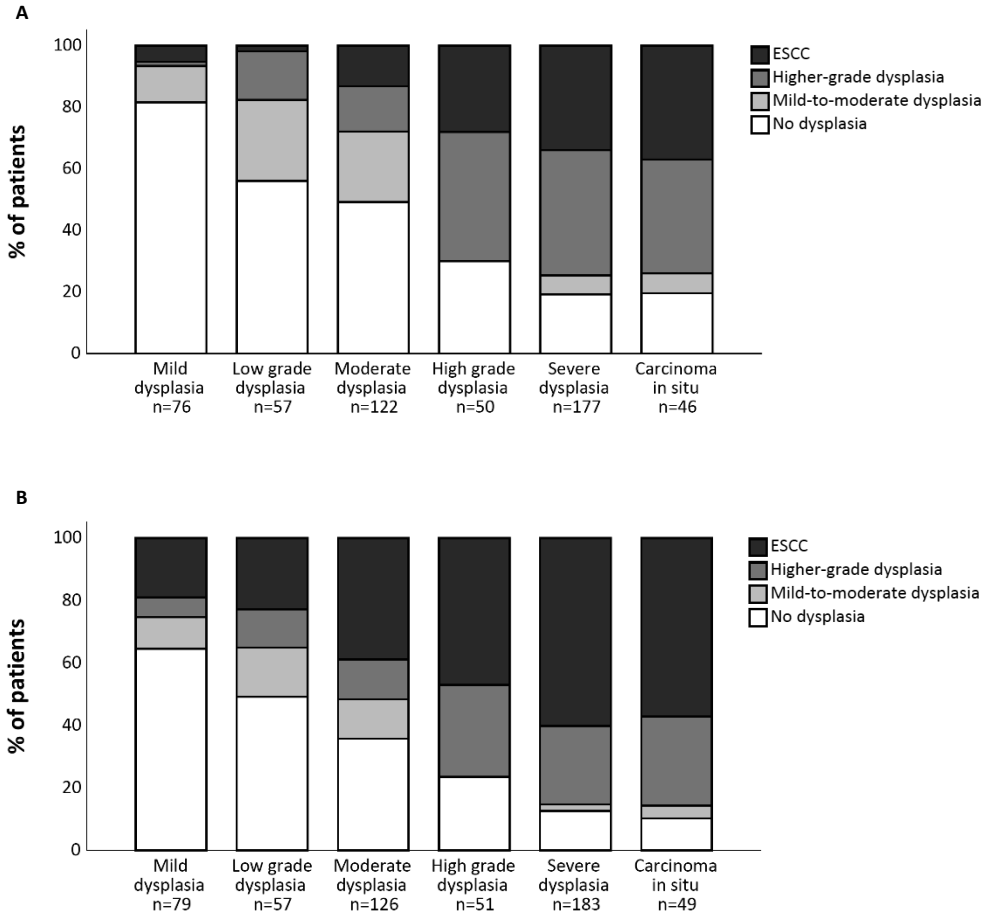


Figure 3. Most advanced lesion detected during first endoscopic re-assessment (A) and complete follow up (B) in patients with distinct grades of squamous dysplasia at baseline. Data presented in groups according to the grade of confirmed first squamous dysplasia diagnosis. A) shows the most advanced lesion detected during first endoscopic reassessment. Patients with dysplasia not otherwise specified as first dysplasia diagnosis (n=24) or detected during first endoscopic re-assessment (n=11) are not shown. Median time to first endoscopic re-assessment with histopathology was 17, 12, 11, 4, 5, and 6 weeks for patients with mild, low grade, moderate, high grade, and severe dysplasia, and carcinoma in situ, respectively. B) shows the most advanced lesions detected during complete follow up. This Figure contains 7 patients with a clinical diagnosis of ESCC without pathology confirmation, based on data from the Netherlands cancer registry. Median follow up time was 20 months for mild dysplasia, 10 months for low grade dysplasia, 7 months for moderate dysplasia, 4 months for high grade dysplasia, 2 months for severe dysplasia, and 5 months for carcinoma in situ.

Association between increasing grades of dysplasia and risk of ESCC

ESCC was diagnosed in 28.4% of included patients with baseline squamous dysplasia. Table 2 depicts the proportions of patients diagnosed with ESCC, according to their distinct grades of baseline squamous dysplasia. Increasing grades of dysplasia were associated with a significantly increased risk of ESCC (*P*<0.001) (Table 3). Patients with moderate dysplasia had a significantly increased risk of ESCC compared with mild dysplasia (HR 2.40, 95%CI: 1.35-4.29) and a showed a trend towards an increased risk compared with low grade dysplasia (HR 1.71, 95%CI: 0.93-3.16). Patients with low grade dysplasia had a tendency towards an increased risk to develop higher-grade dysplasia, compared with patients with mild dysplasia (HR 3.10, 95%CI: 0.98-9.80), but the results were not significant. Baseline high grade dysplasia was associated with a significantly increased risk of ESCC, compared with mild (HR 3.64, 95%CI: 1.91-6.94) and low grade dysplasia (HR 2.59, 95% CI 1.32-5.10). The risk of ESCC between patients with baseline moderate dysplasia and high grade dysplasia did not differ significantly (HR 0.66, 95% CI 0.41-1.08). Results were consistent after adjusting for sex, age, year of first dysplasia diagnosis, primary treatment strategy, and time to first endoscopic re-assessment (Table 3, Table S2).

Table 2. The proportion of patients with distinct grades of baseline squamous dysplasia diagnosed with prevalent and incident ESCC.

Baseline grade of dysplasia	No. of patients	No. of patients with ESCC	Prevalent ESCC	Incident ESCC[1]	Annual ESCC risk per PY[1]	PY at risk[1]
Mild	179	15 (8.4%)	9 (5.0%)	6 (3.5%)	2.1%	279.7
Low grade	80	13 (16.3%)	8 (10.0%)	5 (6.9%)	5.1%	97.3
Moderate	197	49 (24.9%)	32 (16.2%)	17 (10.3%)	5.2%	324.4
High grade	77	24 (31.2%)	18 (23.4%)	6 (10.2%)	8.9%	67.5
Severe	244	110 (45.1%)	92 (37.7%)	18 (11.8%)	7.5%	239.7
Carcinoma in situ	72	28 (38.9%)	18 (25.0%)	10 (18.5%)	10.6%	94.6
NOS [2]	24	9 (37.5%)	4 (16.7%)	5 (25.0%)	10.1%	49.6
Total cohort	**873**	**248 (28.4%)**	**181 (20.7%)**	**67 (9.7%)**	**5.8%**	**1152.7**

Data presented as n with (%). ESCC were divided in prevalent (≤ 6 months) and incident (>6 months) after baseline diagnosis of squamous dysplasia. [1] Calculated for patients at risk of ESCC at 6 months after baseline squamous dysplasia (n=692). [2]Grading of squamous dysplasia was not possible, due to biopsy size or orientation. ESCC, esophageal squamous cell carcinoma; no., number; NOS, not otherwise specified, PY, patient-years.

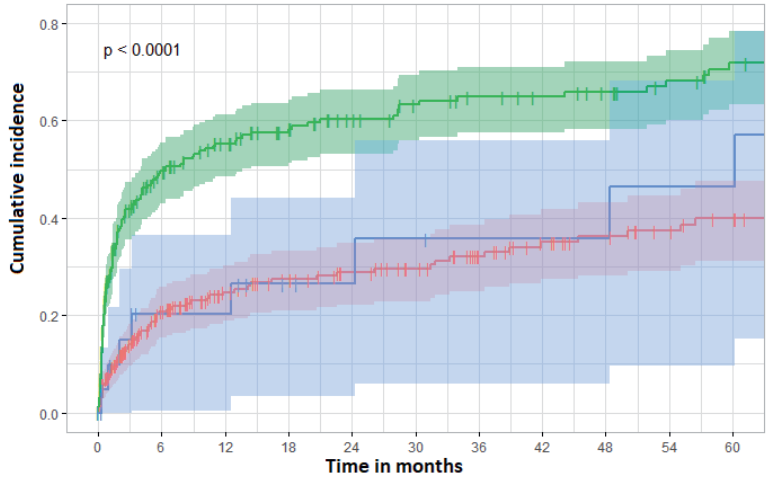
Table 3. Risk factors associated with the detection of ESCC in patients with distinct grades of squamous dysplasia (n=873).

	No. of ESCC/ total cohort	Univariate HR	95% CI	*P*	Adjusted HR	95% CI	*P*
Sex							
Male	139/481	Ref.	-	-	Ref.	-	-
Female	109/392	0.96	0.75-1.24	0.765	0.91	0.71-1.17	0.460
Age (years)	248/873	1.02	1.01-1.03	<0.001	1.02	1.00-1.03	0.009
Year of first dysplasia diagnosis							
1991-2000	50/237	Ref.	-	-	Ref.	-	-
2000-2010	101/296	1.43	1.02-2.00	0.040	1.37	0.98-1.94	0.069
2010-2020	97/340	1.22	0.87-1.72	0.251	1.19	0.83-1.70	0.340
Baseline dysplasia grade							
Mild	15/179	Ref.	-	-	Ref.	-	-
Low grade	13/80	1.40	0.67-2.95	0.373	1.29	0.60-2.75	0.513
Moderate	49/197	2.40	1.35-4.29	0.003	2.23	1.25-3.99	0.007
High grade	24/77	3.64	1.91-6.94	<0.001	2.96	1.52-5.77	0.001
Severe	110/244	5.33	3.10-9.15	<0.001	4.70	2.72-8.11	<0.001
Carcinoma in situ	28/72	4.07	2.17-7.62	<0.001	3.43	1.82-6.49	<0.001
NOS	9/24	2.43	1.06-5.55	0.036	2.34	1.02-5.34	0.045

Results were obtained with univariate and multivariate Cox proportional hazards analyses. Two-side *P*-values <0.05 were considered significant. In multivariate analyses, results were adjusted for sex, age, and grade of baseline dysplasia. For patients with dysplasia NOS, grading of squamous dysplasia was not possible, due to biopsy size or orientation. Data are presented as HR with 95% CI with the detection of ESCC as outcome. CI, confidence interval; ESCC, esophageal squamous cell carcinoma; no., number; HR, hazard ratio; NOS, not otherwise specified; Ref., reference.

Prevalent and incident ESCC

Prevalent ESCC was diagnosed in 181/873 (20.7%) patients and incident ESCC in 67/692 (9.7%) patients (Table 2, Figure 4). Incident ESCC was detected after a median of 23 months (IQR 11-49). After excluding patients with prevalent ESCC, the annual ESCC risk was 2.1%, 5.1%, and 5.2% per patient-year for patients with mild, low grade, and moderate dysplasia (Table 2) with a total of 701.3 patient-years of follow up. The risk for both prevalent and incident ESCC increased with increasing grades of baseline squamous dysplasia (Table 2, Table S3). Multivariable analyses, adjusted for sex and age, showed similar results.



	Number at risk										
Mild-to-moderate dysplasia	456	154	120	106	95	86	74	63	56	50	45
Higher-grade dysplasia	393	104	81	67	55	46	41	38	34	28	22
Dysplasia NOS	24	13	13	9	8	7	6	6	6	5	5
	Cumulative number of events										
Mild-to-moderate dysplasia	0	49	56	60	62	63	66	69	70	71	73
Higher-grade dysplasia	0	128	139	143	147	151	153	153	154	156	159
Dysplasia NOS	0	4	4	5	5	6	6	6	6	7	7

Figure 4. Cumulative incidence of esophageal squamous cell carcinoma in 873 patients with baseline squamous dysplasia. Data is shown for patients with mild-to-moderate dysplasia (n=456), higher-grade dysplasia (n=393) and dysplasia not otherwise specified (n=24). Logrank test between groups: *P*<0.001.

Characteristics of ESCC

Patients diagnosed with ESCC had a mean age at diagnosis of 69.0 years (SD±10.7) and 56.0% was male (characteristics of prevalent and incident ESCC are shown in Table S4). The tumor stage of ESCC was low (0-II) in 48.4% and high (III-IV) in 27.5%. Distant metastases at time of diagnosis were detected in 8.9% of patients. In total, patients with ESCC were treated with ER (14.9%), surgery (35.1%), and chemo-/radiotherapy (47.6%). The median survival after ESCC diagnosis was 25 months (IQR 10-75).

DISCUSSION

Squamous dysplasia is the histological precursor of ESCC and is divided in distinct grades, based on the proportion of squamous epithelium with histopathological abnormalities. In Western countries, the risk of ESCC for these distinct grades of dysplasia is unknown and, consequently, optimal management remains unclear. We performed a nationwide, retrospective study on the risk of ESCC in patients with distinct grades of esophageal squamous dysplasia in the Netherlands. In our study, all patients with squamous dysplasia, including patients with mild, low grade, and moderate dysplasia, had a substantially increased risk of developing ESCC. Therefore, endoscopic surveillance or treatment should be considered for all patients with squamous dysplasia in Western countries.

The currently published studies on squamous dysplasia and the associated risk of ESCC originate from Asian countries.[9-11, 13, 14] These studies report a cumulative 5-year incidence of ESCC ranging from 1% to 24% for patients with mild dysplasia, 5% to 50% for moderate dysplasia and up to 100% for severe dysplasia and CIS.[9-11, 13, 14] In rural areas of China, one-time endoscopic screening and treatment in case of dysplasia resulted in both a decreased incidence and mortality of ESCC in residents aged 40 to 69 years, compared with controls.[18, 19] These findings confirm that in Asian countries, endoscopic surveillance or treatment is warranted for patients with all grades of squamous dysplasia. Unfortunately, comparisons between Asian and Western populations are difficult, caused by the large differences in ESCC incidence between these countries and, therefore, also differences in screening, surveillance, and treatment strategies.[1]

In the current study, we report on prevalent and incident ESCC separately, attempting to distinguish patients with a potentially underlying baseline ESCC, from patients developing ESCC during the follow up. Prevalent ESCC were diagnosed in one fifth of included patients and up to 16% of patients with baseline mild, low grade and moderate dysplasia. A part of the patients with prevalent ESCC potentially had a visible suspicious lesion during endoscopy without histopathological confirmation. In others, the pathology report of

dysplasia may have resulted in an additional endoscopy with ER, during which the diagnosis ESCC was established.

The pathological assessment of esophageal squamous dysplasia can be challenging and may be subject to interobserver variability and sampling bias. To decrease interobserver variability in Western countries, the two-tiered classification into either low grade or high grade dysplasia was introduced in the 5th edition of the WHO classification.[4] In line with the introduction of the two-tiered classification, low grade and high grade dysplasia were diagnosed more frequently in this study during recent years. Nevertheless, we found that both the three-tiered (mild, moderate, and severe dysplasia) and two-tiered classification are currently used in the Netherlands. In line with the recommendation of the WHO, we think that one uniform classification for patients with squamous dysplasia, used by all pathologists in Western countries, would be desirable. Standardized advice for distinct grades of squamous dysplasia with indications for endoscopic surveillance and treatment, will promote exchangeability and comparability of scientific data and may help to improve the outcomes of patients with squamous dysplasia.

Sampling bias, when biopsies do not adequately reflect the grade of dysplasia, can be caused by several endoscopic and histopathological factors. Endoscopic factors include for example the experience of the endoscopist and the number, chosen location, and depth of the biopsies. Histopathological factors include a lack of orientation and presence of other histopathological abnormalities such as active inflammation in case of reflux- or candida esophagitis. The occurrence and clinical relevance of sampling bias is confirmed by previous studies, which reported a discordance of the grade of squamous dysplasia of up to 45% between biopsy and corresponding ER specimen.[20-22] The study of Chen *et al.* (2022) reported on 202 patients with low grade dysplasia in biopsies, of which the corresponding ER specimen showed high grade dysplasia in 33% of patients.[21] These results are in line with the proportion of prevalent ESCC of 20.7% detected in our current study, and emphasize the importance of adequate endoscopic (re-)assessment with representative biopsies and accurate pathological assessment.

This nationwide cohort study is one of the first Western studies reporting on the ESCC risk in patients with squamous dysplasia, but has some inherent limitations. The current study was based on characteristics available in the Palga and NCR databases. The Palga database contains pathology reports from clinical practice. The NCR contains certain characteristics of patients diagnosed with ESCC, but clinical data, including medical history, symptoms of dysphagia and odynophagia, and endoscopy characteristics such as the presence, size, and macroscopic appearance of lesions, are not available. Endoscopic assessment and follow up

or treatment strategies were performed upon clinician's expert opinion and daily clinical practice, and no pathology slides were reassessed. No histopathological follow up was available in a substantial proportion of included patients (i.e. 42% of patients with mild-to-moderate dysplasia and 31% of patients with higher-grade dysplasia), which may have resulted in an underestimation of the risk of ESCC.

In conclusion, all patients with esophageal squamous dysplasia in Western countries, including those with mild, low grade and moderate dysplasia, have a substantial risk of developing ESCC. Consequently, endoscopic surveillance of the esophageal mucosa or ER of dysplasia should be considered for patients with mild-to-moderate dysplasia in Western countries. For patients with high grade dysplasia, severe dysplasia and CIS, adequate endoscopic staging and in case of suspicion for neoplasia, aggressive treatment is required as ESCC is already present in a substantial proportion of patients.

REFERENCES

1. Arnold M, Ferlay J, van Berge Henegouwen MI, et al. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. Gut. 2020;69(9):1564-71.
2. 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;94:138-47.
3. Yokoyama A, Ohmori T, Makuuchi H, et al. Successful screening for early esophageal cancer in alcoholics using endoscopy and mucosa iodine staining. Cancer. 1995;76(6):928-34.
4. World Health O. WHO classification of tumours: digestive system tumours: World Health Organization (WHO); 2019.
5. Savant D, Zhang Q, Yang Z. Squamous neoplasia in the esophagus. Archives of Pathology & Laboratory Medicine. 2021;145(5):554-61.
6. Liu X, Zhang M, Ying S, et al. Genetic alterations in esophageal tissues from squamous dysplasia to carcinoma. Gastroenterology. 2017;153(1):166-77.
7. van de Ven SEM, de Graaf W, Bugter O, et al. Screening for synchronous esophageal second primary tumors in patients with head and neck cancer. Dis Esophagus. 2021.
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(4):1122-30.
9. 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(2):187-92.
10. Li H, Zhang S, Zhou J, et al. Endoscopic surveillance for premalignant esophageal lesions: A community-based multicenter, prospective cohort study. Clinical Gastroenterology and Hepatology. 2022.
11. Dawsey SM, Lewin KJ, Wang GQ, et al. Squamous esophageal histology and subsequent risk of squamous cell carcinoma of the esophagus. A prospective follow-up study from Linxian, China. Cancer. 1994;74(6):1686-92.
12. Liu M, Zhou R, Guo C, et al. Size of Lugol-unstained lesions as a predictor for risk of progression in premalignant lesions of the esophagus. Gastrointestinal endoscopy. 2021;93(5):1065-73. e3.
13. Wei W-Q, Hao C-Q, Guan C-T, et al. Esophageal histological precursor lesions and subsequent 8.5-year cancer risk in a population-based prospective study in China. The American journal of gastroenterology. 2020;115(7):1036.
14. Wen D, Zhang L, Wang X, et al. A 5.5-year surveillance of esophageal and gastric cardia precursors after a population-based screening in China. Journal of gastroenterology and hepatology. 2015;30(12):1720-5.
15. Schlemper RJ, Dawsey SM, Itabashi M, et al. Differences in diagnostic criteria for esophageal squamous cell carcinoma between Japanese and Western pathologists. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2000;88(5):996-1006.
16. Pimentel-Nunes P, Libânio D, Bastiaansen BAJ, et al. Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline–Update 2022. Endoscopy. 2022.
17. Casparie M, Tiebosch A, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Analytical Cellular Pathology. 2007;29(1):19-24.
18. Wei W-Q, Chen Z-F, He Y-T, et al. Long-term follow-up of a community assignment, one-time endoscopic screening study of esophageal cancer in China. Journal of Clinical Oncology. 2015;33(17):1951.
19. Chen R, Liu Y, Song G, et al. Effectiveness of one-time endoscopic screening programme in prevention of upper gastrointestinal cancer in China: a multicentre population-based cohort study. Gut. 2021;70(2):251-60.
20. Park YJ, Kim GH, Park DY, et al. Histopathologic discrepancies between endoscopic forceps biopsy and endoscopic resection specimens in superficial esophageal squamous neoplasms. Journal of Gastroenterology and Hepatology. 2019;34(6):1058-65.
21. Chen H, Zhou XY, Li S, et al. Endoscopic detection of esophageal low-grade squamous dysplasia: How to predict pathologic upgrades before treatment? J Dig Dis. 2022;23(4):209-19.
22. Yang L, Jin H, Xie XL, et al. Endoscopic resections for superficial esophageal squamous cell epithelial neoplasia: focus on histological discrepancies between biopsy and resected specimens. BMC Gastroenterol. 2021;21(1):114.

SUPPLEMENTARY

Table S1. Diagnostic codes of the Palga search strategy.

Item	Specification (diagnostic code)
Location	Esophagus (T62)
Year search	1991-2020
Sample type	Tissue (T)
Morphology	Dysplasia (M7400) Carcinoma in situ (M80102) Atypia (M697) NOT all malignancies except carcinoma in situ (*5*) NOT Barrett (T62310 M73330) NOT Intestinal metaplasia (M73320)

Table S2. Risk factors associated with the detection of ESCC in patients with distinct grades of squamous dysplasia undergoing endoscopic re-assessment with biopsies (n=560).

	No. of ESCC/ total cohort	Adjusted HR	95% CI	*P*
Sex				
Male	134/310	Ref.	-	
Female	107/250	0.95	0.73-1.23	0.690
Age (years)	241/560	1.01	1.00-1.03	0.021
Baseline grade of dysplasia				
Mild dysplasia	14/78	Ref.	-	-
Low grade dysplasia	13/57	1.13	0.52-2.46	0.754
Moderate dysplasia	48/125	1.92	1.05-3.52	0.034
High grade dysplasia	24/51	2.34	1.17-4.67	0.016
Severe dysplasia	106/179	3.63	2.03-6.49	<0.001
Carcinoma in situ	27/48	2.76	1.41-5.43	0.003
Dysplasia NOS	9/22	2.63	1.13-6.14	0.025
Year of first dysplasia diagnosis				
1991-2000	49/133	Ref.	-	-
2000-2010	98/188	1.28	0.90-1.81	0.169
2010-2020	94/239	1.18	0.82-1.71	0.374
Primary strategy				
Endoscopy with biopsy	209/480	Ref.	-	-
Treatment for dysplasia[1]	32/80	0.67	0.45-0.994	0.047
Time to first endoscopy with histopathology				
0-3 months	193/379	Ref.	-	-
4-6 months	21/81	0.40	0.25-0.63	<0.001
6-12 months	9/36	0.35	0.18-0.70	0.003
>12 months	18/64	0.37	0.22-0.61	<0.001

Results were obtained with multivariate Cox proportional hazards analyses and adjusted for sex, age, grade of baseline dysplasia, year of first dysplasia diagnosis, primary treatment strategy and time to first endoscopic re-assessment. Data are presented as HR with 95% CI with the detection of ESCC as outcome. [1]Treatments for squamous dysplasia consisted of endoscopic resection (n=50), surgery (n=18) and chemotherapy and/or radiotherapy (n=12). CI, confidence interval; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; Ref., reference.

Table S3. Risk factors associated with the detection of prevalent and incident ESCC in patients with distinct grades of squamous dysplasia.

	Total cohort	Prevalent ESCC (181/873)				Incident ESCC (67/692)			
		n	Adjusted HR	95% CI	*P*	n	Adjusted HR	95% CI	*P*
Sex									
Male	481	104	Ref.	-		35	Ref.	-	-
Female	392	77	0.88	0.66-1.18	0.395	32	1.03	0.63-1.67	0.915
Age (years)	873	181	1.01	1.00-1.03	0.043	67	1.02	1.00-1.04	0.119
Grade of baseline dysplasia									
Mild dysplasia	179	9	Ref.	-	-	6	Ref.	-	-
Low grade dysplasia	80	8	1.14	0.44-2.96	0.788	5	2.12	0.64-6.99	0.217
Moderate dysplasia	197	32	2.31	1.10-4.84	0.027	17	2.46	0.97-6.25	0.059
High grade dysplasia	77	18	3.37	1.50-7.60	0.003	6	2.65	0.83-8.47	0.100
Severe dysplasia	244	92	5.67	2.85-11.29	<0.001	18	2.98	1.16-7.61	0.023
Carcinoma in situ	72	18	3.55	1.59-7.93	0.002	10	3.98	1.43-11.11	0.008
Dysplasia NOS	24	4	1.72	0.53-5.58	0.368	5	3.54	1.08-11.65	0.037

Results were obtained with multivariate Cox proportional hazards analyses and adjusted for sex, age and grade of baseline dysplasia. ESCC were divided in prevalent (≤ 6 months) and incident (>6 months) after diagnosis of baseline squamous dysplasia. Data are presented as HR with 95% CI with the detection of prevalent and incident ESCC as outcome. CI, confidence interval; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; Ref., reference.

Table S4. Characteristics of patients with baseline squamous dysplasia, diagnosed with prevalent and incident esophageal squamous cell carcinoma (n=248).

Characteristics	Prevalent ESCC n=181	Incident ESCC n=67
Sex, male	104 (57.5%)	35 (52.2%)
Median age, years	69.0 (SD ±9.4)	67.5 (SD ±13.5)
Tumor stage		
0	4 (2.2%)	12 (17.9%)
1	53 (29.3%)	17 (25.4%)
2	25 (13.8%)	9 (13.4%)
3	42 (23.2%)	10 (14.9%)
4	14 (7.7%)	2 (3.0%)
Missing	43 (23.8%)	17 (25.4%)
Distant metastasis at diagnosis	17 (9.4%)	5 (7.5%)
Treatment for ESCC		
ER	18 (9.9%)	6 (9.0%)
Surgery	39 (21.5%)	12 (17.9%)
Chemotherapy	5 (2.8%)	0
Radiotherapy	34 (18.8%)	9 (13.4%)
Chemoradiotherapy	27 (14.9%)	5 (7.5%)
Neoadjuvant chemoradiotherapy + surgery	17 (9.4%)	3 (4.5%)
Neoadjuvant chemotherapy + surgery	5 (2.8%)	2 (3.0%)
ER + chemoradiotherapy	2 (1.1%)	4 (6.0%)
No treatment	20 (11.0%)	22 (32.8%)
Other [1]	8 (4.4%)	1 (1.5%)
Missing	6 (3.3%)	3 (4.5%)
Median survival after ESCC diagnosis (months)	25 (IQR 11-73)	27 (IQR 9-91)
Vital status (31-01-2021)		
Alive	48 (26.5%)	15 (22.4%)
Death	120 (66.3%)	49 (73.1%)
Missing	13 (7.2%)	3 (4.5%)

Data are presented as mean with standard deviation or n (%), according to the nature of the data. ESCC were divided in prevalent (≤ 6 months) and incident (>6 months) after diagnosis of baseline squamous dysplasia. The Tumor, Node, Metastasis (TNM) stage according to the 5th (2000–2002), 6th (2003–2009), 7th (2010–2016) and 8th (2017-2022) stage classification were collected from the Netherlands Cancer Registry, according the year of ESCC diagnosis. [1]Other treatments consisted of ER + neoadjuvant chemoradiotherapy + surgery (n=3), ER + surgery (n=4) and surgery + radiotherapy (n=2). ER, endoscopic resection; ESCC, esophageal squamous cell carcinoma; SD, standard deviation.

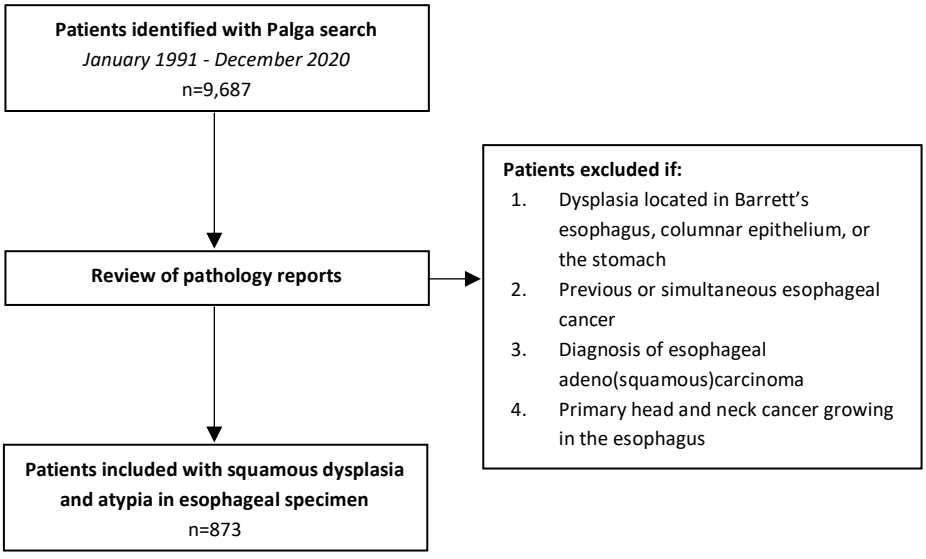


Figure S1. Flowchart of inclusion of patients with esophageal squamous dysplasia (n=873). Palga, Dutch nationwide pathology databank.

Part III

Second primary tumors in the aerodigestive tract

Chapter 4

Prevalence of lung tumors in patients with esophageal squamous cell carcinoma and vice versa: A systematic review and meta-analysis

Laurelle van Tilburg, Steffi E.M. van de Ven, Manon C.W. Spaander, Laurens A. van Kleef, Robin Cornelissen, Marco J. Bruno, Arjun D. Koch

Journal of Cancer Research and Clinical Oncology. 2022

ABSTRACT

Background: Recent reports suggest an increased prevalence of lung second primary tumors (SPTs) in esophageal squamous cell carcinoma (ESCC) patients and vice versa. However, the exact prevalence of SPTs remains unclear and screening for these SPTs is currently not routinely performed in Western countries. We aimed to report on the prevalence of lung SPTs in patients with ESCC and esophageal SPTs in patients with lung cancer (LC).

Methods: Databases were searched until 25 March 2021 for studies reporting the prevalence of lung SPTs in ESCC or vice versa. Pooled prevalences with 95% confidence intervals (CI) of SPTs were calculated with inverse variance, random-effects models and Clopper-Pearson.

Results: 19 studies in ESCC patients and 20 studies in LC patients were included. The pooled prevalence of lung SPTs in patients with ESCC was 1.8% (95% CI 1.4-2.3). For esophageal SPTs in LC patients, the pooled prevalence was 0.2% (95% CI 0.1-0.4). The prevalence of lung SPTs in ESCC patients was significantly higher in patients treated curatively compared to studies also including palliative patients (median 2.5% versus 1.3%). This difference was consistent for the esophageal SPT prevalence in LC patients (treated curatively median 1.3% versus 0.1% for all treatments). Over 50% of the detected SPTs were squamous cell carcinomas and were diagnosed metachronously.

Conclusion: Patients with ESCC and LC have an increased risk of developing SPTs in the lungs and esophagus. However, the relatively low SPT prevalence rates do not justify screening in these patients. Further research should focus on risk stratification to identify subgroups of patients at highest risk of SPT development.

INTRODUCTION

Over half a million esophageal cancers and two million lung cancers (LC) were diagnosed worldwide in 2018.[1-3] The major risk factor for esophageal squamous cell carcinoma (ESCC) and LC is tobacco smoking.[4] The prognosis of both cancers remains poor, although the 5-year survival rate has improved to approximately 22% for ESCC in 2018 and 23% for LC in 2020.[5, 6] The poor survival rates of patients with ESCC and LC could partially be explained by the occurrence of second primary tumors (SPTs).[3, 7, 8]

For patients with ESCC, the occurrence of SPTs is frequently explained by the theory of field cancerization.[9] This theory states that chronic exposure of the epithelium surrounding the primary tumor to carcinogens, especially tobacco, can lead to (pre)malignant changes of the epithelium. Most SPTs in patients with ESCC are located in the upper aero digestive tract, especially in the head and neck region and lungs.[7]

Large incidence differences for both ESCC and LC exist worldwide, with high incidence rates of both cancers reported in Eastern Asia.[2] However, little is known regarding the prevalence of lung SPTs and esophageal SPTs in this patient population, especially in non-Asian countries. Moreover, the potential yield and benefit of screening for SPTs in patients with ESCC and LC remains unclear.

Nowadays, screening for lung SPTs in patients with ESCC and esophageal SPTs in patients with LC is not routinely implemented in Western countries.[10-12] According to current Asian guidelines, a trachea-bronchoscopy to detect SPTs is advised during the diagnostic workup in all patients with ESCC with chronic alcohol and tobacco consumption.[13, 14] The Dutch guidelines suggest screening for lung SPTs in ESCC patients may be considered and does not mention screening for esophageal SPTs in patients with LC.[11]

The primary objective of this systematic review and meta-analysis is to investigate the prevalence of lung SPTs in patients with ESCC and the prevalence of esophageal SPTs in patients with LC. The secondary objectives are to assess the tumor stage of SPTs and time interval between the primary cancer diagnosis and detection of SPTs.

METHODS

Search strategy

The databases PubMed, Embase, Medline, Cochrane Central, Google Scholar, and Web of Science were searched by two independent investigators (L.T. and S.V.) until 25 March 2021. The systematic search contained keywords for second/multiple primary tumor, esophageal cancer and lung cancer. No time restrictions were set. The search was performed in collaboration with the medical library of the Erasmus University Rotterdam, the Netherlands. The complete search strategy is available in Appendix 1. In addition, reference lists of included studies were searched to identify additional relevant studies.

Study inclusion

Studies that reported the proportion of lung SPTs (of all histological types) in patients with ESCC or the proportion of esophageal SPTs (both ESCC and esophageal adenocarcinoma) in patients with LC were included. Studies without original data, case reports, non-human and non-English studies were excluded. Two independent investigators (L.T. and S.V.) screened titles and abstracts followed by full texts of potentially eligible articles identified by the search strategy. In case of any disagreement, a consensus was reached through discussion (with L.T., S.V., and A.K.). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart was used to create an overview of the data screening process.[15]

Data extraction and quality assessment

The extracted information from each study included: study characteristics (author, year of publication, study country, design, and setting) and patient characteristics (gender, number of patients with ESCC and lung SPTs, number of patients with LC and esophageal SPTs, time interval between the primary cancer diagnosis and detection of SPTs, tumor stage, histopathology, and treatment). The methodological quality of each study was assessed with the Newcastle-Ottawa scale for quality assessment for cohort studies.[16] Funnel plots and Egger tests were used to assess the risk of publication bias.[17]

Outcomes and definitions

The primary outcomes were 1) the pooled prevalence of lung SPTs in patients with ESCC and 2) the pooled prevalence of esophageal SPTs in patients with LC. Secondary outcomes included the tumor stage of SPTs and the time from the diagnosis of the primary cancer to the detection of an SPT. The criteria for SPTs from Warren and Gates were used; an SPT must be 1) a malignant tumor based on histopathological assessment, 2) separated from

the primary cancer by normal mucosa, and 3) the possibility of the SPT being a recurrence or metastasis from the primary cancer must be ruled out.[18] The time to the detection of SPTs was classified as a tumor in the history before the diagnosis of ESCC or LC and synchronous and metachronous SPTs.[19] Synchronous SPTs were defined as the detection of an SPT within 6 months of the diagnosis of the primary tumor (this may be referred to as simultaneous). Metachronous SPTs were defined as the detection of an SPT at least 6 months after the diagnosis of the primary tumor.

Data analysis

For the meta-analysis, the SPT prevalence was calculated for each study as the number of SPTs divided by the number of the patient population in that specific study. The heterogeneity between included studies was assessed using the inconsistency index (I^2). The incidence of both ESCC and LC differs strongly worldwide, with the highest incidence rates of both cancers reported in Eastern Asia.[2] Therefore, the random-effects model with inverse variance was used to calculate the pooled prevalence and 95% confidence intervals (CI) were calculated with Clopper-Pearson. Excessive influence of individual studies on the pooled prevalence was investigated in sensitivity analyses. Standardized incidence ratios (SIRs) of the included studies were extracted for a comparison with the risk in the general population to develop lung cancer or esophageal cancer. Data were presented as counts with percentages. Analyses were performed in R version 4.1.1 (The R Foundation Statistical Computing, Vienna, Austria) with *meta* version 4.18-2 and *metafor* version 3.0-2. All tests were performed two-sided and $P < 0.05$ was considered significant.

RESULTS

Study selection and quality assessment

The literature search identified 13,594 records (shown in Figure 1). After removing duplicates, 7,782 articles were assessed for titles and abstracts, of which 171 articles were potentially eligible. After full-text reviewing, 39 studies were included in this systematic review and meta-analysis. The quality assessment according to the Newcastle-Ottawa Scale of included studies is shown in Table S1.

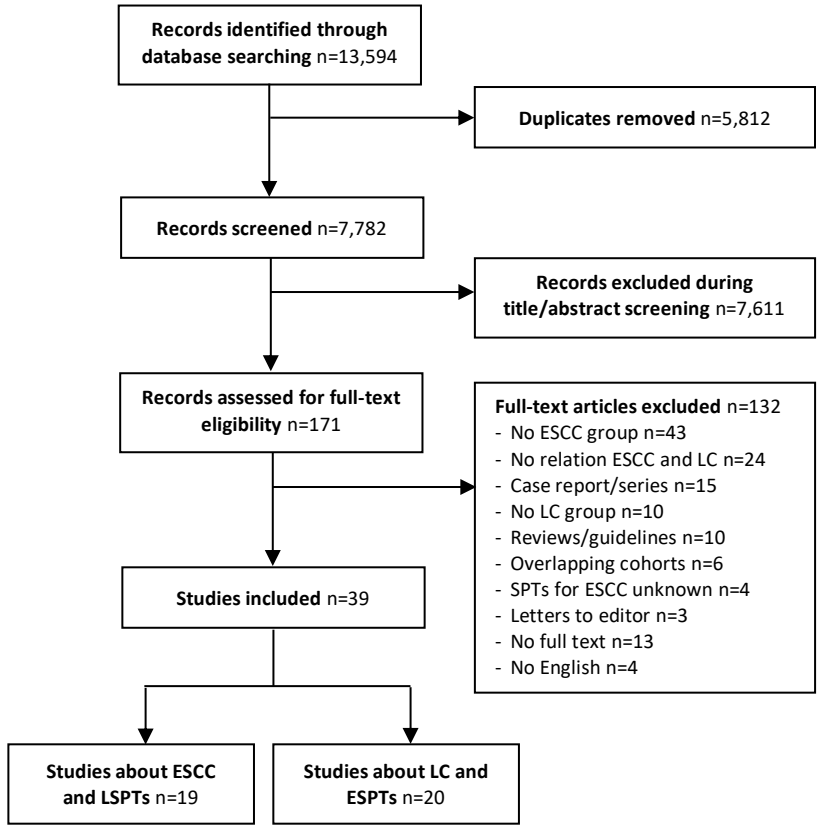


Figure 1. Flowchart of study inclusion. ESCC, esophageal squamous cell carcinoma; LC, lung cancer; SPT, second primary tumor.

Study characteristics

The 39 included studies consisted of 19 studies performed in patients with ESCC (Table S2)[7, 20-37] and 20 studies performed in patients with LC (Table S3).[38-57] The studies comprised a total of 62,924 patients with ESCC (median 601; range 185-30,121) and 648,315 patients with LC (median 4,111; range 32-258,559). Twenty-two studies were performed in Asian countries[20-30, 43-47, 49, 51-54, 56], ten studies in Europe[7, 31, 32, 40-42, 48, 50, 55, 57] and seven studies in other countries.[33-39] Most studies were performed retrospectively.[7, 22-55] Four studies were performed prospectively[20, 21, 56, 57], of which two were screening studies to detect SPTs.[21, 56] The funnel plots and Egger tests showed no proof of publication bias for the prevalence of lung SPTs in patients with ESCC ($P = 0.11$) and the prevalence of esophageal SPTs in patients with LC ($P = 0.16$) (Figure S1).

Prevalence of lung SPTs

The pooled prevalence of lung SPTs in patients with ESCC was 1.8% (95% CI 1.4-2.3) with a high level of heterogeneity (I^2 = 88%, P < 0.01) (Figure 2). In total, 953 lung SPTs were detected in 62,924 patients with ESCC. The pooled prevalence of lung SPTs was significantly higher among ESCC patients treated with curative intent (2.5%; 95% CI 2.0-3.2), compared to studies that also included palliative ESCC patients (1.3%; 95% CI 1.0-1.9) (Figure 3). Sub analyses with only patients treated with palliative care were not possible because lung SPT rates specifically for palliative ESCC patients were not reported in the included studies. The lung SPT prevalence was suggestively higher in ESCC patients from Asian countries (2.1%, 95% CI 1.6-2.8) compared to non-Asian countries (1.5%, 95% CI 1.0-2.1) (Figure S2) and for studies published in the last decade (2010-2021: 2.3%; 95% CI 1.8-3.0) compared to previous decades (before 2000: 1.0%, 95% CI 0.4-2.3; 2000-2010: 1.7%, 95% CI 1.0-2.8) (Figure S3). However, no statistically significant differences could be demonstrated.

Characteristics and time to diagnosis of lung SPTs

Most patients with ESCC that developed lung SPTs were male (98.3%).[24, 32, 35] The tumor stage of lung SPTs was stage 0-I (n=20; 43.5%), stage II-III (n=9; 19.6%), and stage IV (n=17; 37.0%) in three retrospective studies.[25, 32, 35] In one screening study, 6/8 lung SPTs were detected in asymptomatic patients of which five lung SPTs were detected in early and curable stages.[21] Based on four studies, the histology of the lung SPTs was squamous cell carcinoma in 38% to 100% of the lung SPTs per study (total 51/69), adenocarcinoma in 10% to 56% (total 13/69) small cell carcinoma in 0% to 6% (total 3/69) and adenosquamous carcinoma in 0% to 11% (1/69).[21, 24, 32, 36] The time to detection of lung SPTs was reported in 16 studies (Table 1).[7, 20, 22, 24, 26-29, 31, 32, 34-37] The study of Fitzpatrick *et al.* combined lung tumors before ESCC diagnosis with synchronous lung SPTs.[37] Natsugoe *et al.* reported lung tumors before ESCC diagnosis and metachronous lung SPTs together.[27] The studies of Yamaguchi *et al.* and Motoyama *et al.* only reported metachronous LSTPs.[21, 25] Among 12 studies, comprising 44,973 patients with ESCC, lung SPTs were detected synchronously in 198/675 patients and metachronously in 225/675 patients. In 11 studies, 252/456 patients with ESCC had a history of lung cancer.[20, 24, 28, 29, 31, 32, 35-37]

Characteristics of ESCC

Twelve studies reported the tumor stage of ESCC.[7, 20, 22-30, 33] However, only the study of Lee *et al.* reported the numbers of lung SPTs for each ESCC tumor stage.[24] In this study, 6 lung SPTs were detected in 172 patients with ESCC stage 0-I, 3 lung SPTs in 136 patients with ESCC stage II, 4 lung SPTs in 118 patients with ESCC stage III and 1 lung SPT in 5 patients with

ESCC stage IV.[24] In the included studies, treatments for patients with ESCC were surgery (n=13,915), chemo- or radiotherapy (n=15,071) and endoscopic resection (n=275).[7, 20-31, 33-36] Nine studies only included patients with ESCC treated with curative intent.[21-29] The follow up time of patients with ESCC was not reported in eight studies and median shorter than 1.5 years after ESCC diagnosis in two studies.[22, 28-30, 32, 33, 35, 36]

Prevalence of esophageal SPTs

The pooled prevalence of esophageal SPTs in patients with LC was 0.2% (95% CI 0.1-0.4) with significant heterogeneity (I^2 = 97%, P < 0.01) (Figure 4). In total, 575 esophageal SPTs occurred in 648,315 patients. The prevalence of esophageal SPTs was significantly higher among patients with LC treated with curative intent (1.3%, 95% CI 0.4-3.9), compared to studies that also included patients with LC treated with palliative intent (0.1%, 95% CI 0.1-0.2) (Figure 5). The esophageal SPT prevalence in LC patients was significantly higher in Asian countries (0.5%; 95% CI 0.2-1.5), compared to non-Asian countries (0.1%; 95% CI 0.1-0.1) (Figure S4). No trends were observed in esophageal SPT prevalence for studies published between the last decade and previous decades (Figure S5). Sensitivity analyses did not reveal excessive influence of individual studies on the pooled prevalence (Figure S6).

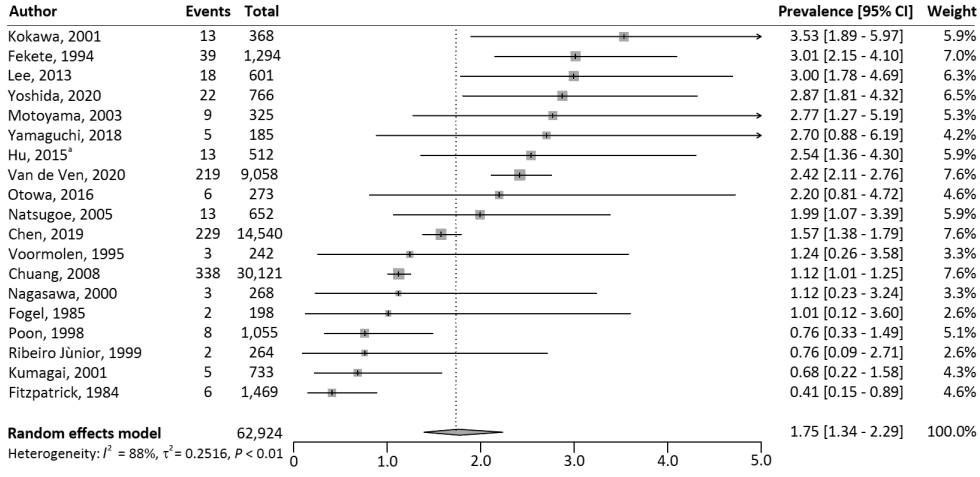


Figure 2. Overview of the prevalence of lung SPTs in patients with ESCC. CI, confidence interval; ESCC, esophageal squamous cell carcinoma; I^2, inconsistency index; τ^2, tau-squared represents the extent of variation among the effects observed in different studies; SPT, second primary tumor.[a] Hu *et al.* excluded all lung squamous cell carcinoma (n=11), which occurred within the first 5 years after the diagnosis of ESCC, as potential lung SPTs.

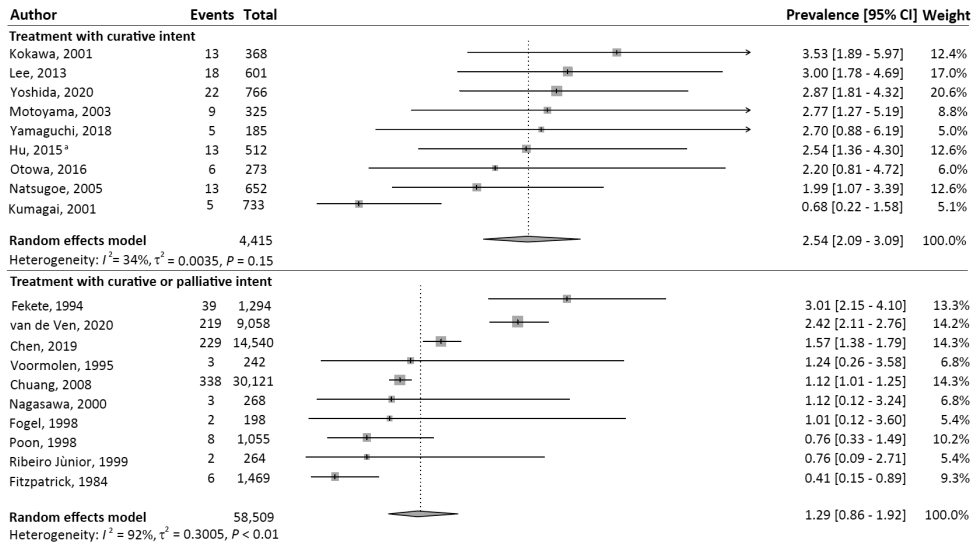


Figure 3. Overview of the prevalence of lung SPTs in patients with ESCC for different treatment intents. CI, confidence interval; ESCC, esophageal squamous cell carcinoma; I^2, inconsistency index; τ^2, tau-squared represents the extent of variation among the effects observed in different studies; SPT, second primary tumor. [a] Hu *et al.* excluded all lung squamous cell carcinoma (n=11), which occurred within the first 5 years after the diagnosis of ESCC, as potential lung SPTs.

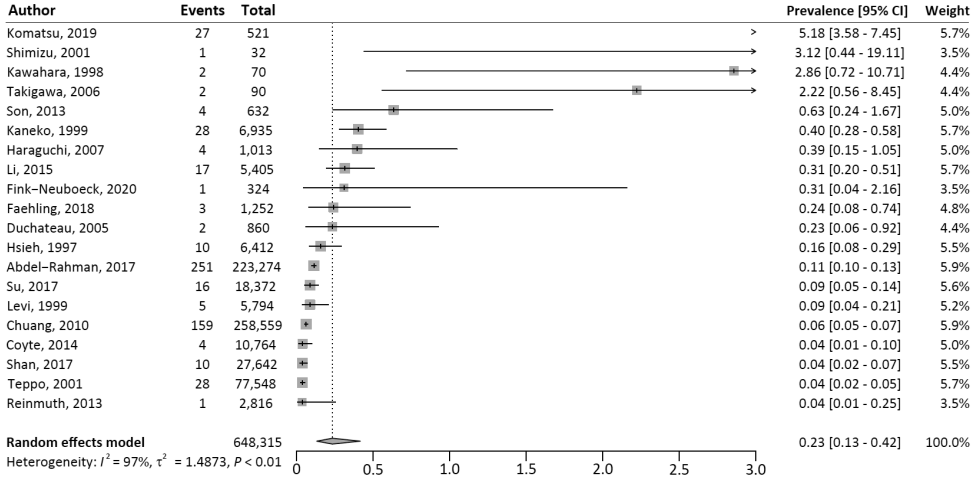


Figure 4. Overview of the prevalence of esophageal SPTs in patients with LC. CI, confidence interval; LC, lung cancer; I^2, inconsistency index; τ^2, tau-squared represents the extent of variation among the effects observed in different studies; SPT, second primary tumor.

Table 1. Follow up time to the detection of lung second primary tumors in patients with ESCC.

Author (year) [ref]	Total lung SPTs, n	History of Lung cancer, n (%)	Synchronous lung SPTs, n (%)	Metachronous lung SPTs, n (%)	Time from LC in history to ESCC	Time to detection of metachronous lung SPTs
Van de Ven *et al*. (2020)[7]	219	NR	123 (56.2)	96 (43.8)	NR	Median 3.2 year (IQR 1.9-4.5)
Yoshida *et al*. (2020)[20]	22	4 (18.2)	2 (9.1)	16 (72.7)	NR	NR
Yamaguchi *et al*. (2018)[21]	5	NR	NR	5 (100.0)	NR	NR
Otowa *et al*. (2016)[22]	6	4 (66.7)	2 (33.3)	0	NR	NR
Lee *et al*. (2013)[23]	18	1 (5.6)	9 (50.0)	8 (44.4)	NR	NR
Chuang *et al*. (2008)[24]	338	226 (66.9)	30 (26.8)	82 (73.2)	<12 months: n=62 1-4 years: n=83 ≥5 years: n=81	6-11 months: n=6 1-4 years: n=43 ≥5 years: n=33
Motoyama *et al*. (2003)[25]	9	NR	NR	9 (100.0)	NR	Reported for n=5: 12, 14, 20, 23, 43 and 112 months
Kokawa *et al*. (2001)[26]	13	2 (15.4)	4 (30.8)	7 (53.8)	NR	Mean 23 months (sd 10.4)
Kumagai *et al*. (2001)[27]	5	1 (20.0)	3 (60.0)	1 (20.0)	NR	NR
Ribeiro Jùnior (1999)[28]	2	1 (50.0)	0	1 (50.0)	2 years	6 year
Poon *et al*. (1998)[29]	8	4 (50.0)	2 (25.0)	2 (25.0)	NR	NR
Voormolen *et al*. (1995)[30]	3	1 (33.3)	1 (33.3)	1 (33.3)	NR	NR
Fekete *et al*. (1995)[31]	39	7 (17.9)	22 (56.4)	10 (25.6)	Mean 46 months (range 18-77)[1]	
Fogel *et al*. (1985)[32]	2	1 (50.0)	0	1 (50.0)	84 months	21 months
Total	**675**	**252**	**198**	**239**		

ESCC, esophageal squamous cell carcinoma; IQR, interquartile range; NR, not reported; sd, standard deviation; SPT, second primary tumor. [1]Time interval between the diagnosis of ESCC and the diagnosis of LC.

Table 2. Follow up time to the detection of esophageal SPTs in patients with lung cancer.

Author (year) [ref]	Total esophageal SPTs, n	History of esophageal cancer, n (%)	Synchronous esophageal SPTs, n (%)	Metachronous esophageal SPTs, n (%)
Faehling *et al.* (2018)[42]	3	3 (100.0)	0	NR
Abdel-Rahman *et al.* (2017)[38]	251[a]	NR	50 (20.1)[b]	199 (79.9)
Shan *et al.* (2017)[51]	10	10 (100.0)	0	NR
Su *et al.* (2017)[53]	16	NR	NR	16 (100.0)
Son *et al.* (2013)[52]	4	1 (25.0)	0	3 (75.0)
Haraguchi *et al.* (2007)[43]	4	NR	3 (75.0)	1 (25.0)
Kaneko *et al.* (1999)[45]	28	NR	28 (100.0)	NR
Kawahara *et al.* (1998)[46]	2	NR	NR	2 (100.0)
Hsieh *et al.* (1997)[44]	10	2 (20.0)	6 (60.0)	2 (20.0)
Total	**328**	**16**	**87**	**223**

SPT, second primary tumor. [a] The time to detection was unknown in two esophageal SPTs. [b] Synchronous esophageal SPTs were defined as esophageal cancer occurring within 1 year of diagnosis of lung cancer

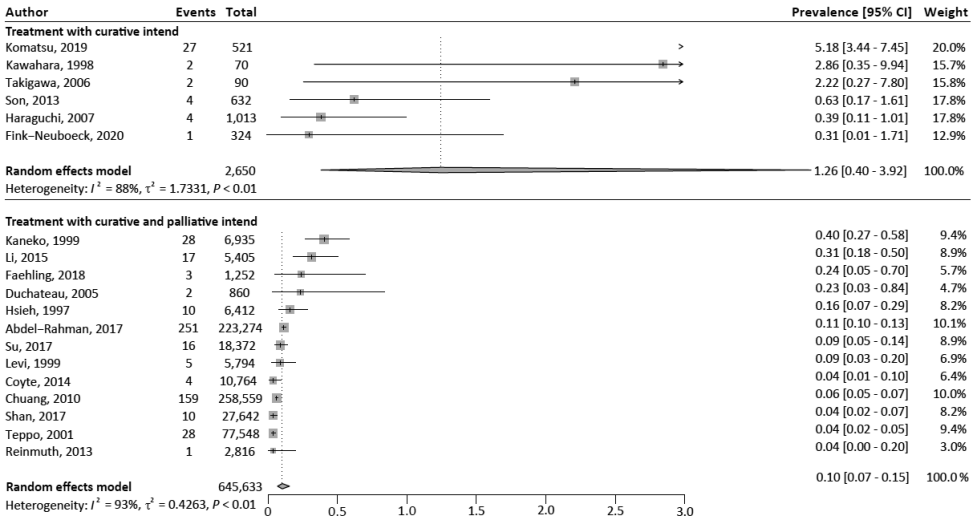


Figure 5. Overview of the prevalence of esophageal SPTs in patients with LC for different treatment intents. CI, confidence interval; LC, lung cancer; I^2, inconsistency index; τ^2, tau-squared represents the extent of variation among the effects observed in different studies; SPT, second primary tumor.

Characteristics and time to diagnosis of esophageal SPTs

Based on six studies, 79.3% of the patients with LC that developed esophageal SPTs were male.[38, 39, 43, 46, 53, 55, 56] The study of Shimizu *et al.* only included male veterans.[56] The tumor stage of esophageal SPTs was known in three studies[38, 56, 57]; the esophageal SPTs (n=97) detected in the study of Abdel-Rahman were stage I in 39.2%, stage II in 23.7%, stage III in 12.3%, and stage IV in 24.7%.[38] The screening study of Shimizu performed esophageal screening with lugol's chromoendoscopy in 32 patients with LC and detected one early stage esophageal SPT. [56] In four studies, the histology of esophageal SPTs was squamous cell carcinoma 59% to 100% of the esophageal SPTs per study (164/267 in total) and adenocarcinoma in 25% to 31% of esophageal SPTs (78/267 in total).[38, 44, 46, 52] The time to detect an SPT was noted in 13 studies. Two studies combined history of EC with metachronous esophageal SPTs [49, 57] and another two studies reported on a history of EC and subsequent esophageal SPTs.[40, 41] The remaining nine studies reported 87 esophageal SPTs that were detected synchronously and 223 esophageal SPTs metachronously (Table 2).[38, 40-44, 49, 51, 52]

Characteristics of LC

The tumor stage of LC was reported in five studies[38, 42, 50, 54, 57]. However, none of these studies reported the number of esophageal SPTs for each LC tumor stage. In six studies, only patients with LC treated with curative intent were included.[43, 47, 52, 54, 56, 57] Reported treatments for LC were surgery (n=61,356) and chemo- or radiotherapy (n=108,961).

Increased standardized incidence ratios compared to general population

Table 3 shows the studies that reported SIRs for the risk of SPTs, compared to the risk of esophageal or LC in the general population.[7, 23, 33, 34, 38, 39, 48, 53, 55] In all four studies in ESCC patients, a significantly increased risk for lung SPTs was reported compared to the general population.[7, 23, 33, 34] In five studies performed in patients with LC, SIRs ranging from 1.45 to 2.40 were reported. The study of Abdel-Rahman *et al.* (2017)[38] reported a significantly increased risk for esophageal SPTs in patients with LC, whereas the smaller studies of Su *et al.* (2017)[53] and Levi *et al.* (1999) did not.[48]

Table 3. Standardized incidence ratios (SIRs) for lung SPTs and esophageal SPTs.

	Author (year)[ref]	Observed (n)	Expected (n)	SIR (95% CI) Total	SIR (95% CI) Males	SIR (95% CI) Females	SIR (95% CI) Time frames
Lung SPTs in ESCC	Van de Ven *et al*. (2020)[7]	123	19	6.42 (5.02-8.06[b])	5.35 (3.90-7.14[b])	9.48 (6.29-13.66[b])	NR
	Chen *et al*. (2019)[36]	229	63	3.63 (3.17–4.13)	NR	NR	NR
	Hu *et al.* (2015)[a 33]	13	5	2.79 (1.60-4.87)	NR	NR	NR
	Chuang *et al*. (2008)[24]	112	72	1.55 (1.28-1.87)	NR	NR	<6mo: 1.47 (0.99-2.10) 6-11mo: 0.60 (0.22-1.31) 1-4year: 1.98 (1.43-2.67) ≥5year: 1.64 (1.13-2.31)
Esophageal SPTs in LC	Abdel-Rahman *et al.* (2017)[38]	251	105	2.40 (1.62-3.43)	RT: 3.60 (2.77-4.61) No RT: 2.05 (1.65-2.53)	RT 5.52 (3.50-8.28) No RT: NR	1-5 year 3.09 (1.85-4.82) 5-9 year: 2.13 (0.92-4.19) ≥10 year: 1.17 (0.24-3.42)
	Su *et al*. (2017)[53]	16	11.05	1.45 (0.83–2.35)	1.55 (0.89-2.52)	0.00 (0.00-4.90)	NR
	Teppo *et al*. (2001)[55]	28	NR	NR	1.23 (0.80-1.79)	0.93 (0.11-3.35)	NR
	Chuang *et al*. (2010)[39]	159	NR	NR	SCC 1.78 (1.44-2.18) SCLC 1.46 (0.75-2.55) Adeno 1.91 (1.26-3.09)	SCC 3.31 (1.81-5.56) SCLC 3.30 (1.21-7.18) Adeno 1.72 (0.69-3.55)	NR
	Levi *et al*. (1999)[48]	5	2.8	1.8 (0.6-4.4)	NR	NR	NR

CI, confidence interval; ESCC, esophageal squamous cell carcinoma; LC, lung cancer; RT, radiotherapy; SIR, standardized incidence ratio; SPT, second primary tumor; NR, not reported. [a] Hu *et al*. excluded all lung squamous cell carcinoma (n=11), which occurred within the first 5 years after the diagnosis of ESCC, as potential lung SPTs. [b] 99% confidence interval.

DISCUSSION

To the best of our knowledge, this is the first systematic review reporting on the prevalence of SPTs in the esophagus and lungs in patients with ESCC and LC. We found a pooled prevalence of lung SPTs of 1.8% in patients with ESCC and a prevalence of esophageal SPTs of 0.2% in patients with LC. More than 50% of the detected SPTs were squamous cell carcinomas and were diagnosed metachronously.

The prevalence rates of SPTs in patients with ESCC and LC in this meta-analysis are most likely an underestimation of the actual prevalence of lung SPTs in patients with ESCC and vice versa for the following reasons. First, the overall survival rates of patients with ESCC and LC remain poor, although they have increased during the recent decades.[3, 5] In 23 of 39 studies, patients treated with palliative intent were also included, while these patients are known to have a median survival of 22 weeks for ESCC and 20 weeks for LC.[3, 5] This short life span after the diagnosis of the primary tumor limits the risk for SPT development, while patients treated with curative intent are known to have better survival rates and, therefore, the cumulative risk of SPT development increases over time. This survival bias is also supported by our finding that patients treated with curative intent are significantly more at risk of developing lung SPTs and esophageal SPTs than patients who received palliative care. One can hypothesize that the cumulative SPT risks increase in the future, if treatment and survival rates of patients with ESCC and LC may continue to rise.

Second, we found a higher prevalence of lung SPTs in patients with ESCC than the prevalence of esophageal SPTs in patients with LC. This difference could be partly explained by the differential use of the positron emission tomography/computed tomography (PET/CT) scan, which is nowadays part of the standard diagnostic work-up up of ESCC and LC to detect metastasis.[10, 11] Contrary to the high sensitivity of the PET/CT for the detection of early LC, the sensitivity of the PET/CT for the detection of early-stage esophageal cancers is only 38% and is inferior to endoscopic screening for esophageal SPTs.[10, 58] Presumably, most esophageal SPTs in patients with LC remained undetected until they reach symptomatic advanced stages, which often cannot be treated with a curative intent. If screening for esophageal SPTs for specific subgroups of patients with LC would ever be considered, an upper gastrointestinal endoscopy would be the examination of choice.

Third, almost all included studies were performed retrospectively, which hampers accurate differentiation between lung SPTs and lung metastases of primary ESCC. This difficulty resulted in conservative definitions of lung SPTs, e.g. one study choose to exclude all lung squamous cell carcinoma detected within the first 5 years after the diagnosis of ESCC as

potential SPTs[23] and another only included squamous cell lung carcinoma as lung SPTs when the tumors showed clear histologic differences.[21]

In our systematic review, nine included studies reported standardized incidence ratios (SIRs) to develop lung SPTs or esophageal SPTs. Most of these studies reported increased SIRs, supporting that SPT prevalence rates found in this study exceed the risk to develop EC and LC in the general population. However, for an adequate comparison with the risk among the general population, matching of all individual patient data of the included studies for parameters, including age, gender, comorbidities, follow up time and alcohol and tobacco use would be essential.

The SPT prevalence rates found in this meta-analysis currently do not support screening for lung SPTs and esophageal SPTs. Future research should focus on identification of subgroups of patients with ESCC and LC with the highest risks for SPT development. Although evidence is limited, patient characteristics with the highest risk for SPTs that can be considered are for example males with chronic tobacco use and early and curable primary tumors. In these patients, the occurrence of SPTs can have major consequences for treatment and prognosis, and screening might potentially be beneficial. Moreover, geographic differences in the incidence of ESCC, LC, and SPTs are an important differentiator in the process of identification of patients with highest risks to develop SPTs. Another issue with regard to screening that needs to be addressed is the optimal timing to screen for SPTs in these patients. This needs to be balanced, between as early as possible to detect SPT at an early and curable stage on one hand and screening of selected patients with improved survival rates on the other hand.

Recently, a large-scale screening study was performed to detect lung cancers among a population of heavy (ex-)smokers.[59] In this study, patients underwent a minimum of 10 years of screening and follow up with CTs at baseline, year 1, year 3, and year 5.5. The incidence of LC was 5.6%, and screening successfully reduced LC-related mortality. With our findings, combined with the fact that 80-90% of ESCC patients are heavy (ex-)smokers[60], one might hypothesize that a subgroup of patients with ESCC would also potentially benefit from CT screening during the ESCC follow up to detect lung SPTs.

Although this systematic review included all available studies reporting on the prevalence of lung SPTs and esophageal SPTs, several limitations need to be discussed: 1) different definitions for the diagnosis and timing for SPTs were used. Synchronous and metachronous SPTs were lumped together as subsequent SPTs in nine studies[23, 30, 33, 40, 47, 48, 54, 56, 57] and varying definitions were used for synchronous and metachronous in eight studies.[28, 38, 41, 43,

[46, 50, 53, 55]; 2) the retrospective study design with limited information regarding the detection method of SPTs and lack of long-term follow up data in most included studies; 3) both ESCC and LC often remain asymptomatic for a long time and therefore are frequently detected in advanced stages; 4) high heterogeneity between the included studies. These limitations in the methodology of included studies resulted in rather low prevalence rates of SPTs.

In conclusion, this meta-analysis showed that patients with ESCC and LC have an increased risk of developing SPTs in the lungs and esophagus. However, based on the rather low SPT prevalence rates found in this systematic review, screening cannot be recommended. Further research focusing on risk stratification for subgroups of patients with ESCC and LC might reveal subgroups with higher risks, potentially making screening more worthwhile.

REFERENCES

1. Arnold M, Ferlay J, van Berge Henegouwen MI, et al. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. Gut. 2020;69(9):1564-71.
2. 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(6):394-424.
3. Lu T, Yang X, Huang Y, et al. Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. Cancer management and research. 2019;11:943.
4. Freedman ND, Abnet CC, Caporaso NE, et al. Impact of changing US cigarette smoking patterns on incident cancer: risks of 20 smoking-related cancers among the women and men of the NIH-AARP cohort. International journal of epidemiology. 2016;45(3):846-56.
5. 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;94:138-47.
6. State of Lung Cancer. 2020 report American Lung Association; 2020. [Accessed 19/06/2022, Available from: https://www.lung.org/getmedia/381ca407-a4e9-4069-b24b-195811f29a00/solc-2020-report-final.pdf].
7. van de Ven SE, Falger JM, Verhoeven RH, et al. Increased risk of second primary tumours in patients with oesophageal squamous cell carcinoma: A nationwide study in a Western population. United European Gastroenterol J. 2020:2050640620977129.
8. van de Ven S, Bugter O, Hardillo JA, et al. 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(10):1304-11.
9. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer. 1953;6(5):963-8.
10. Guideline Non small cell lung cancer (in Dutch: Richtlijn niet kleincellig longcarcinoom): Dutch Association of Physicians in Chest Medicine and Tuberculosis; 2020. [Accessed 17/07/2022, Available from: https://richtlijnendatabase.nl/richtlijn/niet_kleincellig_longcarcinoom/startpagina_-_niet-kleincelling_longcarcinoom.html].
11. Guideline esophageal cancer (in Dutch: Richtlijn Oesofaguscarcinoom): Dutch society of gastroenterologists; Version 3.1. [Accessed 18/08/2022, Available from: https://www.mdl.nl/sites/www.mdl.nl/files/richlijnen/Richtlijn_Oesofaguscarcinoom.pdf].
12. Guideline small cell lung carcinoma (in Dutch: Richtlijn Kleincellig longcarcinoom): Dutch Association of Physicians in Chest Medicine and Tuberculosis; 2011. [Accessed 13/07/2022; Available from: https://richtlijnendatabase.nl/richtlijn/kleincellig_longcarcinoom/kleincellig_longcarcinoom_-_startpagina.html].
13. Lordick F, Mariette C, Haustermans K, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v50-v7.
14. Muro K, Lordick F, Tsushima T, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic oesophageal cancer: a JSMO–ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS. Annals of Oncology. 2019;30(1):34-43.
15. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6(7):e1000097.
16. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Oxford; 2000.
17. Duval S, Tweedie R. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000;56(2):455-63.
18. Warren S. Multiple primary malignant tumors, a survey of the literature and a statistical study. Am J Cancer. 1932;16:1358-414.
19. Cahan WG, Castro EB, Rosen PP, et al. Separate primary carcinomas of the esophagus and head and neck region in the same patient. Cancer. 1976;37(1):85-9.
20. Poon RTP, Law SYK, Chu KM, et al. Multiple primary cancers in esophageal squamous cell carcinoma: Incidence and implications. Ann Thorac Surg. 1998;65(6):1529-34.
21. Motoyama S, Saito R, Kitamura M, et al. 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.
22. Yoshida N, Eto K, Kurashige J, et al. Comprehensive Analysis of Multiple Primary Cancers in Patients with Esophageal Squamous Cell Carcinoma Undergoing Esophagectomy. Ann Surg. 2020.

23. Hu WS, Liu ZJ, Zhang JB, et al. Risk patterns of subsequent primary cancers following esophagectomy in early-stage thoracic esophageal squamous cell cancer patients. Tumori. 2015;101(3):328-33.
24. 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(13):4260-6.
25. Yamaguchi T, Kato K, Nagashima K, et al. Type of second primary malignancy after achieving complete response by definitive chemoradiation therapy in patients with esophageal squamous cell carcinoma. Int J Clin Oncol. 2018;23(4):652-8.
26. Otowa Y, Nakamura T, Takiguchi G, et al. Safety and benefit of curative surgical resection for esophageal squamous cell cancer associated with multiple primary cancers. Eur J Surg Oncol. 2016;42(3):407-11.
27. Natsugoe S, Matsumoto M, Okumura H, et al. Multiple primary carcinomas with esophageal squamous cell cancer: Clinicopathologic outcome. World J Surg. 2005;29(1):46-9.
28. Kumagai Y, Kawano T, Nakajima Y, et al. Multiple primary cancers associated with esophageal carcinoma. Surg Today. 2001;31(10):872-6.
29. Kokawa A, Yamaguchi H, Tachimori Y, et al. Other primary cancers occurring after treatment of superficial oesophageal cancer. Br J Surg. 2001;88(3):439-43.
30. Nagasawa S, Onda M, Sasajima K, et al. Multiple primary malignant neoplasms in patients with esophageal cancer. Dis Esophagus. 2000;13(3):226-30.
31. Voormolen MHJ, Van Deelen RAJ, Tilanus HW, et al. Esophageal carcinoma and multiple primary tumors. DIS ESOPHAGUS. 1995;8(3):218-21.
32. Fekete F, Sauvanet A, Kaisserian G, et al. Associated primary esophageal and lung carcinoma: a study of 39 patients. Ann Thorac Surg. 1994;58(3):837-42.
33. Chen D, Fan N, Mo J, et al. Multiple primary malignancies for squamous cell carcinoma and adenocarcinoma of the esophagus. J Thorac Dis. 2019;11(8):3292-301.
34. 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(6):1543-9.
35. Ribeiro Júnior U, Cecconello I, Safatle-Ribeiro AV, et al. Squamous cell carcinoma of the esophagus and multiple primary tumors of the upper aerodigestive tract. Arq Gastroenterol. 1999;36(4):195-200.
36. Fogel TD, Harrison LB, Son YH. Subsequent upper aerodigestive malignancies following treatment of esophageal cancer. CANCER. 1985;55(9):1882-5.
37. Fitzpatrick PJ, Tepperman BS, DeBoer G. Multiple primary squamous cell carcinomas in the upper digestive tract. INT J RADIAT ONCOL BIOL PHYS. 1984;10(12):2273-9.
38. Abdel-Rahman O, Cheung WY. Subsequent thoracic cancers among patients diagnosed with lung cancer: a SEER database analysis. Curr Med Res Opin. 2017;33(11):2009-17.
39. Chuang SC, Scélo G, Lee YCA, et al. Risks of second primary cancer among patients with major histological types of lung cancers in both men and women. Br J Cancer. 2010;102(7):1190-5.
40. Coyte A, Morrison DS, McLoone P. Second primary cancer risk - The impact of applying different definitions of multiple primaries: Results from a retrospective population-based cancer registry study. BMC Cancer. 2014;14(1).
41. Duchateau CS, Stokkel MP. Second primary tumors involving non-small cell lung cancer: prevalence and its influence on survival. Chest. 2005;127(4):1152-8.
42. Faehling M, Schwenk B, Kramberg S, et al. Second malignancy in non-small cell lung cancer (NSCLC): prevalence and overall survival (OS) in routine clinical practice. J Cancer Res Clin Oncol. 2018;144(10):2059-66.
43. Haraguchi S, Hioki M, Koizumi K, et al. Characteristics of multiple primary malignancies associated with lung cancer by gender. Respiration. 2007;74(2):192-5.
44. Hsieh WC, Chen YM, Perng RP. Temporal relationship between cancers of the lung and upper aerodigestive tract. Jpn J Clin Oncol. 1997;27(2):63-6.
45. Kaneko S, Yamaguchi N. Epidemiological analysis of site relationships of synchronous and metachronous multiple primary cancers in the National Cancer Center, Japan, 1962-1996. Jpn J Clin Oncol. 1999;29(2):96-105.
46. Kawahara M, Ushijima S, Kamimori T, et al. Second primary tumours in more than 2-year disease free survivors of small-cell lung cancer in Japan: The role of smoking cessation. Br J Cancer. 1998;78(3):409-12.
47. Komatsu H, Izumi N, Tsukioka T, et al. Prognosis associated with synchronous or metachronous multiple primary malignancies in patients with completely resected non-small cell lung cancer. Surg Today. 2019;49(4):343-9.
48. Levi F, Randimbison L, Te VC, et al. Second primary cancers in patients with lung carcinoma. Cancer. 1999;86(1):186-90.

49. Li F, Zhong WZ, Niu FY, et al. Multiple primary malignancies involving lung cancer. BMC Cancer. 2015;15(1).
50. Reinmuth N, Stumpf A, Stumpf P, et al. Characteristics and outcome of patients with second primary lung cancer. Eur Respir J. 2013;42(6):1668-76.
51. Shan S, She J, Xue ZQ, et al. Clinical characteristics and survival of lung cancer patients associated with multiple primary malignancies. PLoS ONE. 2017;12(9):e0185485.
52. Son C, Lee SK, Choi PJ, et al. Characteristics of additional primary malignancies in Korean patients with non-small cell lung cancer. J Thorac Dis. 2013;5(6):737-44.
53. Su VYF, Liu CJ, Chen YM, et al. Risk of Second Primary Malignancies in Lung Cancer Survivors – The Influence of Different Treatments. Targeted Oncol. 2017;12(2):219-27.
54. Takigawa N, Kiura K, Segawa Y, et al. Second primary cancer in survivors following concurrent chemoradiation for locally advanced non-small-cell lung cancer. Br J Cancer. 2006;95(9):1142-4.
55. Teppo L, Salminen E, Pukkala E. Risk of a new primary cancer among patients with lung cancer of different histological types. Eur J Cancer. 2001;37(5):613-9.
56. Shimizu Y, Tukagoshi H, Fujita M, et al. Endoscopic screening for early esophageal cancer by iodine staining in patients with other current or prior primary cancers. Gastrointest Endosc. 2001;53(1):1-5.
57. Fink-Neuboeck N, Lindenmann J, Porubsky C, et al. Hazards of Recurrence, Second Primary, or Other Tumor at Ten Years After Surgery for Non–Small-Cell Lung Cancer. Clin Lung Cancer. 2020.
58. Su H-A, Hsiao S-W, Hsu Y-C, 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(1):1-9.
59. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. New England Journal of Medicine. 2020;382(6):503-13.
60. Gruner M, Denis A, Masliah C, et al. Narrow-band imaging versus Lugol chromoendoscopy for esophageal squamous cell cancer screening in normal endoscopic practice: Randomized controlled trial. Endoscopy. 2020.

SUPPLEMENTARY

Table S1. Quality assessment of included studies according to the Newcastle-Ottawa scale for cohort studies.

Author [ref]	Year	Selection	Comparability	Exposure/outcome	Total (9/9)
Van de Ven *et al.*[8]	2020	★★★★	★	★★★	8
Yoshida *et al.*[22]	2020	★★★★	★★	★	7
Chen *et al.*[33]	2019	★★★★	★	★	6
Yamaguchi *et al.*[25]	2018	★★★	★	★★★	7
Otowa *et al.*[26]	2016	★★★★	★★	★★★	9
Hu *et al.*[23]	2015	★★★★	★★	★★★	9
Lee *et al.*[24]	2013	★★★★	★★	★★★	9
Chuang *et al.*[34]	2008	★★★★	★	★	6
Natsugoe *et al.*[27]	2005	★★★★	★★	★★★	9
Motoyama *et al.* [21]	2003	★★★★	★	★★★	9
Kokawa et al[29]	2001	★★★★	★★	★	7
Kumagai *et al.*[28]	2001	★★★★	★★	★	7
Nagasawa *et al.*[30]	2000	★★★★	★★	★	7
Ribeiro Jùnior *et al.*[35]	1999	★★★★	★	★	6
Poon *et al.*[20]	1998	★★★★	★★	★★★	9
Voormolen *et al.*[31]	1995	★★★★	★	★★★	8
Fekete *et al.*[32]	1994	★★	★	★	4
Fogel *et al.*[36]	1985	★★	★	★	4
Fitzpatrick *et al.*[37]	1984	★★★★	★	★	6
Fink-Neuboeck *et al.*[57]	2020	★★★★	★★	★★	8
Komatsu *et al.*[47]	2019	★★★★	★★	★★★	9
Faehling *et al.*[42]	2018	★★★★	★	★★★	8
Abdel-Rahman *et al.*[38]	2017	★★★★	★	★	6
Shan *et al.*[51]	2017	★★★★	★	★	6
Su *et al.*[53]	2017	★★★★	★	★★	7
Li *et al.*[49]	2015	★★★★	★	★	6
Coyte *et al.*[40]	2014	★★★★	★	★	6
Reinmuth *et al.*[50]	2013	★★★★	★	★★★	8
Son *et al.*[52]	2013	★★★★	★★	★	7
Chuang *et al.*[39]	2010	★★★★	★	★	6
Haraguchi *et al.*[43]	2007	★★★★	★★	★	7

Takigawa *et al.*[54]	2006	★★★	0	★★★	6
Duchateau *et al.*[41]	2005	★★★★	★	★	6
Shimizu *et al.*[56]	2001	★★★★	0	★★★	7
Teppo *et al.*[55]	2001	★★★★	★	★★	7
Kaneko *et al.*[45]	1999	★★★★	★	★★	7
Levi *et al.*[48]	1999	★★★★	★	★★★	8
Kawahara *et al.*[46]	1998	★★★★	0	★★★	7
Hsieh *et al.*[44]	1997	★★★★	★	★	6

Table S2. Study characteristics and quality assessment of included studies performed in patients with ESCC.

Author [ref]	Year	Country	Study design	ESCC, n	Lung SPTs, n (%)	Time to SPTs investigated			Quality (NOS)
						History of LC	Synchronous lung SPTs	Metachronous lung SPTs	
Van de Ven *et al.*[8]	2020	Netherlands	Retro	9,058	219 (2.4)	-	+	+	8/9
Yoshida *et al.*[20]	2020	Japan	Retro	766	22 (2.9)	+	+	+	7/9
Chen *et al.*[36]	2019	USA	Retro	14,540	229 (1.6)	-		+[b]	6/9
Yamaguchi *et al.*[21]	2018	Japan	Retro	185	5 (2.7)	-	-	+	7/9
Otowa *et al.*[22]	2016	Japan	Retro	273	6 (2.2)	+	+	+	9/9
Hu *et al.*[33]	2015	China	Retro	512	13 (2.5)[a]	-		+[b]	9/9
Lee *et al.*[23]	2013	Korea	Retro	601	18 (3.0)	+	+	+	9/9
Chuang *et al.*[24]	2008	World	Retro	30,121	338 (1.1)	+	+	+	6/9
Natsugoe *et al.*[34]	2005	Japan	Retro	652	13 (2.0)	+	+	+	9/9
Motoyama *et al.*[25]	2003	Japan	Retro (1972-1988) Pro (1989-2001)	325	9 (2.8)	-	-	+	9/9
Kokawa *et al.*[26]	2001	Japan	Retro	368	13 (3.5)	+	+	+	7/9
Kumagai *et al.*[27]	2001	Japan	Retro	733	5 (0.7)	+	+	+[c]	7/9
Nagasawa *et al.*[35]	2000	Japan	Retro	268	3 (1.1)	+		+[b]	7/9
Ribeiro Jùnior *et al.*[28]	1999	Brazil	Retro	264	2 (0.8)	+	+	+	6/9
Poon *et al.*[29]	1998	China	Pro	1,055	8 (0.8)	+	+	+	9/9
Voormolen *et al.*[30]	1995	Netherlands	Retro	242	3 (1.2)	+	+	+	8/9

Table S2. Study characteristics and quality assessment of included studies performed in patients with ESCC. (continued)

Author [ref]	Year	Country	Study design	ESCC, n	Lung SPTs, n (%)	Time to SPTs investigated			Quality (NOS)
						History of LC	Synchronous lung SPTs	Metachronous lung SPTs	
Fogel *et al.*[32]	1985	USA	Retro	198	2 (1.0)	+	+	+	4/9
Fitzpatrick *et al.*[37]	1984	Canada	Retro	1,469	6 (0.4)	+	+	+	6/9

ESCC, esophageal squamous cell carcinoma; LSPT, lung second primary tumor; NOS, Newcastle-Ottawa Scale quality assessment for cohort studies; Pro, prospective; Retro, retrospective; SPTs, second primary tumor; USA, united States of America. [a]Hu *et al.* excluded all lung squamous cell carcinoma (n=11), which occurred within the first 5 years after the diagnosis of ESCC, as potential LSPTs. [b]Synchronous and metachronous LSPTs were registered jointly as subsequent SPTs. [c]Metachronous LSPTs were defined as SPTs detected more than 1 year after the diagnosis of ESCC.

Table S3. Study characteristics and quality assessment of included studies performed in patients with lung cancer.

Author [ref]	Year	Country	Study design	LC type	LC, n	Esophageal SPTs, n (%)	Time to SPTs investigated			Quality (NOS)
							History of EC	Synchronous esophageal SPTs	Metachronous esophageal SPTs	
Fink-Neuboeck *et al.*[57]	2020	Austria	Pro	NSCLC	324	1 (0.3)	+	+[b]		8/9
Komatsu *et al.*[47]	2019	Japan	Retro	NSCLC	521	27 (5.2)	-	+[b]		9/9
Faehling *et al.*[42]	2018	Germany	Retro	NSCLC	1,252	3 (0.2)	+[a]	+	-	8/9
Abdel-Rahman *et al.*[38]	2017	USA	Retro	LC	223,274	251 (0.1)	-	+	+[c]	6/9
Shan *et al.*[51]	2017	China	Retro	LC	27,642	10 (0.04)	+	+	-	6/9
Su *et al.*[53]	2017	Taiwan	Retro	LC	18,372	16 (0.09)	-	-	+[c]	7/9
Li *et al.*[49]	2015	China	Retro	LC	5,405	17 (0.3)	+	+	+	6/9
Coyte *et al.*[40]	2014	Scotland	Retro	LC	10,764	4 (0.04)	-	+[b]		6/9
Reinmuth *et al.*[50]	2013	Germany	Retro	LC	2,816	1 (0.04)	-	+	+[d]	8/9
Son *et al.*[52]	2013	Korea	Retro	NSCLC	632	4 (0.6)	+	+	+	7/9
Chuang *et al.*[39]	2010	World	Retro	LC	258,559	159 (0.06)	-	+	+	6/9
Haraguchi *et al.*[43]	2007	Japan	Retro	LC	1,013	4 (0.4)	-	+	+[c]	7/9
Takigawa *et al.*[54]	2006	Japan	Retro	NSCLC	90	2 (2.2)	-	+[b]		6/9
Duchateau *et al.*[41]	2005	Netherlands	Retro	NSCLC	860	2 (0.2)	+	+	+[d]	6/9
Shimizu *et al.*[56]	2001	Japan	Pro	LC	32	1 (3.1)	-	+[b]		7/9
Teppo *et al.*[55]	2001	Finland	Retro	LC	77,548	28 (0.04)	-	+	+[e]	7/9

Table S3. Study characteristics and quality assessment of included studies performed in patients with lung cancer.

Author [ref]	Year	Country	Study design	LC type	LC, n	Esophageal SPTs, n (%)	Time to SPTs investigated			Quality (NOS)
							History of EC	Synchronous esophageal SPTs	Metachronous esophageal SPTs	
Kaneko *et al.*[45]	1999	Japan	Retro	LC	6,935	28 (0.4)	-	+	-	7/9
Levi *et al.*[48]	1999	Switzerland	Retro	LC	5,794	5 (0.09)	-	+[b]		8/9
Kawahara *et al.*[46]	1998	Japan	Retro	SCLC	70	2 (2.9)	-	-	+[d]	7/9
Hsieh *et al.*[44]	1997	Taiwan	Retro	LC	6,412	10 (0.2)	+	+	+	6/9

LC, lung cancer; NOS, Newcastle-Ottawa Scale quality assessment for cohort studies; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; Pro, prospective; Retro, retrospective; SPT, second primary tumor; USA, United States of America. [a] History of EC was defined as the detection of EC more than 3 months before the diagnosis of LC. [b] Synchronous and metachronous esophageal SPTs were registered jointly as subsequent SPTs. [c] Metachronous esophageal SPTs were defined as SPTs detected more than 1 year after the diagnosis of LC. [d] Metachronous esophageal SPTs were defined as SPTs detected more than 2 years after the diagnosis of LC. [e] Metachronous esophageal SPTs were defined as SPTs detected during follow up (i.e. after first admission for LC).

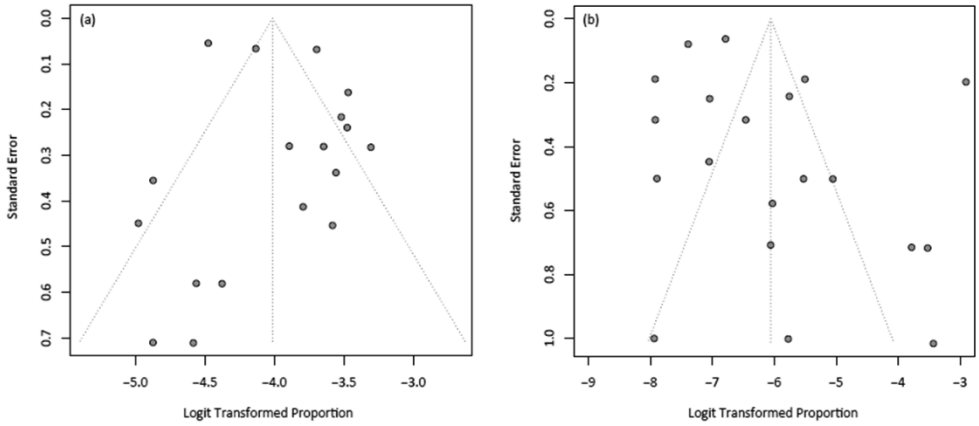


Figure S1. Funnel plots to assess the risk of publication bias. The risk for publication bias for studies (a) performed in patients with ESCC to detect lung SPTs (P = 0.11) and (b) performed in patients with lung cancer to detect esophageal SPTs (P = 0.16). ESCC, esophageal squamous cell carcinoma.

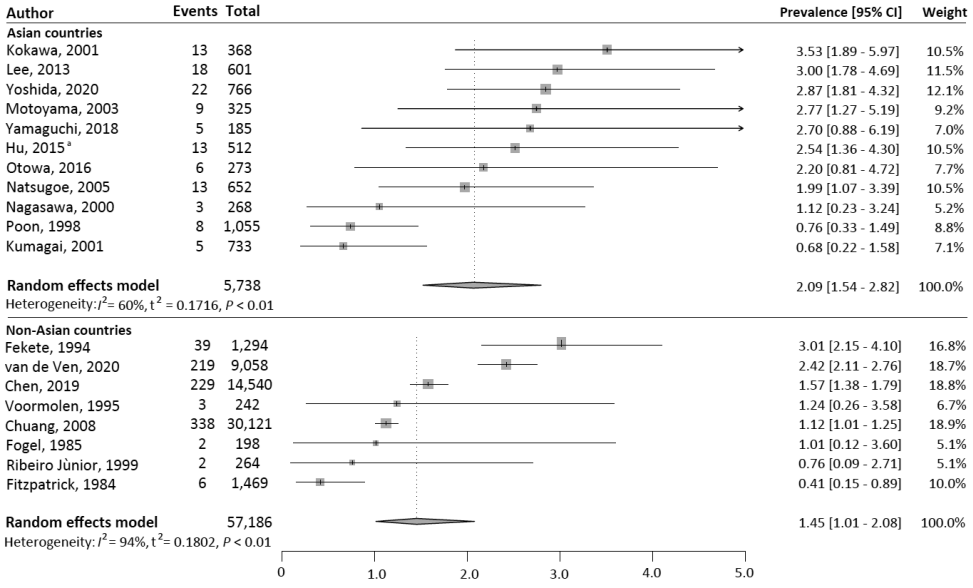


Figure S2. Overview of the prevalence of lung SPTs in patients with ESCC in Asian and non-Asian countries. CI, confidence interval; ESCC, esophageal squamous cell carcinoma; I2, inconsistency index; τ^2, tau-squared represents the extent of variation among the effects observed in different studies; SPT, second primary tumor. [a] Hu *et al.* excluded all lung squamous cell carcinoma (n=11), which occurred within the first 5 years after the diagnosis of ESCC, as potential lung SPTs.[23]

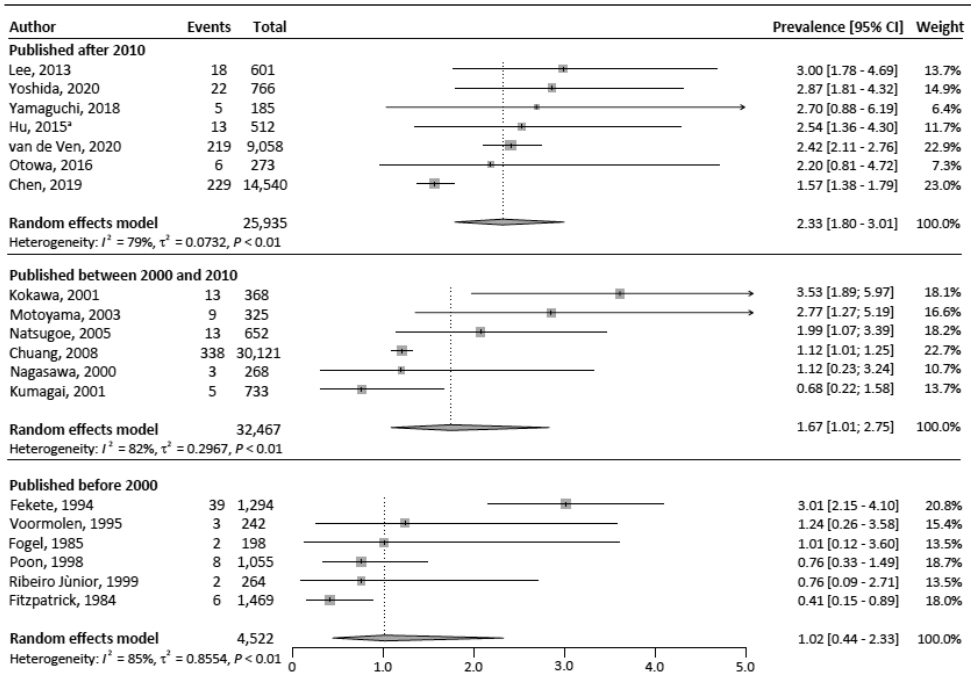


Figure S3. Overview of the prevalence of lung SPTs in patients with ESCC during recent decades. CI, confidence interval; ESCC, esophageal squamous cell carcinoma; I^2, inconsistency index; τ^2, tau-squared represents the extent of variation among the effects observed in different studies; SPT, second primary tumor. [a] Hu *et al.* excluded all lung squamous cell carcinoma (n=11), which occurred within the first 5 years after the diagnosis of ESCC, as potential lung SPTs.[23]

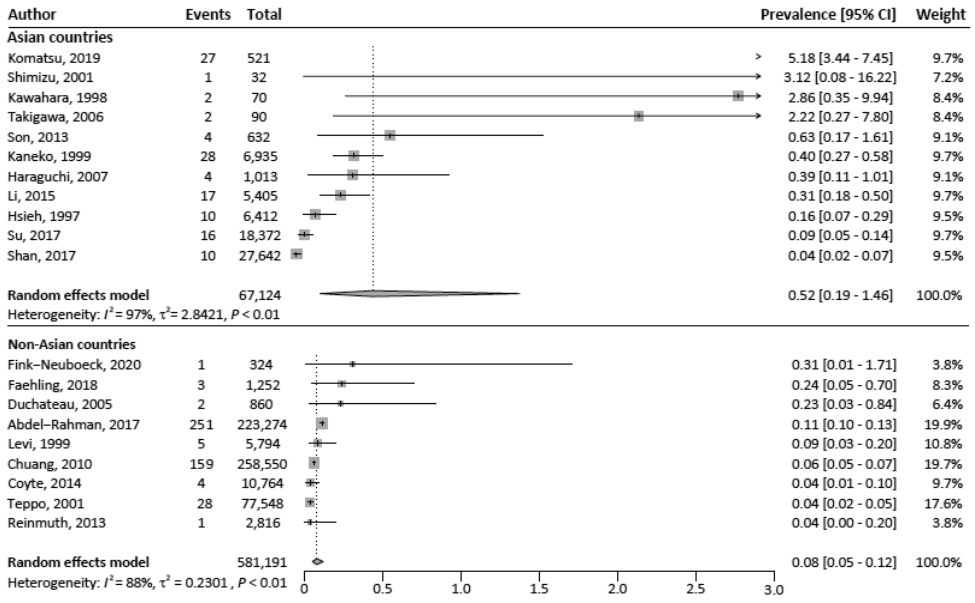


Figure S4. Overview of the prevalence of esophageal SPTs in patients with lung cancer in Asian and non-Asian countries. CI, confidence interval; I^2, inconsistency index; τ^2, tau-squared represents the extent of variation among the effects observed in different studies; SPT, second primary tumor.

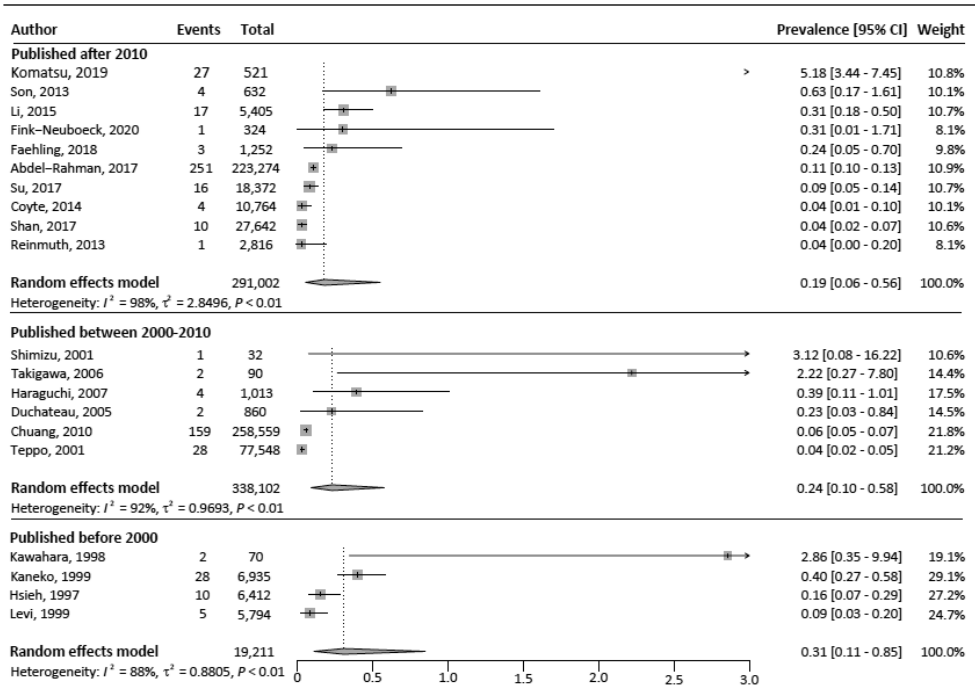


Figure S5. Overview of the prevalence of esophageal SPTs in patients with lung cancer during recent decades. CI, confidence interval; I^2, inconsistency index; τ^2, tau-squared represents the extent of variation among the effects observed in different studies; SPT, second primary tumor.

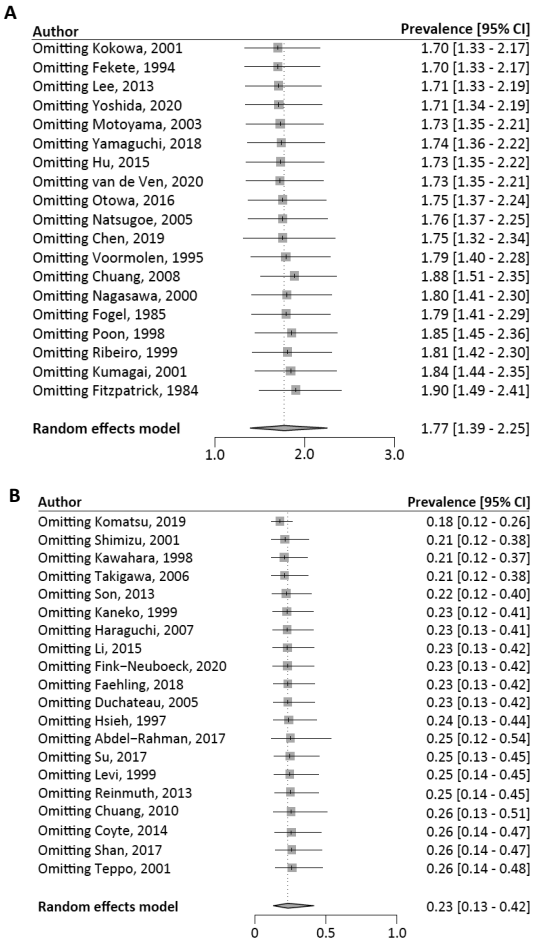


Figure S6. Excessive influence analysis of the included studies. ESCC, esophageal squamous cell carcinoma; LC, lung cancer; SPT, second primary tumor. A) Excessive influence analyses of the included studies performed in patients with ESCC and lung SPTs. B) Excessive influence analyses of the included studies performed in patients with ESCC and lung SPTs.

Appendix 1. The full search strategy

Embase

('second cancer'/de OR (((Metachronous OR Synchronous) NEAR/6 (tumo* OR malignan* OR carcin* OR neoplas* OR cancer*)) OR ((Second OR Multiple OR double OR triple OR quadruple OR quintuple OR subsequen* OR Simultan*) NEAR/3 (primar*) NEAR/6 (tumo* OR malignan* OR carcin* OR neoplas* OR cancer*))):ab,ti,kw) AND ('esophagus tumor'/exp OR 'lung tumor'/exp OR ((esophag* OR oesophag* OR lung OR pulmonar* OR upper-aerodigest* OR upper-digest*) NEAR/6 (tumo* OR cancer* OR neoplas*)):ab,ti,kw) NOT [conference abstract]/lim NOT ([animals]/lim NOT [humans]/lim) AND [English]/lim

Medline

(Neoplasms, Second Primary/ OR Neoplasms, Multiple Primary/ OR (((Metachronous OR Synchronous) ADJ6 (tumo* OR malignan* OR carcin* OR neoplas* OR cancer*)) OR ((Second OR Multiple OR double OR triple OR quadruple OR quintuple OR subsequen* OR Simultan*) ADJ3 (primar*) ADJ6 (tumo* OR malignan* OR carcin* OR neoplas* OR cancer*))).ab,ti,kf.) AND (exp Esophageal Neoplasms/ OR exp Lung Neoplasms/ OR ((esophag* OR oesophag* OR lung OR pulmonar* OR upper-aerodigest* OR upper-digest*) ADJ6 (tumo* OR cancer* OR neoplas*)).ab,ti,kf.) NOT (exp animals/ NOT humans/) AND english.la.

Web of science

TS=(((((Metachronous OR Synchronous) NEAR/5 (tumo* OR malignan* OR carcin* OR neoplas* OR cancer*)) OR ((Second OR Multiple OR double OR triple OR quadruple OR quintuple OR subsequen* OR Simultan*) NEAR/2 (primar*) NEAR/5 (tumo* OR malignan* OR carcin* OR neoplas* OR cancer*)))) AND (((esophag* OR oesophag* OR lung OR pulmonar* OR upper-aerodigest* OR upper-digest*) NEAR/5 (tumo* OR cancer* OR neoplas*)))) AND DT=(Article OR Review OR Letter OR Early Access) AND LA=(english)

Cochrane

((((Metachronous OR Synchronous) NEAR/6 (tumo* OR malignan* OR carcin* OR neoplas* OR cancer*)) OR ((Second OR Multiple OR double OR triple OR quadruple OR quintuple OR subsequen* OR Simultan*) NEAR/3 (primar*) NEAR/6 (tumo* OR malignan* OR carcin* OR neoplas* OR cancer*))):ab,ti,kw) AND (((esophag* OR oesophag* OR lung OR pulmonar* OR upper-aerodigest* OR upper-digest*) NEAR/6 (tumo* OR cancer* OR neoplas*)):ab,ti,kw)

Google scholar

"Metachronous|Synchronous tumors|malignancies|neoplasms|cancers"|"Second|Multiple|double|triple primary tumor|malignancy|carcinoma|neoplasm|cancer"
esophagus|oesophagus|esophageal|oesophageal|lung|pulmonary incidence|prevalence
'Metachronous|Synchronous tumors|malignancies|neoplasms|cancers'|'Second|Multiple|double|triple primary tumor|malignancy|carcinoma|neoplasm|cancer'
esophagus|oesophagus|esophageal|oesophageal|lung|pulmonary incidence|prevalence

Chapter 5

Screening for head and neck tumors in patients with esophageal squamous cell carcinoma and vice versa: a nationwide survey among medical specialists

L. van Tilburg, S.A. van den Ban, S.E.M. van de Ven, A. Sewnaik, M. J. Bruno, M.C.W. Spaander, R.J. Baatenburg de Jong, A.D. Koch

Endoscopy international open. 2022

ABSTRACT

Background: Retrospectively, minimally 5% of patients with esophageal squamous cell carcinoma (ESCC) and 11% with head and neck squamous cell carcinoma (HNSCC) in Western countries developed a second primary tumor (SPT). SPT screening in ESCC and HNSCC patients is not implemented routinely in daily practice in many Western countries. This study aimed to assess medical specialist knowledge and opinions regarding screening for head and neck SPTs in ESCC patients and vice versa in the Netherlands.

Methods: A nationwide survey among gastroenterologists and head and neck (HN) surgeons was conducted between December 2020 and March 2021. The survey consisted of 27 questions and focused on knowledge of medical specialists of the prevalence and opinions toward implementing screening for head and neck SPTs in ESCC patients and vice versa.

Results: One hundred twenty-eight gastroenterologists (20.5%) and 31 HN surgeons (50.0%) completed the survey. The expected median prevalence of head and neck SPTs in ESCC was 7.0% (interquartile range [IQR]: 5.0–15.0) among gastroenterologists and 5.0% (IQR: 3.0–8.0) among HN surgeons. For esophageal SPTs in HNSCC, the expected median prevalence was 9.5% (IQR: 5.0–12.0) among gastroenterologists and 4.0% (IQR: 2.0–5.0) among HN surgeons. Screening for head and neck and esophageal SPTs was considered promising by 35.2% and 39.6%, respectively, which increased to 54.7% of the specialists after providing incidence data on SPTs. Of the HN surgeons, 41.3% felt they were as capable as gastroenterologists of performing esophageal screening.

Conclusions: This Dutch nationwide survey revealed a lack of knowledge and different perspectives among specialists about screening to detect SPTs in ESCC and HNSCC patients. Adequate education seems essential to increase awareness among specialists and improve SPT detection, independent of the need for implementation of screening for SPTs in ESCC and HNSCC patients.

INTRODUCTION

Second primary tumors (SPTs) occur relative frequently in patients diagnosed with primary esophageal (ESCC) and head and neck squamous cell carcinoma (HNSCC).[1-3] Most common SPT locations are the head and neck (HN) region, esophagus, and lungs.[2, 4] Development of SPTs in ESCC and HNSCC patients is often explained by the theory of field cancerization.[5] This theory states that when the mucosa around the primary tumor is exposed to carcinogens (e.g. alcohol and tobacco) for a long time, it is therefore prone to the development of (pre)malignant changes in the epithelium.[6]

SPTs in ESCC and HNSCC patients are frequently diagnosed at advanced stages and are associated with decreased survival rates.[2, 4] Survival rates of ESCC and HNSCC patients could potentially improve with screening to detect SPTs in pre-symptomatic and curable stages. Several screening studies - mainly in Asian countries - have been conducted to detect SPTs in ESCC and HNSCC patients.[1, 3, 7-11] However, conclusions of Asian screening studies may not be applicable to Western countries, because of the large difference in incidence for both ESCC and HNSCC between Western and Asian populations.[12, 13]

In retrospective studies in Western countries, at least 5% of ESCC patients and 11% of HNSCC patients developed an SPT.[2, 4] The minority of published screening studies have been conducted in Western countries with esophageal SPT rates ranging from 5.9% to 10.0% in patients with HNSCC.[14-18] No Western screening studies have been published on head and neck SPTs in patients with ESCC.[3] Currently, screening for SPTs in ESCC and HNSCC patients is not implemented routinely in daily practice in many Western countries.[19, 20]

Regardless of the yield and potential benefit of screening for SPTs, expertise and awareness of the involved medical specialists are essential to accurately detect SPTs in ESCC and HNSCC patients. Especially early-stage esophageal SPTs and head and neck SPTs may be subtle and can be easily missed.[21-23] This study aimed to assess the knowledge about head and neck SPTs in a Western population of ESCC patients and vice versa among gastroenterologists and HN surgeons. The secondary aim was to assess opinions among involved specialists regarding the potential for implementing screening to detect SPTs to improve the outcome of ESCC and HNSCC patients.

METHODS

Study design and participants

A nationwide survey was conducted among gastroenterologists and HN surgeons in the Netherlands. In the Netherlands, there are currently 623 gastroenterologists and 92 HN surgeons. Every gastroenterologist may encounter patients with ESCC, while the diagnostic work-up and treatment of patients with HNSCC is centralized in expert centers. All medical specialists involved in the diagnosis and treatment of ESCC and HNSCC were invited via de Dutch Society of Gastroenterologists (in Dutch: *Nederlandse Vereniging van Maag-Darm-Leverartsen; NVMDL*) and Dutch Head and Neck Society (in Dutch*: Nederlandse Werkgroep Hoofd-Hals Tumoren; NWHHT*). All specialists received the digital survey with up to two reminders via email.

Elements of digital survey

A structured survey was developed in Dutch using LimeSurvey version 2.06 (Supplementary S1). The survey was available from December 2020 till March 2021. The survey consisted of 27 questions and took approximately 4 minutes to complete. Returning to previous questions to change answers during the survey was not possible.

Questions in this survey were divided into three parts. Part 1 consisted of demographic characteristics of specialists, including age, sex, work location and subspecialization. The routine use of optical chromoendoscopy (such as narrow band imaging, i-scan and flexible spectral imaging color enhancement) during upper gastrointestinal endoscopy for gastroenterologists and during panendoscopy with a nasopharyngeal endoscope for HN surgeons was also asked. Part 2 focused on the expectations among medical specialists regarding the prevalence and synchronous proportion of esophageal SPTs in HNSCC patients and head and neck SPTs in ESCC patients in a Western population. The prevalence was defined as the life-time risk for patients with primary ESCC or HNSCC to develop an SPT. Synchronous SPTs were defined as SPTs that were detected within six months of the diagnosis of the primary tumor.[24] In part 3, questions were asked on the possibility of implementing screening for SPTs in a Western country, including the arguments in favor (i.e. to improve early diagnosis of SPTs and increased patient survival) or against embarking on screening (i.e. increased patient burden, increased workload for specialists, more research needed, and limited knowledge of this subject). Next, information from two recent Dutch studies about the prevalence of SPTs in Western patients diagnosed with ESCC and HNSCC was provided (Supplementary S1).[4, 17] With these data provided, the questions about whether screening for SPTs in ESCC and HNSCC patients should be implemented were

repeated, including the reason for the chosen answer(s). Other questions included who should perform esophageal screening and the best screening method for esophageal SPTs.

Statistics and ethics

Anonymized data from fully completed surveys were analyzed using descriptive statistics. Based on Dutch medical ethical regulations, no institutional review board approval, nor informed consent, was necessary.

RESULTS

Respondents

A total of 623 gastroenterologists and 62 HN surgeons were invited; 88 specialists (12.8%) opened or partially completed the survey. The survey was fully completed by 159 specialists; 128 gastroenterologists (20.5%) and 31 HN surgeons (50.0%) (Table 1). Two-thirds of the specialists was male (66.7%). The medical specialists had a median age of 46 years (IQR: 39-54) with 10 years (IQR: 5-19) of professional experience. Specialists were subspecialized within survey-related subspecializations in 63.3% of the gastroenterologists and 83.9% of the HN surgeons. Table S1 lists the responses of specialists with and without survey-related subspecializations. Routine use of chromoendoscopy was reported by most gastroenterologists (91.4%) and half of HN surgeons (51.6%).

Table 1. Baseline characteristics of medical specialists (n=159).

	All n=159	**Gastroenterologists** n=128	**Head and neck surgeons** n=31
Invited specialists, n	862	800	62
Respondents, n (response rate)	159 (18.4%)	128 (16.0%)	31 (50.0%)
Demographics			
Male sex, n (%)	106 (66.7%)	78 (60.9%)	28 (90.3%)
Age (years), median [IQR]	46.0 [39.0-54.0]	44.0 [38.3-52.8]	54.0 [43.0-57.0]
Professional experience (years), median [IQR]	10.0 [5.0-19.0]	9.0 [5.0-16.0]	19.0 [8.0-25.0]
Hospital type, n (%)			
Academic	45 (28.3%)	23 (18.0%)	22 (71.0%)
Top clinical	78 (49.1%)	70 (54.7%)	8 (25.8%)
Peripheral	36 (22.6%)	35 (27.3%)	1 (3.2%)
Subspecialization of specialists, n (%)[1]			
Oncology	62 (39.0%)	48 (37.5%)	14 (45.2%)
Interventional endoscopy	55 (34.6%)	55 (43.0%)	-
Head and neck surgery	26 (16.4%)	-	26 (83.9%)
Routine use of chromoendoscopy, n (%)	133 (83.6)	117 (91.4)	16 (51.6)
Familiar with field cancerization theory, n (%)	67 (42.1)	37 (28.9)	30 (96.8)
Diagnoses per specialist per year, median [IQR]	-	ESCC: 3.0 [2.0-5.0]	HNSCC: 125.0 [70.0-300.0]

Data are presented as median [IQR] or n and percentage. ESCC, esophageal squamous cell carcinoma; IQR, interquartile range; HNSCC, Head and neck squamous cell carcinoma. [1]Medical specialists could have more than one subspecialisation.

Head and neck SPTs in ESCC

Specialists expected the median ***prevalence*** of head and neck SPTs in patients with ESCC to be 5.0% (IQR: 5.0-10.0) (Figure 1). A ***prevalence*** of ≤3% or ≥20% was expected by 38.4% of the specialists. For the subgroups of gastroenterologists and HN surgeons, the expected median ***prevalence*** of head and neck SPTs in ESCC patients was 7.0% (IQR: 5.0-15.0) and 5.0% (IQR: 3.0-8.0), respectively. The expected proportion of ***synchronous*** head and neck SPTs was median 5.0% (IQR: 2.0-5.0) among all specialists, 5.0% (IQR: 2.0-9.5) among gastroenterologists and 2.0% (IQR: 1.0-5.0) among HN surgeons.

Esophageal SPTs in HNSCC

Among all specialists, the expected median ***prevalence*** of esophageal SPTs in patients with HNSCC was 5.0% (IQR: 4.0-10.0). An esophageal SPT ***prevalence*** in HNSCC of ≤3% or ≥20% was expected by 24.5% and 14.5% of all specialists, respectively. The expected median prevalence was 9.5% (IQR: 5.0-12.0) for gastroenterologists and 4.0% (IQR: 2.0-5.0) for HN surgeons. The expected proportion of ***synchronous*** esophageal SPTs in HNSCC was 5.0% (IQR: 3.0-10.0) among gastroenterologists and 2.0% (IQR: 1.0-5.0) among HN surgeons. Sex, age and years of experience of medical specialists were not associated with the expected prevalence and synchronous proportion of SPTs in patients with ESCC and HNSCC (data not shown).

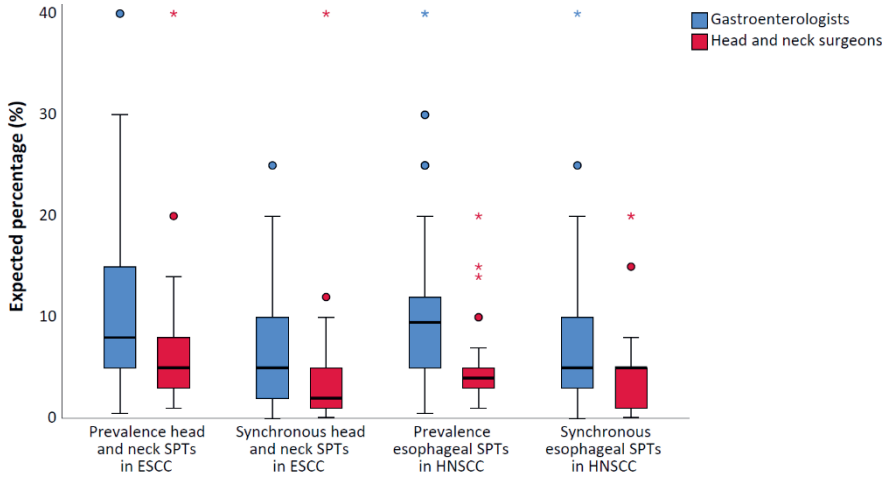


Figure 1. The expected prevalence of head and neck SPTs in patients with ESCC and vice versa in a Western population. ESCC, esophageal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; SPT, second primary tumor. Boxplot legend: median (midline), box (25th to 75th percentiles) and whiskers. Outliers and extreme values beyond the whiskers are shown with circles and asterisks, respectively. Outliers with an expected prevalence of above 40% not shown (n=5).

Risk factors for SPTs

Tobacco and alcohol were identified as risk factors for SPTs in both ESCC and HNSCC patients by 98.1% and 97.5% of the medical specialists, respectively. Furthermore, specialists identified the following risk factors: sex (57.2%), age (47.8%), genetic factors (33.3%), dietary factors (25.2%), ethnicity (24.5%), gastroesophageal reflux disease (17.6%) and body mass index (16.4%). Before providing data about HNSCC locations and the associated risk for esophageal SPTs, 32.1% of all specialists identified the hypopharynx as the primary HNSCC location associated with the highest esophageal SPT risk. The hypopharynx was selected by 80.6% of the HN surgeons and by 20.3% of the gastroenterologists (Table 2). Of the gastroenterologists, 45.3% answered that they did not know which HN sublocation was associated with the highest risk for esophageal SPTs, compared to 3.2% of HN surgeons.

Table 2. Primary HNSCC location associated with the highest risk for esophageal SPTs, according to gastroenterologists and head and neck surgeons.

	All specialists n=159	**Gastroenterologists** n=128	**Head and neck surgeons** n=31
HNSCC location			
Hypopharynx	51 (32.1%)	26 (20.3%)	25 (80.6%)
Oropharynx	20 (12.6%)	18 (14.1%)	2 (6.5%)
Larynx	15 (9.4%)	14 (10.9%)	1 (3.2%)
Oral cavity	14 (8.8%)	12 (9.4%)	2 (6.5%)
Do not know	59 (37.1%)	58 (45.3%)	1 (3.2%)

Data are presented as n and percentage. HNSCC, head and neck squamous cell carcinoma; SPT, second primary tumor.

Screening for SPTs

One-third of all specialists (35.2%) would consider screening for head and neck SPTs in patients with ESCC (Figure 2); 45.9% of the specialists were not sure and 18.9% thought HN screening in ESCC should not be implemented. Half of the specialists (47.2%) expected that implementing HN screening in ESCC patients would lead to both more diagnoses and more early-stage diagnoses head and neck SPTs, 30.8% expected only more diagnoses head and neck SPTs at early stages and 6.3% expected only more diagnoses head and neck SPTs. Sixty-three specialists (39.6%) would consider screening of the esophagus in HNSCC patients; 42.8% was in doubt and 17.6% stated that esophageal screening should not be implemented. If screening were implemented, 61.0% of the specialists expressed the

expectation that more esophageal SPTs would be diagnosed and that these SPTs would be found at early stages.

Of all gastroenterologists, 35.9% would consider implementation of HN screening in ESCC patients and 42.2% would consider esophageal screening in HNSCC patients. After revealing the actual data regarding the incidence of SPTs, 56.3% were willing to consider implementation of screening for esophageal SPTs and head and neck SPTs. Of HN surgeons, 32.3% and 29.0% would consider screening to detect Head and neck SPTs in ESCC and vice versa, respectively. After provided information, 48.4% of HN surgeons was in favor of screening of the esophagus and HN region.

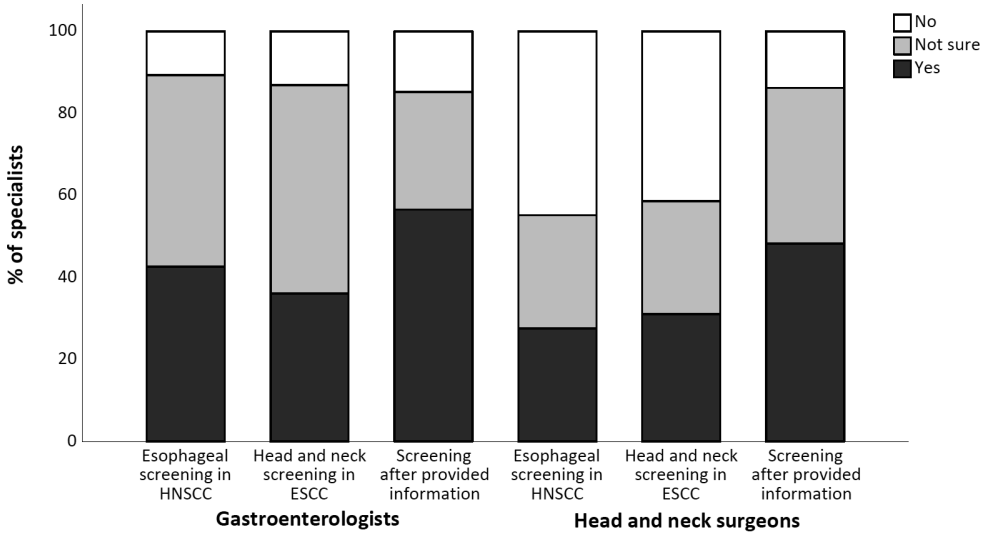


Figure 2. Opinions of specialists on implementing screening for SPTs in ESCC and HNSCC patients. ESCC, esophageal squamous cell carcinoma; HN, head and neck region; HNSCC, Head and neck squamous cell carcinoma; SPT, second primary tumors.

Based on the provided information, 58 specialists (36.4%) changed their opinion regarding esophageal screening in HNSCC patients and 66 specialists (41.5%) changed their opinion regarding HN screening in ESCC patients. Of the specialists that changed their opinion, 58.6% and 72.7% of the specialists were more willing to consider screening to detect esophageal SPTs and head and neck SPTs, respectively. Reasons advocating for implementation of screening of the HN region and esophagus included early SPT diagnosis (before 46.5%; after 63.5%) and increased patient survival (before 42.8%; after 61.0%) (Table 3). Reasons to discourage the implementation of HN and esophageal screening were limited knowledge about this subject (before 35.8%; after 17.0%), need for more research

(before 18.9%; after 18.2%), patient burden associated with screening (before 8.2%; after 6.3%), and increased workload for specialists (before 6.3%; after 3.8%). Of the specialists that did not want to consider screening for SPTs or were unsure after the supplied information (n=73), 37.0% thought more research was needed and another 37.0% had limited knowledge about SPTs in ESCC and HNSCC patients.

If screening for esophageal SPTs in HNSCC patients were to be implemented, gastroenterologists would perform screening with at least chromo endoscopy (48.4%) or lugol's staining (43.8%). In total, 129 specialists (81.1%) reported that gastroenterologists should perform screening of the esophagus to detect esophageal SPTs. Of HN surgeons, 41.9% reported that they should perform esophageal screening in HNSCC patients (16.1%) or felt as capable as gastroenterologists of performing esophageal screening (25.8%) during panendoscopy.

Table 3. Reasons in favor or discouraging screening for SPTs in patients with ESCC or HNSCC, according to the medical specialists.

	All specialists n=159		Gastroenterologists n=128		Head and neck surgeons n=31	
	Before info	After info	Before info	After info	Before info	After info
Reasons in favor of screening						
Early diagnosis	74 (46.5%)	101 (63.5%)	58 (45.3%)	80 (62.5%)	16 (51.6%)	21 (67.7%)
Improved survival	68 (42.8%)	97 (61.0%)	54 (43.4%)	77 (60.2%)	14 (45.2%)	20 (64.5%)
Reasons discouraging screening						
Limited knowledge	57 (35.8%)	27 (17.0%)	54 (42.2%)	26 (20.3%)	3 (9.7%)	1 (3.2%)
More research needed	30 (18.9%)	29 (18.2%)	21 (16.4%)	24 (18.8%)	9 (29.0%)	5 (16.1%)
Patient burden	13 (8.2%)	10 (6.3%)	4 (3.1%)	6 (4.7%)	9 (29.0%)	4 (12.9%)
Increased workload	10 (6.3%)	6 (3.8%)	3 (2.3%)	2 (1.6%)	7 (22.6%)	4 (12.9%)
Other reasons	16 (10.1%)	18 (11.3%)	9 (7.0%)	10 (7.8%)	7 (22.6%)	8 (25.8%)

Data are presented as n and percentage. Specialists could choose multiple reasons via checkboxes. ESCC, esophageal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; info, information; SPT, second primary tumor.

DISCUSSION

SPTs occur relative frequently in patients diagnosed with ESCC and HNSCC in Western countries and are often located in the esophagus and HN region. Adequate knowledge among gastroenterologists and HN surgeons is essential for awareness of the risk of SPTs and accurate detection of SPTs in patients with ESCC and HNSCC.

This nationwide survey enabled us to create an overview of the knowledge and experience of medical specialists about head and neck SPTs in patients with ESCC and vice versa in a Western country. This inventory revealed a lack of knowledge among involved specialists. Perspectives regarding screening to detect SPTs differed strongly among specialists. The information on the incidence of SPTs in a Western population that was provided in our survey increased the willingness to consider screening for SPTs in ESCC and HNSCC patients. This underscores the importance of providing accurate data on the actual occurrence of SPTs.

An important finding of our study was the large variance in the expected prevalence of SPTs in ESCC and HNSCC patients among involved specialists. Four out of 10 medical specialists expected the prevalence of head and neck SPTs in ESCC patients and vice versa to be 3% or less or 20% and above. Median expectations of the prevalence of SPTs in ESCC and HNSCC patients of 5.0% were comparable to numbers reported in recent studies.[4, 15, 17] Our research group performed a retrospective study with 9,058 ESCC patients in the Netherlands and found a 3.0% prevalence of head and neck SPTs in patients with primary ESCC. Synchronous head and neck SPTs were detected in 1.8% of the ESCC patients.[4] Previous non-Asian screening studies detected 6.9% esophageal SPTs in 392 patients with HN or tracheobronchial squamous cell carcinoma in France[15], 10% esophageal SPTs in 40 patients with HN cancer in Switzerland[16] and 7.9% esophageal SPTs in 1888 HNSCC patients in Brazil.[18]

The expected proportion of 2% to 10% for synchronous esophageal SPTs in this study are in line with that found in our previous screening study.[17] Our research group reported 5.9% (95% confidence interval 1.9-13.2%) esophageal SPTs in 85 patients diagnosed with human papillomavirus-negative HNSCC located at the hypopharynx, oropharynx and other HN sublocations in patients with alcohol abuse in the Netherlands.[17]

Before information on the SPT incidence in Western ESCC and HNSCC patients was provided, one-third of the medical specialists expressed that their knowledge of SPTs was limited and almost 20% thought more research was needed. When the actual incidence numbers of SPTs were provided in our survey, the willingness increased from 35% and 39%

to 55% among specialists to consider screening to detect SPTs in ESCC and HNSCC patients. This finding together with the wide range in expectations towards the prevalence and synchronous proportion of SPTs, suggests that knowledge about SPTs in ESCC and HNSCC patients among specialists is still rather limited. Adequate education is key to increase awareness about SPTs in ESCC and HNSCC patients.

Screening for SPTs in ESCC and HNSCC patients is not implemented routinely in daily practice in many Western countries. Current European guidelines show many differences regarding screening for SPTs in ESCC and HNSCC patients. The Dutch guidelines suggest that screening of the HN region and lungs in ESCC patients may be considered.[20] Screening endoscopy for esophageal SPTs in patients with HNSCC is not mentioned in the Dutch guidelines.[25] The French Society of Otorhinolaryngology, on the other hand, recommends endoscopic screening to detect esophageal SPTs in patients with oro- and hypopharyngeal HNSCC or chronic alcohol abuses.[26] The laryngology and HN guideline of the United Kingdom states that the incidence of esophageal SPTs is low and screening with rigid esophagoscopy should be limited to HNSCC patients with highest risks for synchronous esophageal SPTs.[19] Other screening modalities to detect esophageal SPTs, such as positron emission tomography/computed tomography (PET/CT) scan, should not be considered, because the sensitivity of the PET/CT for the detection of early-stage esophageal cancer is only 38%.[27] Therefore, the PET-CT is inferior to endoscopic screening for esophageal SPTs.

For meaningful implementation of screening to detect SPTs, it is crucial that screening eventually results in an improved survival for patients with ESCC or HNSCC and an SPT. An important aspect of achieving survival benefit is the timing of screening. On the one hand synchronous screening also includes patients that will develop early metastatic disease, and therefore, would not benefit from screening and on the other hand metachronous screening may detect SPTs too late (i.e. in advanced stages). Moreover, numbers needed to screen and cost-effectiveness of screening for SPTs in ESCC and HNSCC patients need to be determined. It would also be interesting to investigate which type of specialists should perform esophageal screening, taken into account the yield of screening and associated healthcare costs. Besides large prospective trials on screening, future research should be concentrated on improving knowledge and awareness of SPTs in ESCC and HNSCC patients among involved medical specialists.

Although this is the first survey study investigating knowledge of SPTs among gastroenterologists and HN surgeons in Europe, the following limitations need to be addressed. First, the response rate was 23.2%, which is relatively low, but comparable to other survey studies among medical specialists.[28, 29] Second, two-thirds of specialists

(n=107) were subspecialized in the oncology, interventional endoscopy and HN surgery, implying that we questioned a group of specialists that might encounter this medical problem more frequently in daily clinical practice. As is shown in Table S1, the wide range in expectations towards the prevalence was consistent among medical specialists. Third, findings of this survey were based on surveys completed by medical specialists. Responders could not be compared to non-responders, because the demographics of the responders were obtained in the first questions in the survey and were not available for non-responding specialists. This could potentially result in a selection bias, causing an overestimation of the knowledge among specialists and might limit the generalizability of our results to all gastroenterologists and HN surgeons in Europe. Validation of the results can confirm the reproducibility of our findings.

In conclusion, this Dutch nationwide survey reveals a lack of knowledge about head and neck SPTs in patients with ESCC and vice versa among surveyed specialists. Willingness to consider screening for SPTs in ESCC and HNSCC patients increases after background information was provided on the incidence of SPTs. Future research should focus on the impact on survival and the optimal timing of screening for SPTs in ESCC and HNSCC patients in Western countries. Education for specialists seems essential in order to increase awareness and improve detection of SPTs, independent of the need for implementation of screening for SPTs in ESCC and HNSCC patients.

REFERENCES

1. 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(4):1122-30.
2. 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(6):1648-55.
3. van de Ven S, Bugter O, Hardillo JA, et al. 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(10):1304-11.
4. van de Ven SE, Falger JM, Verhoeven RH, et al. Increased risk of second primary tumours in patients with oesophageal squamous cell carcinoma: A nationwide study in a Western population. United European Gastroenterol J. 2020:2050640620977129.
5. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer. 1953;6(5):963-8.
6. Bugter O, Spaander MCW, Bruno MJ, et al. Optical detection of field cancerization in the buccal mucosa of patients with esophageal cancer. Clin Transl Gastroenterol. 2018;9(4):152.
7. Watanabe A, Hosokawa M, Taniguchi M, et al. Head and neck cancer associated with esophageal cancer. Auris Nasus Larynx. 2007;34(2):207-11.
8. 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(4):e164-e70.
9. 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(6):1750-6.
10. 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):752-9.
11. 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.
12. Arnold M, Ferlay J, van Berge Henegouwen MI, et al. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. Gut. 2020;69(9):1564-71.
13. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. International journal of cancer. 2019;144(8):1941-53.
14. 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(2):275-82.
15. 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.
16. 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(12):2748-54.
17. van de Ven SEM, de Graaf W, Bugter O, et al. Screening for synchronous esophageal second primary tumors in patients with head and neck cancer. Dis Esophagus. 2021.
18. Nobre Moura R, Kuboki Y, Baba ER, et al. Long-term results of an endoscopic screening program for superficial esophageal cancer in patients with head and neck squamous cell carcinoma. Endosc Int Open. 2022;10(2):E200-E8.
19. Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines 5th edition 2016. [Accessed 01/02/2022; Available from: https://www.entuk.org/sites/default/files/files/5th%20edition%20head%20and%20neck%20cancer%20multidisciplinary%20management%20guidelines.pdf].
20. Guideline esophageal cancer (in Dutch: Richtlijn Oesofaguscarcinoom): Dutch society of gastroenterologists; Version 3.1. [Accessed 01/02/2022; Available from: https://www.mdl.nl/sites/www.mdl.nl/files/richlijnen/Richtlijn_Oesofaguscarcinoom.pdf].
21. 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):808-13.

22. Chung CS, Lo WC, Lee YC, et al. 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.
23. Kumai Y, Shono T, Waki K, et al. Detection of hypopharyngeal cancer (Tis, T1 and T2) by ENT physicians vs gastrointestinal endoscopists. Auris Nasus Larynx. 2020;47(1):135-40.
24. Moertel CG, Dockerty MB, Baggenstoss AH. Multiple primary malignant neoplasms. I. Introduction and presentation of data. Cancer. 1961;14(2):221-30.
25. Leemans CR SL, Langendijk JA, et al. Guideline head and neck cancer (in Dutch: richtlijn Hoofd-halstumoren) 2012. [Accessed 01/02/2022; Available from: https://richtlijnendatabase.nl/richtlijn/hoofd-halstumoren/hoofd-halstumoren_-_korte_beschrijving.html].
26. 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(2):107-12.
27. Su H-A, Hsiao S-W, Hsu Y-C, 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(1):1-9.
28. Fowler J, Chin CJ, Massoud E. Rhinitis medicamentosa: a nationwide survey of Canadian otolaryngologists. Journal of Otolaryngology-Head & Neck Surgery. 2019;48(1):1-5.
29. Van Kooten H, de Jonge V, Schreuders E, et al. Awareness of postpolypectomy surveillance guidelines: a nationwide survey of colonoscopists in Canada. Canadian Journal of Gastroenterology. 2012;26(2):79-84.

SUPPLEMENTARY

Supplementary S1. Complete and translated version of the survey.

1. What is your specialization?
   - ☐ Gastroenterology
   - ☐ Otolaryngology
   - ☐ Head and neck surgery
   - ☐ Other: […]

2. At what type of hospital do you work?
   - ☐ Academic hospital
   - ☐ Top clinical hospital
   - ☐ Peripheral hospital

3. How many years have you been working as a medical specialist?
   […] years

4. What is your age?
   […] years

5. What is your sex?
   - ☐ Male
   - ☐ Female

6.
   a. (For gastroenterologists) Do you have a sub specialization within the gastroenterology? Choose what is applicable. Multiple answers are possible.
   - ☐ Inflammatory bowel disease
   - ☐ Gastrointestinal oncology
   - ☐ Interventional endoscopy
   - ☐ Hepatology
   - ☐ Pancreatic disorders
   - ☐ General gastroenterologist
   - ☐ Other: […]

   b. (For head and neck surgeons) Do you have a sub specialization within the otolaryngology and head and neck surgery? Choose what is applicable. Multiple answers are possible.
   - ☐ Head and neck surgery
   - ☐ Otology
   - ☐ Rhinology
   - ☐ Laryngology
   - ☐ Pediatric otorhinolaryngology
   - ☐ Vestibular disorders
   - ☐ Oncological otolaryngology
   - ☐ General otolaryngology
   - ☐ Other: […]

7. Do you routinely use optical chromoendoscopy during endoscopy? (such as NBI, i-scan, or FICE)
   - ☐ Yes
   - ☐ No

8.
   a. (For gastroenterologists) How many esophageal squamous cell carcinoma do you diagnose yearly?
      […]
   b. (For head and neck surgeons) How many head and neck squamous cell carcinomas do you diagnose yearly?
      […]

9. What do you expect the risk for patients with esophageal squamous cell carcinoma to be diagnosed with head and neck cancer **within 6 months** of the diagnosis of esophageal cancer?
   […%]

10. What do you expect the prevalence of head and neck cancer to be in patients diagnosed with esophageal squamous cell carcinoma in Western countries?
    […%]

Please note: the following two questions are similar to the previous two questions, however the question subject is switched.

11. What do you expect the risk for patients with head and neck squamous cell carcinoma to be diagnosed with esophageal cancer **within 6 months** of the diagnosis of head and neck cancer?
    […%]

12. What do you expect the prevalence of esophageal cancer to be in patients diagnosed with head and neck squamous cell carcinoma in Western countries?

13. Do you know shared risk factors for both esophageal squamous cell carcinoma and head and neck squamous cell carcinoma? Multiple answers are possible.
    - ☐ Smoking
    - ☐ Diet
    - ☐ Alcohol abuses
    - ☐ Genetics
    - ☐ BMI
    - ☐ Age
    - ☐ Sex
    - ☐ Gastroesophageal reflux disease
    - ☐ Ethnicity
    - ☐ I do not know
    - ☐ Other: […]

14. Patients with head and neck squamous cell carcinoma have an increased risk to develop an esophageal second primary tumor. Which primary head and neck squamous cell carcinoma location is associated with the highest risk for esophageal second primary tumors?
    - ☐ Larynx
    - ☐ Hypopharynx
    - ☐ Oropharynx
    - ☐ Oral cavity
    - ☐ I do not know

15. Are you familiar with the field cancerization theory?
    - ☐ Yes
    - ☐ No

16. If esophageal screening would be implemented, which specialist do you think that should perform esophageal screening in patients with head and neck cancer?
    - ☐ Gastroenterologist
    - ☐ Otolaryngologist
    - ☐ No preference

17. (For gastroenterologists) Which screening technique is do you think the most suitable for esophageal screening in patients with head and neck squamous cell carcinoma in Western countries? Multiple answers are possible.
    - ☐ White light
    - ☐ Optic chromoendoscopy
    - ☐ Lugol's staining
    - ☐ I do not know

18. What do you expect of esophageal screening in patients with head and neck squamous cell carcinoma?
    - ☐ More diagnoses esophageal cancer
    - ☐ More diagnoses esophageal cancer at early stages
    - ☐ Both more diagnoses esophageal cancer and more diagnoses at early stages
    - ☐ No difference in number of diagnoses

19. Do you think that screening of the esophagus in patients with head and neck cancer in the Netherlands should be considered?
    - ☐ Yes
    - ☐ No
    - ☐ Do not know

20. What do you expect of head and neck screening in patients with esophageal squamous cell carcinoma?
    - ☐ More diagnoses head and neck cancer
    - ☐ More diagnoses head and neck cancer at early stages
    - ☐ Both more diagnoses and more diagnoses head and neck cancer at early stages
    - ☐ No difference in number of diagnoses

21. Do you think that screening of the head and neck region in patients with esophageal cancer in the Netherlands should be considered?
    - ☐ Yes
    - ☐ No
    - ☐ Do not know

22. What are the most important reasons for your answers during previous questions? Multiple answers are possible.
    - ☐ Early diagnosis in stages that can be treated with minimal invasive treatment
    - ☐ Potential improved patient survival
    - ☐ Increased patient burden
    - ☐ Increased work pressure for specialists that perform the screening
    - ☐ Nog enough evidence, more research is needed
    - ☐ I do not have enough knowledge about this subject to judge if screening should be considered
    - ☐ Other: […]

Our research group performed several studies to investigate the prevalence of second primary tumors in patients with squamous cell carcinoma, located in the esophagus and head and neck region.

- In a nationwide retrospective study in the Netherlands (9058 patients with esophageal squamous cell carcinoma; 2000-2016), 270 head and neck second primary tumors were detected, of which 167 were diagnosed within 6 months of the diagnosis esophageal squamous cell carcinoma.
- In 2019, a prospective screening study was performed in head and neck squamous cell carcinoma patients (patients with HPV-negative oropharynx- and hypopharynx carcinoma and other HN locations with alcohol abuses), 5.9% was diagnosed with an esophageal second primary tumor. All second primary tumors in the esophagus were diagnosed in curative stages and most could be treated with endoscopic resection. This supports our hypothesis that screening holds the potential of detect esophageal tumors in a pre-symptomatic early stages that can be treated curatively.

23. Did you know patients with esophageal squamous cell carcinoma have an increased risk for head and neck cancer?
    - ☐ Yes
    - ☐ No

24. Did you know patients with head and neck squamous cell carcinoma have an increased risk for esophageal cancer?
    - ☐ Yes
    - ☐ No

25. Do you think that screening based on this data is justified?
    - ☐ Yes
    - ☐ No
    - ☐ Not sure

26. What are the most important considerations for your answer to the previous question? If applicable, it is possible to choose multiple answers.
    - ☐ Early diagnosis in stages that can be treated with minimal invasive treatment
    - ☐ Potential improved patient survival
    - ☐ Increased patient burden
    - ☐ Increased work pressure for specialists that perform the screening
    - ☐ Nog enough evidence, more research is needed
    - ☐ I do not have enough knowledge about this subject to judge if screening should be considered
    - ☐ Other: […]

27. Do you have any comments on or questions about this survey? […]

Table S1. Characteristics of medical specialists with and without survey-related sub specializations.

	With survey-related sub specializations, n=107	**Without survey-related sub specializations,** n=52
Demographics		
Sex male	78 (72.9%)	28 (53.8%)
Age (years)	47.0 [40.0-55.0]	42.0 [38.0-52.0]
Professional experience (years)	13.0 [5.0-20.0]	6.5 [4.0-16.0]
Hospital type		
Academic	39 (36.4%)	6 (11.5%)
Top clinical	52 (48.6%)	26 (50.0%)
Peripheral	16 (15.0%)	20 (38.5%)
Routine use of chromoendoscopy	92 (86.0%)	41 (78.8%)
Familiar with field cancerization theory	57 (53.3%)	10 (19.2%)
Diagnoses per specialist yearly	ESCC (n=81): 3 [2-5] HNSCC (n=26): 150 [100-300]	ESCC (n=47): 2 [1-3] HNSCC (n=5): 5 [3-23]
Expected occurrence of SPTs		
Prevalence of head and neck SPTs in ESCC	5.0 [5.0-10.0]	5.0 [5.0-14.8]
Synchronous head and neck SPTs in ESCC	5.0 [2.0-5.0]	5.0 [2.0-10.0]
Prevalence of esophageal SPTs in HNSCC	5.0 [2.0-8.0]	5.0 [3.0-10.0]
Synchronous esophageal SPTs in HNSCC	6.0 [4.0-12.0]	5.0 [3.0-10.0]
HNSCC location with the highest risk for esophageal SPTs		
Hypopharynx	41 (38.3%)	10 (19.2%)
Oropharynx	15 (14.0%)	5 (9.6%)
Larynx	10 (9.3%)	5 (9.6%)
Oral cavity	9 (8.4%)	5 (9.6%)
Do not know	32 (29.9%)	27 (51.9%)

Data are presented as n and percentage or median [IQR]. Survey-related specializations were considered the fields within gastroenterology and otorhinolaryngology that relatively frequently encounter ESCC and HNSCC during clinical practice, i.e. oncology, interventional endoscopy and head and neck surgery. ESCC, esophageal squamous cell carcinoma; HNSCC, Head and neck squamous cell carcinoma; SPT, second primary tumor.

Chapter 6

Endoscopic screening of the upper gastrointestinal tract for second primary tumors in patients with head and neck cancer in a Western country

Laurelle van Tilburg, Steffi E.M. van de Ven, Pieter Jan F. de Jonge, Wilmar de Graaf, Manon C.W. Spaander, Suzan Nikkessen, José A. Hardillo, Aniel Sewnaik, Dominiek A. Monserez, Hetty Mast, Stijn Keereweer, Marco J. Bruno, Robert J. Baatenburg de Jong, Arjun D. Koch

Endoscopy. 2023

ABSTRACT

Background: Patients with head and neck squamous cell carcinoma (HNSCC) can develop second primary tumors (SPTs) in the esophagus. Endoscopic screening could lead to detection of SPTs at early stages and improve the survival.

Methods: We performed a prospective endoscopic screening study in patients with curably treated HNSCC diagnosed between January 2017 and July 2021 in a Western country. Screening was performed synchronously (< 6 months) or metachronously (≥ 6 months) after HNSCC diagnosis. Routine imaging for HNSCC consisted of flexible transnasal endoscopy with positron emission tomography/computed tomography or magnetic resonance imaging, depending on primary HNSCC location. The primary outcome was prevalence of SPTs, defined as presence of esophageal high grade dysplasia or squamous cell carcinoma.

Results: 202 patients (mean age 65 years, 80.7% male) underwent 250 screening endoscopies. HNSCC was located in the oropharynx (31.9%), hypopharynx (26.9%), larynx (22.2%), and oral cavity (18.5%). Endoscopic screening was performed within 6 months (34.0%), 6 months to 1 year (8.0%), 1 to 2 years (33.6%), and 2 to 5 years (24.4%) after HNSCC diagnosis. We detected 11 SPTs in 10 patients (5.0%, 95% CI 2.4-8.9) during synchronous (6/85) and metachronous (5/165) screening. Most patients had early stage SPTs (90%) and were treated with curative intent with endoscopic resection (80%). No SPTs in screened patients were detected with routine imaging for HNSCC before endoscopic screening.

Conclusion: In 5% of patients with HNSCC, an SPT was detected with endoscopic screening. Endoscopic screening should be considered in selected HNSCC patients to detect early stage SPTs, based on highest SPT-risk and life expectancy according to HNSCC and comorbidities.

INTRODUCTION

In Western countries, approximately 11% of patients with head and neck squamous cell carcinoma (HNSCC) develop a second primary tumor (SPT).[1] These SPTs are often located in the upper aerodigestive tract, which consists of the head and neck region, lungs, and esophagus.[1] in particular, esophageal SPTs frequently remain undetected until reaching advanced stages and are therefore associated with decreased survival rates.[2]

Endoscopic screening of the upper gastrointestinal (GI) tract allows for timely detection of SPTs at early and curable stages.[3, 4] Early-stage SPTs can be treated with minimally invasive endoscopic resection, potentially improving the survival of patients with HNSCC.[5] Consequently, endoscopic screening in patients with HNSCC is routinely implemented in countries with a high incidence of esophageal and gastric cancer, such as China and Japan.[6-8] In Asian countries, several screening studies in patients with HNSCC have been conducted, reporting a prevalence of 3% to 41% esophageal SPTs.[7, 9-12]

Conversely, in Western countries, the incidence of esophageal squamous cell carcinoma (ESCC) is relatively low (age-standardized incidence rate of <3.5 per 100.000), compared with Asia.[8] Thus, the results from Asian studies in patients with HNSCC should not be generalized and so far, most Western countries have not implemented routine screening for SPTs in the upper GI tract has been implemented so far in most Western countries.[13, 14] Data from screening studies originating from Western countries are scarce and consist mainly of studies with small numbers of patients with HNSCC. These published studies report detection of esophageal SPT in up to 10% of patients with HNSCC.[3, 15-17] Risk factors for the development of SPTs in patients with HNSCC include human papillomavirus (HPV)-negative tumors located at the oropharynx or hypopharynx and patients with excessive alcohol consumption and tobacco use.[2, 18]

The detection of SPTs can be divided into synchronous (within 6 months) and metachronous (after more than 6 months), according to the time interval between HNSCC diagnosis and endoscopic screening. In 2019, our group started a prospective screening program for synchronous SPTs in the upper GI tract in patients with HNSCC.[3] The current study is an extension of the aforementioned study, presenting the results of both synchronous and metachronous endoscopic screening in a selected group of patients with HNSCC in a Western country.

METHODS

Study design and patients

We performed a prospective endoscopic screening study of patients who were diagnosed with HNSCC between January 2017 and July 2021 in a tertiary referral center in the Netherlands. Patients with HNSCC with an increased risk of SPTs, based on previously published studies[4], were eligible for endoscopic screening. This consisted of patients with HNSCC located in the oropharynx, hypopharynx, and other subsites combined with alcohol abuse (≥14 units per week for males and ≥7 units per week for females).[3, 19] The eligibility criteria and results of patients included in the synchronous screening program have been described in detail previously.[3] Exclusion criteria were 1) cancer at an incurable stage, 2) upper GI cancer detected before endoscopic screening, 3) severe comorbidities, preventing patients from undergoing endoscopic screening, and 4) follow up performed in other hospitals. Patients with human papillomavirus-associated oropharyngeal carcinoma were also excluded, as these patients often present without common risk-factors for SPTs such as smoking and alcohol and are known to have a lower risk-profile for SPTs.[20] High risk human papillomavirus testing was performed in patients with oropharyngeal carcinoma with immunohistochemistry for a surrogate p16 marker.[21]

HNSCC staging and follow up

All included patients received routine staging and follow up for HNSCC, according to current Dutch guidelines.[21] In the Netherlands, care for all patients with HNSCC is centralized in 14 expert centers, which perform the diagnostic work-up and discuss treatment options in multidisciplinary meetings. The diagnostic work-up of HNSCC includes a panendoscopy (i.e. flexible transnasal endoscopy examining the oral cavity, nasopharynx, hypopharynx, oropharynx, and larynx) and computed tomography (CT) scan or magnetic resonance imaging (MRI) scan, depending on HNSCC location. Patients with an increased risk of distant metastasis (i.e. patients with low jugular, bilateral or N3 lymph node metastasis) receive a positron emission tomography/CT (PET/CT) scan. Routine follow up visits after HNSCC treatment include physical examination and pandendoscopy. The aim of follow up for HNSCC is early detection of disease recurrence and SPTs in the head and neck region. In cases of suspected HNSCC recurrence or SPTs, staging and treatment is performed within daily clinical practice.

Endoscopic screening

Endoscopic screening was performed with high definition (HD) endoscopes by expert endoscopists (AK, MS, PJ, SN, and WG), who each had more than 5 years' experience in the

detection of neoplasia in the upper GI tract. All endoscopists participated in a dedicated upper GI screening program and had extensive experience in the detection of premalignant lesions in the upper GI tract. Endoscopic screening was performed with HD white light endoscopy (WLE), optical chromoendoscopy (narrow band imaging, NBI), and Lugol's staining. First, the mucosae of the stomach, duodenum, and esophagus were carefully inspected with WLE. Second, the esophageal and gastric mucosae were inspected again with NBI. After switching back to WLE, 10-30mL of Lugol's staining (1.2% iodine solution) was applied to the esophageal mucosa with a spray catheter or syringe. Visible lesions were classified according to the Paris and IPCL classification and assessed for endoscopic resectability.[22] No routine target biopsies were taken of SPTs amendable to ER and no random biopsies of the esophagus were taken. In cases of suspected SPT that could not be treated with ER, targeted biopsies were taken. Adverse events that occurred as a result of endoscopic screening were recorded.

Timing of endoscopic screening

All included patients received at least one screening endoscopy. The study cohort consisted of three screening groups: synchronous screening only, synchronous with subsequent metachronous screening, and metachronous screening only. First, synchronous screening was performed in included patients diagnosed with HNSCC between February 2019 and February 2020.[3] Second, among patients that had at least 1 year of follow up for HNSCC and fulfilled the eligibility criteria, we performed a follow up screening endoscopy (i.e. metachronous screening 1 year after synchronous screening). Third, it was decided to include eligible patients diagnosed between January 2017 and February 2019 and between February 2020 and July 2021 to increase patient inclusion in the metachronous screening cohort. These patients were approached for metachronous screening 1 to 5 years after HNSCC diagnosis (i.e. metachronous screening alone).

Second primary tumors

SPTs were defined as the presence of esophageal high grade dysplasia (HGD) or ESCC. The detection of squamous low grade dysplasia (LGD), a precursor lesion of ESCC, was also monitored. All cases of LGD were reviewed by an expert team of three experienced upper GI pathologists until consensus regarding the grade of dysplasia was reached. Lesions larger than 5mm detected during endoscopic screening with WLE, NBI, and/or Lugol's staining, were considered suspicious for SPT or LGD. In cases of confirmed SPT, treatment was discussed in a multidisciplinary tumor board meeting with the gastroenterologist, GI surgeon, head and neck surgeon, radiologist, and oncologist. Treatment options for SPTs included endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD),

surgery, and chemoradiotherapy. Other findings, including GI tract cancers such as esophageal adenocarcinoma and gastric cancer, Barrett's esophagus, reflux esophagitis (according to the Los Angeles classification), and gastritis, were treated as per standard clinical care.

Study end points

The primary end point was the prevalence of SPTs, detected during endoscopic screening of the upper GI tract. Secondary end points were 1) histology and tumor stage of SPTs, 2) time to detection, treatment, and outcomes of patients with HNSCC and SPTs, and 3) proportion of SPTs detected during a follow up endoscopy after 1 year. Additionally, we also report on the proportion, histology, and stage of SPTs diagnosed on imaging for HNSCC or in symptomatic patients.

Statistics and ethics

Descriptive statistics are presented as mean with standard deviations (SD), median with interquartile range (IQR), and count with percentage, according to the nature of the data. The detection rates of SPTs were reported with 95% confidence intervals and follow up data were obtained to December 2022. Statistical analysis was performed using IBM SPSS for Windows version 28 (SPSS Inc). Informed consent was obtained from all included patients. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The study was registered in the Netherlands Trial Register (NL7299) and approved by the Medical Ethical Review Committee of the Erasmus Medical Center, Rotterdam, the Netherlands (MEC-2018-1243).

RESULTS

Patients

A total of 518 eligible patients were diagnosed with HNSCC between January 2017 and July 2021 (Figure 1, Figure S1). Of these patients, 222 patients were excluded, because of cancer at an incurable stage (n=133), severe comorbidities (n=43), treatment and follow up in other hospitals (n=24), a history of esophageal cancer before HNSCC diagnosis (n=12), and detection of an SPT before endoscopic screening could be performed (n=10). In total, 296 patients with HNSCC were approached for inclusion, of whom 202 (68.2%) were included and underwent successful endoscopic screening. Most patients included were male (80.7%) with a median age of 65 years (IQR 59-69 years) (Table 1, Table S1). The majority of the patients consumed alcohol (78.2%) and were current (43.6%) or former (51.0%) tobacco

smokers. The HNSCC of included patients was located in the oropharynx (31.9%), hypopharynx (26.9%), larynx (22.2%), and oral cavity (18.5%).

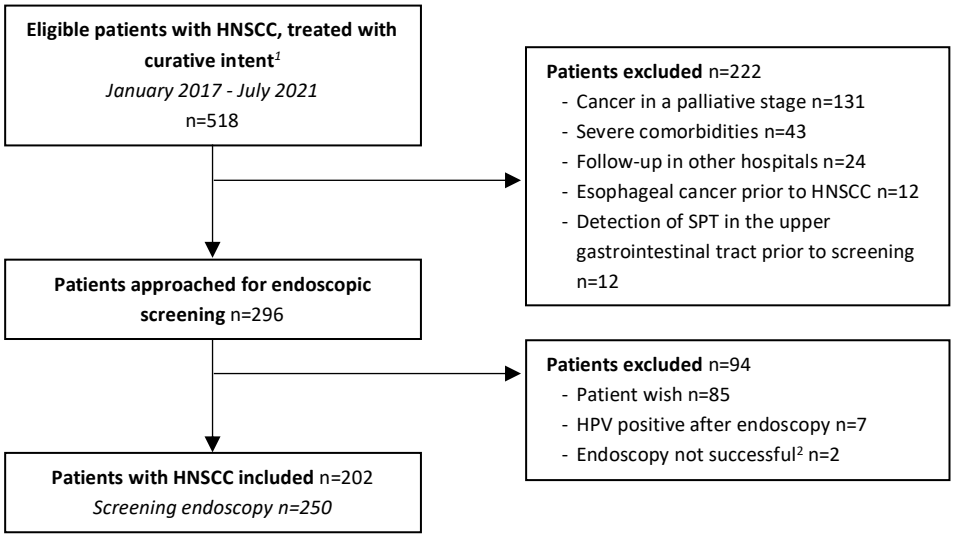


Figure 1. **Flowchart of patient inclusion.** [1]Patients diagnosed with HNSCC between February 2019 and February 2020 were approached for synchronous and metachronous screening, if fulfilling the eligibility criteria. [2]Endoscopy not successful, due to neopharyngeal stricture (n=1) and need for sedation (n=1). HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; SPT, second primary tumor.

Table 1. Baseline and HNSCC characteristics of the included patients (n=202).

Patient characteristics	**Total cohort,** n=202
Demographics	
Male sex	163 (80.7%)
Age, years	65 [59-69]
ASA classification ≥III	44 (21.8%)
Alcohol consumption	
Yes	158 (78.2%)
Units per week	21 [14-28]
No	44 (21.8%)
Alcohol use in the past	29
Units per week	38 [20-70]
Tobacco use	
Current, pack years	88 (43.6%), 40 [30-55]
Former, pack years	103 (51.0%), 40 [20-50]
Never	11 (5.4%)
HNSCC characteristics	n=216
HNSCC location [1]	
Nasopharynx	1 (0.5%)
Hypopharynx	58 (26.9%)
Oropharynx	69 (31.9%)
Oral cavity	40 (18.5%)
Larynx	48 (22.2%)
T stage [1]	
Tis	18 (8.3%)
T1	46 (21.3%)
T2	70 (32.4%)
T3	46 (21.3%)
T4	36 (16.7%)
N stage [1]	
N0	130 (60.2%)
N1	27 (12.5%)
N2/N2a/N2b/N2c	4 (1.9%) / 5 (2.3%) / 31 (14.4%) / 13 (6.0%)
N3b	6 (2.8%)

Table 1. Baseline and HNSCC characteristics of the included patients (n=202). (continued)

HNSCC characteristics	n=216
M0 stage	202 (100%)
HNSCC treatment	
Chemotherapy and/or radiotherapy	131 (64.9%)
Surgery	33 (16.3%)
Surgery + (chemo)radiotherapy	19 (9.4%)
Laser	17 (8.4%)
No treatment	2 (1.0%)

Data presented as n with percentage or median [IQR]. [1] Calculated for the total number of head and neck squamous cell carcinoma (n=216), excluding recurrences. HNSCC, head and neck squamous cell carcinoma.

Endoscopic screening

We performed 250 screening endoscopies of the upper GI tract in 202 patients with HNSCC. First endoscopic screening was performed in all patients and 48 patients underwent follow up endoscopic screening after 1 year (Figure S2). In 85 patients, we performed synchronous screening (34.0% of all screening endoscopies) with a median time between HNSCC diagnosis and screening of 9 days (IQR 6-20 days). Of the synchronously screened patients, 52 (61.2%) underwent a follow up endoscopy after 1 year. Indications for the follow up endoscopy were screening (n=48) and surveillance after treatment of a synchronous SPT (n=4). The remaining patients (38.8%) could not be included in metachronous screening, as these patients were no longer eligible (83.9%) or did not wish to undergo follow up screening (16.1%) (Figure S1). Subsequently, we performed metachronous screening only in 117 patients. In total, metachronous screening endoscopies (n=165) were performed 6 months to 1 year (n=20; 8.0% of all screening endoscopies), 1 to 2 years (n=84; 33.6%), and 2-5 years (n=61; 24.4%) after HNSCC diagnosis. No adverse events occurred as a result of endoscopic screening.

SPTs detected with endoscopic screening

A total of 11 esophageal SPTs were detected in 10/202 patients (5.0%, 95% CI 2.4-8.9) during 250 screening endoscopies (Table 2, patients 1-10). The SPTs had a median size of 20mm (IQR 15-30mm). First endoscopic screening detected 10 SPTs in 9 patients during 202 screening endoscopies (4.5%). Follow up endoscopic screening resulted in the detection of 1 SPT during 48 screening endoscopies (2.1%). During synchronous screening (n=85), SPTs were detected in six patients (7.1%). One of the synchronous SPTs was identified during pathology re-assessment of LGD, which was performed by three experienced pathologists 1 year after ER, revealing HGD (patient 2). During metachronous screening (n=165), five SPTs were detected in four patients (2.4%). Metachronous screening performed 1 year after

synchronous screening resulted in the detection of one SPT (1/48; 2.1%), while metachronous screening alone led to the detection of four SPTs in three patients (3/117; 2.6%). None of the SPTs detected during endoscopic screening (0/11) were detected during the diagnostic work-up (including MRI or PET/CT-scan) or routine follow up for HNSCC prior to endoscopic screening.

Increased detection of early-stage SPTs with endoscopic screening

Of the 10 patients with an SPT, 90.0% were diagnosed with an early stage SPT (Table 2, patients 1-9). The SPTs in patients 1-8 were treated with ER (EMR n=4, ESD n=4) with curative intent (Table 2, Figure 2). Histopathological assessment of the ER specimen showed HGD (n=4), pT1a (n=3), and pT1b cancer (n=1). In two patients, the radiotherapy field for HNSCC was extended to include a synchronous esophageal SPT, because of the presence of lymphovascular invasion in the ER specimen (patient 5) and for a T2 SPT (patient 9). One patient without clinical signs of dysphagia or odynophagia was diagnosed with both a T4 and T2 SPT during endoscopic screening (patient 10). Besides the detection of SPTs, LGD was detected in two patients (1.0%) and treated with EMR in one patient. The second patient died due to HNSCC before ER was performed.

Table 2. Characteristics of patients with HNSCC and an esophageal SPT, detected during endoscopic screening.

Patient characteristics					HNSCC characteristics		SPT characteristics						
ID	Sex	Age (years)	Alcohol (U/wk)	Smoking (PY)	Sub-location	TN stage	Time to detection (months)	Location (cm)	Paris classification + diameter (mm)	IPCL + AVA classification	SPT stage	Tx	Outcome (time after SPT diagnosis in months)
1	M	62	21	20	Oropharynx + hypopharynx	T4N2c +T2N2c	0	38	0-IIa (20)	B2 + AVA-middle	HGD	EMR	Endo FU: no recurrence (31)
2	F	67	28	0	Larynx	T2N0	0	24	0-IIb (5)	B1 + no AVA	HGD[1]	EMR	Endo FU: nu recurrence (12)
3[2]	M	67	0	0	Oropharynx	T2N0	0	21-24	0-IIb (30)	B1 + no AVA	HGD	ESD	Endo FU: 2nd esophageal SPT (16); Tx ESD (HGD)
4[2]	F	62	9	30	Hypopharynx	T4N2b	0	23-31	0-IIb +0-IIa (80)	B2 + no AVA	HGD	ESD	Endo FU: 2nd SPT (16); Tx ESD (HGD) 3rd SPT (31); Tx EMR (pT1a)
5	M	67	14	50	Oral cavity	T2N0	18	30	0-IIa (15)	B2 + no AVA	T1a	EMR	Endo FU has been planned
6	M	74	20	10	Oral cavity	T2N0	15	21	0-IIa (10)	B2 + no AVA	T1a	EMR	No FU (patient wish)
7	M	67	0	13	Oropharynx + hypopharynx	T2N2c +T2N2c	0	20	0-IIa (20)	B2 + no AVA	T1a	ESD + CRT	No FU. Patient died (19) due to palliative HNSCC
8	F	77	3	43	Oropharynx	T4aN2	32	15-17	0-IIa + 0-IIc (15)	B2 + AVA-large	T1b	ESD	No FU, because no Tx options in case of recurrence
9	M	48	42	31	Hypopharynx	T2N2c	0	20	0-Is + 0-II (20)	-	T2	CRT	Recurrence ESCC (9): Tx surgery Patient died (18) due to surgical complications
10	M	69	48	100	Hypopharynx	T1N3b	27 27	27-28 18-22	0-IIa + 0-IIc (15) Stricturing tumor (40)	-	T2 T4	RT	Patient died (6) due to ESCC

AVA, avascular areas; CRT, chemoradiotherapy; endo endoscopic; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; FU, follow up; HGD, high grade dysplasia; HNSCC, head and neck squamous cell carcinoma; IPCL, Intrapapillary capillary loops according to the Japese Esophageal Society classification; PY, pack years; RFA, radio frequency ablation; RT, radiotherapy; SPT, second primary tumor; Tx, treatment; U/wk, units/week. [1]In the previously published synchronous screening study[3], the grade of dysplasia was reported as LGD. Pathological re-assessment revealed was performed by three expert pathologists after 1 year and revealed HGD. [2]Only the characteristics of the first second primary tumor in the upper gastrointestinal tract are shown for this patient.

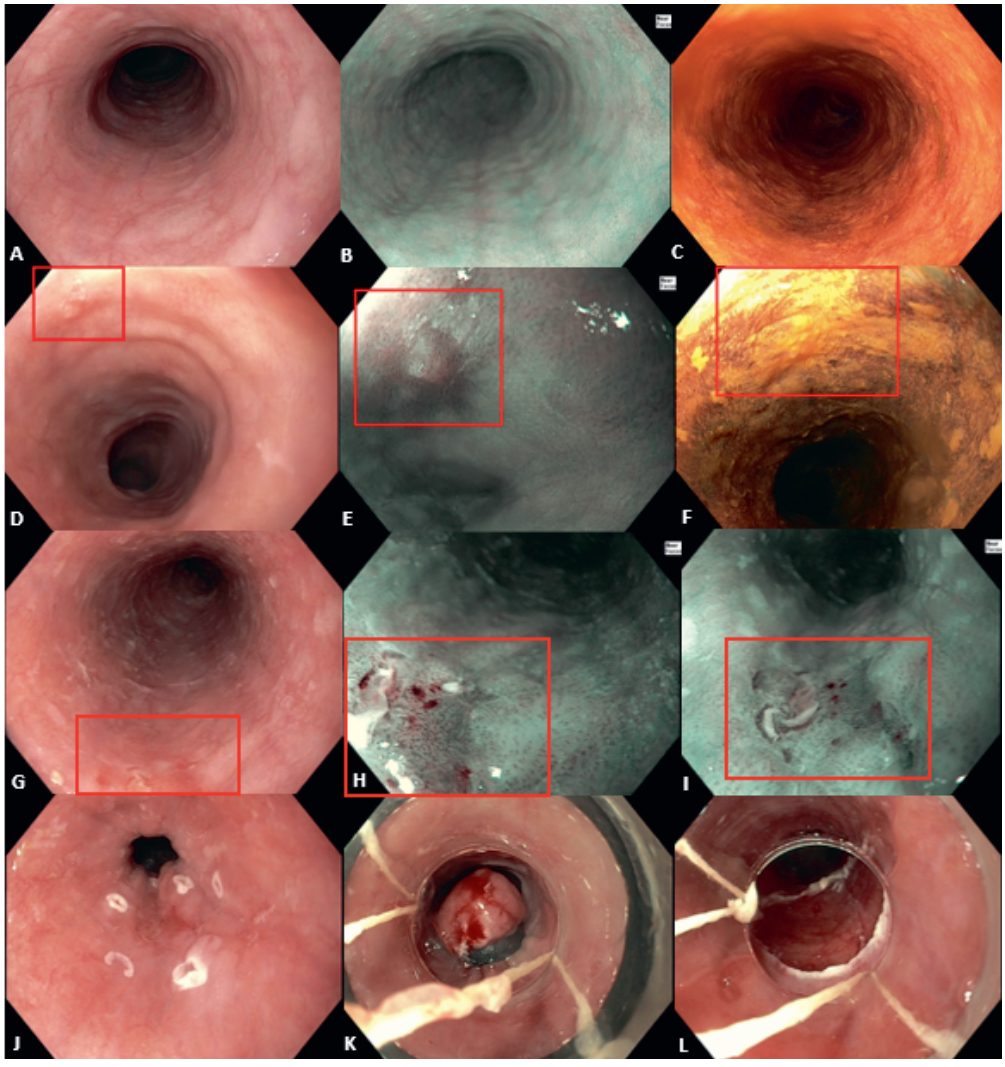


Figure 2. Endoscopic screening of the esophagus. Endoscopic images with white light endoscopy (A, D, G, J-L), optical chromoendoscopy (B, E, and H), and lugol's staining (C and F). Image A-C show no abnormalities. Images D-F show an early esophageal squamous cell carcinoma detected during endoscopic screening (patient 5). Endoscopic mucosal resection confirmed a pT1a esophageal squamous cell carcinoma. Images G-I show squamous high grade dysplasia, which could be removed with endoscopic mucosal resection (images J-L) (patient 1).

Other relevant GI findings detected with endoscopic screening

During endoscopic screening, one patient was diagnosed with an esophageal adenocarcinoma and one patient with gastric cancer. Both patients could be treated curatively with ER (EMR n=1, ESD n=1) and histopathological assessment revealed T1a cancer (n=2). Both patients received endoscopic follow up without recurrence. The patient diagnosed with esophageal adenocarcinoma was also treated with radiofrequency ablation. Other findings included the presence of gastroesophageal reflux disease (13.4%; grade A in 5.0%, grade B in 5.9%, grade C in 1.0%, and grade D in 0.5%), Barrett's esophagus (10.4%), and gastric intestinal metaplasia or confirmed Helicobacter pylori infection (5.4%).

Endoscopic detection techniques

Confirmed SPTs in the esophagus were detected with WLE (9/11), NBI (10/11) and Lugol's staining (6/7) (Table 3). No Lugol's staining was used in the assessment of four SPTs, as it was deemed not to have additional diagnostic value in the SPT diagnosis. All SPTs were detected with WLE combined with NBI. The additional value of Lugol's staining after WLE and NBI in expert hands was the detection of HGD in one patient and LGD in one patient. The positive predictive value was the highest for NBI (57.9%) and lowest for Lugol's staining (15.7%). The false positive detection rate of Lugol's staining was 84.3%. Figure S3 depicts different Lugol voiding lesions detected during endoscopic screening, with corresponding grades of dysplasia confirmed during pathological assessment.

Table 3. Detection of second primary tumors and low grade dysplasia in the upper gastrointestinal tract with different endoscopic screening techniques.

	WLE	NBI	Lugol's staining
Total screening endoscopies	250	249[1]	238[2]
Total suspected lesions n (%)	18 lesions during 15 (6.0%) endoscopies	19 lesions during 16 (6.4%) endoscopies	52 lesions during 38 (16.0%) endoscopies
Pathology[3]			
ESCC	7/7	7/7	2/3[2]
HGD	2/4	3/4	4/4
LGD	1/2	1/2	2/2
No dysplasia	8	8	43
No pathology	0	0	1
Positive predictive value, %			
For the detection of an SPT	9/18 (50.0%)	10/19 (52.6%)	6/51 (11.8%)[4]
For the detection of an SPT/LGD	10/18 (55.6%)	11/19 (57.9%)	8/51 (15.7%)[4]
False positives, %	8/18 (44.4%)	6/19 (42.1%)	43/51 (84.3%)[4]

[1] No NBI was used during one endoscopy, owing to patient discomfort. [2] No lugol's staining was used during 12 endoscopies because it had no additional diagnostic value for the assessment of SPTs, patient discomfort, or allergy. [3] Number of SPTs detected with endoscopic screening technique/total number of SPTs detected in the included patients.[4] Calculated for the total number of lesions with pathological confirmation (n=51). Patients with non-squamous lesions, including esophageal adenocarcinoma or gastric cancer, are not shown (n=2). ESCC, esophageal squamous cell carcinoma; HGD, high grade dysplasia; LGD, low grade dysplasia; NBI, narrow band imaging; narrow; SPT, second primary tumor; WLE, white light endoscopy.

SPTs detected on HNSCC imaging and in symptomatic patients

Among patients eligible for metachronous screening only (n=389, figure S1), 10 patients with HNSCC had already been diagnosed with an esophageal SPT, before these patients could be approached for endoscopic screening (Table S2, patients 11-20). These SPTs were detected during the HNSCC diagnostic work-up (n=6) and follow up (n=1) and in patients with symptoms of dysphagia and odynophagia (n=3). Unlike the SPTs in screened patients with HNSCC, SPTs among those not screened were detected more often at advanced stages (50.0%) (Figure 3) and no SPTs could be treated with ER. Esophageal SPT-related deaths occurred in 6/10 patients, all within 12 months after SPT diagnosis.

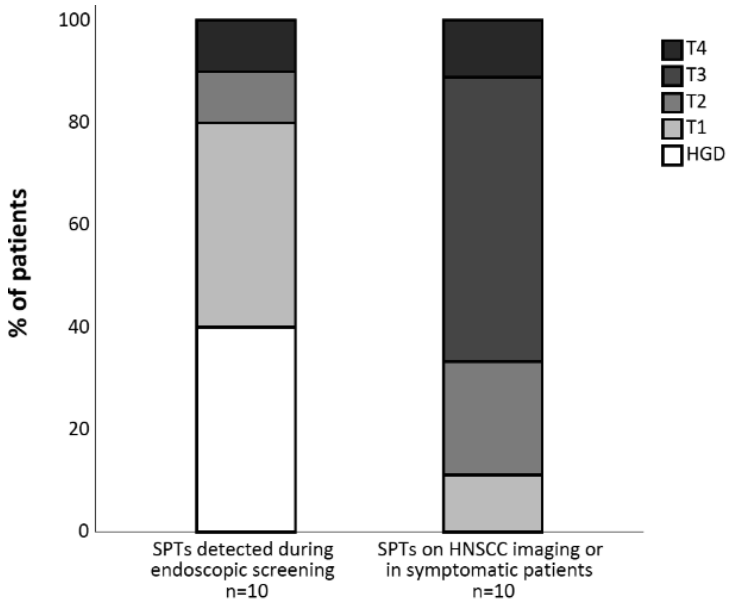


Figure 3. Tumor stage of second primary tumors (SPTs) of eligible patients with HNSCC. For one patient with two SPTs detected during endoscopic screening (patient 10), only the most advanced SPT was shown. The tumors stage of one patient (patient 20) was unknown. HGD, high grade dysplasia; SPTs, second primary tumors.

DISCUSSION

Endoscopic screening in patients with HNSCC holds the potential to detect SPTs in the esophagus at early stages. Currently, no routine screening for SPTs in patients with HNSCC has been implemented in most Western countries and the yield and benefit of endoscopic screening are yet to be determined.[13, 21] We conducted a prospective endoscopic screening study and detected SPTs in 5% of 202 patients with HNSCC in the Netherlands. Most SPTs were detected in an early stage and could be treated curatively with ER.

Our SPT prevalence of 5% is in line with previous endoscopic screening studies originating from European countries, reporting a prevalence ranging from 3% to 10% SPTs in patients with HNSCC.[15-17] We also reported on other GI tract cancers, detected during endoscopic screening. Although risk-profiles of different types of cancer in the upper GI tract differ strongly, we believe that these cancers should also be reported in Western screening studies for SPTs. The incidence of esophageal adenocarcinomas is rising in Western

countries [8] and early detection of upper GI tract cancers potentially has substantial positive consequences with regard to prognosis and survival of patients with HNSCC.
Screening in patients with HNSCC should focus on the detection of SPTs at early stages, as timely detection of SPTs may improve the survival rates of these patients. Previous literature assessing the use of PET/CT as the screening modality for the detection of SPTs reported a limited sensitivity of up to 38%, particularly for the detection of early-stage esophageal cancers.[13, 23, 24] This is in line with our study, as none of the SPTs detected on routine cross-sectional imaging for HNSCC were detected in early stages or could be treated with ER. In contrast, 80% of the patients with SPTs detected during endoscopic screening could be treated with ER.

The frequency and timing are key aspects of endoscopic screening in patients with HNSCC. Based on current data, one-time endoscopic screening may be preferable above repeat endoscopic screening, as follow up endoscopic screening in synchronously screened patients had a relatively limited SPT yield of 2%. The timing of one-time endoscopic screening should be further investigated, as synchronous endoscopic screening performed as part of the HNSCC diagnostic work-up has the potential to discover asymptomatic SPTs in the earliest stage possible. In the current study, however, 22% of synchronously screened patients developed metastatic HNSCC within 1 year after diagnosis and therefore did not benefit from synchronous screening. An advantage of metachronous screening is that a smaller selection of HNSCC patients with a favorable prognosis from HNSCC remain. Screening a smaller selection of HNSCC survivors is likely to be more cost effective than screening the entire HNSCC population and these patients probably have more benefit from early detection of SPTs. Therefore, a key aspect of the timing of screening are HNSCC-related survival rates, which depend on HNSCC staging and subsite. The 2-year survival rates vary between 62% for hypopharyngeal and oropharyngeal cancer to 81% for laryngeal cancer.[25] Based on previous literature and current data, we hypothesize that the optimal timing of screening might potentially be 1-2 years after HNSCC diagnosis, whereas potentially synchronous SPTs are still discovered at curable stages.

In the current study, systematic endoscopic screening was performed with WLE, NBI, and Lugol's staining. In expert hands using HD endoscopes, Lugol's staining often resulted in additional biopsies and ER, while the detection of additional SPTs was limited. These results are in line with the 2022 update of the European Society of GI Endoscopy, which recommends the use of HD endoscopy with WLE and NBI to screen for esophageal neoplasia.[26]

Although this was a large endoscopic screening study in patients with HNSCC in a Western country, some limitations need to be addressed. This was a single-center study including a selection of patients with HNSCC with presumed highest risk of SPTs based on previous Asian studies. This may limit the generalizability to all patients with HNSCC in daily clinical practice. In the Netherlands, care for patients with HNSCC is centralized in 14 experienced centers with uniform staging and treatment. We therefore expect that our results also apply to patients in other Western experienced HNSCC centers with experienced endoscopists. However, awareness and perspectives regarding endoscopic screening for SPTs may differ between specialists.[27]

The timing of endoscopic screening differed between included patients. Further studies should investigate individual risk-benefit profiles of all patients with HNSCC in Western countries. The ideal setting would be the combination of a nationwide endoscopic screening and the development of a risk prediction model, both including all patients treated curatively for HNSCC. Based on current guidelines, endoscopic screening should be performed with WLE and NBI and Lugol's staining may potentially be used based on endoscopists' preference.

In conclusion, endoscopic screening resulted in the detection of an esophageal SPT in 5% of patients with HNSCC. Most SPTs were detected at an early stage and could be treated with curative intent. Therefore, endoscopic screening for SPTs should be considered in selected patients with HNSCC. This selection should include patients with highest risk for SPTs (e.g. alcohol and tobacco consumption, hypopharyngeal and human papillomavirus-negative oropharyngeal carcinomas) with an acceptable life expectancy according to HNSCC prognosis and comorbidities. Metachronous one-time screening after curative treatment and adequate follow up time seems preferable for patients with HNSCC in Western countries. Based on our data combined with a patient selection with favorable survival, we suggest a timing between 12 to 24 months after HNSCC diagnosis.

REFERENCES

1. 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(6):1648-55.
2. Overwater A, Rueb K, Elias SG, et al. Esophageal Second Primary Tumors in Patients With Head and Neck Squamous Cell Carcinoma: Incidence, Risk Factors, and Overall Survival. Am J Gastroenterol. 2022;117(5):794-7.
3. van de Ven SEM, de Graaf W, Bugter O, et al. Screening for synchronous esophageal second primary tumors in patients with head and neck cancer. Dis Esophagus. 2021.
4. 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(4):1122-30.
5. Zhang N, Li Y, Chang X, et al. Long-term effectiveness of one-time endoscopic screening for esophageal cancer: A community-based study in rural China. Cancer. 2020;126(20):4511-20.
6. 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):752-9.
7. Thakur K, Singh CA, Thakar A, et al. Prevalence of Synchronous ESCN in Head and Neck Cancer: A Single-Institution Perspective. Laryngoscope. 2021;131(3):E807-E14.
8. Arnold M, Ferlay J, van Berge Henegouwen MI, et al. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. Gut. 2020;69(9):1564-71.
9. 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):938-43.
10. 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 Pt 1):408-17.
11. 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.
12. Chen YH, Wang YK, Chuang YS, et al. Endoscopic Surveillance for Metachronous Esophageal Squamous Cell Neoplasms among Head and Neck Cancer Patients. Cancers (Basel). 2020;12(12).
13. Guideline esophageal cancer (in Dutch: Richtlijn Oesofaguscarcinoom): Dutch society of gastroenterologists; Version 3.1. [Accessed 01/07/2023; Available from: https://www.mdl.nl/sites/www.mdl.nl/files/richlijnen/Richtlijn_Oesofaguscarcinoom.pdf].
14. Săftoiu A, Hassan C, Areia M, et al. Role of gastrointestinal endoscopy in the screening of digestive tract cancers in Europe: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2020;52(04):293-304.
15. Petit T, Georges C, Jung GM, et al. Systematic esophageal endoscopy screening in patients previously treated for head and neck squamous-cell carcinoma. Annals of oncology. 2001;12(5):643-6.
16. 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.
17. 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(12):2748-54.
18. Salcedo-Bellido I, Requena P, Mateos R, et al. Factors associated with the development of second primary tumours in head and neck cancer patients. European Journal of Cancer Care. 2022:e13699.
19. National Institute on Alcohol A, Alcoholism. Helping Patients Who Drink Too Much, A Clinician's Guide2007.
20. Adjei Boakye E, Buchanan P, Hinyard L, et al. Risk and outcomes for second primary human papillomavirus–related and–unrelated head and neck malignancy. The Laryngoscope. 2019;129(8):1828-35.
21. Leemans CR SL, Langendijk JA, et al. Guideline head and neck cancer (in Dutch: richtlijn Hoofd-halstumoren) 2012. [Accessed 01/07/2023; Available from: https://richtlijnendatabase.nl/richtlijn/hoofd-halstumoren/hoofd-halstumoren_-_korte_beschrijving.html].

22. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc. 2003;58(6 Suppl):S3-43.
23. Kondo N, Tsukuda M, Nishimura G. Diagnostic sensitivity of (1)(8)fluorodeoxyglucose positron emission tomography for detecting synchronous multiple primary cancers in head and neck cancer patients. Eur Arch Otorhinolaryngol. 2012;269(5):1503-7.
24. Su H-A, Hsiao S-W, Hsu Y-C, 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(1):1-9.
25. IKNL. Netherlands Cancer Registry - Netherlands Comprehensive Cancer Organisation [Accessed 01/07/2023; Available from: https://iknl.nl/nkr-cijfers].
26. Pimentel-Nunes P, Libânio D, Bastiaansen BAJ, et al. Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline–Update 2022. Endoscopy. 2022.
27. van Tilburg L, van den Ban SA, van de Ven SEM, et al. Screening for head and neck tumors in patients with esophageal squamous cell carcinoma and vice versa: a nationwide survey among medical specialists. Endoscopy International Open. 2022;10(09):E1268-E74.

SUPPLEMENTARY

Table S1. Baseline and HNSCC characteristics of the included patients with (n=10) and without (n=192) an esophageal SPT, detected during endoscopic screening.

Patient characteristics	**Patients without SPT,** n=192	**Patients with SPT,** n=10
Demographics		
Male sex	156 (81.3%)	7 (70.0%)
Age, years	65 [58-69]	67 (62-68)
ASA classification ≥III	42 (21.9%)	2 (20.0%)
Alcohol consumption		
Yes	150 (78.1%)	8 (80.0%)
Units per week	21 (14-35)	25 [10-39]
No	42 (21.9%)	2 (20.0%)
Alcohol use in the past	27	2
Units per week	40 [20-70]	84 [84-84]
Tobacco use		
Current	80 (41.7%)	8 (80.0%)
Pack years	40 [30-55]	31 [23-50]
Former	102 (53.1%)	1 (10.0%)
Pack years	40 [20-50]	50 [50-50]
Never	10 (5.2%)	1 (10.0%)
HNSCC characteristics	n=204	n=12
HNSCC location [1]		
Nasopharynx	1 (0.5%)	0
Hypopharynx	53 (26.0%)	5 (41.7%)
Oropharynx	65 (31.9%)	4 (33.3%)
Oral cavity	38 (18.6%)	2 (16.7%)
Larynx	47 (23.0%)	1 (8.3%)
T stage [1]		
Tis	18 (8.8%)	0
T1	45 (22.1%)	1 (8.3%)
T2	63 (30.9%)	7 (58.3%)
T3	45 (22.1%)	1 (8.3%)
T4	33 (16.2%)	3 (25.0%)
N stage [1]		
N0	126 (61.8%)	4 (33.3%)
N1	27 (13.2%)	0
N2	47 (23.0%)	8 (66.7%)
N3b	6 (2.9%)	0
M stage		
M0	192 (100%)	10 (100%)

Table S1. Baseline and HNSCC characteristics of the included patients with (n=10) and without (n=192) an esophageal SPT, detected during endoscopic screening. (continued)

HNSCC characteristics	n=204	n=12
HNSCC treatment		
Chemo- and/or radiotherapy	124 (64.5%)	7 (70.0%)
Surgery	31 (16.1%)	2 (20.0%)
Surgery + radiotherapy	16 (8.3%)	1 (10.0%)
Surgery + chemoradiotherapy	2 (1.0%)	0
Laser	17 (8.9%)	0
No treatment	2 (1.0%)	0

Data presented as n with percentage or median [p25-p75]. [1] Calculated for the total number of head and neck squamous cell carcinoma with SPTs (n=12) and without SPTs (n=204), excluding recurrences. HNSCC, head and neck squamous cell carcinoma; SPT, second primary tumor.

Table S2. Characteristics of patients with HNSCC and an esophageal SPT, diagnosed on HNSCC imaging or in symptomatic patients (n=10).

Patient			HNSCC characteristics		SPT characteristics						
ID	Sex	Age	Sub-location	TN stage	Symptoms	Indication	Primary detection method	Time to detection (months)	Tumor stage	Treatment	Outcome (follow up period in months)
11	M	67	Larynx	T3N2c	Dysphagia	HNSCC diagnostic work-up	PET/CT	2	T1	CRT + surgery	Patient died (15), due to ESCC or HNSCC
12	M	65	Larynx	T3N2c	None	HNSCC diagnostic work-up	CT	0	T2	CRT	No recurrence (24)
13	M	55	Oropharynx	T4aN2c	Dysphagia + odynophagia	HNSCC diagnostic work-up	PET/CT	1	T2	CRT	No recurrence (53)
14	F	78	Oropharynx	T1N2c	None	HNSCC diagnostic work-up	CT	1	T3	RT	Patient died (9), due to ESCC
15	M	62	Oropharynx	T2N3	None	HNSCC diagnostic work-up	CT	0	T3	No treatment	Patient died (7), due to ESCC
16	F	70	Oropharynx + oral cavity	T2N0 + T1bN0	None	HNSCC diagnostic work-up	PET/CT	37	T3	RT	Patient died (5), due to ESCC
17	M	54	Hypopharynx	T3N2b	Dysphagia + odynophagia	Symptoms	CT	35	T3	RT	Patient died (3), due to ESCC
18	M	65	Oropharynx	T3N2a	Dysphagia	Symptoms	CT	11	T3	CRT	Patient died (10), due to ESCC
19	M	62	Hypopharynx	T2N2c	Odynophagia	HNSCC recurrence	PET/CT	21	T4a	RT	Patient died (5), due to ESCC
20	F	67	Hypopharynx	T3N0	Dysphagia + odynophagia	Symptoms	Endoscopy	19	Tx	CRT	No recurrence (30)

CT, computed tomography; CRT, chemo- and radiotherapy; ESCC, esophageal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; PET/CT, Positron Emission Tomography/Computed Tomography; SPT, second primary tumor; RT, radiotherapy.

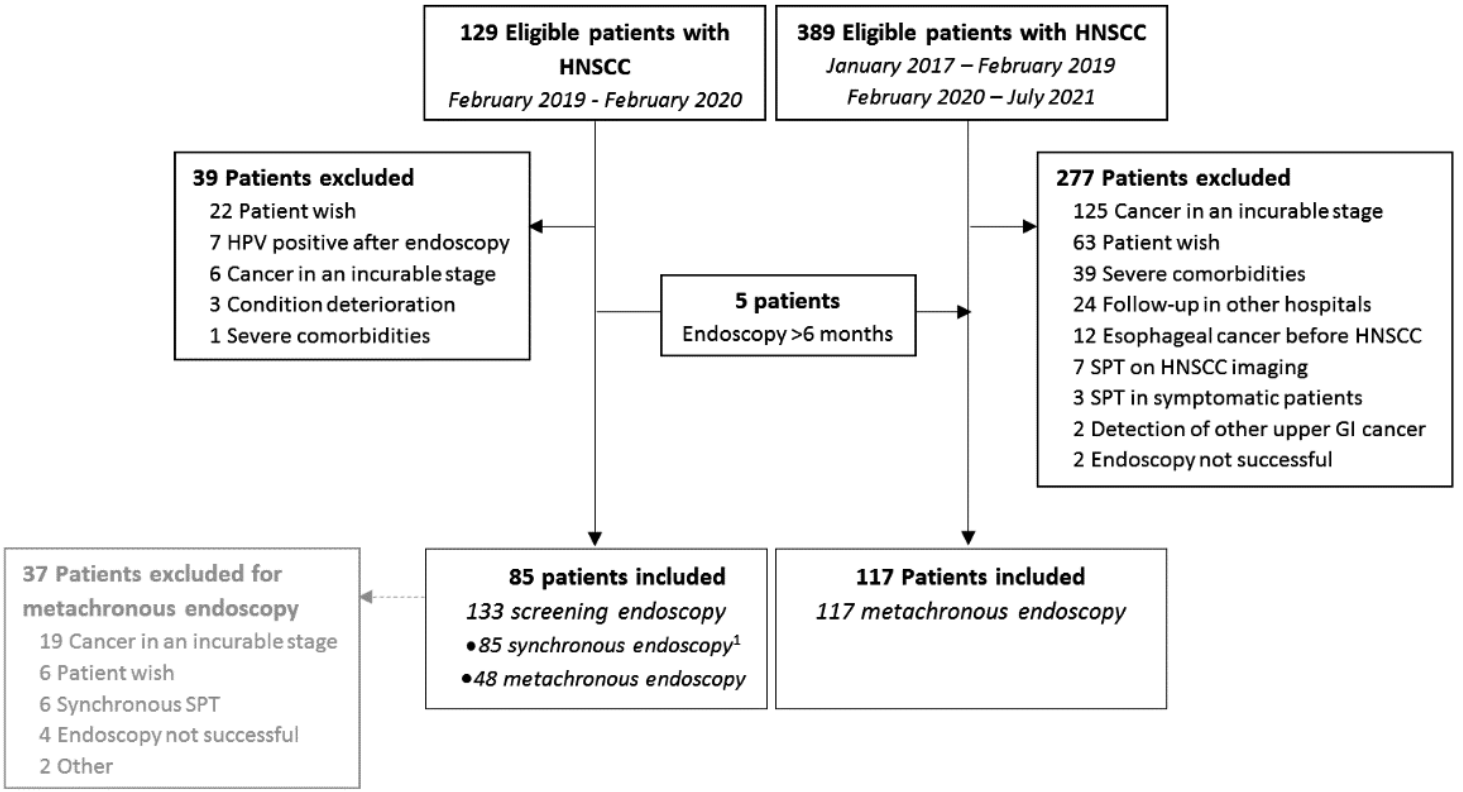


Figure S1. Flowchart of patient inclusion in the synchronous and metachronous endoscopic screening. HNSCC, head and neck squamous cell carcinoma; GI, gastrointestinal; HPV, human papillomavirus; SPT, second primary tumor. [1] Also included in the synchronous endoscopic screening study, published by van de Ven et al. (2021). The time between HNSCC diagnosis and endoscopic screening was divided in synchronous (without 6 months) and metachronous (after more than 6 months).

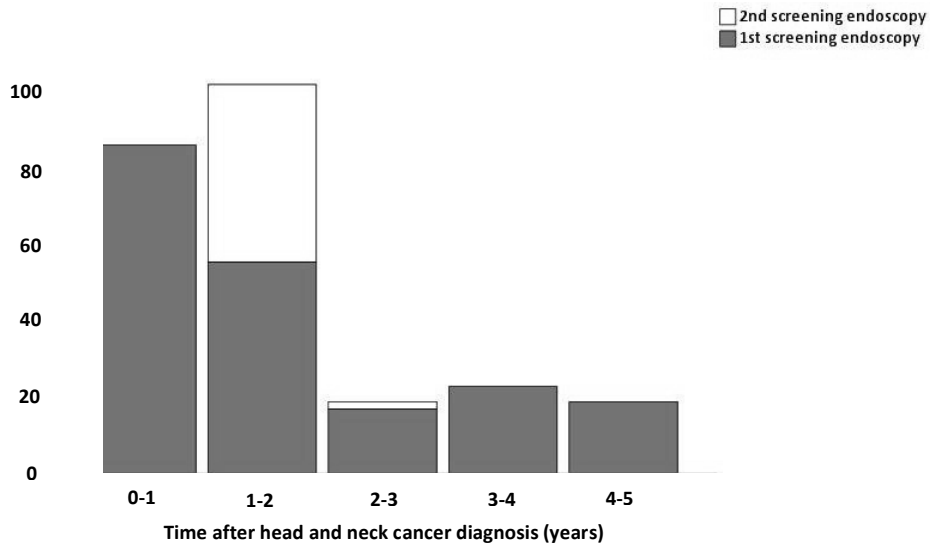
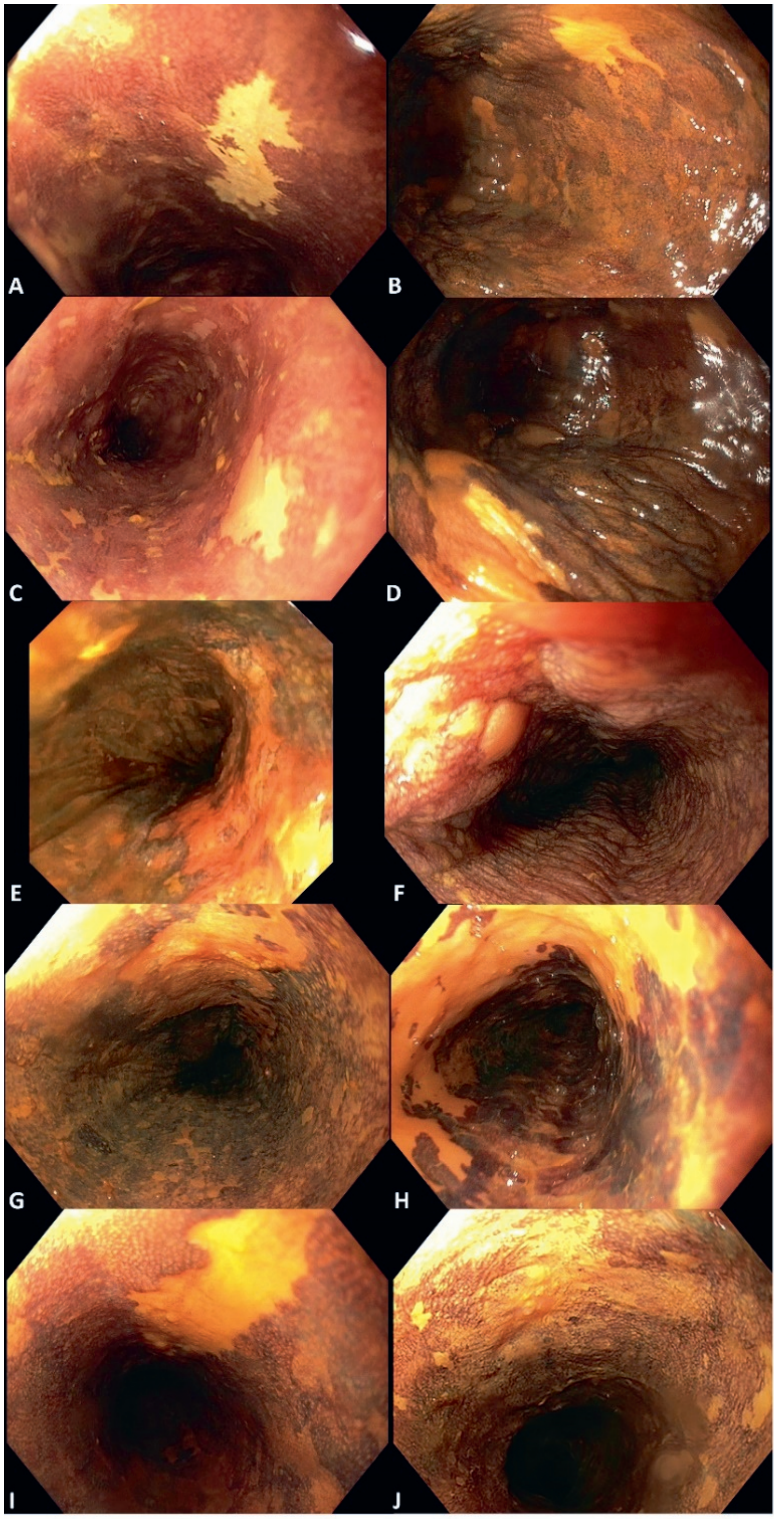


Figure S2. Timing of endoscopic screening of the upper gastrointestinal tract in patients with head and neck cancer.

Figure S3. Endoscopic images of lugol voiding lesions, detected during endoscopic screening of the esophagus (shown on page 155). Endoscopic images of lugol voiding lesions in the esophagus, detected during endoscopic screening in patients with HNSCC. Most lesions were removed with endoscopic resection (all lesions except E). The pathology assessment revealed no dysplasia for the lesions showed in images A-D, low grade dysplasia for lesions E and F, high grade dysplasia for lesions G and H and a T1a esophageal squamous cell carcinoma for I and J.


A
B
C
D
E
F
G
H
I
J

Chapter 6
(Appendix)

To screen or not to screen: Reply to “Long-term results of an endoscopic screening program for superficial esophageal cancer in patients with head and neck squamous cell carcinoma”

Laurelle van Tilburg, Marieke T. Brands, Arjun D. Koch

Endoscopy International Open. 2022

Reply letter

Esophageal second primary tumors (SPTs) frequently occur in patients with head and neck squamous cell carcinoma (HNSCC), with strongly varying incidences worldwide.[1, 2] Therefore, different screening strategies are used, from annual screening for every patient with HNSCC in some countries, including Brazil, to no standardized esophageal screening in Western countries. With great interest, we have read the article by Nobre Moura *et al.*[3] investigating endoscopic screening for superficial esophageal cancer in patients with HNSCC in Brazil. We compliment the authors for the large sample size of 1,888 patients with HNSCC with a relatively long median follow up time. The authors reported a detection rate of 7.9% esophageal SPTs by annual endoscopic screening and most esophageal SPTs (77.8%) were early stage lesions. The detection of advanced esophageal SPTs was associated with a significantly shorter overall survival in patients with HNSCC, while early esophageal SPTs showed no survival difference compared to those with HNSCC only. These results are promising and emphasize the need for further studies about screening patients with HNSCC for esophageal SPTs.

Even in countries with a high esophageal SPT incidence the absolute numbers are low, therefore many HNSCC patients will not benefit from screening. For each individual patient, the benefits of screening (i.e. the detection of early esophageal SPTs with potentially improved survival) should always be balanced against the harms of screening (i.e. the physical and psychological burden for patients and costs associated with screening). In the study by Nobre Moura *et al.*[3] patients with advanced HNSCC were excluded, however, both patients with and without treatment with curative intend were included. The expected benefits and harms balance of screening is likely unfavorable in patients with a limited life expectancy and these patients often do not opt for further treatment if an esophageal SPT is detected. We therefore believe that risk-based patient selection is essential for the effectiveness of esophageal screening in HNSCC patients.

The criteria of Wilson and Jungner assess the appropriateness of a population-based screening.[4] In the study by Nobre Moura *et al.*[3], it is questionable whether the criteria of an accepted treatment and costs of case-finding in relation to the total health care costs can be met for all HNSCC patients. We believe an individual approach based on the potential benefits and harms is essential. Given the low absolute numbers and the long timeframe over which esophageal SPTs occur, proper risk-assessment can only be achieved with the use of population-based data with a long follow up such as those found in national cancer registries.[5]

In conclusion, this interesting study showed that annual esophageal screening in HNSCC patients resulted in an increased detection of esophageal SPTs, mostly in early stages. Further studies should focus on a risk stratification of patients with HNSCC, taking into account all currently known risk factors and population-based data, to identify patients that will benefit the most of esophageal screening.

REFERENCES

1. 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(4):1122-30.
2. Arnold M, Ferlay J, van Berge Henegouwen MI, et al. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. Gut. 2020;69(9):1564-71.
3. Nobre Moura R, Kuboki Y, Baba ER, et al. Long-term results of an endoscopic screening program for superficial esophageal cancer in patients with head and neck squamous cell carcinoma. Endosc Int Open. 2022;10(2):E200-E8.
4. Wilson JMG, Jungner G, World Health O. Principles and practice of screening for disease. 1968.
5. Brands MT, Campschroer G, Merkx MAW, et al. Second primary tumours after squamous cell carcinoma of the oral cavity. Eur J Surg Oncol. 2021;47(8):1934-9.

Part IV

Endoscopic treatment
of esophageal neoplasia

Chapter 7

Western outcomes of circumferential endoscopic submucosal dissection for early esophageal squamous cell carcinoma

Enrique Rodríguez de Santiago*, Laurelle van Tilburg*, Pierre H. Deprez, Mathieu Pioche, Roos E. Pouw, Michael J. Bourke, Stefan Seewald, Bas L.A.M. Weusten, Jeremie Jacques, Sara Leblanc, Pedro Barreiro, Arnaud Lemmers, Adolfo Parra-Blanco, Ricardo Küttner-Magalhães, Diogo Libânio, Helmut Messmann, Eduardo Albéniz, Michal F. Kaminski, Noor Mohammed, Felipe Ramos Zabala, Alberto Herreros-de-Tejada, Hugo Uchima Koecklin, Timothée Wallenhorst, João Santos-Antunes, João A. Cunha Neves, Arjun D. Koch, Myriam Ayari, Rodrigo Garces Duran, Thierry Ponchon, Jérôme Rivory, Jacques J.G.H.M. Bergman, Eva P.D. Verheij, Sunil Gupta, Stefan Groth, Vincent Lepilliez, Ana R. Franco, Sanaa Belkhir, Jonathan White, Alanna Ebigbo, Andreas Probst, Romain Legros, Nastazja D. Pilonis, Diego de Frutos, Raquel Muñoz González, Mario Dinis-Ribeiro

* Shared first authorship

Gastrointestinal Endoscopy. 2023

ABSTRACT

Background and aims: Circumferential endoscopic submucosal dissection (cESD) in the esophagus has been reported to be feasible in small Eastern case series. We assessed the outcomes of cESD in the treatment of early esophageal squamous cell carcinoma (ESCC) in Western countries.

Methods: We conducted an international study at 25 referral centers in Europe and Australia using prospective databases. We included all patients with ESCC treated with cESD before November 2022. Our main outcomes were curative resection according to European guidelines and adverse events.

Results: A total of 171 cESDs were performed on 165 patients. En bloc and R0 resections rates were 98.2% (95% CI 95.0–99.4) and 69.6% (95% CI 62.3–76.0), respectively. Curative resection was achieved in 49.1% (95% CI 41.7–56.6) of the lesions. The most common reason for non-curative resection was deep submucosal invasion (21.6%). The risk of stricture requiring six or more dilations or additional techniques (incisional therapy/stent) was high (70.8%), despite the use of prophylactic measures in 93.4% of the procedures. The rates of intraprocedural perforation, delayed bleeding and adverse cardiorespiratory events were 4.1%, 0.6% and 4.7%, respectively. Two patients died (1.2%) from a cESD-related adverse event. Overall and disease-free survival rates at 2 years were 91.4% and 79.2%, respectively.

Conclusions: In Western referral centers, cESD for ESCC is curative in approximately half of the lesions. It can be considered a feasible treatment in selected patients. Our results suggest the need to improve patient selection and to develop more effective therapies to prevent esophageal strictures.

INTRODUCTION

Esophageal squamous cell carcinoma (ESCC) remains one of the leading causes of cancer-related mortality worldwide.[1] When detected at an early stage and endoscopically treated, ESCC survival rates exceed 90% in expert centers.[2] Endoscopic submucosal dissection (ESD) is less invasive and better tolerated than surgery (2% to 4% mortality[3]) and achieves higher en bloc and R0 resection rates than endoscopic mucosal resection.[1] Thus, most recent guidelines advocate ESD as the first-line treatment for early lesions confined to the mucosa or superficial submucosa when the predicted risk of regional lymphatic spread is low.[1, 4] The indication for endoscopic resection is usually based on size, optical diagnosis features and the circumferential extension of the lesion.[1, 4]

In particular, the use of ESD in patients with circumferential lesions remains controversial due to the paucity of data. It is currently unknown if the potential benefit in terms of curative resection outweighs the burden of severe esophageal strictures and other adverse events (AEs). The available scientific evidence stems from Eastern cohorts suggesting the technique to be feasible, with curative resection and local recurrence rates ranging from 60% to 100% and 0% to 12%, respectively.[5-8] The interpretation of these results in our setting is further limited by the small size of all available case series and because ESD outcomes differ between the East and the West.[9] Circumferential ESD (cESD) poses a technical challenge and its feasibility outside Asia remains to be defined. Consequently, European guidelines emphasize the need to gather more data to determine the outcomes of ESD in this complex scenario.[1, 4]

In this international study, we assessed the effectiveness and safety of cESD for the treatment of early ESCC in Western centers. Secondarily, we estimated overall and disease-free survival and evaluated predictors of non-curative resection and difficult-to-treat stenosis.

METHODS

Study design

This retrospective study was promoted by the Mucosal Resection Working Group of the Spanish Society of Gastrointestinal Endoscopy and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[10] Only Western centers with prospectively collected databases were allowed to participate in the study. We included all patients with early ESCC treated by cESD at each institution before November 2022. No exclusion criteria were applied. A total of 26 patients had been included in

previous publications but were also analyzed here to provide the complete picture of cESD.[11-15]

The study was approved by the ethics committees for clinical research of the participating centers (Institutional Review Board code at the promoting institution: HRYC-DSE-19). Written informed consent was obtained from all patients before their inclusion in the prospectively maintained ESD registries. Additional study-specific informed consent was obtained when deemed necessary by local regulations.

ESD procedure and histopathological assessment

The ESD technique and material used were at the discretion of each endoscopist. The need for complementary treatment (surgery, radiotherapy or chemotherapy) was agreed upon in the multidisciplinary committees of the participating institutions. All specimens were fixed in formalin after ESD for histopathological analysis. Histology was evaluated in each of the centers by an experienced pathologist dedicated to gastrointestinal lesions.

Definitions and outcomes

Study definitions were based on recent clinical guidelines and previous reports.[1, 4] Our primary outcome was curative resection according to the 2022 guidelines of the European Society of Gastrointestinal Endoscopy (ESGE)[1], defined as a free-margin resection (R0) and the absence of high risk histological criteria for lymph node metastasis. We considered the following to be curative: very low-risk resections (R0, no lymphovascular invasion, dysplasia or intramucosal carcinoma [m1-m2], well-to-moderately differentiated tumor and no ulceration) and low-risk resections (R0, no lymphovascular invasion, intramucosal carcinoma [m3] or submucosal invasion < 200 µm [sm1], well-to-moderately differentiated tumor, no ulceration and carcinoma size < 2 cm). Lesions fulfilling all the following criteria were classified as local-risk resection: horizontal margin R1 for dysplastic or cancer cells or not assessable (Rx), vertical margin free, no lymphovascular invasion, dysplasia or intramucosal carcinoma [m1-m2], well-to-moderately differentiated tumor and no ulceration. Finally, the resection was considered high risk (non-curative) if any of the following criteria were present: vertical margin R1, poorly differentiated tumor, lymphovascular invasion, ulceration, submucosal invasion > 200 µm (sm2/sm3) or submucosal invasion < 200 µm and carcinoma size > 2 cm.

Delayed bleeding was defined as bleeding within the first 30 days meeting any of the following: a) hematemesis or melena, b) > 2 g/dL drop in hemoglobin or c) endoscopic, radiological or surgical procedure due to suspicion of bleeding.[14] Esophageal stricture was

defined as narrowing of the lumen that required endoscopic dilation or caused clinical symptoms such as dysphagia or odynophagia. Strictures were defined as difficult-to-treat if the patient underwent six or more sessions of endoscopic dilation or required incisional therapy, stent placement or stenosis surgery.[8, 16] AEs were graded using the Adverse events in GastRointEstinal Endoscopy (AGREE) classification.[17]

Data collection

Data were collected using REDCap™. The investigators approved an electronic study-specific case report form before the study outset that included: a) endoscopist and center data, b) comorbidity and antithrombotic medication, c) pre-operative staging, d) ESD procedural data, e) lesion characteristics (size, location, morphology according to the Paris classification and optical diagnosis including the Japan Esophageal Classification [JES][18]), f) histology, g) AEs, and h) follow up. A central data review was performed between December 2022 and April 2023. In this review, we double-checked the primary and secondary outcomes, identified outliers, conducted a follow up update and reviewed all missing values. The final anonymized database was closed in May 2023 and was available to all the investigators.

Statistical analysis

Means and standard deviations were calculated for continuous variables while medians and ranges were used for variables with skewed distribution. We used frequency counts and percentages to describe categorical data**.** Predictors of non-curative resection and difficult-to-treat stricture were assessed using logistic regression and the 'all possible equations' method as the variable selection strategy.[19] Survival rates were estimated using the Kaplan-Meier method and a binary data framework. Cox regression was used to estimate the impact of curative resection on survival outcomes. Patients were right-censored at their last available visit.

No sample size estimation was made because the main objective of the study was descriptive (i.e., estimating the curative resection rate and AEs). We conducted the following exploratory analyses: a) calculation of the diagnostic yield of the JES classification to predict the depth of invasion based on intrapapillary capillary loop (IPCL) morphology; and b) comparison of the curative resection rate between lesions within (< 5 cm and clinically predicted T1a m1-m2) and beyond (> 5 cm or clinically predicted T1a m3/T1b) the Japanese guideline recommendations.[4] Missing values are presented in Tables. A p-value < 0.05 was considered significant. The statistical analysis was performed using Stata 14.2 (StataCorp, TX).

RESULTS

Study population

We invited 47 referral centers from Europe (n=40), America (n=6) and Australia (n=1) to take part. Of these, 25 participated in the study. A total of 171 cESDs in 165 patients were performed between March 2010 and November 2022 (Figure 1). Six patients underwent cESDs twice. The median Charlson Comorbidity Index was 4 points and 15.2% of the patients were considered unfit for surgery by a local multidisciplinary team. Additional characteristics are detailed in Table 1.

Preprocedural assessment

Most included lesions had a flat morphology (Table 2). Horizontal margins were delineated using virtual chromoendoscopy (n=102, 59.8%), Lugol's staining (n=8, 4.7%) and both methods (n=61, 35.7%). Dual focus technology was used in 99 lesions (57.9%) to assess the microvascular pattern, magnification in 20 (11.7%) and no zoom method in 52 (30.4%). The JES classification was available for 101 lesions (59.1%). The overall accuracy of the depth of invasion prediction was less than 80% for all IPCL subcategories (Table S1). Pre-operative imaging tests are detailed in Table S2.

Intramucosal carcinoma was the most common histology before cESD (n=81, 47.4%) (Table 2). The findings of the pre-ESD biopsy and the final specimen were concordant in 68 lesions (39.8%) but 99 were upstaged (57.9%) and 4 were downstaged (2.3%). A total of 32 lesions (39.5%) with a pre-ESD biopsy showing intramucosal carcinoma had submucosal invasion in the final specimen.

ESD procedure and en bloc resection rates

The procedures were performed by 31 endoscopists, most of whom performed more than 25 ESDs per year (n=28, 90.3%). The number of included procedures per center ranged between 1 and 22 (Figure 2). The en bloc resection rate was 98.2% (n=168, 95% CI 95.0–99.4). A multi-tunneling strategy was used in 122 lesions (71.4%). The median hospital stay was 2 days (range, 0–22 days). Additional details are provided in Table 2.

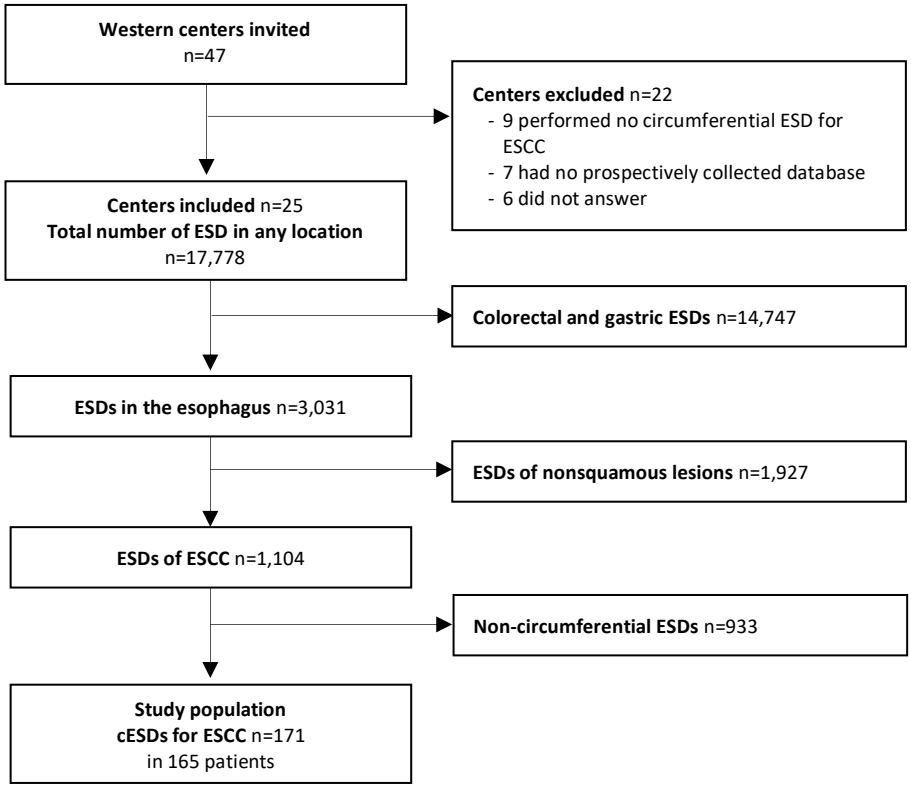


Figure 1. Study flowchart. ESD, endoscopic submucosal dissection; ESCC, esophageal squamous cell carcinoma.

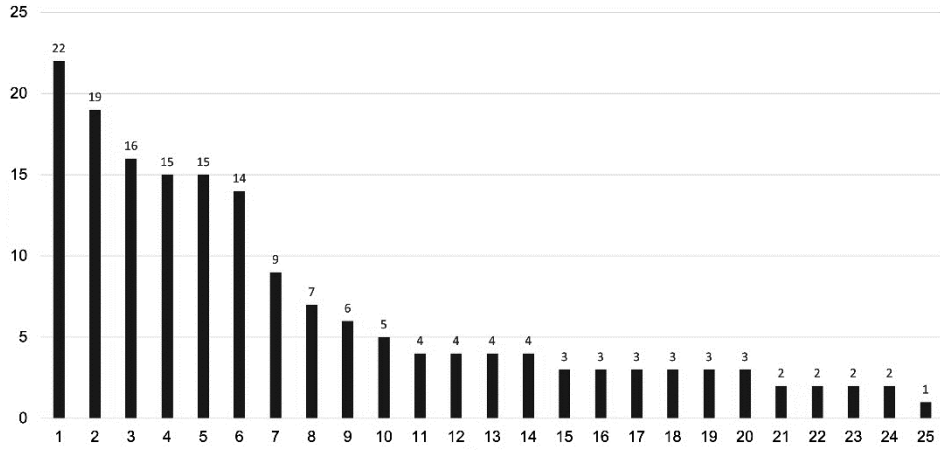


Figure 2. Number of circumferential ESDs performed per center. ESD, endoscopic submucosal dissection.

Table 1. Study population: characteristics of the included patients.

Characteristic	n = 165
Age, years	70.3 (34.0 – 91.8)
Female sex	74 (44.9%)
ASA functional status	
I	11 (6.7%)
II	83 (50.3%)
III	71 (43.0%)
Charlson Comorbidity Index	4 (0 -12)
Missing	1
Presence of liver cirrhosis	
No	150 (90.9%)
Yes, with esophageal varices	10 (6.1%)
Yes, without esophageal varices	5 (3.0%)
Unfit for surgery according to a formal MDT assessment	
No	131 (79.4%)
Yes	25 (15.2%)
Missing	9 (5.4%)
History of radiotherapy for head and neck cancer	18 (10.9%)
Use of anticoagulants	
No	145 (87.9%)
Vitamin K antagonists	8 (4.9%)
Apixaban	5 (3.0%)
Rivaroxaban	4 (2.4%)
Edoxaban	2 (1.2%)
Tinzaparin	1 (0.6%)
Use of antiplatelet therapy	
No	128 (77.6%)
Aspirin	31 (18.8%)
Clopidogrel	6 (3.6%)

Data presented as n (%) or median (range). ASA, American Society of Anesthesiologists; MDT, multidisciplinary team.

Table 2: Study population: baseline procedure and pathology characteristics.

Procedure characteristics	n = 171
Nº of circumferential ESD per patient	
1	165
2	6
Predominant location	
Upper esophagus (< 23 cm from the incisors)	29 (17.0%)
Mid esophagus (23 – 32 cm from incisors)	92 (53.8%)
Lower esophagus (> 32 cm to esophagogastric junction)	50 (29.2%)
Morphology according to the Paris classification	
IIa	52 (30.4%)
IIb	47 (27.5%)
IIc	4 (2.3%)
IIa + IIb	37 (21.7%)
IIa + IIc	18 (10.5%)
IIb + IIa	5 (2.8%)
Other	3 (3.6%)
Missing	2 (1.2%)
Preprocedural biopsy	
Not performed	13 (7.6%)
Indefinite for neoplasia	2 (1.2%)
Low grade dysplasia	4 (2.3%)
High grade dysplasia	71 (41.5%)
Intramucosal carcinoma	81 (47.4%)
Procedural time in minutes	143 (40 – 450)
CO2 insufflation	166 (97.1%)
Orotracheal intubation	150 (87.7%)
Non lifting sign	7 (4.1%)
Fibrosis	
F0	128 (74.9%)
F1	25 (14.6%)
F2	18 (10.5%)
Traction	
No	97 (56.7%)
Clip and line	55 (32.2%)
Clip and band	10 (5.9%)
Other	9 (5.3%)

Table 2: Study population: baseline procedure and pathology characteristics. (continued)

Pathology characteristics	
Size	
Long axis of the resection specimen, mm	60 (15 – 220)
Long axis of the carcinoma, mm	20 (1 – 145)
Invasion depth	
Low grade dysplasia	1 (0.6%)
High grade dysplasia	31 (18.1%)
T1a	89 (52.0%)
T1m2	54 (31.6%)
T1m3	33 (19.3%
Mucosal invasion depth missing	2 (1.2%)
T1b	50 (29.2%)
T1sm1 (<200 μm)	13 (7.6%)
T1sm2/3 (> 200 μm)	37 (21.6%)
Differentiation grade (for carcinoma only, n = 139)	
Well-moderate (G1-G2)	112 (80.6%)
Poor (G3)	22 (15.8%)
Missing	5 (3.6%)
Presence of lymphovascular invasion	27 (15.9%)
Vertical resection margin	
R0	144 (84.2%)
Rx	5 (2.9%)
R1	22 (12.9%)
Lateral resection margin	
R0	134 (78.4%)
Rx	5 (2.9%)
R1	32 (18.7%)
Ulceration in histology	17 (9.9%)

Data presented as n (%) or (range). ESD, endoscopic submucosal dissection.

Histology findings and curative resection

The most common histology in ESD specimens was intramucosal carcinoma (n=89, 52%), followed by carcinoma with submucosal invasion (Table 2). A total of 119 lesions had free margins (R0 resection rate 69.6%, 95% CI 62.3–76.0). From the 52 lesions with affected margins: 23 were horizontal margin positive, 13 vertical margin positive, 9 had both margins affected and 7 were Rx. Eighty-four cESDs (49.1%, 95% CI 41.7–56.5) were curative: 66 (38.6%, 95% CI 31.6–46.1) were classified as very low-risk resections and 18 (10.5%, 95% CI 6.8–16.1) as low-risk resections. Fifteen lesions (8.8%, 95% CI 5.4–14.0) had R1/Rx horizontal margins without other high-risk histological factors (local-risk resection). Seventy-two lesions (42.1%, 95% CI 35.0–49.6) were high-risk non-curative. Deep submucosal invasion was the most common reason for a high-risk non-curative resection (n=37, 21.6%) (Table 2). There was more than one histological finding associated with poor prognosis in 31 lesions (18.1%).

Only 14 lesions (8.2%) had a clinical indication for cESD according to Japanese guidelines. The risk of non-curative resection did not significantly differ by guideline indication (71.4% vs 46.9%, p = 0.09). In the multivariable analysis, a preprocedural biopsy harboring intramucosal carcinoma was the only variable associated with non-curative resection (Table 3).

Esophageal strictures and other AEs

Most included patients received stricture prophylaxis (n=156, 93.4%), and the strategies were highly heterogeneous (Table 4). Monotherapy with oral (41.5%) or topical (20.5%) steroids were the most common regimens. Of 165 patients, 139 (84.2%, 95% CI 77.8–89.4) developed esophageal stenosis. Of these, 121 strictures (70.8%, 95% CI 63.5–77.1) were difficult-to-treat.

Balloon dilation was the most common treatment (Table 4). The median time to the first dilation session was 27 days (range, 1–275 days). Eight patients developed esophageal perforation during 1327 follow up dilation sessions (0.6% risk per dilation session): five were treated with temporary stent placement, two with hemoclips and one did not require endoscopic treatment. A total of 119 patients (69.7%) were able to tolerate a regular solid diet at the last follow up after a median postprocedural time of 4.7 months (range, 1–59 months). In the multivariable analysis, the major axis of the lesion was the only variable associated with difficult-to-treat stenosis (Table 5, Table S3).

Table 3. Predictors for a noncurative resection.

	Curative resection		Univariable		Multivariable	
	Yes	No	OR (95% CI)	P value	OR (95% CI)	P value
Age, years	70.9 (34.0 – 91.8)	69.7 (49.4 - 88.1)	1.02 (0.99 – 1.06)	0.134	-	-
Location						
Middle esophagus	47 (51.1%)	45 (48.9%)	Ref.	-	-	-
Upper esophagus	14 (48.3%)	15 (51.7%)	0.89 (0.39 – 2.06)	0.792		
Lower esophagus	23 (46.0%)	27 (54.0%)	0.82 (0.41 – 1.63)	0.563		
Specimen long axis, mm	60 (23 – 220)	60 (15 – 138)	1.00 (0.99 – 1.01)	0.661		
ESD expertise						
> 200 procedures	79 (51.0%)	76 (49.0%)	Ref.	-	-	-
≤ 200 procedures	5 (31.3%)	11 (68.7%)	0.43 (0.15 – 1.32)	0.142		
Morphology						
IIc component						
No	72 (48.6%)	76 (51.4%)	Ref.	-		
Yes	12 (52.2%)	11 (47.8%)	0.87 (0.36 – 2.10)	0.753		
Center volume						
Low volume	58 (50.9%)	56 (49.1%)	Ref.	-	-	-
High-volume*	26 (45.6%)	31 (54.4%)	0.81 (0.43 – 1.53)	0.517		
Fibrosis						
No	60 (46.9%)	68 (53.1%)	Ref.	-	-	-
Yes	24 (55.8%)	19 (44.2%)	1.43 (0.71 – 2.87)	0.312		

Table 3. Predictors for a noncurative resection. (continued)

	Curative resection		Univariable		Multivariable	
	Yes	No	OR (95% CI)	P value	OR (95% CI)	P value
JES guideline indication						
Beyond guidelines (> 5 cm or IPCL B2-B3)	61 (46.9%)	69 (53.1%)	Ref.	-	-	-
Within guidelines (< 5 cm & IPCL B1)	10 (71.4%)	4 (28.6%)	2.82 (0.84 – 9.48)	0.092		
Not assessable (< 5 cm, IPCL unavailable)	13 (48.2%)	14 (51.8%)	1.05 (0.46 – 2.41)	0.908		
Preprocedural biopsy (n = 158)						
Carcinoma	32 (39.5%)	49 (60.5%)	Ref.	-	Reference	
LGD/HGD	46 (59.7%)	31 (40.3%)	2.27 (1.20 – 4.30)	0.012	2.27 (1.20 – 4.30)	0.012
JES IPCL classification (n = 101)						
B1	22 (66.7%)	11 (33.3%)	1.94 (0.81 – 4.64)	0.136	-	-
B2	34 (50.8%)	33 (49.3%)	Ref.	-		
B3	0 (0%)	1 (100%)	0.32 (0.01 – 8.23)	0.494		

Data presented as n (%) or median (range). CI, confidence interval; ESD, endoscopic submucosal dissection; HGD, high grade dysplasia; IPCL, intrapapillary capillary loop, LGD, low grade dysplasia; JES, Japan Esophageal Society; OR, odds ratio. *The high-volume group was comprised of the three centers with the highest nº of cases performed to compare the first quartile with the rest of the population

Postprocedural pain requiring opioids occurred in 21.6% of cESDs (n=37). One patient experienced delayed bleeding (0.6%, 95% CI 0.1–3.2) and was managed without endoscopic intervention. Intraprocedural perforation occurred during seven cESDs (4.1%, 95% CI 2.0–8.2): six were successfully closed with hemoclips and one did not receive any specific treatment due to the small size of the perforation. One patient developed a delayed perforation (0.6%, 95% CI 0.1–3.2) that was successfully treated with a fully covered stent. Eight patients experienced a respiratory or cardiovascular event (4.7%, 95% CI 2.4–8.9). No patient required surgery due to an ESD-related AE. The severity of all AEs is detailed in Table S4.

Two patients died due to an ESD-related AE (1.2%, 95% CI 0.3–4.2). One patient experienced esophageal perforation during balloon dilation and was treated with a fully covered stent. This patient developed an esophageal-respiratory fistula and heart failure causing death 53 days after the perforation. A patient with liver cirrhosis receiving prophylactic oral steroids was readmitted 3 weeks after the cESD with orbital mucormycosis that caused death 25 days after the cESD. Because steroids are a risk factor for systemic mucormycosis, the cause of death was considered ESD-related.

Follow up, complementary treatments and survival rates

The median follow up was 18.8 months (range, 0.4–122.5 months). A total of 161 (97.6%) and 118 patients (71.5%) had available follow up data at day 30 and 1 year, respectively. The complementary treatments received and outcomes stratified by curative resection are presented in Table 6. Twenty-nine patients (17.6%) received chemo- and/or radiotherapy. Fourteen patients (8.5%) underwent elective surgery because of non-curative resection: seven had no residual disease, three had lymph node metastases without intraluminal disease, two had intraluminal disease and lymph node metastasis and two had intraluminal disease. Sixteen patients died during follow up: nine deaths were unrelated to ESD or cancer, four were cancer-related deaths, two were secondary to an above-mentioned ESD-related AE and one was due to unknown reasons.

Overall survival rates at 1 and 2 years were 98.0% (95% CI 94.0–99.4) and 91.4% (95% CI 83.9–95.5). A total of 115 out of 118 (97.5%) and 74 out of 83 (89.2%) patients with available follow up were alive at 1 and 2 years, respectively. Disease-free survival rates at 1 and 2 years were 93.0% (95% CI 86.9–96.3) and 79.2% (95% CI 69.9-85.7). Curative resection had a beneficial impact on 2-year disease-free survival (89.4% vs 71.1%, adjusted hazard ratio 0.22, 95% CI 0.08–0.62), but not on 2-year overall survival (94.8% vs 88.5%, adjusted hazard ratio 0.30, 95% CI 0.08–1.09) (Figure 3 and Table S5).

Table 4. Prophylaxis and management of esophageal strictures.

Prophylaxis of esophageal strictures[1]	**n = 171**
Oral steroids	71 (41.5%)
Topical steroids	35 (20.5%)
Oral steroids + local steroid injection	14 (8.2%)
Local steroid injection	12 (7.0%)
Oral steroids + topical steroids	7 (4.1%)
Local steroid injection + topical steroids	7 (4.1%)
Oral steroids + topical steroids + PEG before ESD	5 (2.9%)
Prophylactic self-dilation with Savary before ESD	2 (1.2%)
Oral steroids + topical steroids + PEG before ESD + prophylactic stent	1 (0.6%)
Oral steroids + local steroid injection + topical steroids	1 (0.6%)
Oral steroids + local steroid injection + prophylactic stent	1 (0.6%)
Oral steroids + prophylactic stent	1 (0.6%)
Prophylactic stent	1 (0.6%)
No stricture prophylaxis	11 (6.4%)
Duration of oral steroids, weeks	8 (1 – 36)
Management of esophageal strictures	
Nº of patients that developed esophageal stricture	142 (83.0%)
Balloon dilation	132 (77.2%)
Nº of dilations	6 (1 – 59)
Initial balloon diameter, mm	12 (5 – 18)
Maximum balloon diameter, mm	15 (8 – 20)
Local injection of steroids	35 (20.5%)
Savary dilation	33 (19.3%)
Stent placement	31 (18.1%)
Repeated self-dilation at home	6 (3.5%)
Incisional therapy	5 (2.9%)

Data presented as n (%) or median (range). ESD, endoscopic submucosal dissection; PEG, percutaneous endoscopic gastrostomy. [1] The prophylactic regimen could not be disclosed in four patients, as they were included in a double-blinded randomized controlled trial comparing oral budesonide versus placebo.

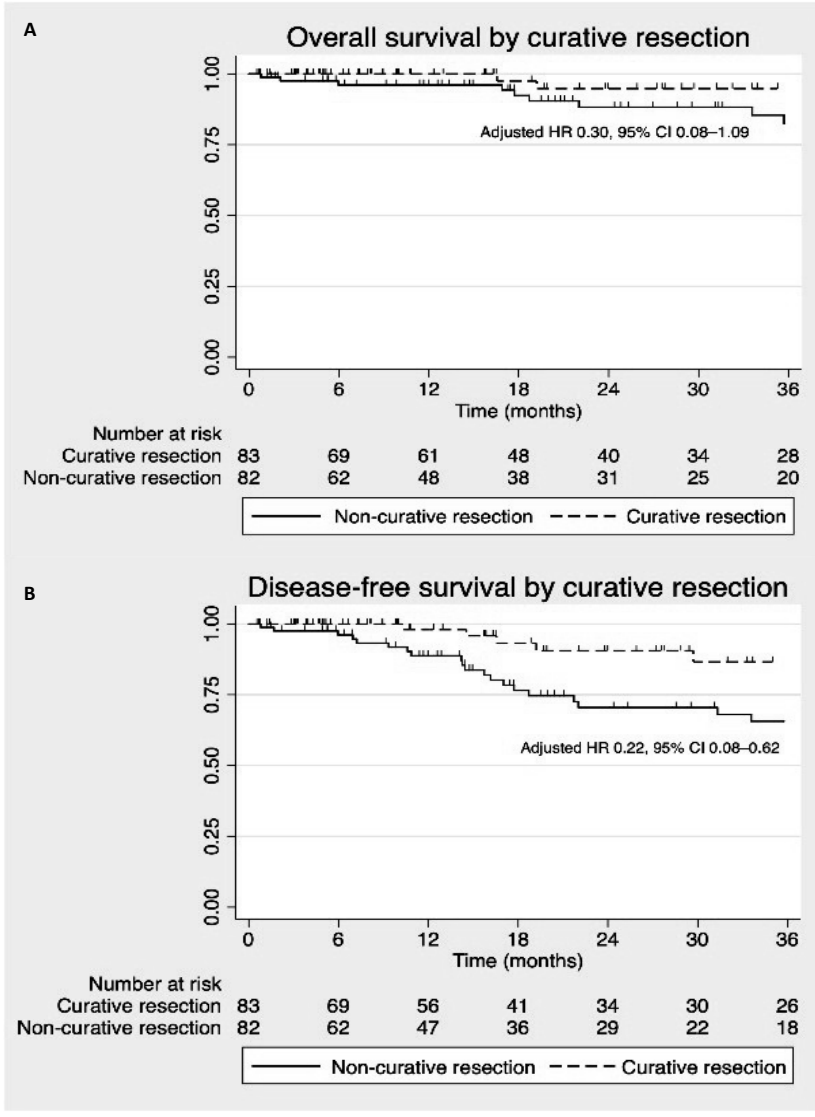


Figure 3. A) Overall survival. B) Disease-free survival. HR, hazard ratio.

Table 5. Predictors of difficult-to-treat esophageal stricture.

	Difficult-to-treat esophageal stenosis		Univariable		Multivariable	
	Yes	No	OR (95% CI)	P value	OR (95% CI)	P value
Age, years	70.3 (34.0 – 87.8)	70.5 (49.6 – 91.8)	0.99 (0.96 - 1.03)	0.838	-	-
Location						
Middle esophagus	64 (69.6%)	28 (30.4%)	Ref.		-	-
Upper esophagus	21 (72.4%)	8 (27.6%)	1.15 (0.45 – 2.90)	0.770		
Lower esophagus	36 (72.0%)	14 (28.0%)	1.13 (0.53 – 2.40)	0.761		
Stenosis prophylaxis (n = 167)						
No	8 (72.7%)	3 (27.4%)	Ref.	-	-	-
Yes	110 (70.5%)	46 (29.5%)	0.90 (0.23 – 3.53)	0.876		
Longitudinal axis of the lesion, mm	60 (15 – 200)	50 (15 – 160)s	1.02 (1.00 – 1.03)	0.016	1.02 (1.00 – 1.03)	0.016
Longitudinal axis of the mucosal defect, mm	80 (30 – 220)	75 (10 – 200)	1.01 (1.00 – 1.02)	0.087	Excluded due to collinearity	
Radiotherapy						
No	106 (71.1%)	43 (28.9%)	Ref.	-	-	-
Yes	15 (68.2%)	7 (31.8%)	0.87 (0.33 – 2.28)	0.776		
Morphology with IIc component						
No	106 (71.6%)	42 (28.4%)	Ref.	-	-	-
Yes	15 (65.2%)	8 (34.8%)	0.74 (0.29 – 1.88)	0.531		
Submucosal invasion						
No	87 (71.9%)	34 (28.1%)	Ref.	-	-	-
Yes	34 (68.0%)	16 (32%)	0.83 (0.41 – 1.70)	0.610		

Data presented as n (%) or median (range). CI, confidence interval; OR, odds ratio.

Table 6. Complementary treatments and outcomes stratified by curative resection.

	Very-low risk resection n=66	Low-risk resection n=18	High-risk non curative resection n=72	Local-risk resection n=15
Strategy after cESD				
No further treatment	65 (98.5%)	17 (94.4%)	35 (48.6%)	0
Definitive chemoradiotherapy	0	1 (5.6%)	12 (16.7%)	0
Radiotherapy	0	0	7 (9.7%)	0
Chemotherapy	1 (1.5%)[2]	0	4 (5.5%)	1 (6.7%)[3]
Surgery	0	0	11 (15.3%)	0
Chemoradiotherapy + surgery	0	0	2 (2.8%)	0
Chemotherapy + surgery	0	0	1 (1.4%)	0
Intraluminal recurrence	3 (4.5%)[1]	0	10 (13.9%)	1 (6.7%)
Metastatic disease during FU	1 (1.5%)[2]	0	12 (16.7%)	1 (6.7%)[3]
Death during FU	4 (6.1%)	0	9 (12.5%)	3 (20%)
ESD-related	0	0	2 (2.8%)	0
Cancer-related	1 (1.5%)[2]	0	3 (4.2%)[4]	0
Other	3 (4.5%)	0	4 (5.6%)	3 (20%)

Data presented as n (%). Median follow up was 18.8 months. [1]In two of the three patients it could not be clarified whether the intraluminal recurrence was a metachronous lesion or a recurrence of the index lesion. [2] The patient had history of oral squamous cell carcinoma treated by surgery and radiotherapy. The patient died due to metastatic disease of squamous carcinoma, although the exact origin (oral vs esophageal) could not be stablished. [3] Metastatic disease from lung squamous cell carcinoma. [4] Patient 1: carcinoma with deep submucosal invasion (1.750 µm). Died of metastatic disease despite adjuvant chemoradiotherapy. Patient 2: intramucosal poorly differentiated carcinoma with lymphovascular invasion. Died of concomitant metastatic head and neck cancer. Patient 3: carcinoma with deep submucosal invasion (640 µm). Underwent elective surgery, and no evidence of residual disease was found in the surgical specimen. Liver metastases were diagnosed 15 months after endoscopic submucosal dissection. Died of metastatic disease 2 months after. ESD, endoscopic submucosal dissection.

DISCUSSION

Balancing expected benefits and risks is key to defining the role of ESD in the management of early circumferential ESCC. In this international study, we found that cESD is feasible and associated with a high en bloc resection rate. The procedure was curative in approximately half of the patients and 79% were alive and cancer free after 2 years. Nonetheless, it was associated with a high risk of difficult-to-treat stenosis and a meaningful risk of procedure-related AEs.

Our curative resection rate (49.1%) was below that reported in Eastern studies (60%–100%) (Table S6). This is in line with the difference in the curative resection rates of noncircumferential esophageal ESDs between the East and the West[14, 15] and may have several explanations. First, our cohort often overlooked the guideline indications, given the high proportion of lesions with B2 IPCL (i.e., clinically predicted T1a-m3/T1b) or with a longitudinal axis exceeding 50 mm. This is an important point, as it implies that Western centers may be more willing to perform cESD as an "excisional biopsy". The Japanese guidelines make a weak recommendation for cESD in patients with clinical T1a-m1/m2 circumferential ESCC with a longitudinal axis less than 50 mm.[4] Meanwhile, ESGE guidelines label cESD an 'expanded' indication for T1a-m1/m2 but do not provide a longitudinal axis cut-off. Our results endorse the concept of cESD as an 'expanded' indication because the curative resection rate was below the figures expected for an 'absolute' indication[1, 20], even in the few lesions meeting guideline recommendations. Going beyond guidelines also happens in the East. In a recent Japanese survey conducted at 16 expert centers, 44% to 50% of institutions declared the use of cESD beyond guidelines for lesions > 50 mm and 56% to 70% for lesions < 50 mm T1a-m3/T1b.[7]

Second, the high rate of en bloc resection in our cohort suggests that the reason for the lower curative resection rate might be related to patient selection, rather than a technical ESD factor. It is likely that some physicians opted for cESD instead of surgery despite the presence of worrisome features, given the comorbidity burden of our cohort (median Charlson Comorbidity Index, 4). Third, Western endoscopists may be less familiar with the optical diagnosis of early ESCC and have less access to endoscopes with magnification, which could explain why nearly one-third of the lesions were not evaluated with any zoom method. The JES classification for estimating the invasion depth based on microvessel morphology can achieve an overall accuracy of about 90% in Japan.[18] However, its accuracy outside the East and in circumferential lesions has not been formally assessed.[18] When IPCLs were assessed (59%), our exploratory analysis found that the overall accuracy was low. The findings of this subanalysis should be interpreted with caution and need to be validated in Western studies. Moreover, affected horizontal margins were the main reason for R1

resection, which may be due to difficulties in delineating the lesion and reinforce the need to improve the pre-ESD optical assessment. Finally, biopsy before cESD underestimated the final pathology in nearly 60% of the lesions. Intramucosal carcinoma in the preprocedural biopsy was the sole preprocedural factor associated with a non-curative resection. From a clinical perspective, this finding can be regarded as an 'alarm sign' prompting a thorough mucosal interrogation with magnification in search of signs of deep submucosal invasion.

Esophageal stricture is a major concern after cESD that can severely impact patients' quality of life.[21] Our results confirm that most patients treated with cESD developed stenosis despite prophylaxis, and nearly 75% required frequent endoscopic dilations or more complex techniques such as incisional therapy or stent placement. Thus, all patients should be informed about the high risk of stenosis and its consequences before cESD. We chose difficult-to-treat stricture as the outcome of interest because it seemed more clinically relevant than simple stricture and because the risk factors for the latter are already known.[22] Interestingly, the long axis of the lesion did not correlate with the curative resection rate but did predict the development of difficult-to-treat stricture.

The best prophylactic regimen remains unknown, which explains the highly heterogeneous strategies found in our study. Oral steroids were the most common prophylactic treatment, despite the lack of randomized controlled trials supporting their use. When oral steroids are used, physicians should be aware of life-threatening drug-related AEs such as diabetes mellitus imbalance or immunosuppression. Indeed, one patient with liver cirrhosis died due to systemic fungal infection, an AE previously reported in patients on systemic steroid therapy prescribed to prevent esophageal strictures.[23] The Japanese guidelines weakly recommend local steroid injection for mucosal defects affecting more than three-quarters of the circumference, but it seems of limited efficacy after cESD.[4, 24] Topical steroids (e.g., budesonide) were also frequently used and represent an attractive alternative due to their ease of use and safety.[13] Whether prophylactic stenting, early postprocedural dilations before the stenosis becomes fibrotic or self-dilation ambulatory programs are of any benefit is yet to be clarified. New biomaterials, cell sheet engineering and autologous transplantation are currently being explored.[25]

The best treatment upon stenosis development also remains unclear. In our study, repeated balloon dilatation was the preferred method, and eight patients experienced esophageal perforation (one fatal case). Thus, patients undergoing cESD should also be well informed about the expected risks of stenosis treatment. An important finding of our study is that nearly 70% were able to tolerate a regular diet after 5 months, underscoring the fact that stenosis treatment is burdensome but often achieves an adequate response.

AEs beyond stenosis are also a concern. The incidence of intraprocedural perforation and bleeding are within an acceptable range and mirror those of previous reports.[5-8] Multi-tunneling and traction were frequently used, which may have helped to reduce the perforation risk and increase the procedural speed.[26, 27] We believe that a combination of the two strategies is probably the best ESD strategy for circumferential lesions.[11] Delayed perforation is another known AE of cESD and occurred in one patient.[28] Importantly, all these periprocedural AEs were successfully managed without surgery. The risk of respiratory and cardiovascular events was noticeable and should also be taken into consideration. This finding can be partially explained by the frequent use of antithrombotics, by the comorbidity burden and by the prolonged hospital stay often required for cESD.

The lack of long-term outcomes also explains the current controversy about the management of early circumferential ESCC. The cohort with the longest follow up (4 years) provides favorable results regarding overall (96%) and disease-free (86%) survival.[6] Our follow up was shorter, but we have already found slightly lower 2-year overall (91%) and disease-free (79%) survival rates. Nonetheless, a 'black-and-white' view is inadequate to consider our curative yield (50%) and survival rates disappointing, given the complexity of circumferential ESCC management and the morbidity of surgery. In addition, it is essential to delineate the reason for non-curative resection. In local-risk resections, endoscopic surveillance without further treatment was the most common strategy and we found no cancer-related deaths in this subgroup. High-risk non-curative resections entailed significant recurrence risk, but many patients can achieve long-term survival with subsequent complementary treatments.[29-31] Finally, photodynamic therapy could be an alternative to ESD in patients with early ESCC and has been approved after local failure to chemoradiotherapy. However, it does not allow a prognostic histological assessment and is not currently approved for circumferential lesions.[32]

The main strengths of this study are that it represents the largest cohort of cESD for ESCC, involving 25 Western referral centers, and that the data are derived from prospectively collected databases. However, several limitations must be acknowledged. First, the findings of our multivariable analysis lack external validation. Second, the high heterogeneity in stricture prophylaxis impeded elucidation of the benefit of each individual treatment. Third, we did not include a control group with other therapies because prospectively collected databases for surgery and chemoradiotherapy were often lacking, which anticipated a high risk of selection bias. Finally, a longer follow up is needed to determine the role of cESD in oncological terms.

In conclusion, our study shows that cESD for ESCC is technically feasible and can be curative in approximately 50% of lesions at high-volume Western centers. The risk of difficult-to-treat stenosis and other AEs further reinforces the need to improve optical diagnosis assessment and thereby refine patient selection. More effective prophylactic stricture regimens should be made a research priority to optimize outcomes. Until prospective data are available, cESD should be regarded as an 'expanded' indication and considered in well-selected patients with early ESCC at expert centers.

REFERENCES

1. Pimentel-Nunes P, Libânio D, Bastiaansen BAJ, et al. Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline–Update 2022. Endoscopy. 2022.
2. Nishizawa T, Suzuki H. Long-Term Outcomes of Endoscopic Submucosal Dissection for Superficial Esophageal Squamous Cell Carcinoma. Cancers (Basel). 2020;12(10).
3. D'Journo XB, Boulate D, Fourdrain A, et al. Risk Prediction Model of 90-Day Mortality After Esophagectomy for Cancer. JAMA Surg. 2021;156(9):836-45.
4. Ishihara R, Arima M, Iizuka T, et al. Endoscopic submucosal dissection/endoscopic mucosal resection guidelines for esophageal cancer. Dig Endosc. 2020;32(4):452-93.
5. Sato H, Inoue H, Kobayashi Y, et al. Control of severe strictures after circumferential endoscopic submucosal dissection for esophageal carcinoma: oral steroid therapy with balloon dilation or balloon dilation alone. Gastrointestinal Endoscopy. 2013;78(2):250-7.
6. Minamide T, Kawata N, Maeda Y, et al. Clinical outcomes of endoscopic submucosal dissection for superficial circumferential esophageal squamous cell carcinoma. Gastrointest Endosc. 2023;97(2):232-40 e4.
7. Kadota T, Ishihara R, Hatta W, et al. Multi-institutional questionnaire on treatment strategies for superficial entire circumferential esophageal squamous cell carcinoma. DEN Open. 2023;3(1):e206.
8. Kadota T, Yoda Y, Hori K, et al. Prophylactic steroid administration against strictures is not enough for mucosal defects involving the entire circumference of the esophageal lumen after esophageal endoscopic submucosal dissection (ESD). Esophagus. 2020;17:440-7.
9. Daoud DC, Suter N, Durand M, et al. Comparing outcomes for endoscopic submucosal dissection between Eastern and Western countries: A systematic review and meta-analysis. World J Gastroenterol. 2018;24(23):2518-36.
10. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-9.
11. Stephant S, Jacques J, Brochard C, et al. High proficiency of esophageal endoscopic submucosal dissection with a "tunnel + clip traction" strategy: a large French multicentric study. Surg Endosc. 2023;37(3):2359-66.
12. Fraile-Lopez M, Parra-Blanco A. Double-tunnel circumferential endoscopic submucosal dissection with double clip-band-line traction for an esophageal squamous neoplasm. Endoscopy. 2020;52(8):E303-E5.
13. van de Ven SEM, Snijders M, Bruno MJ, et al. Effectiveness of topical budesonide in preventing esophageal strictures after endoscopic resection of esophageal cancer. Endosc Int Open. 2020;8(12):E1795-E803.
14. Rodriguez de Santiago E, Herreros-de-Tejada A, Albeniz E, et al. Implementation of esophageal endoscopic submucosal dissection in Spain: Results from the nationwide registry. Implementacion de la diseccion endoscopica submucosa esofagica en Espana: resultados del registro nacional. Gastroenterol Hepatol. 2023.
15. Fleischmann C, Probst A, Ebigbo A, et al. Endoscopic Submucosal Dissection in Europe: Results of 1000 Neoplastic Lesions From the German Endoscopic Submucosal Dissection Registry. Gastroenterology. 2021;161(4):1168-78.
16. Kochman ML, McClave SA, Boyce HW. The refractory and the recurrent esophageal stricture: a definition. Gastrointest Endosc. 2005;62(3):474-5.
17. Nass KJ, Zwager LW, van der Vlugt M, et al. Novel classification for adverse events in GI endoscopy: the AGREE classification. Gastrointest Endosc. 2022;95(6):1078-85 e8.
18. Oyama T, Inoue H, Arima M, et al. Prediction of the invasion depth of superficial squamous cell carcinoma based on microvessel morphology: magnifying endoscopic classification of the Japan Esophageal Society. Esophagus. 2017;14(2):105-12.
19. Doménech JM, Navarro JB. Find the best subset for linear, logistic and cox regression: user-written command confound for Stata [computer program]. Bellaterra: Universitat Autònoma de Barcelona. 2020;1.
20. Ono H, Yao K, Fujishiro M, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer (second edition). Dig Endosc. 2021;33(1):4-20.

21. Libanio D, Pimentel-Nunes P, Bastiaansen B, et al. Endoscopic submucosal dissection techniques and technology: European Society of Gastrointestinal Endoscopy (ESGE) Technical Review. Endoscopy. 2023;55(4):361-89.
22. Lin N, Lin J, Gong J. Risk factors of postoperative stricture after endoscopic submucosal dissection for superficial esophageal neoplasms: A meta-analysis. Medicine (Baltimore). 2021;100(51):e28396.
23. Ishida T, Morita Y, Hoshi N, et al. Disseminated nocardiosis during systemic steroid therapy for the prevention of esophageal stricture after endoscopic submucosal dissection. Dig Endosc. 2015;27(3):388-91.
24. Miyake M, Ishihara R, Matsuura N, et al. Predictors of stricture after non-circumferential endoscopic submucosal dissection of the esophagus and single-dose triamcinolone injection immediately after the procedure. Gastrointest Endosc. 2023;98(2):170-7.
25. Zhou XB, Xu SW, Ye LP, et al. Progress of esophageal stricture prevention after endoscopic submucosal dissection by regenerative medicine and tissue engineering. Regen Ther. 2021;17:51-60.
26. Lopimpisuth C, Simons M, Akshintala VS, et al. Traction-assisted endoscopic submucosal dissection reduces procedure time and risk of serious adverse events: a systematic review and meta-analysis. Surg Endosc. 2022;36(3):1775-88.
27. Fan X, Wu Q, Li R, et al. Clinical benefit of tunnel endoscopic submucosal dissection for esophageal squamous cancer: a multicenter, randomized controlled trial. Gastrointest Endosc. 2022;96(3):436-44.
28. Yano T, Tanabe S, Ishido K, et al. Delayed perforation after endoscopic submucosal dissection for early gastric cancer: Clinical features and treatment. World J Gastrointest Endosc. 2016;8(8):368-73.
29. Berger A, Perrod G, Pioche M, et al. Efficacy of Organ Preservation Strategy by Adjuvant Chemoradiotherapy after Non-Curative Endoscopic Resection for Superficial SCC: A Multicenter Western Study. Cancers (Basel). 2023;15(3).
30. Minashi K, Nihei K, Mizusawa J, et al. Efficacy of Endoscopic Resection and Selective Chemoradiotherapy for Stage I Esophageal Squamous Cell Carcinoma. Gastroenterology. 2019;157(2):382-90 e3.
31. Flor de Lima M, Castro B, Rodriguez-Carrasco M, et al. Best additional management after non-curative endoscopic resection of esophageal squamous cell carcinoma: a systematic review and meta-analysis. Scand J Gastroenterol. 2022;57(5):525-33.
32. Inoue T, Ishihara R. Photodynamic Therapy for Esophageal Cancer. Clin Endosc. 2021;54(4):494-8.

Table S1. Japan Esophageal Classification IPCL assessment (n = 101).

IPCL	Invasion depth			Overall accuracy	Sensitivity	Specificity	Positive predictive value	Negative predictive value
	<T1a m3	T1m3/T1sm1	>T1sm1					
B1	21 (63.6%)	11 (33.3%)	1 (3.0%)	58.4%, 95%CI: 48.7-67.5%	41.2% 95%CI: 28.8-54.8%	76.0% 95%CI: 62.6-85.7%	63.6% 95%CI: 46.6-77.8%	55.9% 95%CI: 44.1-67.1%
B2	30 (44.7%)	17 (25.4%)	20 (29.8%)	39.6% 95%CI: 30.6-49.4%	60.7% 95%CI: 42.4-76.4%	31.5% 95%CI: 22.0-42.9%	25.4% 95%CI: 16.5-39.5%	67.6% 95%CI: 50.8-80.9%
B3	0 (0%)	0 (0%)	1 (100%)	79.2% 95%CI: 70.3-86.0%	4.6% 95%CI: 0.8-21.8%	100% 95%CI: 95.4-100%	100% 95%CI: 20.7-100%	79.0% 95%CI: 70.0-85.8%

Data presented as n (%). CI, confidence interval; IPCL, intrapapillary capillary loop.

Table S2. Preprocedural imaging.

Imaging performed before ESD	
None	48 (28.1%)
Endoscopic ultrasonography	18 (10.5%)
CT scan	30 (17.5%)
Endoscopic ultrasonography + CT scan	70 (40.9%)
PET scan	54 (31.6%)
Endoscopic ultrasonography	**n = 88**
Tx	19 (21.8%)
Tis	15 (17.2%)
T1	49 (56.3%)
T2	4 (4.6%)
Missing	1 (1.1%)
Nx	4 (4.5%)
N0	78 (88.6%)
N1[1]	4 (4.5%)
N2[2]	1 (1.2%)
Missing	1 (1.1%)
CT scan	**n = 100**
Tx	67 (67.0%)
Tis	14 (14.0%)
T1	16 (16.0.%)
T2	1 (1.0%)
Missing	2 (2.0%)
Nx	2 (2.0%)
N0	92 (92.0%)
N1	3 (3.0%)
Missing	3 (3.0%)
PET scan	**n = 54**
Intraluminal uptake	20 (37.1%)
N0	53 (98.2%)
Suspicious lymph nodes	1 (1.9%)

Data presented as n (%). CT, computed tomography; ESD, endoscopic submucosal dissection; PET, positron emission tomography. [1]In three patients endoscopic ultrasonography-guided biopsy was negative for malignant cells. In the remaining patient, the PET scan did not show pathologic uptake and ESD was agreed upon in the multidisciplinary committee. [2]Endoscopic ultrasonography-guided biopsy was negative for malignant cells.

Table S3. Risk of difficult-to-treat stricture after categorizing lesion size in 3 groups.

Major axis	Difficult-to-treat stricture rate
0-50 mm	63.1% (95% CI 52.4-72.6)
51-100 mm	76.5% (95% CI 65.1-85.0)
>100 mm	93.8% (95% CI 71.6-98.9)

CI, confidence interval.

Table S4. Adverse events and their severity according to the AGREE classification.

Significant intraprocedural bleeding	
No	168 (98.2%)
Grade II	1 (0.6%)
Grade IIIa	2 (1.2%)
Delayed bleeding	
No	170 (99.4%)
Grade II	1 (0.6%)
Intraprocedural perforation	
No	164 (95.9%)
Grade I	1 (5.8%)
Grade IIIa	6 (3.5%)
Delayed perforation	
No	170 (99.4%)
Grade IVa	1 (0.6%)
Perforation during follow up dilations	
No	163 (95.3%)
Grade II	1 (0.6%)
Grade III	6 (3.5%)
Grade V	1 (0.6%)
Other adverse events	
Grade II	
Pain requiring opioids	37 (21.6%)
Transient fever	7 (4.1%)
Pulmonary embolism	2 (1.2%)
Chronic obstructive pulmonary disease exacerbation	1 (0.6%)
Temporary respiratory distress	1 (0.6%)
Pneumoperitoneum	1 (0.6%)
Pneumomediastinum	1 (0.6%)
Grade IV	
Acute coronary syndrome	1 (0.6%)
Grade V	
Systemic mucormycosis	1 (0.6%)

AGREE, Adverse events in GastRointEstinal Endoscopy.

Table S5. Impact of curative resection on overall and disease-free survival, adjusted by age, comorbidity and complementary treatments.

	Overall survival		
	Hazard Ratio	**95% CI**	***P* value**
Age	1.01	0.96 – 1.07	0.668
Charlson Comorbidity Index	1.28	0.98 – 1.66	0.070
Curative resection	0.30	0.08 – 1.09	0.068
Elective adjuvant surgery	0.44	0.05 – 3.54	0.439
Chemoradiotherapy	0.92	0.19 – 4.57	0.926
	Disease-free survival		
	Hazard Ratio	**95% CI**	***P* value**
Age	1.00	0.96 – 1.04	0.912
Charlson Comorbidity Index	1.15	0.95 – 1.41	0.147
Curative resection	0.22	0.08 – 0.62	0.004
Elective adjuvant surgery	0.70	0.23 – 2.07	0.516
Chemoradiotherapy	1.52	0.62 – 3.77	0.357

CI, confidence interval.

Table S6. Summary of studies evaluating circumferential esophageal endoscopic submucosal dissection for early squamous cell carcinoma.

Author (year)	Country	Study design	n	Technical success	Curative resection	Stenosis rate	Other adverse events	Follow-up	Local recurrence	Distant metastasis
Isomoto *et al. (2011)*	Japan	Retro	7	100%	100% (≤Sm1)	100%	No adverse events related to ESD technique	11 months (mean)	0%	0%
Sato *et al. (2013)*	Japan	Retro	22	100%	NR	100%	No adverse events related to ESD technique	NR	0%	NR
Miwata *et al.(2015)*	Japan	Retro	19	NR	100%	100%	Perforation or scratched muscularis propria (n=10)	NR	NR	0%
Ye *et al.(2015)*	China	Pro	23	100%	100%	NR for cESD. Overall: 17.4%	NR for cESD. Overall: Mediastinal emphysema 8.7%; Pneumothorax 4.3%	16 months (median)	0%	0%
Gan *et al. (2016)*	China	Case series	7	100%	100%	100%	Scratched muscularis propria without need of intervention (n=2)	1-12 months	0%	NR
Iizuka *et al.(2018)*	Japan	Retro	22	100%	90.9%	59%	No adverse events related to ESD technique. Adverse events related to corticotherapy.	20 weeks	0%	0%
Liao *et al.(2018)*	China	Retro	9	100%	100%	88.9%	None	Mean 16.8 months	NR	11%
Longsong *et al.(2019)*	China	Pro	8	100%	100%	12.5%	None	Median: 7.3	0%	NR

Table S6. Summary of studies evaluating circumferential esophageal endoscopic submucosal dissection for early squamous cell carcinoma. (continued)

Author (year)	Country	Study design	n	Technical success	Curative resection	Stenosis rate	Other adverse events	Follow-up	Local recurrence	Distant metastasis
Chai *et al.(2019)*	China	Pro	8	100%	100%	37.5%	None	Median follow-up: 7 months	NR	NR
Kadota *et al.(2020)*	Japan	Pro	26	NR	92%	62%	Bleeding (n=1)	NR	NR	NR
Liu *et al.(2021)*	China	Pro	25	100%	80%.	44%	Stent migration (n=2)	10 months (median)	NR	NR
Lian *et al.(2022)*	China	Pro	25	100%	100%	12%	NR	6 months	NR	NR
Minamide *et al.(2023)*	Japan	Retro	52	100%	59.6%	85.7%	Perforation (7.7%) Delayed bleeding (1.9%)	49 months (median)	11.5%	1.9%

cESD, circumferential submucosal dissection; pro, prospective; retro, retrospective.

Chapter 8

Vertical tumor-positive resection margins and the risk of residual neoplasia after endoscopic resection of Barrett's neoplasia: a nationwide cohort with pathology reassessment

Laurelle van Tilburg*, Eva P.D. Verheij*, Steffi E.M. van de Ven, Sanne N. van Munster, Bas L.A.M. Weusten, Lorenza Alvarez Herrero, Wouter B. Nagengast, Erik J. Schoon, Alaa Alkhalaf, Jacques J.G.H.M. Bergman, Roos E. Pouw, Lindsey Oudijk, Sybren L. Meijer, Marnix Jansen, Michail Doukas*, Arjun D. Koch*

On behalf of the Dutch Barrett Expert Centers and the Dutch Barrett Expert Centers study group.

* Shared first/last authorship

Endoscopy, 2024

ABSTRACT

Background: This study evaluated the proportion of patients with residual neoplasia after endoscopic resection (ER) for Barrett's neoplasia with confirmed tumor-positive vertical resection margin (R1v).

Methods: This retrospective cohort study included patients undergoing ER for Barrett's neoplasia with histologically documented R1v since 2008 in the Dutch Barrett Expert Centers. We defined R1v as cancer cells touching vertical resection margins and Rx as nonassessable margins. Reassessment of R1v specimens was performed by experienced pathologists until consensus was reached regarding vertical margins.

Results: 101/110 included patients had macroscopically complete resections (17 T1a, 84 T1b), and 99/101 (98%) ER specimens were histologically reassessed. Reassessment confirmed R1v in 74 (75%) patients and found Rx in 16% and R0 in 9%. Presence/absence of residual neoplasia could be assessed in 66/74 patients during endoscopic reassessment (n=52) and/or in the surgical resection specimen (n=14), and 33/66 (50%) had residual neoplasia. Residual neoplasia detected during endoscopy was always endoscopically visible and biopsies from a normal-appearing ER scar did not detect additional neoplasia. Of 25 patients who underwent endoscopic follow-up (median 37 months [IQR 12–50]), 4 developed a local recurrence (16.0%), all detected as visible abnormalities.

Conclusions: Histological evaluation of ER margins appears challenging, as 75% of documented R1v cases were confirmed during reassessment. After ER with R1v, 50% of patients had no residual neoplasia. Endoscopic reassessment 8–12 weeks after ER seems to accurately detect residual neoplasia and can help to determine the most appropriate strategy for patients with R1v.

INTRODUCTION

Endoscopic resection (ER) has become the first-line curative treatment for early neoplasia in Barrett's esophagus (BE), because of its safety and low cancer recurrence risk during long-term follow up.[1-3] Histopathological assessment of the ER specimen predicts the risks for lymph node metastasis (LNM) and residual neoplasia. This assessment drives further clinical decision-making, ranging from endoscopic follow up to surgery.[2, 4] Endoscopic follow up is justified in patients with a low-risk of LNM (i.e. mucosal or superficial submucosal cancer (≤sm1) with good to moderate tumor differentiation and no lymphovascular invasion) and a low-risk of residual neoplasia, characterized by tumor-negative resection margins.[1]

Current guidelines recommend adjunct surgery in patients with tumor-positive vertical resection margins (R1v).[1, 2] However, residual neoplasia is not always present in the surgical resection specimen of patients with R1v.[5] Moreover, surgical resection is – even in high-volume centers – associated with substantial mortality (0-5%), morbidity (20-50%), and decreased quality of life.[6-8] Surgery may thus be unwanted overtreatment in a subset of patients with documented R1v. We hypothesize that endoscopic reassessment after R1v may be able to discern patients with residual neoplasia who should be offered surgery, from those without residual neoplasia, who can be followed up endoscopically.

Published studies on residual cancer after R1v resections are scarce and review small numbers of patients.[9-12] Even though varying definitions of R1 have been used and accurate histopathological assessment of the vertical margin of ER specimens has proven to be challenging, even by experienced pathologists, these studies report lower risks of residual cancer than generally has been assumed (range: 0-57%).[9-12] Recently, our research group reported outcomes of 138 endoscopic submucosal dissections (ESDs) performed between 2008 and 2019 in the Barrett Expert Centers (BEC) in the Netherlands.[5] Vertical and/or lateral R1 resections were found in 38 ESD specimen. In 71% of these patients, no residual cancer was present during first endoscopic reassessment, performed 8 to 12 weeks after ESD.[5]

Studies involving systematic reassessment of R1v margins by an experienced pathology board are currently lacking. Consequently, the risk of residual cancer following R1v resections remains unclear. This study aimed to evaluate the risk of residual neoplasia following endoscopic mucosal resection (EMR) or ESD of BE neoplasia with documented R1v. Our second aim was to report the characteristics and outcomes of R1v resections.

METHODS

This retrospective, nationwide study used data from the Dutch BEC registry (Netherlands Trial Register, NL7039), which has been described in detail previously.[3, 13] The registry contains outcomes of all patients receiving endoscopic treatment for BE neoplasia in the Netherlands since 2008. This care is centralized in the Netherlands: endoscopists and pathologists from all nine expert centers participate in a joint training program, adhere to a unified protocol and attend annual clinical and scientific meetings to guarantee uniform clinical management. Each BEC has a minimum caseload of 10 new patients undergoing endoscopic treatment for BE neoplasia yearly. The Medical Ethical Research Committee of Amsterdam University Medical Centers decided that the registry was not subject to Medical Research Involving Human Subjects and waived the need for formal ethical review and informed consent.

Study population

All patients treated with ER for early BE neoplasia with documented R1v margins in pathology reports were included. Patients were included from January 2008 till May 2019 for EMRs and till December 2020 for ESDs. This study also included 32 ESDs with documented R1v that have been described previously.[5]

Histopathological evaluation

ER specimens were pinned down on cork or hard wax and fixed in formalin solution for 24 hours. Specimens were then cut to 4 µm thickness at 2 mm interval for ER specimens and at 5mm intervals for surgery specimens. Subsequently, the slides were stained with hematoxylin and eosin (H&E). Other stainings (e.g. p53, desmin, and pan-keratin) were performed upon the pathologist's preference. The tumor invasion depth was classified as at least mucosal (T1a; m1-m3) or submucosal (T1b; sm1-sm3). Tumor differentiation grade was reported as well (G1), moderate (G2), or poor-undifferentiated (G3-4). Lymphovascular invasion (LVI) was present or absent.

Reassessment of ER specimens

Documented pathology assessment and reassessment were performed by experienced BE pathologists. All available pathology slides of resection specimens were retrieved and up to five relevant slides regarding the vertical margin were selected by two pathologists (MD, SM). In case of missing pathology slides or insufficient quality, formalin-fixed paraffin-embedded tissue blocks of resection specimens were retrieved and new slides were cut. In equivocal cases regarding the maximum invasion depth or vertical margin, additional slides

were cut at the pathologist's request. Relevant R1v slides were digitized for reassessment, anonymized, and stored on a secure server.

Vertical resection margin. The resection margins were assessed as either cancer cells unequivocally infiltrating the resection margin (R1), absence of cancer cells in the margins (R0); or not assessable margins (Rx). All digital pathology slides were reassessed independently by one of the four participating experienced gastrointestinal pathologists (LO, MD, MJ, SM). The pathologists were blinded to patient, treatment, and outcomes of prior pathology assessment. Outcomes of vertical margin reassessment were compared with prior pathology reports. In case of disagreement between the vertical margin outcome of reassessment and initially documented pathology, a second pathologist blindly reassessed the slides. For cases in which the second pathologist was not in agreement with either the initial pathology report or the reassessment of the first pathologist, a consensus meeting was held with all four pathologists present. In equivocal cases or in case of Rx margins, the reasons were discussed (e.g. tangential cutting, suboptimal embedding, curled lateral margins, cauterization artifacts). For confirmed R1v margins, the following characteristics were assessed: tumor width at the vertical margin (i.e. maximum width of the tumor in contact with the vertical resection margin in μm), number of R1v sites, ER specimen depth at the R1v site and tumor differentiation at the invasive front, according to the WHO classification for tumor grading.[14]

Reassessment of surgical specimens. For patients who underwent surgery after R1v, adjunct review of the surgical specimen was performed by an experienced pathologist (LO, MD, SM). The presence and, if applicable, tumor stage of BE neoplasia (HGD or esophageal adenocarcinoma, EAC) were reassessed to ensure all patients with residual neoplasia were detected. The presence of submucosal fibrosis, which may suggest the previous ER location, was also evaluated.

Treatment and follow up strategy

An ER with R1v margin is generally considered a high-risk resection (i.e. non-curative). Guidelines recommend that complete staging, including (PET/)CT and endoscopic ultrasound to detect any LNM or distant metastasis, should be performed before additional treatment is initiated.[1] Additional treatment, including surgery and/or chemoradiotherapy (CRT), is strongly recommended, because of the presumed high-risk of residual cancer.[1] The risk of LNM is based on histopathological characteristics of the ER specimen (i.e. high-risk if deep submucosal invasion (sm2/3), G3/4 or LVI+).[1] Patients deemed unfit or who refused surgery without signs of metastasis, were offered endoscopic follow up. In absence of residual neoplasia and metastasis, additional radiofrequency ablation (RFA) of the residual

BE segment was considered during endoscopic follow up, to prevent possible malignant progression.[3]

Study end points

The primary end point was presence of residual neoplasia after ER with R1v margin for BE neoplasia. Residual neoplasia was defined as the presence of HGD or EAC detected during first endoscopic reassessment within 1 cm of the ER scar or in the surgical resection specimen (Table S1). Secondary end points included: 1) outcomes of pathology reassessment of documented R1v margins; 2) accuracy of first endoscopic reassessment in detecting residual neoplasia; and, 3) clinical outcomes including long-term follow up with local recurrences. Local recurrence was defined as HGD or EAC detected during endoscopic follow up within 1 cm of the ER scar, with at least one prior endoscopy without abnormalities.

Statistics

Descriptive statistics were presented as means with standard deviations (SD), medians with inter-quartile ranges (IQR) and counts with percentages, when appropriate. Statistical analyses were performed using IBM SPSS for Windows version 25 (SPSS Inc). Logistic regression was used to compare outcomes among different subgroups.

RESULTS

Baseline and procedure characteristics

A total of 1442 patients were treated with ER for BE neoplasia at the expert centers since 2008 (Figure S1). Pathology reports showed documented R1v margins in 110 patients (7.6%). Baseline patient, ER and documented pathology characteristics are shown in Table 1. Documented R1v was reported in 5.8% of patients treated with EMR (73/1263) and in 20.7% of patients treated with ESD (37/179). Most EMRs were performed in piecemeal fashion (93.2%), while most ESDs were en bloc resections (91.9%). For en bloc resections (n=39; 34 ESDs and 5 EMRs), lateral R1 margins positive for cancer were present in 14/39 patients (35.9%). High-risk characteristics for LNM (i.e. ≥T1sm2, G3/4, or LVI+) were present in 61.8% of patients with documented R1v. Most procedures (n=101; 91.8%) were considered endoscopically successful (i.e. macroscopically complete). Macroscopically incomplete resections (n=9) are described in Supplementary text S1 and were not included in histological reassessment or evaluations for residual neoplasia.

Outcomes of experienced pathologist reassessment

Pathology slides of 99/101 (98.0%) macroscopically complete resections could be retrieved for reassessment. A median of 3 slides (range 1-5) were used for a maximum of 2 rounds of reassessment and consensus meeting by experienced pathologists (Figure 1). The presence of R1v margins was confirmed in 74.7% of the documented cases (74/99; 95% CI 65.0-82.0), while the remaining vertical margins were reassessed as Rx (n=16, 16.2%) and R0 (n=9, 9.1%). R1v margins were confirmed in 90.9% of ESDs (30/33) and in 66.7% of EMRs (44/66) (Figure S1). In patients with mucosal carcinoma, 56.3% had confirmed R1v margins, while in patients with submucosal carcinoma confirmed R1v was diagnosed in 78.3%. In patients with confirmed R1v (n=74), the median R1 tumor width at the vertical margin was 1140 µm (IQR 500-1978)(Table S3) and 39.2% had more than one R1v site in the resection specimen.

During reassessment of 48/99 cases of documented R1v, the pathologist could not assess the vertical margin (Rx n=16, 16.2%) or had some doubt regarding their assessment of radicality (n= 32, 32.3%). Reasons preventing optimal histological assessment included tangential cutting (28.3%), suboptimal embedding (22.2%), curled lateral margins (15.2%), cauterization artifacts (15.2%), and pinning artifacts (15.2%). Pathology images demonstrating these features that prevented optimal histopathological assessment are shown in Figure S2 and were present in 62.1% of the EMR specimens and 21.2% of the ESD specimens (Table S4).

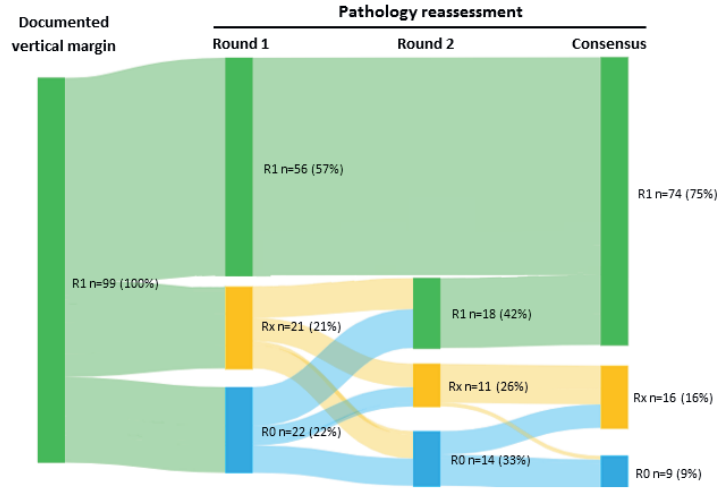


Figure 1. Outcomes of pathology reassessment of macroscopically complete ER with documented R1v (n=99). Data shown as n with % in a Sankey diagram. ER specimen with documented R1v could be retrieved for pathology reassessment in 99/101 (98.0%) patients with macroscopically complete resections. R1, tumor-positive vertical resection margins; Rx, not assessable margins; R0, tumor-free resection margins.

Table 1. Baseline characteristics of patients with documented R1v (n=110).

Patient and ER characteristics	n=110
Male sex	89 (80.9%)
Age in years	69.5 (±10.1)
ASA classification ≥3	31 (28.2%)
BE length in cm	
Circumferential extent	2 (0-5)
Maximum extent	4 (3-7)
Paris classification (primary component)	
0-Ip/Is	37 (33.6%)
0-IIa	63 (57.2%)
0-IIb	6 (5.5%)
0-IIc	3 (2.7%)
Missing	1 (0.9%)
Prior treatment	6 (5.5%)
ER	3 (2.7%)
ER + subsequent RFA	2 (1.8%)
RFA	1 (0.9%)
Technique	
MBM	56 (50.9%)
Cap-assisted EMR	17 (15.5%)
ESD	37 (33.6%)
En bloc	39 (35.5%)
Piecemeal	71 (64.5%)
Number of pieces	5 (4-7)
Macroscopically successful resection	101 (91.8%)

Table 1. Baseline characteristics of patients with documented R1v (n=110). (continued)

Documented pathology characteristics	
Maximum measured invasion depth	
T1m3	20 (18.2%)
Tsm1 (<500 microns)	37 (33.6%)
T1sm2/3 (≥ 500 microns)	52 (47.3%)
T2[1]	1 (0.9%)
Differentiation grade	
G1	18 (16.4%)
G2	50 (45.4%)
G3/4	42 (38.2%)
Presence of LVI	
No	74 (67.3%)
Yes	36 (32.7%)
Lateral resection margins[2]	
Tumor-negative (R0)	23 (59.0%)
Not assessable (Rx)	2 (5.1%)
Tumor-positive (R1)	14 (35.9%)

Data presented as n with %, median (IQR) or mean with SD, according to the nature of the data. [1]ESD with partial removal of the muscularis propria containing Barrett's neoplasia. [2]For en bloc resections only. ER, endoscopic resection; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LVI, lymphovascular invasion MBM, multiband mucosectomy; RFA, radiofrequency ablation.

Findings of endoscopic reassessment

Among the patients with confirmed R1v, 52/74 (70.3%) underwent endoscopic reassessment after median 10 weeks (IQR 6-15). During first endoscopic reassessment, a visible suspicious lesion within 1 cm of the ER scar was detected in 25/52 patients (48.1%). Of these, residual neoplasia was confirmed in 22/25 visible lesions (positive predictive value 88.0%, Table 2), while no dysplasia was detected in three patients with target biopsies. These three patients underwent subsequent surgery showing no neoplasia (n=1), CRT because of LNM (n=1), and endoscopic follow up during 48 months without detection of a local recurrence (n=1). In patients without visible lesions (27/52; 51.9%), target biopsies of the regularly healed ER scar were taken in nine patients, and did not result in additional detection of neoplasia (Figure 2). The negative predictive value of first endoscopic reassessment was 79.2% (95% CI 57.9-92.9, Table 2), taking into account all patients treated with subsequent surgery or undergoing endoscopic follow up. Even though no residual neoplasia was observed, six patients were referred for subsequent surgery, which resulted in the detection of HGD in one patient and no residual neoplasia in the other patients.

Table 2. Predictive value of first endoscopic reassessment for the detection of residual neoplasia or local recurrence in the esophagus.

First endoscopic reassessment	**Outcome**		**Total**
	Residual neoplasia or local recurrence	*No neoplasia*	
Suspicious lesion	22	3	25
No lesion	5[1]	19	24
	27	22	49

The absence of residual neoplasia could be confirmed in surgical resection specimens or during endoscopic follow up. Patients without visible lesions during first endoscopic reassessment who were directly referred for chemoradiotherapy (n=2) or had no endoscopic follow up (n=1) were excluded in this analysis. [1]Consisting of 1 residual neoplasia (HGD) and 4 local recurrences detected after 7, 9, 10, and 19 months after ER with R1v resection margin.

Clinical outcomes after confirmed R1v resection

The presence of residual neoplasia could be assessed in 66/74 patients with confirmed R1v, of whom 50.0% (33/66; 95% CI 37.4-62.6) had residual neoplasia in the surgical resection specimen (n=11) or during the first endoscopic reassessment (n=22) (Figure 3; Table 3). Reasons preventing surgical treatment after R1v are shown in Table S5. The tumor stages of detected residual neoplasia were HGD (n=3), T1a (n=10), T1b (n=4), and ≥T2 carcinoma (n=16) (Figure S3). In the remaining eight patients (8/74), the presence of residual neoplasia was unknown, due to treatment with CRT before endoscopic reassessment (n=2), CRT and surgery (n=1), or no follow up (n=5).

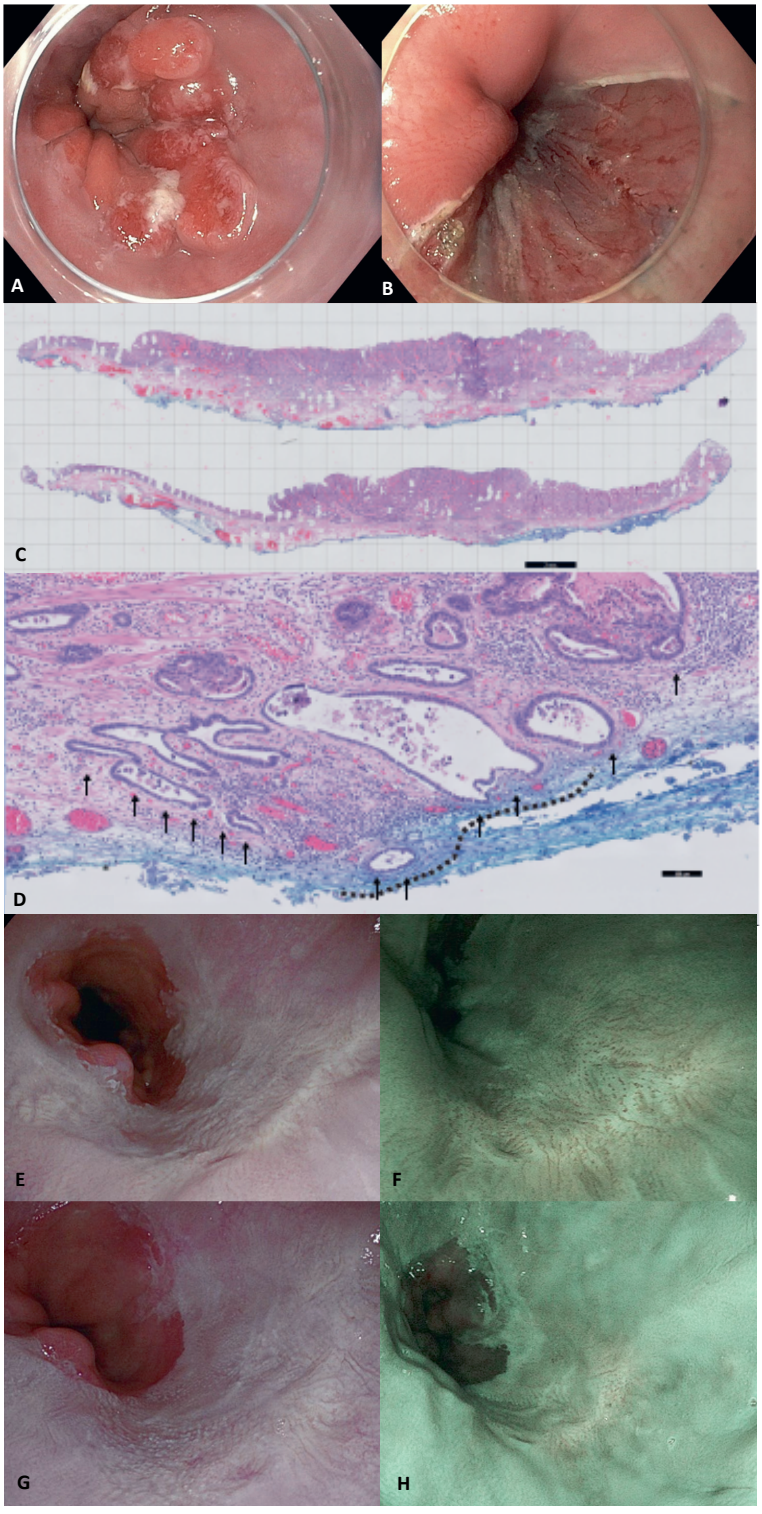
Residual neoplasia occurred less often after ESD (33.3%) than after EMR (61.5%) with confirmed R1v margin. The risk of residual neoplasia was higher, but not statistically significantly increased with increasing tumor width in the vertical margin of ER specimen (odds ratio 1.52, 95% CI 0.95-2.42 for every increase of 1000 µm). The specimen depth at the R1v site was limited to the muscularis mucosa in 24 patients (32.4%), of whom 17 had submucosal carcinoma in other ER specimen parts. Of these, 14/17 underwent first endoscopic reassessment, of whom 7/14 (50.0%) had residual neoplasia.

Table 3. Presence of residual neoplasia after ER of BE neoplasia according to the tumor invasion depth and vertical margin status, as assessed by endoscopic reassessment or in the surgical resection specimen.

Documented invasion depth and vertical margin status according to reassessment	n (%)	No residual neoplasia	Residual neoplasia	Could not be assessed[1]
R1v	74	33 (50%)	33 (50.0%)	8
T1m3	9/74	6 (75.0%)	2 (25.0%)	1
T1sm1	28/74	10 (38.5%)	16 (61.5%)	2
T1sm2/3	37/74	17 (53.1%)	15 (46.9%)	5
Rx	16	9 (75.0%)	3 (25.0%)	4
R0	9	5 (62.5%)	4 (44.4%)	0

BE, Barrett esophagus; ER, endoscopic resection; FU, follow up; [1]Presence of residual neoplasia not could be assessed, due to absence of endoscopic reassessment after R1v or treatment with primary chemoradiotherapy.

Figure 2. No residual neoplasia or recurrence during follow up in a patient with confirmed tumor-positive vertical resection margin (shown on page 209). Paris type 0-IIa-IIc lesion with suspicion of submucosal invasion (image A). The lesion was resected by ESD (image B). Histopathology assessment showed a T1bsm1 adenocarcinoma with G1 LVI+ R1v. Reassessment of the vertical margin by a panel of experienced pathologists confirmed R1v with a width of 1500 µm cancer cells in the vertical margin (images C, D; dashed line indicating vertical R1 segment and arrows indicating the invasion depth). Lymphovascular invasion is not shown. This patient had no residual neoplasia during first endoscopic reassessment (images E, F), which was confirmed with target biopsies of the resection scar. No additional treatment was performed and no local recurrence was detected during a follow-up of 36 months with five endoscopies (images G, H).


A
B
C
D
E
F
G
H

Treatment of residual neoplasia

Of the patients with residual neoplasia (n=33), 14 underwent adjunct surgery revealing HGD (n=2), T1a (n=7), T1b (n=3), and T2 (n=3) carcinoma (Figure 3). Nine patients received CRT after endoscopic reassessment with residual neoplasia, because of a high-risk of LNM. Two patients were treated with CRT and surgery (T1a (n=1) and T1b carcinoma (n=1)) after endoscopic reassessment. In 5 patients, re-ER was performed and histopathology showed HGD (n=1), T1a (n=3), and T1b (sm2; n=1) EAC. Four of the patients treated with re-ER, received endoscopic follow up after re-ER (range: 31-90 months of follow up with 6-13 endoscopies) and had no local recurrences or metachronous lesions. In one patient, metastasized EAC was detected shortly after re-ER and this patient died of EAC after 7 months. Outcomes of surgical specimen reassessment are shown in Figure S2.

Endoscopic follow up

In total, 25 patients received endoscopic follow up for a median of 37 months (IQR 12-50) with 6 (IQR 3-11) endoscopies after the ER with confirmed R1v (Figure 3). Of these, 4 patients were previously treated with re-ER for residual neoplasia, who are described above. During follow up, 4 local recurrences (16.0%) were detected within 1 cm of the ER scar after 7, 9, 10, and 19 months. These patients had T1m3 (n=2), T1sm1 (n=1) and Tsm2/3 (n=1) carcinoma at baseline. Prior to detection of the local recurrence, target biopsies of the nonsuspicious ER scar were taken in 3/4 patients and showed no dysplasia. Most local recurrences (75.0%) could be treated curatively with re-ER (n=2, histology HGD and T1a) and CRT with surgery (n=1, histology no neoplasia). One patient with a local recurrence did not receive treatment due to the diagnosis of metastasized lung cancer. None of the patients were diagnosed with metachronous lesions and 11/25 patients were treated with RFA for eradication of the residual BE epithelium.

Outcomes of R0 and Rx diagnosis after reassessment

During reassessment by the central experienced pathologist panel, vertical margins were reassessed as Rx (n=16) or R0 (n=9). Among vertical Rx (n=16), presence of residual neoplasia could be assessed in 13 patients, in whom 4 (30.8%) had residual neoplasia (Figure S4). Among vertical R0 (n=9), residual neoplasia was detected in four patients (44.4%). These latter four patients had ER with lateral R1 margins (n=2), poor tumor differentiation (n=2), and/or LVI+ (n=1). Residual neoplasia after Rx (n=4) or R0 (n=4) was treated curatively in 7/8 patients with surgery (n=3, histology 2 T1a), CRT with surgery (n=1; histology T1a), re-ER (n=1, histology HGD), and re-ER with CRT (n=2, histology 1 T1a and 1 T1b). One patient was diagnosed with metastasized EAC shortly after endoscopic reassessment and died after 16 months.

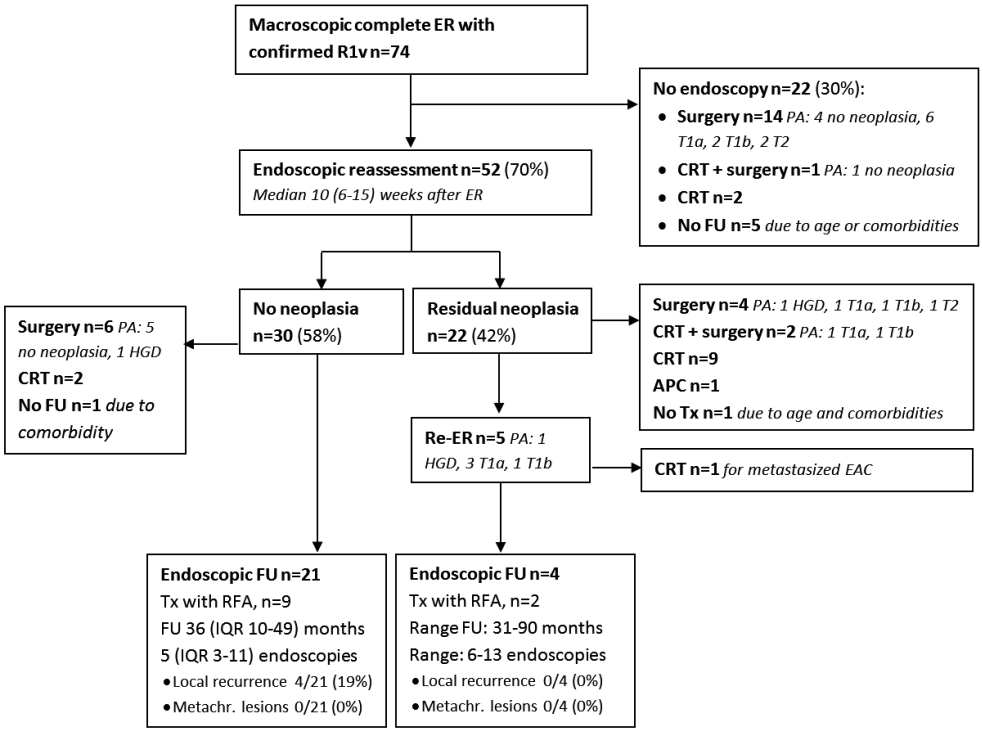


Figure 3. Outcomes of ER for Barrett's neoplasia with histological R1v margin (n=74). APC, argon plasma coagulation; CRT, chemo- and/or radiotherapy; EAC, esophageal adenocarcinoma; FU, follow-up; metachr, metachronous; HGD, high grade dysplasia; IQR, interquartile range; PA, pathology assessment; RFA, radiofrequency ablation; Tx, treatment.

DISCUSSION

Our results show that when histological assessment of endoscopic resection specimens reveals tumor-positive vertical resection margins (R1v), half of the patients had no residual neoplasia afterwards. In this study, we report on all 110 ERs with documented R1v margins that were retrospectively included in the Dutch BEC registry and underwent histopathological reassessment by experienced pathologists. In 50% of our patients with R1v confirmed by a panel of experienced pathologists, residual neoplasia was present in the surgical resection specimen or during first endoscopic reassessment. This is important, as an R1v is usually considered equal to presence of residual cancer after ER of BE neoplasia. If residual neoplasia was present, 39% of patients had HGD or mucosal carcinoma, which could be re-treated successfully. Residual neoplasia was accurately detected with endoscopic reassessment after 8 to 12 weeks.

Our findings are in line with previous studies, which have reported up to 57% residual cancer after R1v ER.[9-12] This study provides new insights, as previous studies comprised small series or lacked reassessment by experienced pathologists. Our results confirm the apparent contradiction between a histological R1v margin after ER and absence of residual neoplasia in 50% of the patients. The absence of residual neoplasia after R1v might be explained by: 1) ablative effects of electrocoagulation during ER; 2) compromised vascularization of the mucosal defect and effects of the immune system potentially resulting in apoptosis of cells with residual neoplasia; and 3) inaccuracy of the histological diagnosis of R1v, potentially caused by faulty endoscopy pinning, suboptimal embedding, tangential cutting, or cauterization artifacts. The latter is also reflected in the relatively large number of Rx margins (n=16) found during reassessment. We found that most equivocal specimens revealed a combination of the aforementioned factors.

Histopathological assessment of the vertical resection margin is challenging, especially in cases of piecemeal resection. In this study, reassessment by experienced pathologists confirmed R1v in 67% of EMRs and 91% of ESDs. A recent study reported the concordance of different histopathological characteristics of 62 ER-specimens by 9 experienced pathologists.[15] Agreement among all nine pathologists regarding the vertical margin radicality was achieved in 68% of cases.[15] In Table S6, we provide clinical recommendations for optimal handling of ER specimens to allow more accurate evaluation of vertical resection margins.

This study showed that residual neoplasia occurred more frequently after EMR (62%) than after ESD (33%) with confirmed R1v margin. This difference might reflect the technical aspects of ESD compared with EMR. First, during ESD, continuous submucosal lifting is

performed and each separate submucosal cut is aimed underneath the lesion. At this stage the lesion might be touched unintentionally at the submucosal side resulting in an R1 resection at the vertical margin without dissecting *through* tumor tissue. This will leave no tumor cells at the patient's side of the resection. During cap-based resection, i.e. EMR, the depth of resection is less controlled and the snare takes the shortest cut while closing. The snare will cut through any tumorous tissue in its path potentially leaving residual neoplasia in the bottom of the resection. Second, differences in patient and tumor selection between ESD and EMR may also reflect the difference in residual neoplasia after R1v.

Some limitations of this study should be addressed. The study was performed retrospectively, resulting in heterogeneous treatment and follow up strategies. This is reflected in the relatively limited number of patients who underwent subsequent surgery after R1v given that guidelines recommend surgery in all fit patients.[1] This may be explained by increasing insights into the limited proportion of patients with residual neoplasia after R1v resections and ongoing studies assessing the potential of endoscopic follow up in high-risk patients. Follow up strategies were not performed according to a standardized protocol, resulting in differences in timing and intervals of surveillance. Endoscopic reassessment was not available in 22 patients and biopsies were not performed in 24 patients. For piecemeal resections, lateral radicality was assessed endoscopically. This is known to be challenging, even for experienced endoscopists. Thus, plausible undocumented lateral R1 resections might partly explain cases with residual neoplasia, as re-ER was technically feasible in some patients.

The indications for ER of BE neoplasia have been gradually expanding, resulting in more resections of high-risk lesions, including submucosal EAC. This may result in an increasing rate of R1 resections in clinical care in the near future. In this study, including all documented R1v after EMR or ESD for BE neoplasia in the Netherlands, subsequent surgery often resulted in overtreatment, as no residual cancer was detected in the surgical resection specimen of 46% of the patients referred for surgery. Additionally, no residual neoplasia was detected in 58% of patients during endoscopic reassessment. If guidelines were followed, this would result in "unnecessary esophagectomy" in 58% of patients. However, this is only the case in patients without signs of LNM.

Based on previous studies and our current data, we recommend an endoscopic reassessment 8 to 12 weeks after ER with R1v to detect residual neoplasia and identify patients who should be referred for additional step-up treatment. Our retrospective data suggest that endoscopic assessment may be able to reliably detect residual neoplasia. In the absence of LNM and residual neoplasia, strict endoscopic surveillance might be

considered as a valid alternative strategy for patients with R1v after ER. In line with new insights on other high-risk patient groups, 3-monthly endoscopic surveillance with high-definition endoscopy and ultrasound (according to the PREFER study protocol ClinicalTrials.gov Identifier NCT03222635) may be considered for patients with R1v without residual neoplasia during endoscopic reassessment. Future prospective studies with homogeneous and standardized treatment and follow-up protocols would provide evidence for an individualized approach for patients with R1v resections after ER for BE neoplasia.

In conclusion, upon confirmed vertical R1 margin after macroscopically complete ER for BE neoplasia, half of the patients had no residual neoplasia. The pathological evaluation of vertical resection margins appears challenging, especially for piecemeal resections, as only 75% of documented R1v cases were confirmed and 16% were re-diagnosed as Rx during reassessment. Without signs of LNM, endoscopic reassessment can be considered after 8-12 weeks to detect residual neoplasia and decide on the most appropriate management strategy. If no abnormalities are present during first endoscopic reassessment, biopsies of the ER scar seem of limited value in detecting additional neoplasia.

REFERENCES

1. Pimentel-Nunes P, Libânio D, Bastiaansen BAJ, et al. Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline–Update 2022. Endoscopy. 2022.
2. Weusten B, Bisschops R, Coron E, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. 2017.
3. Van Munster S, Nieuwenhuis E, Weusten BLAM, et al. 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. 2022;71(2):265-76.
4. Gotink AW, van de Ven SEM, Ten Kate FJ, et al. Individual risk calculator to predict lymph node metastases in patients with submucosal (T1b) esophageal adenocarcinoma: a multicenter cohort study. Endoscopy. 2021.
5. van Munster S, Verheij E, Nieuwenhuis E, et al. Extending treatment criteria for Barrett's neoplasia: results of a nationwide cohort of 138 ESDs. Endoscopy. 2021.
6. Low DE, Kuppusamy MK, Alderson D, et al. Benchmarking complications associated with esophagectomy. Annals of surgery. 2019;269(2):291-8.
7. Pech O, Bollschweiler E, Manner H, et al. Comparison between endoscopic and surgical resection of mucosal esophageal adenocarcinoma in Barrett's esophagus at two high-volume centers. Annals of surgery. 2011;254(1):67-72.
8. Voeten DM, Busweiler LAD, van der Werf LR, et al. Outcomes of Esophagogastric Cancer Surgery During Eight Years of Surgical Auditing by the Dutch Upper Gastrointestinal Cancer Audit (DUCA). Annals of Surgery. 2021;274(5):866-73.
9. Kunzli HT, Belghazi K, Pouw RE, et al. Endoscopic management and follow-up of patients with a submucosal esophageal adenocarcinoma. United European Gastroenterol J. 2018;6(5):669-77.
10. Subramaniam S, Chedgy F, Longcroft-Wheaton G, et al. Complex early Barrett's neoplasia at 3 Western centers: European Barrett's Endoscopic Submucosal Dissection Trial (E-BEST). Gastrointest Endosc. 2017;86(4):608-18.
11. 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(4):600-7.
12. Prasad GA, Buttar NS, Wongkeesong LM, et al. Significance of neoplastic involvement of margins obtained by endoscopic mucosal resection in Barrett's esophagus. Am J Gastroenterol. 2007;102(11):2380-6.
13. van Munster SN, Nieuwenhuis EA, Weusten B, et al. Endoscopic Resection Without Subsequent Ablation Therapy for Early Barrett's Neoplasia: Endoscopic Findings and Long-Term Mortality. J Gastrointest Surg. 2020.
14. World Health O. WHO classification of tumours: digestive system tumours: World Health Organization (WHO); 2019.
15. van der Wel MJ, Klaver E, Pouw RE, et al. Significant variation in histopathological assessment of endoscopic resections for Barrett's neoplasia suggests need for consensus reporting: propositions for improvement. Dis Esophagus. 2021;34(12).

SUPPLEMENTARY

Table S1. Definitions.

Characteristics	Definition
BE neoplasia	Low grade dysplasia, high grade dysplasia, or esophageal adenocarcinoma located in a Barrett's esophagus.
Endoscopic follow up	All endoscopies performed after the ER with tumor-positive vertical resection margin, excluding endoscopic dilatations.
Endoscopic reassessment	The first endoscopy after ER with tumor-positive vertical resection margin during which the scar of the ER was assessed for residual neoplasia.
Local recurrence	After ER, the patient had at least one endoscopy with a non-suspicious ER scar and no BE neoplasia during histopathology assessment (if applicable) AND 1) Presence of a visible lesion within 1cm of the ER scar with suspicion of high grade dysplasia or esophageal adenocarcinoma detected during endoscopic follow up OR 2) Absence of a visible lesion during endoscopic follow up but histopathology within 1cm of the ER scar showing high grade dysplasia or esophageal adenocarcinoma.
Metachronous lesions	Development of high grade dysplasia or esophageal adenocarcinoma in the residual BE segment, at least >1cm from the ER scar.
Residual neoplasia	1) Presence of a visible lesion within 1cm of the ER scar with suspicion of high grade dysplasia or esophageal adenocarcinoma detected during first endoscopic reassessment 2) Absence of a visible lesion during first endoscopic reassessment but histopathology within 1cm of the ER scar showing high grade dysplasia or esophageal adenocarcinoma 3) Presence of high grade dysplasia or esophageal adenocarcinoma detected in the surgical resection specimen performed within 6 months after ER with R1v margin.
Vertical margin tumor-positive (R1v)	Presence of cancer cells in the vertical (i.e. deep) ER margin, i.e. an irradical resection.
Vertical margin not assessable (Rx)	Not assessable vertical ER margin, due to endoscopy and/or histopathological factors.
Vertical margin tumor-negative (R0)	Absence of cancer cells in the vertical ER margin. A radical resection.
Visible lesion	Abnormality with suspicion for BE neoplasia detected during endoscopy.

BE, Barrett's esophagus; ER, endoscopic resection.

Table S2. Baseline documented pathology characteristics of EMR and ESD (n=110).

	Total n=110	EMR n=73	ESD n=37
Maximal measured invasion depth			
T1m3	20 (18.2%)	16 (21.9%)	4 (10.8%)
T1b			
Sm1 (<500 microns)	37 (33.6%)	28 (38.4%)	9 (24.3%)
Sm2/3 (≥ 500 microns)	52 (47.3%)	29 (39.7%)	23 (62.2%)
T2[1]	1 (0.9%)	0	1 (2.7%)
Differentiation grade			
G1	18 (16.4%)	14 (19.2%)	4 (10.8%)
G2	50 (45.5%)	30 (41.4%)	20 (54.1%)
G3/4	42 (38.2%)	29 (39.8%)	13 (35.1%)
Presence of LVI			
No	74 (67.3%)	53 (72.6%)	21 (56.8%)
Yes	36 (32.7%)	20 (27.4%)	16 (43.2%)
Lateral resection margins[2]			
Tumor-negative (R0)	23 (59.0%)	1 (20.0%)	22 (64.7%)
Not assessable (Rx)	2 (5.1%)	1 (1.4%)	1 (2.9%)
Tumor-positive (R1)	14 (35.9%)	3 (60.0%)	11 (32.4%)

Data presented as n with %, median (IQR) or mean with SD, according to the nature of the data. R1 defined as cancer cells present in the resection margin, Rx defined as not assessable margins, R0 defined as absence of cancers cells in the resection margin. [1]Endoscopic submucosal resection with partial removal of the muscularis propria containing BE neoplasia. [2]For en bloc resections only. Abbreviations: EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LVI, lymphovascular invasion MBM, multiband mucosectomy.

Table S3. Additional histopathological characteristics of macroscopic complete ER with confirmed R1v during reassessment (n=74).

Characteristics	n=74
Tumor width in the vertical margin in µm (IQR)	1140 (500-1978)
Number of R1v sites	
1	45 (60.8%)
2	18 (24.3%)
3	8 (10.8%)
4	3 (4.1%)
Differentiation grade at the invasive front	
G1	20 (27.0%)
G2	41 (55.4%)
G3/4	13 (17.6%)
ER specimen depth at R1v	
Mucosa	0
Muscularis mucosa	24 (32.4%)
Submucosa	50 (67.6%)

Data presented as n with % or median (IQR), according to the nature of the data. ER, endoscopic resection; R1v defined as cancer cells in the vertical resection margin.

Table S4. Reasons preventing accurate pathology assessment of the vertical resection margin of the ER specimen.

Characteristic	Total n=99	EMR n=66	ESD n=33
≥1 reason preventing accurate pathology assessment of the vertical resection margin	48 (48.5%)	41 (62.1%)	7 (21.2%)
Tangential cutting	28 (28.3%)	26 (39.4%)	2 (6.1%)
Suboptimal embedding	22 (22.2%)	21 (31.8%)	1 (3.0%)
Curled lateral resection margin	15 (15.2%)	14 (21.2%)	1 (3.0%)
Cauterization artifact	15 (15.2%)	13 (19.7%)	2 (6.1%)
Pinning artifact	15 (15.2%)	13 (19.7%)	2 (6.1%)
Superficial or irregular extending specimen	5 (5.1%)	5 (7.6%)	0
Fragmentation	4 (4.0%)	3 (4.5%)	1 (3.0%)

Data presented as n with %. EMR, endoscopic mucosal resection; ER, endoscopic resection; ESD, endoscopic submucosal dissection.

Table S5. Reasons preventing subsequent surgery in patients with macroscopic complete ER with confirmed R1v during reassessment (n=47).

Characteristic	Total n=47
Patients unfit for surgery	28 (59.6%)
Due to comorbidities	27 (57.4%)
Due to advanced age	8 (17.0%)
Patient wish	18 (38.3%)
Considered low-risk EAC (i.e. absence of risk factors for lymph node metastasis)	2 (4.3%)

Data presented as n with %. More than one reason preventing surgery can be present per patient.

Table S6. Clinical recommendations for optimal handling of endoscopic resections of Barrett's neoplasia.

Clinical recommendation	Purpose and findings in the current study
In case of piecemeal resection, the completeness of the resection at the lateral margin should be determined by the endoscopist.	To prevent residual cancer or local recurrence located at the lateral resection margins.
The ER specimen should include a sufficient amount of submucosa.	To prevent vertical R1 resections of Barrett's neoplasia. In this study, the specimen depth at the R1v site was limited to the muscularis mucosa in 24 patients, of whom 17/24 patients had BE neoplasia invading the submucosa in other parts of the same ER specimen.
The ER specimen should be pinned on a hard surface (e.g. on cork) with the mucosal side up, preferably performed by the endoscopist directly after ER.	Immediate pinning and fixation of the ER specimen allows for adequate orientation and tissue preservation (size and shape) to prevent curling of the lateral borders and shrinkage. In this study, curling of the lateral margins prevented accurate pathology assessment of the vertical margin in 15/99 cases.
Overstretching by pinning down the ER specimen should be avoided.	To prevent tears in the ER specimen.
The pins should preferably not perforate Barrett's neoplasia and especially the area with suspicion of the deepest tumor invasion should be avoided.	To prevent artifacts and allow for accurate assessment of the resection margin(s). In this study, a needle mark was present at the potential location of the vertical R1 resection in 15/99 cases.
Photographs of the ER specimen should be taken directly after pinning down.	For adequate orientation with mapping of the lesion and margins in order to compare the macroscopic appearance with endoscopy findings.
The vertical margin (and for en bloc lateral margins) should be inked.	

ER, endoscopic resection; R1, irradical resection, i.e. tumor cells infiltrating the resection margin; R1v, tumor-positive vertical resection specimen

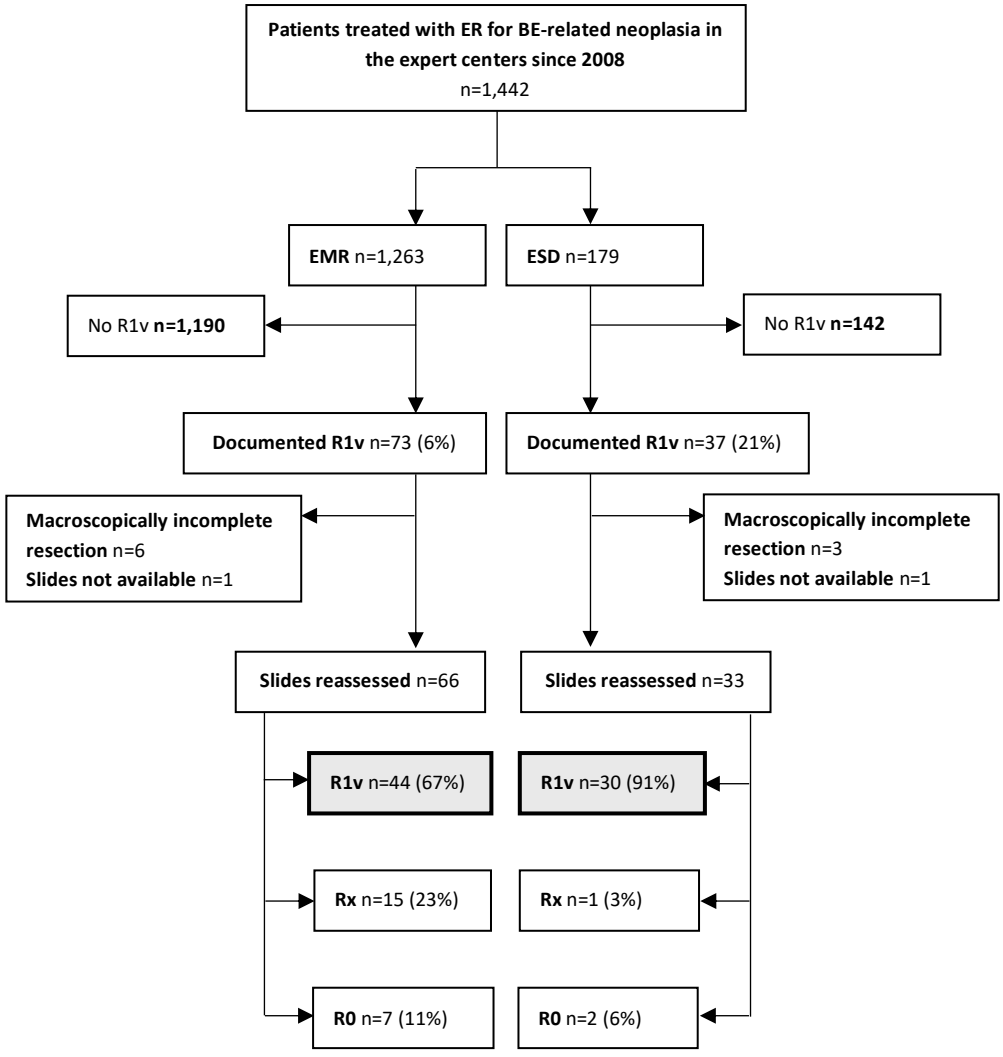


Figure S1. Flowchart of patient inclusion and outcome of histopathological assessment of the vertical resection margin. BE, Barrett's esophagus; EMR, endoscopic mucosal resection; ER, endoscopic resection; ESD, endoscopic submucosal dissection; R1v, tumor-positive vertical resection margin defined as cancers cells in the vertical resection margin; Rx, not assessable vertical resection margin; R0, tumor-negative vertical resection margin.

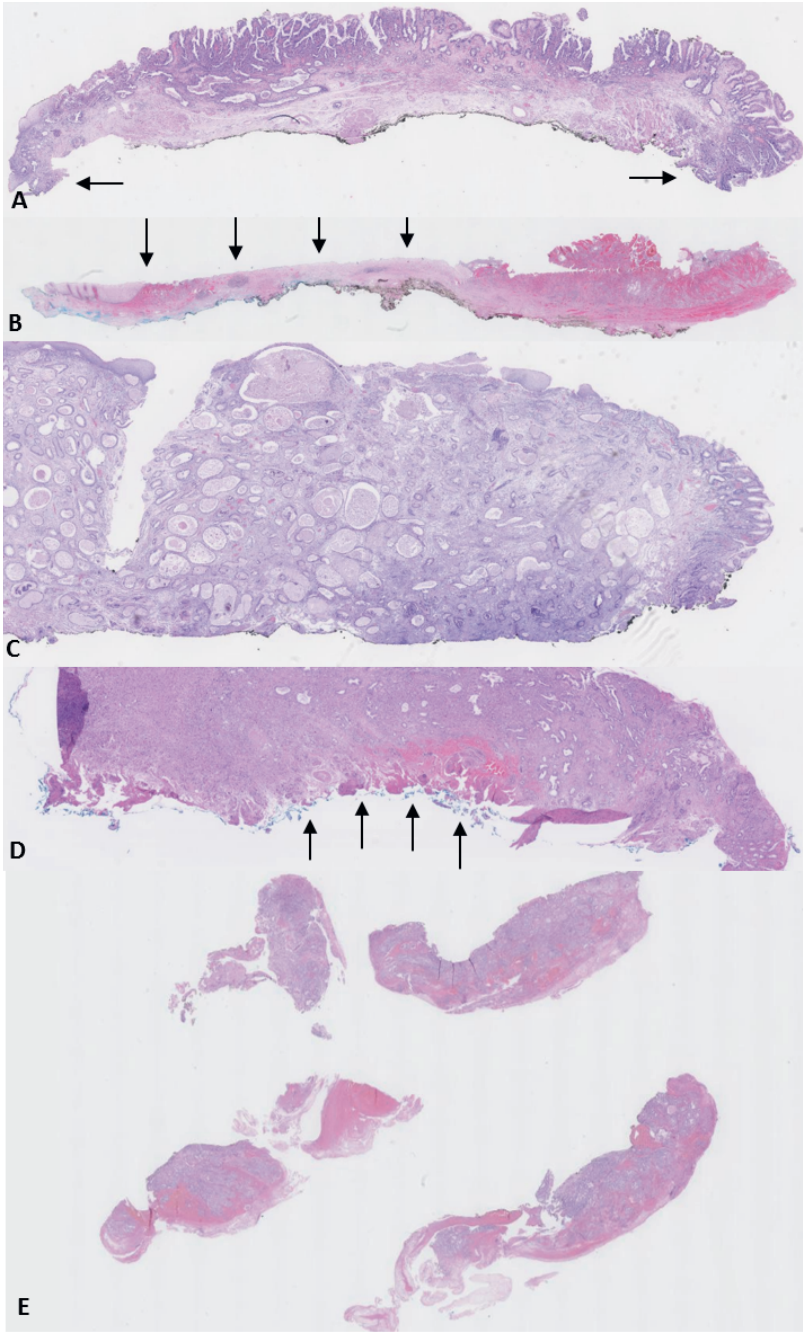


Figure S2. Images of pathology slides with reasons preventing optimal histopathological assessment of vertical resection margins after endoscopic resection of BE neoplasia; A) curled margin, B) suboptimal embedding, C) tangential cutting, D) cauterization artifacts and E) fragmentation.

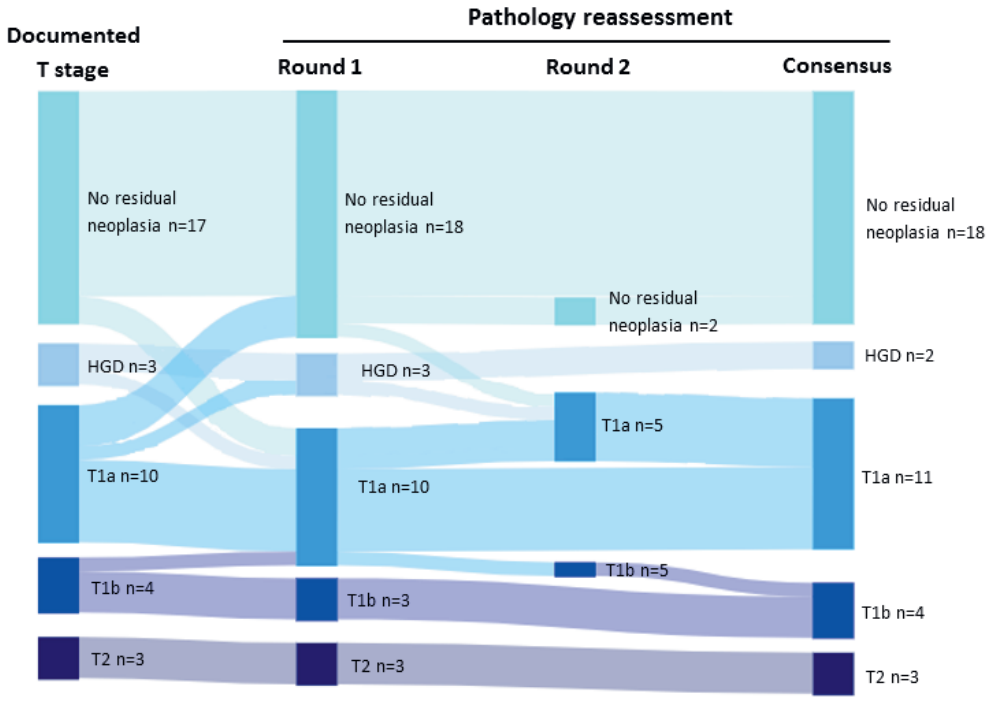


Figure S3. Outcomes of pathology reassessment of patients treated with additional surgery after a macroscopic complete ER with documented R1v (n=37*), either directly after R1v resection or after endoscopic reassessment. Data shown as n with % in a Sankey diagram. *The esophagectomy specimens could be retrieved for pathology reassessment in 37/39 patients. ER, endoscopic resection.

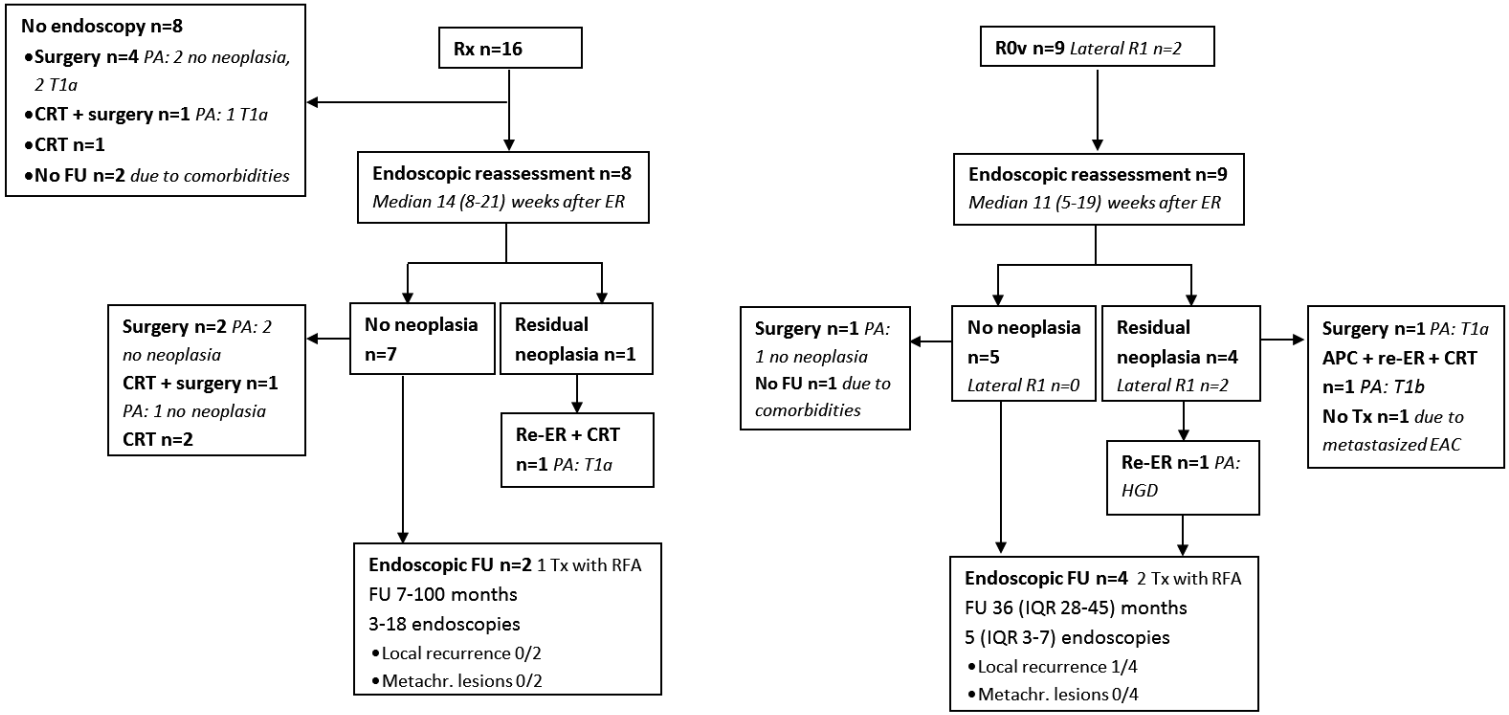


Figure S4. Outcomes of ER for BE neoplasia with Rx (n=16) or R0 (n=9) vertical margin during pathology reassessment. BE, Barrett's esophagus, CRT, chemo- and/or radiotherapy; EAC, esophageal adenocarcinoma; ER, endoscopic resection; FU, follow-up; metachr., metachronous; PA, pathology assessment; RFA, radio frequent ablation; Tx, treatment. The local recurrence after R0 resection was treated with re-ER (PA: T1a carcinoma).

Text S1. Outcomes of macroscopic incomplete resections.

The majority of procedures (n=101; 91.8%) were considered endoscopically successful (i.e. macroscopically complete resections). The remaining procedures (n=9; 6 EMRs and 3 ESDs) were macroscopically incomplete due to severe fibrosis and/or deep invasion. In 8 of these 9 patients (88.9%), residual neoplasia was confirmed and could be treated with additional surgery (n=4; revealing T1a (n=1), T2 (n=1), and T3 carcinoma (n=2)), CRT (n=1), or palliative care (n=3)). In the remaining patient with a macroscopic incomplete ER (PA T2), no residual neoplasia was detected during the first endoscopic reassessment; a T2 local recurrence was detected after 33 months of endoscopic follow up with 8 endoscopies for which palliative radiotherapy was offered due to advanced age and comorbidities.

Part V

Summary and discussion

Chapter 9

Summary and general discussion

This thesis focuses on different aspects of the detection and endoscopic treatment of patients with esophageal neoplasia. The first aim of this thesis is to improve the diagnosis of early esophageal cancer among patients at high risk, including patients with current or previous head and neck squamous cell carcinoma (HNSCC) and patients with esophageal squamous dysplasia. The second aim is to report on outcomes of endoscopic resection (ER) for esophageal neoplasia in Western countries.

Chapter 1 contains the general introduction and aims and outline of this thesis. This Chapter describes the incidence, risk factors, clinical presentation, histological precursors, endoscopic detection, and ER of esophageal neoplasia. Moreover, the occurrence of second primary tumors (SPTs) in the upper aerodigestive tract is discussed.

Part II. Endoscopic detection and risk for esophageal cancer

Artificial intelligence during upper gastrointestinal endoscopy

Chapter 2 describes the current state of artificial intelligence (AI) for the accurate detection and staging of neoplasia during upper gastrointestinal (GI) endoscopy. Recent years, the field of AI during endoscopy has developed rapidly. In 2020, the first studies with AI during live endoscopy for the detection of Barrett's neoplasia have been conducted.[1, 2] This review shows that AI has been investigated for several indications, including the detection and delineation of early cancers and their precursors, prediction of the invasion depth, and endoscopic detection of a *Helicobacter pylori* infection. The included studies report a high diagnostic performance and accuracy up to 99% for the detection of neoplasia by AI. Several included studies compared the performance of AI with endoscopists with different levels of clinical experience. These studies showed that AI systems can potentially outperform all endoscopists, even the expert endoscopists, in upper GI endoscopy.[3-6]

Although all studies included in **Chapter 2** show promising results, a pitfall may be that most AI models were developed in an ideal setting with high-quality images only. This setting does not always reflect the daily clinical practice during live endoscopy, as good visualization of the mucosa and abnormalities also depend on the skills and experience of the endoscopist. For example, blurry imagery was excluded in most studies, while this may influence the diagnostic performance of AI models during live endoscopic procedures. AI systems may also be used for quality control during upper GI endoscopy, including the completeness of mucosal inspection, as discussed in the position statement of the European Society of Gastrointestinal Endoscopy (ESGE) about the expected value of AI.[7] AI could assist in the identification of blind spots during the mucosal inspection and potentially decrease miss rates of neoplasia and post-endoscopy cancers. Based on the currently published

studies, we expect that AI will be implemented during live endoscopy in the near future. Before AI can be implemented, larger studies assessing AI used by endoscopists with different levels of experience during real-time endoscopy are needed.

Risk of esophageal squamous cell carcinoma in patients with squamous dysplasia

Previous studies assessing the risk of ESCC in patients with squamous dysplasia were conducted in Asian countries.[8-13] In Western countries, the risk of ESCC for distinct grades of squamous dysplasia remains unclear. The current ESGE guideline advocates treatment with ER for high grade dysplasia and mucosal carcinoma, but it remains controversial whether endoscopic surveillance or treatment is indicated for low grade dysplasia.[14]

Chapter 3 contains a retrospective study in patients diagnosed with esophageal squamous dysplasia between 1991 and 2020 in the Dutch nationwide pathology databank (Palga). In this study, the risk of esophageal squamous cell carcinoma (ESCC) was assessed for patients with distinct grades of squamous dysplasia. We included 873 patients with baseline mild (n=179), low grade (n=80), moderate (n=197), high grade (n=77), and severe (n=244) dysplasia, and carcinoma in situ (n=72). Of these, 181 (20.7%) patients were diagnosed with prevalent ESCC (within 6 months) and 67 (9.7%) patients were diagnosed with incident ESCC (> 6 months after baseline diagnosis of esophageal squamous dysplasia). After excluding patients with prevalent ESCC, the annual risk of ESCC was increased in all patients with esophageal squamous dysplasia; 2.1% for patients with mild dysplasia, 5.1% for low grade dysplasia, and 5.2% for moderate dysplasia. As all patients with squamous dysplasia had a substantial risk of developing ESCC, we conclude that endoscopic surveillance with careful inspection of the esophageal mucosa or endoscopic treatment should be considered for all patients with mild, low grade, or moderate dysplasia in Western countries.

Based on the number of included patients with squamous dysplasia (n=873), we expect that most pathologists in Western countries rarely diagnose squamous dysplasia in the esophagus. Previous studies showed that the diagnosis and grading of esophageal squamous dysplasia can be challenging, reflected by discrepancies between the pathology diagnosis of biopsies and corresponding ER specimen.[15-17] Since **Chapter 3** shows that different classifications of squamous dysplasia are currently used, we suggest that all pathologists in Western countries should adopt one uniform classifications for squamous dysplasia. This is in line with the recommendation of the World Health Organization, that advises to classify squamous dysplasia in two distinct classes, i.e. low grade and high grade dysplasia, to increase the uniformity in diagnosis between pathologists.[18] Secondly, the

value of assessment by a second pathologist or an expert panel, in line with the pathological diagnosis of Barrett's dysplasia[19], should also be investigated in future studies.

For the interpretation of the results described in **Chapter 3**, it is important to note that this study was performed retrospectively based on data from Palga and the Netherlands Cancer Registry. This resulted in missing data such as the patient history, clinical symptoms, and the endoscopy indication and findings. Furthermore, a standardized protocol regarding the endoscopic treatment or follow up after squamous dysplasia is currently lacking, resulting in heterogeneity of such data in the current study. Future prospective studies should be designed with a standardized protocol regarding 1) the diagnosis and grading of squamous dysplasia and 2) indications for endoscopic surveillance and timing of treatment. Data from the current study can be useful to provide standards for distinct grades of squamous dysplasia with specific indications for and timing of endoscopic surveillance and treatment. This may allow for early detection or even prevent development of ESCC and thereby help to improve the outcomes of patients with squamous dysplasia in Western countries.

Part III. Second primary tumors in the aerodigestive tract

Lung second primary tumors in patients with esophageal squamous cell carcinoma and vice versa

Chapter 4 describes a systematic review and meta-analysis assessing the prevalence of lung SPTs in patients with primary ESCC and the prevalence of esophageal SPTs in patients with primary lung cancer. This analysis included 19 studies with 62,924 patients with primary ESCC and 20 studies with 648,315 patients with primary lung cancer. The pooled prevalence of lung SPTs in patients with ESCC was 1.8% (95% CI 1.4-2.3) and the pooled prevalence of esophageal SPTs in patients with lung cancer was 0.2% (95% CI 0.1-0.4). The prevalence of SPTs was significantly higher in patients treated curatively, compared to studies that also included patients receiving palliative care. We conclude that patients with primary esophageal or lung cancer have an increased risk to develop esophageal or lung SPTs, but the relatively low SPT prevalence rates currently do not justify screening.

Limitations of most included studies were the retrospective design and lack of information regarding the detection method for SPTs. We hypothesize that most synchronous SPTs were detected during the routine diagnostic work-up of the primary cancer, such as the PET/CT-scan, CT, or trachea-bronchoscopy. Metachronous SPTs were likely detected in symptomatic and advanced stages, as most countries did not have a routine screening program to detect SPTs in these patients. Based on **Chapter 4**, we suggest that further studies should focus on the identification of high risk subgroups for SPTs with an acceptable

survival rate based on primary esophageal or lung cancer characteristics and other comorbidities. For these subgroups, screening might result in early detection of asymptomatic SPTs and thereby potentially improve the survival rate of these patients.

Knowledge of medical specialists about head and neck and esophageal second primary tumors

Chapter 5 reports on a nationwide survey completed by 128 gastroenterologists and 31 head and neck surgeons in the Netherlands. The survey focused on the knowledge of the expected prevalence and their opinions on implementing screening for SPTs in patients with primary ESCC or HNSCC. The expected prevalence of head and neck was 5.0% (IQR 5.0-10.0%) among the specialists with a wide range of up to 40.0%, while a retrospective study showed 2.9% head and neck SPTs in patients with ESCC in the Netherlands between 2000 and 2016.[20] For esophageal SPTs in HNSCC, the expected prevalence was 5.0% (IQR 4.0-10.0%), which is in line with our detection rate of 5.0% esophageal SPTs in 202 patients with HNSCC in Chapter 6. Approximately one third of the specialists would consider screening for SPTs in the head and neck region or esophagus, which increased after providing incidence data on SPTs. Interestingly, 41.3% of the head and neck surgeons considered themselves as capable as gastroenterologists to perform screening of the esophagus.

In **Chapter 5**, we revealed a lack of knowledge among medical specialists and showed that perspectives regarding screening for SPTs in patients with ESCC or HNSCC differed. As additional information on SPTs increased the willingness to perform screening, we hypothesize that adequate education could lead to increased awareness and decreased miss rates of early and subtle SPTs. We suggest that the need for education should be addressed separately from the question whether screening for SPTs in patients with ESCC or HNSCC should be considered in Western countries.

Endoscopic screening for esophageal second primary tumors in patients with head and neck cancer

In **Chapter 6**, we performed a prospective endoscopic screening study to detect SPTs in patients with HNSCC in a single tertiary referral center in the Netherlands. In total, 202 patients with HNSCC were included and underwent 250 screening endoscopies. Endoscopic screening was performed within 6 months (34.0%), 6 months to 1 year (8.0%), 1 to 2 years (33.6%), and 2 to 5 years (24.4%) after HNSCC diagnosis. We detected 11 esophageal SPTs in 10 patients (5.0%; 95% CI 2.4-8.9) with endoscopic screening. Synchronous screening resulted in the detection of 6 SPTs during 85 endoscopies (7.1%). Metachronous screening performed 1 year after synchronous screening resulted in the detection of one SPT (1/48;

2.1%), while metachronous screening alone led to the detection of 4 SPTs in 3 patients (3/117; 2.6%). Most patients with SPTs were diagnosed with SPTs in early stages (90.0%) that could be treated with curative intent by ER. No SPTs in the screened patients were detected with routine imaging (i.e. panendoscopy, MRI or PET/CT scan) for HNSCC before endoscopic screening was conducted. In this Chapter, we conclude that endoscopic screening detected 5.0% esophageal SPTs in patients with HNSCC. Endoscopic screening should be considered in selected HNSCC patients to detect early stage SPTs, based on highest SPT-risk and life expectancy according to HNSCC and comorbidities.

In **Chapter 6**, we included a selection of high risk patients with HNSCC, consisting of patients with hypopharyngeal carcinoma, human papillomavirus-negative oropharyngeal carcinoma, and patients with other HNSCC combined with alcohol abuses. This selection of patients with a presumed high risk for SPTs was based on studies originating from Eastern countries[21], which likely does not reflect the entire population of patients with HNSCC in Western countries. Both the selection of high risk patients with HNSCC and the detected number of SPTs (n=11) did not allow for risk factor analysis.

Before screening for esophageal SPTs can be considered for implementation in daily clinical practice, several aspects should be investigated in future studies. An important requirement for the implementation of screening is that screening for SPTs needs to result in an improved survival of patients with HNSCC. We hypothesize that screening the entire population of patients with HNSCC is not likely to be beneficial in Western countries, and therefore further studies should identify risk factors for SPTs in patients with HNSCC. Potential risk factors may include HNSCC located in the hypopharynx or oropharynx, absence of human papillomavirus, and alcohol and tobacco consumption, based on Eastern studies.[21] The development of a risk calculator could assist clinicians to identify patients with highest SPTs risk. This risk should be balanced against the expected survival rate based on the HNSCC prognosis and other comorbidities to identify patients that will benefit most from endoscopic screening. Other aspects that should be investigated are the cost-effectiveness, patient burden and the load of screening on endoscopy programs.

Recommendations for future studies assessing screening for esophageal SPTs in Western countries;

1) A future study should consist of a large multicenter and preferably nationwide screening study, including all patients with HNSCC who are treated curatively for HNSCC. Patients with severe comorbidities should be excluded.
2) Screening should be performed with high definition endoscopy with white light imaging and virtual chromoendoscopy, such as narrow band imaging. If virtual

chromoendoscopy is not available, Lugol's staining may be considered.[14] As early esophageal SPTs can be subtle, endoscopic screening should preferably be performed by endoscopists with experience regarding the detection of premalignancies in the upper GI tract. During endoscopic screening, careful inspection of the entire upper GI tract should be performed to also detect potential Barrett's neoplasia or gastric abnormalities. The PET/CT-scan should not be used as screening modality for SPTs, as the sensitivity for early esophageal neoplasia is limited up to 38%.[22-24] This is in line with our findings in Chapter 6, as no early stage SPTs were detected on routine cross-sectional imaging for HNSCC.

3) One-time screening may be preferable above repeated screening in Western countries with low incidence rates of esophageal neoplasia.[25] In Chapter 7, follow up endoscopic screening after 1 year in synchronously screened patients seemed to have a relatively limited yield of 2% for the detection of SPTs.
4) Metachronous screening seems preferable above synchronous screening for STs in patients with HNSCC. In Chapter 6, 22% of the synchronously screened patients developed metastatic HNSCC within 1 year after diagnosis and therefore did not benefit from synchronous screening. We hypothesize that the optimal timing of screening may be 1 to 2 years after HNSCC diagnosis, whereas selected patients with HSCC with a favorable prognosis remain and synchronous SPTs are still discovered at curable stages. This patient selection of HNSCC survivors is likely to be more cost effective than screening the entire HNSCC population and these patients are also more likely to have survival benefit from early detection of SPTs.

The appendix also contains a reply letter to the study by Nobre Moura *et al.* investigating endoscopic screening for early esophageal cancer in patients with HNSCC in Brazil.[26] This appendix discusses the yield of screening for esophageal SPTs in patients with HNSCC. The study of Nobre Moura *et al.* included 1,888 patients with HNSCC with median 43 months of follow up and detected 7.9% esophageal SPTs with yearly endoscopic screening. Most esophageal SPTs (78%) were detected at early stages. Although patients with advanced HNSCC were excluded, both patients with and without treatment with curative intent were included in endoscopic screening. In our letter, we discuss that the benefits of screening (i.e. early detection with potentially improved survival) should always be balanced against the harms (i.e. physical and psychological burden, costs) of screening for SPTs. We believe that endoscopic screening should not include patients with HNSCC receiving best supportive care.

Part IV. Endoscopic treatment of early esophageal neoplasia

Circumferential endoscopic submucosal dissection for the treatment of esophageal squamous cell carcinoma

In **Chapter 7**, we report on clinical outcomes of 171 circumferential endoscopic submucosal dissections (cESDs) of ESCC performed in 25 tertiary centers in Western countries. The en bloc and R0 resection rates were 98.2% (95% CI 95.0-99.4) and 69.6% (95% CI 62.3-76.0), respectively. A curative resection (i.e. en bloc, R0, and absence of high risk characteristics for lymph node metastasis) was achieved in 49.1% of the cESDs. Despite the fact that stricture prophylaxis was applied in 93.4% of the procedures, the risk of strictures requiring ≥six dilatations or additional treatment with incision therapy or stent placement was 70.8%. The rates of adverse events were 4.1% for intraprocedural perforation, 0.6% for delayed bleeding, and 4.7% for cardiorespiratory events. Two patients died (1.2%, 95% CI 0.3–4.2) from a cESD-related adverse event. Overall and disease-free survival rates at 2 years were 91.4% and 79.2%, respectively. In this study, cESD was considered curative treatment in approximately half of the lesions and can therefore be considered as feasible treatment option in selected patients with ESCC in Western centers. However, improvement of the patient selection treated with cESD and development of more effective therapies to prevent esophageal strictures are required.

Chapter 7 reports that 49.1% of the cESDs were considered curative treatment, which is lower than reported in Eastern studies.[27-29] This is in line with the difference in curative resection rates of noncircumferential ESDs between Eastern and Western countries. Partly, this may be explained by differences in the patient selection in which ESD is performed. The 2022 update of the ESGE guideline suggests cESD may be considered for high grade dysplasia and ESCC with superficial mucosal invasion (i.e. T1m1-2).[14] This guideline does not mention a maximum longitudinal axis for the expected mucosa defect[14], while the Eastern guideline suggests cESD can be considered for T1m1-2 ESCC with a longitudinal axis of less than 50mm.[30] As the indications of ER for the treatment of esophageal neoplasia are expanding recently[14], one can image that the indications of cESD may also expand in the near future.

A major burden is that most patients develop an esophageal stricture after cESD, despite the applied stricture prophylaxis. Esophageal strictures can require frequent endoscopic dilatations and can have a severe impact on the patients' quality of life.[31] Although several studies have been performed to prevent esophageal strictures, the optimal prophylactic regime is still unknown. This is also reflected by the heterogeneity in the applied strategies in **Chapter 7**. The current guideline does not mention 1) in which cases stricture prophylaxis

should be applied, 2) a choice for a specific steroid and application method, and 3) time period during which the prophylaxis should be applied after ESD of esophageal neoplasia.[14] In most centers in Western countries, endoscopists prescribe off-label steroids after ESD involving ≥75% of the esophageal circumference as esophageal stricture prophylaxis. Several non-randomized studies reviewing a small numbers of patients have investigated stricture prevention in the esophagus with oral prednisolone, triamcinolone injections, and topical budesonide, but no standardized regime is available in most Western countries.[32, 33] Future studies, preferably in a randomized controlled trial setting, should assess the optimal strategy to prevent esophageal strictures.

Outcomes of endoscopic resection for Barrett's neoplasia with tumor-positive vertical resection margin

In **Chapter 8**, we report on 110 patients with documented tumor-positive vertical resection margin (R1v) after ER of Barrett's neoplasia and assessed the proportion of patients with residual neoplasia. 101/110 patients (92%) had macroscopic complete resections, of which 99 ER specimens were reassessed by experienced pathologists. Reassessment confirmed R1v in 75% of the patients and showed Rx in 16% and R0 in 9% of the patients. The presence of residual neoplasia could be assessed in 66/74 patients with confirmed R1v margin, of whom 50% of the patients had residual neoplasia in the surgical specimen or during first endoscopic reassessment. No additional neoplasia was detected with biopsies of the ER scar in the absence of visible abnormalities. Twenty-five patients with no residual neoplasia were followed for a median of 37 months (IQR 12-50), in which 4 patients developed a local recurrence (16%), all within the first 2 years of follow up. In this study, we conclude that 50% of the patients with confirmed R1v margin had no residual neoplasia after ER. Based on previous studies and this data, we suggest that in patients without signs of lymph node metastasis, endoscopic reassessment may be considered 8 to 12 weeks after ER with R1v to detect residual neoplasia and identify patients requiring additional treatment.

The pathological evaluation of vertical resection margins appears challenging, especially for piecemeal resections, as only 67% of EMRs with documented R1v were confirmed. A recent study also showed that agreement among 9 experienced pathologists regarding the vertical resection margin radicality was achieved in 68% of the ER cases.[34]

Based on previous studies and **Chapter 8**, we suggest that endoscopic reassessment 8 to 12 weeks after ER with R1v can detect residual neoplasia, and identify patients that should be referred for additional treatment. Our retrospective data support the hypothesis that endoscopic assessment may be able to detect presence or absence of residual neoplasia reliably. In the absence of lymph node metastasis and residual neoplasia, strict endoscopic

surveillance might be considered as an alternative strategy for patients after ER with R1v. In line with new insights on other high-risk patient groups[35-38], three-monthly endoscopic surveillance with high definition endoscopy and endoscopic ultrasound (according to the PREFER study protocol ClinicalTrials.gov Identifier NCT03222635) may be considered for patients with R1v without residual neoplasia during first endoscopic reassessment. Future prospective studies can provide evidence for a more individualized approach for patients with R1v resections after ER of Barrett's neoplasia.

REFERENCES

1. Ebigbo A, Mendel R, Probst A, et al. Real-time use of artificial intelligence in the evaluation of cancer in Barrett's oesophagus. Gut. 2020;69(4):615-6.
2. de Groof AJ, Struyvenberg MR, Fockens KN, et al. Deep learning algorithm detection of Barrett's neoplasia with high accuracy during live endoscopic procedures: a pilot study (with video). Gastrointest Endosc. 2020;91(6):1242-50.
3. de Groof AJ, Struyvenberg MR, van der Putten J, et al. Deep-Learning System Detects Neoplasia in Patients With Barrett's Esophagus With Higher Accuracy Than Endoscopists in a Multistep Training and Validation Study With Benchmarking. Gastroenterology. 2020;158(4):915-29 e4.
4. Cai SL, Li B, Tan WM, et al. Using a deep learning system in endoscopy for screening of early esophageal squamous cell carcinoma (with video). Gastrointest Endosc. 2019;90(5):745-53 e2.
5. Zhao YY, Xue DX, Wang YL, et al. Computer-assisted diagnosis of early esophageal squamous cell carcinoma using narrow-band imaging magnifying endoscopy. Endoscopy. 2019;51(4):333-41.
6. Guimaraes P, Keller A, Fehlmann T, et al. Deep-learning based detection of gastric precancerous conditions. Gut. 2020;69(1):4-6.
7. Messmann H, Bisschops R, Antonelli G, et al. Expected value of artificial intelligence in gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2022;54(12):1211-31.
8. 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(2):187-92.
9. Li H, Zhang S, Zhou J, et al. Endoscopic surveillance for premalignant esophageal lesions: A community-based multicenter, prospective cohort study. Clinical Gastroenterology and Hepatology. 2022.
10. Dawsey SM, Lewin KJ, Wang GQ, et al. Squamous esophageal histology and subsequent risk of squamous cell carcinoma of the esophagus. A prospective follow-up study from Linxian, China. Cancer. 1994;74(6):1686-92.
11. Liu M, Zhou R, Guo C, et al. Size of Lugol-unstained lesions as a predictor for risk of progression in premalignant lesions of the esophagus. Gastrointestinal endoscopy. 2021;93(5):1065-73. e3.
12. Wei W-Q, Hao C-Q, Guan C-T, et al. Esophageal histological precursor lesions and subsequent 8.5-year cancer risk in a population-based prospective study in China. The American journal of gastroenterology. 2020;115(7):1036.
13. Wen D, Zhang L, Wang X, et al. A 5.5-year surveillance of esophageal and gastric cardia precursors after a population-based screening in China. Journal of gastroenterology and hepatology. 2015;30(12):1720-5.
14. Pimentel-Nunes P, Libânio D, Bastiaansen BAJ, et al. Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline–Update 2022. Endoscopy. 2022.
15. Chen H, Zhou XY, Li S, et al. Endoscopic detection of esophageal low-grade squamous dysplasia: How to predict pathologic upgrades before treatment? J Dig Dis. 2022;23(4):209-19.
16. Yang L, Jin H, Xie XL, et al. Endoscopic resections for superficial esophageal squamous cell epithelial neoplasia: focus on histological discrepancies between biopsy and resected specimens. BMC Gastroenterol. 2021;21(1):114.
17. Park YJ, Kim GH, Park DY, et al. Histopathologic discrepancies between endoscopic forceps biopsy and endoscopic resection specimens in superficial esophageal squamous neoplasms. Journal of Gastroenterology and Hepatology. 2019;34(6):1058-65.
18. World Health O. WHO classification of tumours: digestive system tumours: World Health Organization (WHO); 2019.
19. Weusten B, Bisschops R, Coron E, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. 2017.
20. van de Ven SE, Falger JM, Verhoeven RH, et al. Increased risk of second primary tumours in patients with oesophageal squamous cell carcinoma: A nationwide study in a Western population. United European Gastroenterol J. 2020:2050640620977129.
21. 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(4):1122-30.

22. Kondo N, Tsukuda M, Nishimura G. Diagnostic sensitivity of (1)(8)fluorodeoxyglucose positron emission tomography for detecting synchronous multiple primary cancers in head and neck cancer patients. Eur Arch Otorhinolaryngol. 2012;269(5):1503-7.
23. Su H-A, Hsiao S-W, Hsu Y-C, 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(1):1-9.
24. Guideline esophageal cancer (in Dutch: Richtlijn Oesofaguscarcinoom): Dutch society of gastroenterologists; Version 3.1. [Available from: https://www.mdl.nl/sites/www.mdl.nl/files/richlijnen/Richtlijn_Oesofaguscarcinoom.pdf].
25. Arnold M, Ferlay J, van Berge Henegouwen MI, et al. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. Gut. 2020;69(9):1564-71.
26. Nobre Moura R, Kuboki Y, Baba ER, et al. Long-term results of an endoscopic screening program for superficial esophageal cancer in patients with head and neck squamous cell carcinoma. Endosc Int Open. 2022;10(2):E200-E8.
27. Minamide T, Kawata N, Maeda Y, et al. Clinical outcomes of endoscopic submucosal dissection for superficial circumferential esophageal squamous cell carcinoma. Gastrointestinal Endoscopy. 2023;97(2):232-40. e4.
28. Lian J, Chu Y, Chen T, et al. Outcome of a novel self-control stricture-preventing water balloon for complete circular esophageal endoscopic submucosal dissection. Surgical Endoscopy. 2023;37(1):290-7.
29. Liu Y, Li Z, Dou L, et al. Autologous esophageal mucosa with polyglycolic acid transplantation and temporary stent implantation can prevent stenosis after circumferential endoscopic submucosal dissection. Annals of Translational Medicine. 2021;9(7).
30. Ishihara R, Arima M, Iizuka T, et al. Endoscopic submucosal dissection/endoscopic mucosal resection guidelines for esophageal cancer. Dig Endosc. 2020;32(4):452-93.
31. van de Ven SEM, Snijders M, Bruno MJ, et al. Effectiveness of topical budesonide in preventing esophageal strictures after endoscopic resection of esophageal cancer. Endosc Int Open. 2020;8(12):E1795-E803.
32. 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(6):1389-93.
33. Melillo N, Corrado A, Quarta L, et al. Corticosteroids, a review. Panminerva Med. 2007;49(1):29-33.
34. van der Wel MJ, Klaver E, Pouw RE, et al. Significant variation in histopathological assessment of endoscopic resections for Barrett's neoplasia suggests need for consensus reporting: propositions for improvement. Dis Esophagus. 2021;34(12).
35. Van Munster S, Nieuwenhuis E, Weusten BLAM, et al. 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. 2022;71(2):265-76.
36. van Munster S, Verheij E, Nieuwenhuis E, et al. Extending treatment criteria for Barrett's neoplasia: results of a nationwide cohort of 138 ESDs. Endoscopy. 2021.
37. van Munster SN, Nieuwenhuis EA, Weusten B, et al. Endoscopic Resection Without Subsequent Ablation Therapy for Early Barrett's Neoplasia: Endoscopic Findings and Long-Term Mortality. J Gastrointest Surg. 2020.
38. Nieuwenhuis EA, van Munster SN, Meijer SL, et al. Analysis of metastases rates during follow-up after endoscopic resection of early "high-risk" esophageal adenocarcinoma. Gastrointestinal endoscopy. 2022;96(2):237-47. e3.

Chapter 10

Conclusions

Artificial intelligence (AI) has been investigated for several indications in upper gastrointestinal endoscopy, including the detection and delineation of early cancers and their precursors, prediction of the invasion depth, and endoscopic detection of *Helicobacter pylori*. We expect that AI will be implemented in routine daily endoscopy in the near future, but that larger studies assessing AI used by endoscopists with different levels of experience during real-time endoscopy are needed.

Based on a retrospective study in the Netherlands, we showed that all patients with squamous dysplasia in the esophagus, including patients with mild, low grade, moderate dysplasia, have an increased risk of esophageal squamous cell carcinoma (ESCC). We conclude that endoscopic surveillance of the esophageal mucosa or endoscopic resection of dysplasia should be considered for patients with mild, low grade, or moderate dysplasia in Western countries.

With a nationwide survey among gastroenterologists and head and neck surgeons in the Netherlands, we revealed a lack of knowledge about head and neck second primary tumors (SPTs) in patients with ESCC and vice versa. Perspectives about screening for SPTs differed among the included specialists. Based on these findings, adequate education seems important to increase the awareness and thereby improve detection rates of SPTs, independent from the need for implementation of screening for SPTs.

We report a pooled prevalence of 1.8% (95% CI 1.4-2.3) lung SPTs in patients with ESCC and 0.2% (95% CI 0.1-0.4) esophageal SPTs in patients with lung cancer in a systematic review and meta-analysis. Thus, patients with esophageal cancer and patients with lung cancer have an increased risk of developing SPTs in the lungs and esophagus, but these relatively low prevalence rates of SPTs do not justify screening in these patients.

In a prospective screening study, we detected an esophageal SPT in 5.0% (95% CI 2.4-8.9) of the patients with current or previous head and neck squamous cell carcinoma (HNSCC) in the Netherlands. Most patients with an SPT were diagnosed with an early stage SPT (90%) and treated with curative intent by means of an endoscopic resection (80%). No SPTs in screened patients were detected with routine imaging for HNSCC before endoscopic screening. We conclude that endoscopic screening should be considered in a selection of patients with HNSCC. We hypothesize that this selection should include patients with highest risk of SPTs (e.g. alcohol and tobacco consumption, hypopharyngeal carcinomas and human papillomavirus-negative oropharyngeal carcinomas) with an acceptable life expectancy depending on the HNSCC prognosis and other comorbidities.

Circumferential endoscopic submucosal dissection (cESD) can be considered as potentially curative treatment option for circumferential early ESCC, but future studies should focus on the patient selection eligible for cESD and improve the strategies to prevent severe esophageal strictures.

In a nationwide retrospective study, no residual neoplasia was present in 50% of the patients with a confirmed tumor-positive vertical resection margin after endoscopic resection for Barrett's neoplasia. Without signs of lymph node metastasis, endoscopic reassessment may be considered after 8 to 12 weeks to detect residual neoplasia and subsequently decide on the most appropriate treatment strategy. If during endoscopic reassessment no abnormalities are present, biopsies of the ER scar seem of limited value in the detection of additional neoplasia.

Appendices

Nederlandse samenvatting

Dit proefschrift richt zich op de verschillende aspecten van het vaststellen en endoscopisch behandelen van patiënten met een vroegcarcinoom in de slokdarm. Het eerste doel van dit proefschrift is het verbeteren van de detectie van slokdarm vroegcarcinomen in hoog risico patiënten, zoals patiënten met een plaveiselcelcarcinoom (PCC) in het hoofd-halsgebied en patiënten met squameuze dysplasie in de slokdarm. Het tweede doel van dit proefschrift is het beschrijven van de uitkomsten na endoscopische resectie van vroegcarcinomen in de slokdarm in Westerse landen.

Hoofdstuk 1 bevat een overzicht van de incidentie, klinische presentatie, risicofactoren, histopathologische voorlopers, en endoscopische detectie en resectie van vroegcarcinomen in de slokdarm. Daarnaast worden tweede primaire tumoren in de slokdarm, hoofd-halsgebied en longen besproken. Ook bevat dit hoofdstuk de doelen en inhoudsopgave van dit proefschrift.

Deel II. Hoog risico patiënten en endoscopische detectie van neoplasie in de slokdarm en maag

Kunstmatige intelligentie tijdens de endoscopie van de bovenste tractus digestivus

Hoofdstuk 2 beschrijft de huidige status van kunstmatige intelligentie voor het accuraat vaststellen van kankers en voorlopers van deze carcinomen tijdens de endoscopie van de slokdarm en maag. De afgelopen jaren hebben grote ontwikkelingen plaatsgevonden op het gebied van kunstmatige intelligentie tijdens endoscopische onderzoeken. Zo werden in 2020 de eerste studies uitgevoerd waarbij kunstmatige intelligentie werd gebruikt tijdens live endoscopische procedures voor de detectie van Barrett neoplasie.[1, 2] In deze review beschrijven we dat kunstmatige intelligentie wordt onderzocht voor 1) de detectie en afgrenzing van vroegcarcinomen en hun voorlopers, 2) het voorspellen van de invasiediepte van vroegcarcinomen, en 3) het endoscopisch vaststellen van een *Helicobacter pylori* infectie. Alle geïncludeerde studies laten een hoge accuratesse zien tot wel 99% voor de detectie van neoplasie in de slokdarm en maag door kunstmatige intelligentie. In verschillende studies wordt kunstmatige intelligentie vergeleken met endoscopisten met verschillende niveaus van endoscopie ervaring. Hierbij zien we dat kunstmatige intelligentie mogelijk endoscopisten van alle niveaus, inclusief de ervaren endoscopisten, kan overtreffen in de detectie van neoplasie tijdens de endoscopie van de bovenste tractus digestivus. In deze review verwachten we dat kunstmatige intelligentie routinematig zal worden toegepast tijdens endoscopische procedures van de slokdarm en maag in de nabije

toekomst. Echter zijn grote studies nodig om het effect van kunstmatige intelligentie gebruikt door endoscopisten met verschillende niveaus in ervaring en expertise te onderzoeken tijdens live endoscopische procedures.

Squameuze dysplasie en het risico op een plaveiselcelcarcinoom in de slokdarm

De meeste gepubliceerde studies over squameuze dysplasie en het risico op slokdarmkanker zijn uitgevoerd in Oosterse landen.[3-8] In Westerse landen is het risico op slokdarmkanker voor verschillende maten van squameuze dysplasie nog onbekend. De huidige Europese richtlijn raadt aan dat endoscopische resectie voor hooggradige dysplasie en mucosale kankers wordt uitgevoerd, echter is onduidelijk of endoscopische behandeling of follow up zou moeten worden uitgevoerd voor patiënten met laaggradige dysplasie in de slokdarm.[9]

Hoofdstuk 3 bevat een nationale, retrospectieve, cohortstudie naar patiënten met squameuze dysplasie in slokdarm biopsie of resectie preparaten tussen 1991 en 2020 in Nederland. In deze studie hebben we het risico onderzocht op het krijgen van een PCC in de slokdarm voor verschillende maten van squameuze dysplasie. Deze studie is uitgevoerd in samenwerking met de Nederlandse pathologie databank (Palga) en Nederlandse Kanker Registratie (NKR). In totaal werden 873 patiënten met een begin diagnose milde (n=179), laaggradige (n=80), matige (n=197), hooggradige (n=77), en ernstige (n=244) dysplasie of carcinoom in situ (n=72) geïncludeerd. Van alle geïncludeerde patiënten werd 20.7% gediagnosticeerd met een prevalent PCC en 9.7% met een incident PCC in de slokdarm. Na exclusie van patiënten met prevalente slokdarmcarcinomen, was het jaarlijkse risico op slokdarmkanker verhoogd bij alle patiënten met squameuze dysplasie (2.1% voor milde dysplasie, 5.1% voor laaggradige dysplasie, en 5.2% voor matige dysplasie). Aangezien alle patiënten met squameuze dysplasie een aanzienlijk risico hadden op het ontwikkelen van een slokdarmcarcinoom, concluderen we dat endoscopie controle met nauwkeurige inspectie van het slokdarmslijmvlies of endoscopische behandeling moet worden overwogen bij alle patiënten met milde, laaggradige, of matige dysplasie in de slokdarm in Westerse landen.

Deel III. Tweede primaire tumoren

Long tweede primaire tumoren in patiënten met slokdarmkanker en vice versa

Hoofdstuk 4 beschrijft een systematische review en meta-analyse waarin de prevalentie van tweede primaire tumoren in de long bij patiënten met een primaire PCC in de slokdarm en andersom wordt onderzocht. In deze systematische review zijn 19 studies met 62,924 patiënten met primaire slokdarmkanker en 20 studies met 648,315 patiënten met primaire

longkanker geïncludeerd. De gepoolde prevalentie van tweede primaire tumoren in de long in patiënten met een slokdarm PCC was 1.8% (95% betrouwbaarheidsinterval (BI) 1.4-2.3). Voor slokdarm tweede primaire tumoren in patiënten met primaire longkanker was de gepoolde prevalentie 0.2% (95% BI 0.1-0.4). Tweede primaire tumoren werden significant vaker gezien in patiënten die curatief behandeld werden voor de primaire kanker (mediaan 2.5% versus 1.3%), vergeleken met studies die zowel curatief als palliatief behandelde patiënten includeerden. We concluderen dat de geïncludeerde patiënten een hoger risico hebben op het ontwikkelen van een tweede primaire tumor in de slokdarm of longen. Gezien de relatief lage prevalentie cijfers, lijkt screening voor tweede primaire tumoren in de slokdarm en longen momenteel niet aangewezen in deze patiëntengroepen.

Kennis van medische specialisten van hoofd-hals en slokdarm tweede primaire tumoren

Hoofdstuk 5 beschrijft de uitkomsten van een landelijke vragenlijst, die compleet werd ingevuld door 128 maag-, darm-, en leverartsen en 31 hoofd-hals chirurgen in Nederland. De vragenlijst richtte zich op de kennis van de verwachtte prevalentie en de opinie over het implementeren van screening voor tweede primaire tumoren in patiënten met een primaire PCC in de slokdarm of het hoofd-halsgebied. De specialisten verwachten een prevalentie van 5.0% (IQR 5.0-10.0%) hoofd-hals tweede primaire tumoren in patiënten met een slokdarmcarcinoom en 5.0% (IQR 4.0-10.0%) slokdarm tweede primaire tumoren in patiënten met een hoofd-hals carcinoom. Ongeveer een derde van de specialisten zou screening voor tweede primaire tumoren in de slokdarm of het hoofd-halsgebied overwegen. Dit aandeel nam toe na toelichting met de geschatte incidentie cijfers van tweede primaire tumoren in Nederland gebaseerd op recente studies. Van de hoofd-hals chirurgen achtte 41.3% zichzelf goed in staat de screening van de slokdarm te verrichten.

Endoscopische screening voor slokdarm tweede primaire tumoren in patiënten met hoofd-halskanker

In **Hoofdstuk 6** hebben we een prospectieve endoscopische screening studie uitgevoerd om slokdarm tweede primaire tumoren te detecteren in patiënten met hoofd-halskanker. Patiënten met een hypofarynx carcinoom, human papillomavirus-negatieve orofarynx carcinoom of andere hoofd-halskanker locatie in combinatie met overmatig alcoholgebruik werden geïncludeerd in het Erasmus Medisch Centrum. In totaal werden 202 patiënten met een primaire PCC in het hoofd-halsgebied geïncludeerd en werden 250 screening endoscopieën uitgevoerd. Endoscopische screening werd uitgevoerd binnen 6 maanden (34.0%), 6 maanden tot 1 jaar (8.0%), 1 tot 2 jaar (33.6%) en 2 tot 5 jaar (24.4%) na de diagnose hoofd-halskanker. Endoscopische screening leidde tot de detectie van 11

slokdarm tweede primaire tumoren in 10 patiënten (5.0%, 95% BI 2.4-8.9). Synchrone screening leidde tot de detectie van 6 tweede primaire tumoren tijdens 85 endoscopieën (7.1%). Metachrone screening uitgevoerd 1 jaar na synchrone screening leidde tot de detectie van 1 tweede primaire tumor (1/48, 2.1%), terwijl metachrone screening alleen leidde tot de detectie van 4 tweede primaire tumoren in 3 patiënten (3/117; 2.6%). Daarnaast werden met metachrone screening 1 maagcarcinoom en 1 adenocarcinoom in de slokdarm gevonden (1.7%). De meeste patiënten met een tweede primaire tumor werden gediagnosticeerd met een tweede primaire tumor in vroege stadia (90.0%), waarvoor behandeling met endoscopische resectie met curatieve intentie kon worden uitgevoerd (80.0%). Geen tweede primaire tumoren in de gescreende patiënten werden gevonden met routine beeldvorming zoals de panendoscopie, MRI of PET/CT-scan voor hoofd-halskanker voordat endoscopische screening werd uitgevoerd. In dit Hoofdstuk concluderen we dat endoscopische screening leidde tot de detectie van slokdarm tweede primaire tumoren in 5% van deze selectie van patiënten met een hoog risico. Daarom zou screening in een selectie van de patiënten met een PCC in het hoofd-halsgebied moeten worden overwogen, gebaseerd op het hoogste risico op tweede primaire tumoren en de levensverwachting gebaseerd op de hoofd-halskanker prognose en andere comorbiditeiten.

De bijlage van Hoofdstuk 6 bevat ook de reactie op de studie van Nobre Moura *et al.* waarin endoscopische screening in patiënten met een primaire PCC in het hoofd-halsgebied in Brazilië werd onderzocht.[10] In deze bijlage wordt de opbrengst van screening voor slokdarm tweede primaire tumoren in patiënten met hoofd-halskanker bediscussieerd. Deze studie includeerde 1,888 patiënten met hoofd-halskanker met mediaan 43 maanden follow up en detecteerde 7.9% slokdarm tweede primaire tumoren met jaarlijkse endoscopische screening. De meeste slokdarm tweede primaire tumoren (77.8%) werden gevonden in vroege stadia. Alhoewel patiënten met gevorderde hoofd-halskanker werden geëxcludeerd, werden zowel patiënten met curatieve als palliatieve behandelintentie geïncludeerd in de endoscopische screening. In deze letter bediscussiëren we dat de voordelen van screening (vroege detectie met potentieel een langere overleving) altijd afgewogen moeten worden tegen de nadelen (lichamelijke en psychische belasting en kosten voor de maatschappij) van screening. Daarom vinden we dat endoscopische screening niet uitgevoerd zou moeten worden in patiënten met een primaire PCC in het hoofd-halsgebied met een palliatief beleid.

Deel IV. Endoscopische behandeling van slokdarm neoplasie

Circumferentiële endoscopische submucosale dissectie voor de behandeling van plaveiselcelcarcinomen in de slokdarm

In **Hoofdstuk 7** rapporten we de klinische uitkomsten van 171 circumferentiële endoscopische submucosale dissecties (cESDs) voor PCC in de slokdarm uitgevoerd in 25 tertiaire centra in Westerse landen. De cESD werd compleet in één geheel uitgevoerd in 98.2% (95% BI 95.0-99.4) en had vrije snijvlakken in 69.6% (95% BI 62.3-76.0) van de procedures. Een curatieve resectie (resectie bestaand uit één geheel, met vrije snijvlakken en zonder hoog risico factoren voor lymfekliermetastasen) werd bereikt in 49.1% van de cESDs. Stricturen waarvoor ≥6 endoscopische dilataties of additionele incisie therapie of stentplaatsing nodig ontstonden na 70.8% van de cESDs, ondanks dat strictuur profylaxe werd toegepast na 93.4% van de cESDs. De cESD gerelateerde complicaties bestonden uit intra-procedureel bloedverlies (4.1%), post-procedureel bloedverlies (0.6%), cardiale of respiratoire klachten (4.7%) en gerelateerde sterfte (1.2%). In deze studie concluderen we dat cESD kan worden overwogen als potentieel curatieve behandeling in patiënten met een PCC in de slokdarm in Westerse landen. Echter zijn een verbetering van de patiënten selectie voor cESD en meer effectieve strategieën ter preventie van ernstige slokdarmstricturen.

Uitkomsten voor endoscopische resectie voor Barrett neoplasie met een tumor-positief verticale resectie marge

In **Hoofdstuk 8** beschrijven we 110 patiënten met een gedocumenteerde tumor-positief verticale resectie marge (R1v) na endoscopische resectie van Barrett neoplasie. In deze studie werd de proportie van patiënten met residu neoplasie onderzocht. 101 van de 110 (91.8%) van de patiënten had een macroscopisch complete resectie, waarvan de coupes van 99 casussen werden herbeoordeeld door ervaren Barrett pathologen. Pathologische herbeoordeling leidden tot bevestiging van het R1v snijvlak in 74.7% van de patiënten en liet een niet te beoordelen snijvlak (Rx) in 16.2% en tumor-negatief snijvlak (R0) in 9.1% van de patiënten zien. De aanwezigheid van residu neoplasie kon worden beoordeeld in 66/74 patiënten met een bevestigd R1v snijvlak, waarvan 50.0% (95% BI 37.4-62.6) van de patiënten residu neoplasie had in het aanvullende slokdarm resectie preparaat of tijdens eerste endoscopische herbeoordeling. Biopsie van het litteken van de eerdere endoscopische resectie in afwezigheid van afwijkingen leidde niet tot detectie van extra patiënten met neoplasie. Vijfentwintig patiënten zonder residu neoplasie ondergingen endoscopische follow up voor mediaan 37 maanden (IQR 12-50), waarin 4 patiënten een lokaal recidief ontwikkelden. Alle 4 deze lokale recidieven ontstonden binnen 48 maanden

na de endoscopische resectie met R1v. In deze studie concluderen we dat 50.0% van de patiënten met een bevestigde R1v marge geen residu neoplasie had na endoscopische resectie. Gebaseerd op deze bevindingen en eerdere gepubliceerde studies raden we aan dat in patiënten zonder aanwijzingen voor lymfekliermetastasen, endoscopische herbeoordeling zou moeten worden overwogen 8 tot 12 weken na endoscopische resectie met R1v om residu neoplasie te detecteren en patiënten te identificeren die additionele behandeling nodig hebben.

REFERENCES

1. Ebigbo A, Mendel R, Probst A, et al. Real-time use of artificial intelligence in the evaluation of cancer in Barrett's oesophagus. Gut. 2020;69(4):615-6.
2. de Groof AJ, Struyvenberg MR, Fockens KN, et al. Deep learning algorithm detection of Barrett's neoplasia with high accuracy during live endoscopic procedures: a pilot study (with video). Gastrointest Endosc. 2020;91(6):1242-50.
3. 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(2):187-92.
4. Li H, Zhang S, Zhou J, et al. Endoscopic surveillance for premalignant esophageal lesions: A community-based multicenter, prospective cohort study. Clinical Gastroenterology and Hepatology. 2022.
5. Dawsey SM, Lewin KJ, Wang GQ, et al. Squamous esophageal histology and subsequent risk of squamous cell carcinoma of the esophagus. A prospective follow-up study from Linxian, China. Cancer. 1994;74(6):1686-92.
6. Liu M, Zhou R, Guo C, et al. Size of Lugol-unstained lesions as a predictor for risk of progression in premalignant lesions of the esophagus. Gastrointestinal endoscopy. 2021;93(5):1065-73. e3.
7. Wei W-Q, Hao C-Q, Guan C-T, et al. Esophageal histological precursor lesions and subsequent 8.5-year cancer risk in a population-based prospective study in China. The American journal of gastroenterology. 2020;115(7):1036.
8. Wen D, Zhang L, Wang X, et al. A 5.5-year surveillance of esophageal and gastric cardia precursors after a population-based screening in China. Journal of gastroenterology and hepatology. 2015;30(12):1720-5.
9. Pimentel-Nunes P, Libânio D, Bastiaansen BAJ, et al. Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline–Update 2022. Endoscopy. 2022.
10. Nobre Moura R, Kuboki Y, Baba ER, et al. Long-term results of an endoscopic screening program for superficial esophageal cancer in patients with head and neck squamous cell carcinoma. Endosc Int Open. 2022;10(2):E200-E8.

List of abbreviations

AE	Adverse event
AI	Artificial intelligence
AUC	Area under the curve
ASA	American Society of Anesthesiologists
BE	Barrett's esophagus
BLI	Blue light imaging
BMI	Body mass index
CAD	Computer-aided detection
CAG	Chronic atrophic gastritis
cESD	Circumferential endoscopic submucosal dissection
CI	Confidence interval
CIS	Carcinoma in situ
CNN	Conventional neural network
CRT	Chemoradiotherapy
CT	Computed tomography
dCRT	Definitive chemoradiotherapy
df	Degree of freedom
DL	Deep learning
EAC	Esophageal adenocarcinoma
EC	Esophageal cancer
EGC	Early gastric cancer
ER	Endoscopic resection
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
ESCC	Esophageal squamous cell carcinoma
ESGE	European Society of Gastrointestinal Endoscopy
EUS	Endoscopic ultrasound
FICE	Flexible spectral imaging color enhancement

GC	Gastric cancer
GI	Gastrointestinal
GIM	Gastric intestinal metaplasia
HGD	High grade dysplasia
H&E	Hematoxylin and eosin stained
HD	High definition
HN	Head and neck region
HNSCC	Head and neck squamous cell carcinoma
HNSPT	Head and neck second primary tumor
HP	*Helicobacter pylori*
HPV	Human papillomavirus
HR	Hazard ratio
I^2	Inconsistency index
IQR	Interquartile range
IPCL	Intraepithelial papillary capillary loop
JES	Japanese Esophageal Society classification
LC	Lung cancer
LGD	Low grade dysplasia
LNM	Lymph node metastasis
LVI	Lymphovascular invasion
MBM	Multiband mucosectomy
MDT	Multidisciplinary team
ME	Magnified endoscopy
ML	Machine learning
MRI	Magnetic resonance imaging
NBI	Narrow band imaging
NCR	Netherlands Cancer Registry
nCRT	Neo-adjuvant chemoradiotherapy
NDBE	Non-dysplastic Barrett's esophagus

NOS	Not otherwise specified
NR	Not reported
NSCLC	Non-small cell lung cancer
NVMDL	Nederlandse vereniging van Maag-, Darm-,Leverartsen
NWHHT	Nederlandse Werkgroep Hoofd-Hals Tumoren
OR	Odds ratio
Palga	Dutch nationwide pathology databank
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
PET/CT	Positron emission tomography/computed tomography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
Pro	Prospective
Pt	Patient
PY	Pack years
Retro	Retrospective
RT	Radiotherapy
Rx	Not assessable resection margin
R0v	Tumor-negative vertical resection margin
R1v	Tumor-positive vertical resection margin
SCC	Squamous cell carcinoma
SD	Standard deviation
SIR	Standardized incidence ratio
Sens	Sensitivity
Spec	Specificity
SCLC	Small Cell Lung Cancer
SPSS	Statistical Package for the Social Sciences
SPT	Second primary tumor
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TNM	Tumor Node Metastasis

WHO	World health organization
WLE	White light endoscopy

Contributing authors

List of contributing authors in alphabetical order. Presented with the affiliations at the time that this research was conducted.

Alaa Alkhalaf
Gastroenterology and Hepatology
Isala Clinics
Zwolle, The Netherlands

Eduardo Albéniz
Endoscopy Unit, Gastroenterology
Hospital Universitario de Navarra (HUN)
Pamplona, Spain

Lorenza Alvarez Herrero
Gastroenterology and Hepatology
St. Antonius Hospital
Nieuwegein, The Netherlands

Myriam Ayari
Hepatogastroenterology
Cliniques Universitaires Saint-Luc
Brussels, Belgium

Robert J. Baatenburg de Jong
Otorhinolaryngology and Head & Neck Surgery
Erasmus Medical Center
Rotterdam, The Netherlands

Sophie A. van den Ban
Gastroenterology and Hepatology
Erasmus Medical Center
Rotterdam, The Netherlands

Pedro Barreiro
Gastroenterology Department of Centro Hospitalar Lisboa Ocidental
Lisboa, Portugal

Sanaa Belkhir
Gastroenterology, Hepatopancreatology and Digestive Oncology
CUB Erasme Hospital
Brussels, Belgium

Jacques J.G.H.M. Bergman
Gastroenterology and Hepatology
Amsterdam University Medical Centers
Amsterdam, The Netherlands

Michael J. Bourke
Gastroenterology and Hepatology
Westmead Hospital
Sydney, NSW, Australia

Marco J. Bruno
Gastroenterology and Hepatology
Erasmus Medical Center
Rotterdam, The Netherlands

Robin Cornelissen
Pulmonary Medicine
Erasmus Medical Center
Rotterdam, The Netherlands

Pierre H. Deprez
Hepatogastroenterology
Cliniques Universitaires Saint-Luc
Brussels, Belgium

Michael Doukas
Pathology
Erasmus Medical Center
Rotterdam, The Netherlands

Rodrigo G. Duran
Hepatogastroenterology, Cliniques Universitaires Saint-Luc
Brussels, Belgium

Mario Dinis-Ribeiro
Gastroenterology, Porto Comprehensive Cancer Center, Porto, Portugal
MEDCIDS, Faculty of Medicine, University of Porto, Porto, Portugal

Alanna Ebigbo
Gastroenterology and Infectious Diseases, University Hospital
Augsburg, Germany

Ana R. Franco
Gastroenterology Department of Centro Hospitalar Lisboa Ocidental, Advanced Endoscopy Center of Hospital Lusíadas, Lisboa, Portugal

Diego de Frutos
Puerta de Hierro University Hospital Majadahonda IDIPHISA Instituto de Investigacion Segovia Arana, Majadahonda, Spain

Wilmar de Graaf
Gastroenterology and Hepatology
Erasmus Medical Center
Rotterdam, The Netherlands

Sunil Gupta
Department of Gastroenterology and Hepatology, Westmead Hospital, Sydney, NSW, Australia

Stefan Groth
Center of Gastroenterology, Klinik Hirslanden, Zurich, Switzerland

Jose A. Hardillo
Otorhinolaryngology and Head and Neck Surgery
Erasmus Medical Center
Rotterdam, The Netherlands

Lara R. Heij
Pathology
Erasmus Medical Center
Rotterdam, The Netherlands

Alberto Herreros-de-Tejada
Puerta de Hierro University Hospital Majadahonda IDIPHISA Instituto de Investigacion Segovia Arana, Majadahonda, Spain

Jeremie Jacques
Service d'Hépato-Gastro-Entérologie
CHU Dupuytren
Limoges, France

Marnix Jansen
Pathology
University College London Hospital
London, UK.

Pieter Jan F. de Jonge
Gastroenterology and Hepatology
Erasmus Medical Center
Rotterdam, The Netherlands

Michal F. Kaminski
Cancer Prevention and Oncological Gastroenterology, The Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Stijn Keereweer
Otorhinolaryngology and Head and Neck Surgery
Erasmus Medical Center
Rotterdam, The Netherlands

Laurens A. van Kleef
Gastroenterology and Hepatology
Erasmus Medical Center
Rotterdam, The Netherlands

Arjun D. Koch
Gastroenterology and Hepatology
Erasmus Medical Center
Rotterdam, The Netherlands

Hugo U. Koecklin
Endoscopy Unit, Hospital Universitari
Germans Trias i Pujol
Barcelona, Spain

Ricardo Küttner-Magalhães
Santo António Hospital, Porto University
Hospital Center
Porto, Portugal

Sara Leblanc
Gastroenterology and Hepatology
Hôpital Privé Jean Mermoz, Ramsay Santé,
Lyon, France

Arnaud Lemmers
Gastroenterology, Hepatopancreatology and
Digestive Oncology, CUB Erasme Hospital,
HUB (Hôpital Universitaire de Bruxelles),
Université Libre de Bruxelles (ULB), Brussels,
Belgium

Romain Legros
Service d'Hépato-Gastro-Entérologie CHU
Dupuytren, Limoges, France

Vincent Lepilliez
Hôpital Privé Jean Mermoz, Ramsay Santé,
Lyon, France

Diogo Libânio
Gastroenterology, Porto Comprehensive
Cancer Center, and RISE@CI-IPOP (Health
Research Network), Porto, Portugal
MEDCIDS, Faculty of Medicine, University
of Porto, Porto, Portugal

Hetty Mast
Oral and Maxillofacial Surgery
Erasmus Medical Center
Rotterdam, The Netherlands

Sybren L. Meijer
Pathology
Amsterdam University Medical Centers
Amsterdam, The Netherlands

Helmut Messmann
Gastroenterology and Infectious Diseases,
University Hospital, Augsburg, Germany

Noor Mohammed
Leeds Gastroenterology Institute, St
James's University Hospital, Leeds, UK

Dominiek A. Monserez
Otorhinolaryngology and Head and Neck
Surgery
Erasmus Medical Center
Rotterdam, The Netherlands

Raquel Muñoz González
Endoscopy Unit, Hospital Universitari
Germans Trias i Pujol, Barcelona, Spain

Sanne N. van Munster
Gastroenterology and Hepatology
Amsterdam University Medical Centers
Amsterdam, The Netherlands

Wouter B. Nagengast
Gastroenterology and Hepatology
University Medical Center Groningen
Groningen, The Netherlands

Suzan Nikkessen
Gastroenterology and Hepatology
Erasmus Medical Center
Rotterdam, The Netherlands

Adolfo Parra-Blanco
Gastroenterology, NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham, UK

Mathieu Pioche
Endoscopy and Gastroenterology Unit
Edouard Herriot Hospital
Lyon, France

Nastazja D. Pilonis
Cancer Prevention and Oncological Gastroenterology, The Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Roos E. Pouw
Gastroenterology and Hepatology
Amsterdam University Medical Centers
Amsterdam, The Netherlands

Thierry Ponchon
Endoscopy and Gastroenterology Unit, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France

Andreas Probst
Gastroenterology and Infectious Diseases, University Hospital, Augsburg, Germany

Lindsey Oudijk
Pathology
Erasmus Medical Center
Rotterdam, The Netherlands

Jérôme Rivory
Endoscopy and Gastroenterology Unit, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France

Enrique Rodríguez de Santiago
Gastroenterology and Hepatology
Hospital Universitario Ramón y Cajal
Madrid, Spain

João Santos-Antunes
Gastroenterology Department, Faculty of Medicine, Centro Hospitalar S. João, Porto, Portugal

Erik J. Schoon
Gastroenterology and Hepatology
Catharina Hospital
Eindhoven, The Netherlands

Stefan Seewald
Center of Gastroenterology
Klinik Hirslanden
Zurich, Switzerland

Aniel Sewnaik
Otorhinolaryngology and Head and Neck Surgery
Erasmus Medical Center
Rotterdam, The Netherlands

Manon C.W. Spaander
Gastroenterology and Hepatology
Erasmus Medical Center
Rotterdam, The Netherlands

Meltem Tokat
Gastroenterology and Hepatology
Erasmus Medical Center
Rotterdam, The Netherlands

Eva P.D. Verheij
Gastroenterology and Hepatology
Amsterdam University Medical Centers
Amsterdam, The Netherlands

Bas L.A.M. Weusten
Gastroenterology and Hepatology
University Medical Center Utrecht
Utrecht, The Netherlands

St. Antonius Hospital
Nieuwegein, The Netherlands

Felipe R Zabala
Gastroenterology Department, Hospital Universitario HM Montepríncipe, Grupo HM Hospitales, Boadilla del Monte, Madrid, Spain

Steffi E.M. van de Ven
Gastroenterology and Hepatology
Erasmus Medical Center
Rotterdam, The Netherlands

Timothée Wallenhorst
Service des Maladies de l'Appareil Digestif
CHU Pontchaillou, Rennes, France

Jonathan White
Gastroenterology, NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham, UK

Bibliography

** Indicates shared first/last authorship.*

1. **The Yield and Safety of Screening Colonoscopy in Patients Evaluated for Liver Transplantation.** van Tilburg L*, Oey RC*, Erler NS, Metselaar HJ, Spaander MCW, van Buuren HR, de Man RA. *Hepatology. 2019*

2. **Artificial Intelligence in Upper Gastrointestinal Endoscopy.** van Tilburg L*, Tokat M*, Koch AD, Spaander MCW. *Dig dis. 2022*

3. **Prevalence of lung tumors in patients with esophageal squamous cell carcinoma and vice versa: a systematic review and meta-analysis.** van Tilburg L, van de Ven SEM, Spaander MCW, van Kleef LA, Cornelissen R, Bruno MJ, Koch AD. *J Cancer Res Clin Oncol. 2022*

4. **Screening for head and neck tumors in patients with esophageal squamous cell carcinoma and vice versa: a nationwide survey among medical specialists.** van Tilburg L, van den Ban SA, van de Ven SEM, Sewnaik A, Bruno MJ, Spaander MCW, Baatenburg de Jong RJ, Koch AD. *Endosc Int Open. 2022*

5. **Extending treatment criteria for Barrett's neoplasia: results of a nationwide cohort of 138 endoscopic submucosal dissection procedures.** van Munster SN, Verheij EPD, Nieuwenhuis EA, Offerhaus JGJA, Meijer SL, Brosens LAA, Weusten BLAM, Alkhalaf A, Schenk EBE, Schoon EJ, Curvers WL, van Tilburg L, van de Ven SEM, Tang TJ, Nagengast WB, Houben MHMG, Seldenrijk KCA, Bergman JJGHM, Koch AD*, Pouw RE*; Dutch Barrett Expert Centers. *Endoscopy. 2022*

6. **Predicting procedure duration of colorectal endoscopic submucosal dissection at Western endoscopy centers.** Dang H, Dekkers N, Steyerberg E, Baldaque-Silva F, Omae M, Haasnoot K, van Tilburg L, van der Kraan J, Langers A, van Hooft J, de Graaf W, Koch AD, Didden P, Moons L, Hardwick J, Boonstra J. *Endosc Int Open. 2022*

7. **To screen or not to screen: Reply to: Long-term results of an endoscopic screening program for superficial esophageal cancer in patients with head and neck squamous cell carcinoma.** van Tilburg L, Brands MT, Koch AD. *Endosc Int Open. 2022*

8. **Endoscopic screening of the upper gastrointestinal tract for second primary tumors in patients with head and neck cancer in a Western country.** van Tilburg L, van de Ven SEM, de Jonge PJF, de Graaf W, Spaander MCW, Nikkessen S, Hardillo J, Sewnaik A, Monserez DA, Mast H, Keereweer S, Bruno MJ, Baatenburg de Jong RJ, Koch AD. *Endoscopy. 2023*

9. **Increased risk of esophageal squamous cell carcinoma in patients with squamous dysplasia: a nationwide cohort study in the Netherlands.** van Tilburg L, Spaander MCW, Bruno MJ, Oudijk L, Heij LR, Doukas M, Koch AD. *Dis Esophagus. 2023*

10. **Low risk of local recurrence after a successful en bloc endoscopic submucosal dissection for noninvasive colorectal lesions with positive horizontal resection margins (R-ESD study).** Haasnoot KJC, Baldaque-Silva F, Koch A, Figueiredo Ferreira M, Santos-Antunes J, Dias E, Omae M, van Tilburg L, Dang H, Lemmers A, Boonstra JJ, Moons LMG. *Endoscopy. 2023*

11. **Western outcomes of circumferential endoscopic submucosal dissection for early esophageal squamous cell carcinoma.** Rodríguez de Santiago E*, van Tilburg L*, Deprez PH, Pioche M, Pouw RE, Bourke MJ, Seewald S, Weusten BLAM, Jacques J, Leblanc S, Barreiro P, Lemmers A, Parra-Blanco A, Küttner-Magalhães R, Libânio D, Messmann H, Albéniz E, Kaminski MF, Mohammed N, Zabala FR, Herreros-de-Tejada A, Koecklin HU, Wallenhorst T, Santos-Antunes J, Cunha Neves J, Koch AD, Ayari M, Duran RG, Ponchon T, Rivory J, Bermang JJGHM, Verheij EPD, Gupta S, Groth S, Lepilliez V, Franco AF, Belkhir S, White J, Ebigbo A, Probst A, Legros R, Pilonis ND, de Frutos D, Muñoz González R, Dinis-Ribeiro M. *Gastrointest Endosc. 2023*

12. **Vertical R1 margins are not always associated with residual neoplasia after endoscopic resection of Barrett's neoplasia: a nationwide cohort with dedicated pathology reassessment.** van Tilburg L*, Verheij EPD*, van de Ven SEM, van Munster SN, Weusten BLAM, Alvarez Herrero L, Nagengast WB, Schoon EJ, Alkhalaf A, Bergman JJGHM, Pouw RE, Oudijk L, Meijer SL, Jansen M, Doukas M*, Koch AD*. *Endoscopy. 2024*

13. **Reply letter to Jiang et al.** van Tilburg L, Koch AD. *Endoscopy. 2024*

14. **Neoplastic progression risk in females with Barrett's esophagus: a systematic review and meta-analysis of individual patient data.** Zellenrath PA, van Tilburg L, Pouw RA, Yadlapati R, Peters Y, Ujiki MB, Thota PN, Ishimura N, Meltzer SJ, Peleg N, Choi W, Reynolds JV, Polydorides AD, Koch AD, Honing J, Spaander MCW. *Submitted*

PhD portfolio

PhD candidate	Laurèlle van Tilburg
PhD period	March 2020 – May 2024
Supervisors	Prof. dr. Marco J. Bruno Dr. Arjun D. Koch
Department	Gastroenterology and Hepatology

Courses and workshops	**Year**
Endnote workshop, Erasmus MC, Rotterdam	2020
Systematic Literature Retrieval in PubMed workshop, Erasmus MC, Rotterdam	2020
Systematic Literature Retrieval in other databases workshop, Erasmus MC, Rotterdam	2020
Basic introduction on SPSS, Molecular medicine postgraduate school, Rotterdam	2020
BROK cursus, Consultatiecentrum Patiëntgebonden Onderzoek, Erasmus MC, Rotterdam	2020
Microsoft Excel 2016 basic workshop, The Erasmus Postgraduate School Molecular Medicine, Rotterdam	2020
Microsoft Excel 2016 advanced workshop, The Erasmus Postgraduate School Molecular Medicine, Rotterdam	2020
Biostatistics I, Erasmus MC, Rotterdam	2021
Personal leadership and communication workshop, Erasmus MC, Rotterdam	2021
The Photoshop and Illustrator CC 2021 Workshop for PhD-students and other researchers, The Erasmus Postgraduate School Molecular Medicine, Rotterdam	2021
English Biomedical Writing for PhD students, Erasmus MC, Rotterdam	2022
Integrity in scientific research, dept. of Medical ethics and Philosophy, Erasmus MC, Rotterdam	2022

Oral presentations	
Endoscopic screening of the upper gastrointestinal tract for second primary tumors in patients with head and neck cancer in a Western country. Digestive Disease Days, Veldhoven, the Netherlands	2022
Increased risk of esophageal squamous cell carcinoma in patients with squamous dysplasia: a nationwide cohort study in the Netherlands. Digestive Disease Days, Veldhoven, the Netherlands	2023

Risk of residual cancer after endoscopic resection of early Barrett's neoplasia with confirmed vertical R1 margin: a nationwide cohort in the Netherlands. Digestive Disease Days, Veldhoven, the Netherlands	2023
Endoscopic screening of the upper gastrointestinal tract for second primary tumors in patients with head and neck cancer in a Western country. European Society for Gastrointestinal Endoscopy Days, Dublin, Ireland	2023
Increased risk of esophageal squamous cell carcinoma in patients with squamous dysplasia: a nationwide cohort study in the Netherlands. Digestive Disease Days, Veldhoven, the Netherlands. Awarded with a travel grant	2023
Risk of residual cancer after endoscopic resection of early Barrett's neoplasia with confirmed vertical R1 margin: a nationwide cohort in the Netherlands. Digestive Disease Week, Chicago, United States of America	2023
Risk of residual cancer after endoscopic resection of early Barrett's neoplasia with confirmed vertical R1 margin: a nationwide cohort in the Netherlands. United European Gastroenterology Week, Copenhagen, Denmark. Awarded with a travel grant	2023

Poster presentations	
Screening for head and neck tumors in patients with esophageal squamous cell carcinoma and vice versa: a nationwide survey among medical specialists. European Society for Gastrointestinal Endoscopy Days, online and Prague, Czech Republic	2022
Endoscopic screening of the upper gastrointestinal tract for second primary tumors in patients with head and neck cancer in a Western country. United European Gastroenterology Week, Vienna, Austria. Awarded with a travel grant	2022
Risk of residual cancer after endoscopic resection of early Barrett's neoplasia with confirmed vertical R1 margin: a nationwide cohort in the Netherlands. European Society for Gastrointestinal Endoscopy Days, Dublin, Ireland	2023
Increased risk of esophageal squamous cell carcinoma in patients with squamous dysplasia: a nationwide cohort study in the Netherlands. United European Gastroenterology Week, Copenhagen, Denmark	2023

Attended (inter)national conferences	
European Society for Gastrointestinal Endoscopy Days, virtual attendance	2022
Digestive Disease Days, Veldhoven, the Netherlands	2022
United European Gastroenterology Week, Vienna, Austria	2022
Digestive Disease Days, Veldhoven, the Netherlands	2023
European Society for Gastrointestinal Endoscopy Days, Dublin, Ireland	2023
Digestive Disease Week, Chicago, United States of America	2023

United European Gastroenterology Week, Copenhagen, Denmark	2023

Attended seminars	
Journal clubs, department of Gastroenterology and Hepatology, Erasmus MC, Rotterdam	2020-2023
Upper GI research meeting, departments of Gastroenterology and Hepatology, Pathology, Oncology and Surgery, Erasmus MC, Rotterdam	2020-2023
Barret Expert Center Meeting, Barrett Expert Centers in the Netherlands (two times a year, in 2020 cancelled due to COVID-19)	2021-2023
Casuïstische patiënten besprekingen, NVGE (4x)	2020-2023

Supervision	
Supervising graduation project Sophie A. van den Ban, medical student Erasmus University Rotterdam: Screening for head and neck tumors in patients with esophageal squamous cell carcinoma and vice versa: a nationwide survey among medical specialists.	2021
Coach of 4 bachelor medicine students, Erasmus University Rotterdam, Rotterdam, the Netherlands	2020-2023

Dankwoord

Graag wil ik iedereen bedanken die heeft geholpen bij de totstandkoming van dit proefschrift. Zonder jullie hulp en steun was dit niet gelukt!

Prof. dr. Bruno, beste Marco, bedankt voor jouw begeleiding als promotor tijdens mijn promotietraject. Ik heb jouw pragmatische blik en efficiëntie tijdens onze gesprekken gewaardeerd. Met jouw helikopter view bewaarde jij op een prettige manier het overzicht in mijn PhD en stuurde je bij waar nodig. Zo hielden Arjun en jij samen altijd het einddoel voor ogen. **Dr. Koch**, beste Arjun, bedankt voor jouw begeleiding als copromotor en je nuchtere en relativerende blik. Jij liet mij de afgelopen jaren vrij om mezelf te ontwikkelen. Het was fijn dat ik altijd bij jou kon aankloppen, wanneer een van onze projecten spaak leek te lopen. Vaak ging ik na onze gesprekken weer met enthousiasme en hernieuwd vertrouwen aan de slag. Dank je wel!

Mijn dank gaat uit naar de leescommissie, **prof. dr. K.K. Krishnadath, prof. dr. J.B. van Lanschot en dr. J. Honing** voor het beoordelen van dit proefschrift. Daarnaast dank ik ook graag de andere leden van de promotie commissie; **prof. dr. M.C.W. Spaander, prof. dr. E.J. Schoon en dr. Meijer**. Ik kijk uit naar onze gedachtewisselingen op 29 mei.

Graag bedank ik alle patiënten die aan de verschillende studies hebben meegedaan, zonder jullie was dit proefschrift niet mogelijk! Ook bedank ik graag alle **co-auteurs** voor de prettige samenwerking. Het heeft geleidt tot een aantal mooie publicaties.

Bedankt voor de samenwerking binnen de **Barrett Expert Centers** met leerzame research meetings. In het bijzonder wil ik de **endoscopisten vanuit de Barrett Expert Centers** en **endoscopisten voor de SCOPE studie** bedanken. Ook dank ik de **Maag Lever Darm Stichting** voor het financieel mogelijk maken van de SCOPE studie.

Andrea Lubeek, dank je wel voor alle hulp. Als secretaresse sta jij altijd klaar met hulp, advies of tips. Dat heb ik zeer gewaardeerd. Graag bedank ik ook de collega's die onderdeel zijn geweest van de **upper GI besprekingen**, de voormalige slokdarmbesprekingen, voor alle nuttige feedback en tips.

Steffi van de Ven, bedankt dat ik onze PhD lijn mocht voortzetten. Onze 9 maanden overlap waren voor mij een ideaal begin, waarin jij me wegwijs hebt gemaakt in de onderzoekswereld. Jouw antwoorden op al mijn praktische vragen over o.a. de SCOPE studie en PEGASUS-1 studie en handige tips kwamen goed van pas. Dank je wel voor alles!

Annemijn Maan, mijn PhD stokje heb ik aan jou mogen overdragen. Fijn om te zien dat alle projecten bij jou in de goede handen zijn en jij met enthousiasme aan de slag bent gegaan.

Eva Verheij, dank je wel voor onze fijne samenwerking. Jij was betrokken en stond altijd klaar om even tussendoor te bellen of te mailen, wanneer nodig. Ik denk dat we trots mogen zijn op het resultaat van ons R1-project!

Collega's van de **interne van het Reinier de Graaf Gasthuis**, bedankt voor alles wat ik hier als ANIOS interne al heb mogen leren. Graag bedank ik **dr. H. Boom** als opleider, voor de interesse en wijze adviezen op de werkvloer. Ik heb me altijd welkom gevoeld en hoop terug te komen als AIOS. Lieve **collega arts-assistenten**, bedankt voor de gezelligheid, steun en natuurlijk ook de vrijdag middag borrels. Vergeet niet om tijdig de biertjes koud te zetten.

R.J. de Knegt, beste Rob, bedankt dat ik de kans krijg in het Erasmus MC bij de MDL te komen werken als ANIOS. Ik kijk uit naar alles wat ik hier ga kunnen leren.

Graag bedank ik mijn collega **arts-onderzoekers op Na-6**. Lieve **Sylvia** en **Laurens**, mijn paranimfen! Bedankt dat jullie mij vandaag bij willen staan. Dankzij jullie was mijn promotie tijd zoveel leuker. Lieve **Sylvia**, jouw enthousiasme werkt aanstekelijk. Al vrij snel nadat ik jou leerde kennen, kregen wij een bondje, ontstaan door onze gedeelde liefde voor planten, onze katten en (online) koffiemomentjes met wat zelfgebakken lekkers erbij. Ik waardeer onze kletsmomentjes en mede dankzij jouw enthousiasme ben ik ook in het RdGG gestart. Wat een goede keuze en super leuk dat we daar weer collega's waren.
Lieve **Laurens**, wat een topper ben jij! Ik heb genoten van onze vele gesprekken en spelletjes avonden onder het genot van een koffietje of biertje. De avonden bierbrouwen waren gezellige avonden, met name omdat er daardoor nog meer tijd was voor veel gezellige momenten en spelletjes. Het is mega knap hoe jij jouw eigen promotie traject hebt aangepakt, wat een manuscriptenmachine ben jij. Hopelijk komen we elkaar in de toekomst weer tegen op de werkvloer in de kliniek!

David, wat hebben wij veel gelachen. Ik waardeer jouw positieve houding, waar ik zelf soms meer aan de realistische zijde zit. Ik heb genoten van onze hardlooprondjes en gezamenlijke trainingen bij de C groep van Rotterdam Atletiek (wie weet kom ik weer terug binnenkort…). Op congressen waren we vaak kameraden op de borrels, waar we vele biertjes aan jouw Untappd hebben toegevoegd. **Pieter**, onze congres ervaringen waren meestal onvergetelijk. Ik heb genoten van onze toffe reis naar IJsland, waarin we met een gigantische jetlag in onze schakelauto richting indrukwekkende watervallen reden. Wat een prachtige dagen waren dat! Ook de fietstochtjes richting het RdGG vond ik heel waardevol, waarin we interessante

casussen en onze levens bespraken. Ik vind het tof dat ik een inkijkje heb gekregen in jouw blik en manier van aanpak wat betreft research en klinisch werk. **Pauline,** bedankt voor jouw bijdrage als mede-slokdarm promovendus. **Edo,** leuk dat jij op de valreep bent aangesloten op ons Na-6 computereiland!

Sjoerd en **Taihra**, leuk dat wij als oud co-genoten contact hebben gehouden. **Taihra**, super knap hoe jij jouw PhD vervolgd hebt na de coschappen! **Sjoerd**, dank je wel voor onze koffiepauzes, wandelingen door het Euromast park en vele discussies. Zet hem op met de Chinees lessen! Ik hoop binnenkort ook jullie proefschrift verdedigingen in mijn agenda te mogen zetten.

Eva ten Velden, wat bijzonder dat we contact hebben gehouden nadat we samen op de basisschool en middelbare school zaten. We zijn ieder volledig een eigen pad ingeslagen; tof om te zien dat jij zelf je eigen tiny house hebt ontworpen en gebouwd. Wat super knap! Dank je wel voor jouw verfrissende blik op mijn leven.

Sophie van den Ban, bedankt voor jouw huisgenootschap en dat je bij mij jouw masteronderzoek wilde komen doen. Ik moet nog regelmatig lachen als ik van jou een foto herinnering krijg doorgestuurd van ons gezamelijke bijbaantje of van ons thuis in pyjama op de bank.

Lieve **Charlie, Laura en Claire**, mijn medegangsters van onze eerstejaarsstudiegroep van Geneeskunde. Leuk om te zien dat iedereen een eigen kant op is gegaan. Ik kijk uit naar een volgende keer sushi of Loetje met jullie. **Charlie**, ontzettend stoer hoe jij je mannetje staat als AIOS chirurgie en daarnaast jouw onderzoekslijn voortzet. **Claire**, jouw grapjes en gekkigheid hoor ik altijd graag. Ik kijk uit naar een volgende pornstar martini. Wij kunnen nog wat leren van de arbeidsvoorwaarden bij de verzekeringsgeneeskunde. **Laura**, onze tropenarts in spé, wat een topper ben je. Wat hebben we genoten toen Pris en ik je opzochten op Bonaire om daar te surfen, duiken en snorkelen. Ik ben benieuwd wat jouw volgende bestemming gaat worden. Lieve **Priscilla,** de leukste Lekkerkerker die ik ken. Ik denk dat jij een hele goede fijne huisarts gaat worden. En wat is het super tof om iedere keer jullie kleine meid **Sophie** weer een beetje groter te zien worden.

Lieve mede-Puntegalers, **Olivier**, **Sanne**, **Maarten** en **Elise**. Bedankt voor jullie vriendschap waarin we samen genieten van dinertjes, oud en nieuw en Puntegale ontbijtjes. Lieve **Thomas en Eveline**, soms bijna bonus Puntegalers, onze nasi Mondays zijn inmiddels uitgegroeid tot heerlijke etentjes met een lekker drankje en discussies over onze levens.

Wat was het tof om met jullie door de Dolomieten te wandelen! Ik waardeer jullie gezelligheid en luisterend oor. Wij kunnen bij jullie altijd terecht. Dank voor alles!

Lieve schoonfamilie, **Maaike, Jeroen, Mark, Celine** en **Annemarie,** bij jullie voel ik me altijd welkom. Ik kijk uit naar ons volgende etentje of boswandeling met **Flynn**. Dank jullie wel!

Lieve **pap** en **mam**, bedankt voor jullie onvoorwaardelijke liefde en steun. Jullie hebben ons alle drie een fijne jeugd gegeven, waarin wij onze eigen weg konden gaan en ons hebben kunnen ontwikkelen tot wie we nu zijn. Nog altijd kom ik heel graag weer bij jullie langs om een weekend samen bij te praten, vaak ook met een lekkere lunch bij Evertsen of met een fietstocht met reigers tellen vanaf de boulevard van Vlissingen. Bedankt voor het aanhoren van al mijn promotieverhalen. Wie had ooit gedacht dat ik doctor, binnen onze familie ook wel boktor genoemd, zou worden.

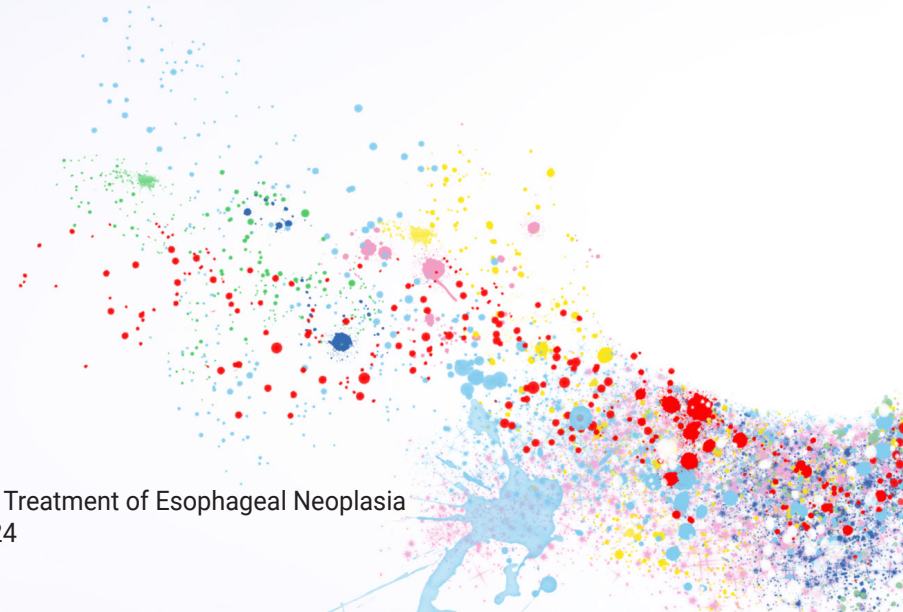
Fabian en **Ronetto,** dank jullie wel dat wij het onderling weinig over mijn promotie traject hoefden te hebben. **Fabian**, leuk om te zien hoe jij bent gegroeid in jouw rol als tutor voor de psychologie studenten. Samen met **Eva** kijk jij uit naar de bruiloft en werken jullie aan een fijn thuis. Ik ben benieuwd wat er de komende jaren op jullie pad gaat komen. **Ronetto**, ik bewonder jouw doorzettingsvermogen en het feit dat jij jouw dromen volgt, waarin je nu jouw tenniscarrière najaagt en in Amsterdam bent gaan wonen.

Lieve **Tom**, dank je wel dat je er altijd voor mij bent. Je bent mijn maatje en begrijpt mij door en door. Samen hebben we onze PhD-trajecten mogen doorlopen en tegenwoordig mis ik soms de dagen waarin we allebei als arts-onderzoekers thuiswerkten, samen vibend op de muziek met **Nienke** op schoot en tussendoor een lunchwandeling door het Euromast park. Ik ben benieuwd wat het leven voor ons in petto heeft en ben blij en trots jou aan mijn zijde te hebben. Ik hou van je!

About the author

Laurèlle van Tilburg was born on 25th of March 1995 in Tilburg, the Netherlands. She completed pre-university education at the Nehalennia in Middelburg in 2013. That same year, she started medical school at the Erasmus University of Rotterdam. During her bachelor and master, she investigated the yield and safety of screening colonoscopy in patients evaluated for liver transplantation. She obtained her medical degree in 2020.

After graduating, she started her PhD program as described in this thesis under the supervision of dr. Arjun D. Koch and prof. Marco J. Bruno at the Gastroenterology and Hepatology department of the Erasmus Medical Center. Afterwards, she started as a resident at the department of Internal medicine of the Reinier de Graaf Gasthuis in Delft and subsequently at the department of Gastroenterology and Hepatology of the Erasmus Medical Center in Rotterdam.



Detection and Endoscopic Treatment of Esophageal Neoplasia