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

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ABSTRACT

Background and study aims 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 (HNSPTs) 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 HNSPTs 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 HNSPTs 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 ESPTs 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 HNSPTs and ESPTs 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 squamous cell carcinoma (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 therefore is prone to 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 in 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 second primary tumor (ESPT) 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 (HNSPTs) 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 ESPTs and HNSPTs may be subtle and can be easily missed [21–23].

This study aimed to assess knowledge about HNSPTs 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 the 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 to 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, gender, work location and subspecialization. Questions were also asked about 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. Part 2 focused on the expectations among medical specialists regarding the prevalence and synchronous proportion of ESPTs in HNSCC patients and HNSPTs 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 6 months of the diagnosis of the primary tumor [24]. In Part 3, questions were asked about 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 (**Suppementary 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 ESPTs.

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**, **Supplementary Fig. S1**). Two-thirds of the specia-

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

	All specialists 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 subspecialization.

lists were 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 subspecialization. Routine use of chromoendoscopy was reported by most gastroenterologists (91.4 %) and half of the HN surgeons (51.6%).

HNSPTs in ESCC

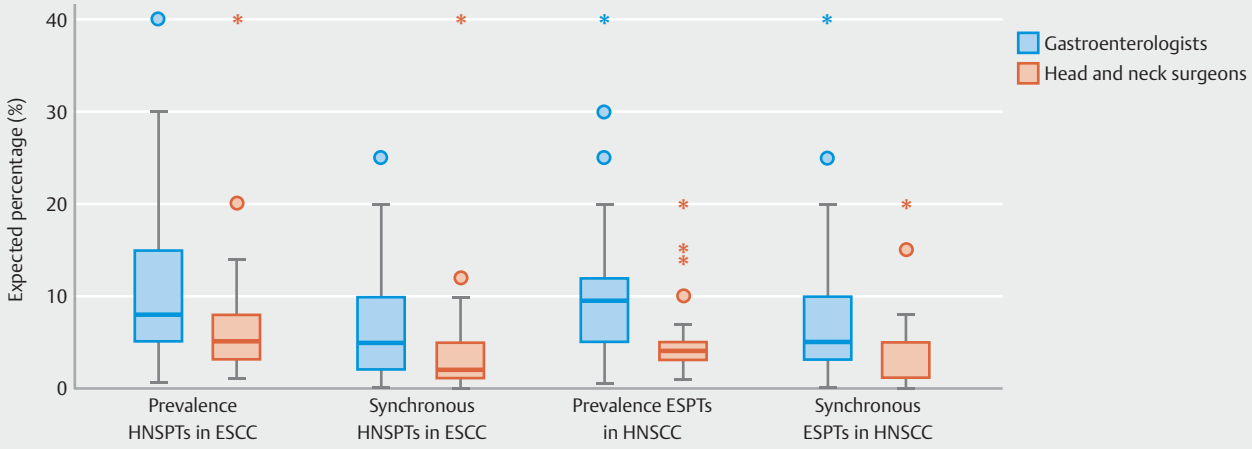
Specialists expected the median prevalence of HNSPTs in patients with ESCC to be 5.0 % (IQR: 5.0–10.0) (▶ **Fig. 1**). A prevalence ≤ 3 % or ≥ 20 % was expected by 38.4 % of the specialists. For the subgroups of gastroenterologists and HN surgeons, the expected median prevalence of HNSPTs in ESCC patients was 7.0 % (IQR: 5.0–15.0) and 5.0 % (IQR: 3.0–8.0), respectively. The expected proportion of synchronous HNSPTs 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.

ESPTs in HNSCC

Among all specialists, the expected median prevalence of ESPTs in patients with HNSCC was 5.0 % (IQR: 4.0–10.0). An ESPT 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 ESPTs 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).

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 ESPTs, 32.1 % of all specialists identified the hypopharynx as the primary HNSCC location associated



▶ **Fig. 1** The expected prevalence of HNSPTs in patients with ESCC and vice versa in a Western population. ESCC, esophageal squamous cell carcinoma; ESPT, esophageal second primary tumor; HNSPT, head and neck second primary tumor; HNSCC, head and neck squamous cell carcinoma; HNSPT, head and neck second primary tumors. 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)

▶ **Table 2** Primary HNSCC location associated with the highest risk for ESPTs, 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.
ESPTs, esophageal second primary tumors; HNSCC, head and neck squamous cell carcinoma.

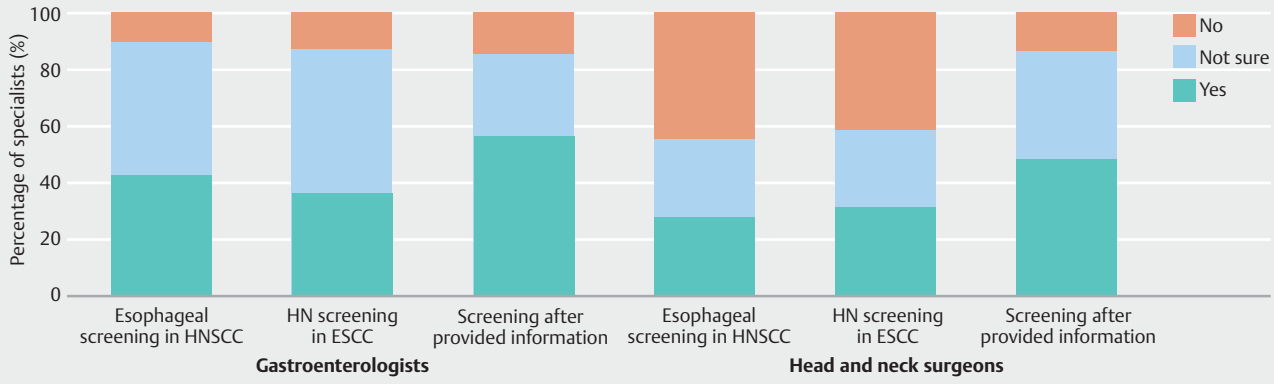
with the highest ESPT risk. The hypopharynx was selected by 80.6 % of the HN surgeons and by 20.3 % of the gastroenterologists (▶ **Table 2**). Of the gastroenterologists, 45.3 % answered that they did not know which HN sublocation was associated with the highest risk for ESPTs, compared to 3.2 % of HN surgeons.

Screening for SPTs

One-third of all specialists (35.2 %) would consider screening for HNSPTs in patients with ESCC (▶ **Fig. 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 of HNSPTs, 30.8 % expected only more diagnoses HNSPTs at early stages and 6.3 % expected only more diagnoses of HNSPTs. Sixty-three specialists (39.6 %) would consider screening of the esophagus in HNSCC patients; 42.8 % were in doubt and 17.6 % stated that esophageal screening should not be implemented. If screening were to be implemented, 61.0 % of the specialists expressed the expectation that more ESPTs would be diagnosed and that these SPTs would be found at early stages.

Of all gastroenterologists, 35.9 % would consider implementing 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 ESPTs and HNSPTs. Of HN surgeons, 32.3 % and 29.0 % would consider screening to detect HNSPTs in ESCC and vice versa, respectively. After incidence information was provided 48.4 % of HN surgeons were in favor of screening of the esophagus and HN region.

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



▶ **Fig. 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.

that changed their opinion, 58.6 % and 72.7 % of the specialists were more willing to consider screening to detect ESPTs and HNSPTs, 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 ESPTs in HNSCC patients were to be implemented, gastroenterologists would perform screening with at least chromoendoscopy (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 ESPTs. 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.

Discussion

SPTs occur relatively 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

▶ **Table 3** Reasons for and against screening for SPTs in ESCC and HNSCC patients, 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)
▪ Need for more research	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.

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 HNSPTs 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 perception of expected prevalence of SPTs in ESCC and HNSCC patients among involved specialists. Four of 10 medical specialists expected the prevalence of HNSPTs in ESCC patients and vice versa to be ≤ 3 % or ≥ 20 %. 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 HNSPTs in patients with primary ESCC. Synchronous HNSPTs were detected in 1.8 % of the ESCC patients [4]. Previous non-Asian screening studies detected ESPTs in 6.9 % of 392 patients with HN or tracheobronchial squamous cell carcinoma in France [15], ESPTs in 10 % of 40 patients with HN cancer in Switzerland [16], and ESPTs in 7.9 % of 1,888 HNSCC patients in Brazil [18].

The expected incidence of 2 % to 10 % for synchronous ESPTs in this study is in line with that found in our previous screening study [17]. Our research group reported a 5.9 % (95 % confidence interval 1.9 %–13.2 %) incidence of ESPTs in 85 patients diagnosed with human papillomavirus-negative HNSCC located in 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 for 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 about 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 ESPTs 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 ESPTs in patients with oropharyngeal and hypopharyngeal HNSCC or chronic alcohol abuse [26]. The laryngology and HN guideline from the United Kingdom states that the incidence of ESPTs is low and screening with rigid esophagoscopy should be limited to HNSCC patients with the highest risk for synchronous ESPTs [19]. Other screening modalities to detect ESPTs, such as positron emission tomography/computed tomography (PET/CT) scan, should not be considered, because the sensitivity of PET/CT for detection of early-stage esophageal cancer is only 38 % [27]. Therefore, PET/CT is inferior to endoscopic screening for ESPTs.

For meaningful implementation of screening to detect SPTs, it is crucial that screening eventually results in 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; 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 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 of expectations about prevalence was consistent among medical specialists. Third, findings from 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 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.

Conclusions

In conclusion, this Dutch nationwide survey reveals a lack of knowledge about HNSPTs in patients with ESCC and vice versa among surveyed specialists. Willingness to consider screening for SPTs in ESCC and HNSCC patients increased after back-

ground information was provided about 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 to increase awareness and improve detection of SPTs, independent of the need for implementation of screening for SPTs in ESCC and HNSCC patients.

Competing interests

Dr. Bruno received research support from and is consultant for Boston Scientific, Cook Medical, InterScope, Mylan, 3M and Pentax Medical. Dr. Spander received research support from Medtronics, Boston Scientific, Norgine, Informed, Sentinel and Sysmex. Dr. Koch received research support from DrFalk Pharma and consultancy fees from ERBE Elektromedizin and Pentax Medical.

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