Oral Oncology 145 (2023) 106529

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Head and neck cancer with synchronous nodules of the lung as a diagnostic and therapeutic challenge – A systematic review

Marc Müller [a,b], Jinji Li [a], Roland Giger [c,1], Olgun Elicin [d,1,*]

[a] HMS Hospital, Ear Nose and Throat Department, Mirdif, Dubai, United Arab Emirates
[b] Freie Universität Liechtenstein, Triesen, Liechtenstein
[c] Department of Otorhinolaryngology, Head and Neck Surgery, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[d] Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

ARTICLE INFO

Keywords:
Head and neck cancer
Squamous cell carcinoma
Second primary malignancies
Pulmonary nodules
Lung cancer
Metastases
Synchronous pulmonary malignancies

ABSTRACT

Head and neck squamous cell carcinoma (HNSCC) often presents with synchronous nodules of the lung (sNL), which may be benign nodules, second primary malignancies or metastases of HNSCC. We sought to gain an insight into the incidence of sNL and synchronous second primary of the lung (sSPML) in HNSCC patients and current opinions on useful diagnostic and therapeutic approaches. We conducted a systematic search of the PubMed database for articles that reported the simultaneous detection of HNSCC and sNL/sPML, within the timeframe of diagnosis and staging. Only studies involving humans were included, without restrictions for sex, age, ethnicity, or smoking history. All articles were categorised according to the Oxford Centre of Evidence-Based Medicine levels and their data collected. Data from 24 studies were analysed. Amongst HNSCC, the mean overall incidence rate of sNL and sSPML was 11.4% (range: 1.3–27%) and 2.95% (range: 0.4–7.4%), respectively. The possibility of a sNL to be a sSPML cannot be ignored (mean: 35.2%). Studies investigating smoking habits showed that the majority (98–100%) of HNSCC patients with sSPML were previous or active smokers. Detection of human papillomavirus through DNA analysis, p16 immunohistochemistry, and identification of clonal evolution were useful in differentiating metastasis from sSPML. ^{18}FDG-PET scan was the most reliable method to diagnose sSPML (sensitivity: 95%; specificity: 96%; positive predictive value: 80%). With early sSPML detection and curative treatment, the 5-year overall survival rate is 34–47%. However, the proposed advantage of early detection warrants further evidence-based justification.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth leading cancer worldwide [1]. Smoking, heavy alcohol consumption, and poor diet are the cause of over 90% of the cases [2]. The relation between smoking and risk of cancer as well as cancer-related mortality have been well established in a multitude of studies [3–5]. Moreover, smoking has been implicated as a causative factor in various types of other malignancies, such as pulmonary, gastric, bladder [6] and pancreatic cancers [7].

Smoking-related cancers have also been reported to entail a high risk of second primary malignancies (SPM) in HNSCC patients [8]. There is a cumulative +2–4% per year risk of SPM due to common carcinogenesis and in-field cancerization (mostly for non-viral HNSCC) [9–11]. The most common sites of SPM are the lung (60%) and the superior aerodigestive tract (20%). Important differences exist in the clinical behaviour (response, pattern, and timing of SPM) between HPV-positive and -negative oropharyngeal cancer. Patients with HPV-positive cancer without significant smoking history have a lower risk of SPM development [12].

HNSCC patients often present with additional synchronous nodules of the lung (sNL) [13]. These sNL may be benign [14] or malignant (synchronous SPM of the lung (sSPML) or metastases from the primary HNSCC). Therefore, sNL in patients with HNSCC are a challenge in terms of both, diagnosis and treatment.

Proper detection and evaluation of sNL and the differentiation between sSPML and metastatic disease is important, since the treatment approaches and the oncologic outcomes are different. Patients may

* Corresponding author at: Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse, 3010 Bern, Switzerland.
E-mail address: olgun.elicin@insel.ch (O. Elicin).
[1] Equal contribution of both last authors.

https://doi.org/10.1016/j.oraloncology.2023.106529
Received 6 February 2023; Received in revised form 20 July 2023; Accepted 21 July 2023
Available online 26 July 2023

benefit from a curative intended (timely performed surgery or radiotherapy with/or without risk-adapted systemic treatment) or systemic palliative treatment.

However, the exact incidence of sNL/sSPML in HNSCC patients is not yet known, and there is still a lack of consensus on the most appropriate diagnostic procedures and management. With the aim to bridge this knowledge gap about the incidence of sNL/sSPML and their optimal management, we surveyed the current practice and opinions regarding the work-up of sNL/sSPML in HNSCC patients through a systematic literature review.

Material and methods

The search strategy was designed by OE, MM and JL. The literature was systematically reviewed through a search in the PubMed database up to September 2020. The search terms were head and neck squamous cell cancer, oral cavity cancer, oropharynx cancer, hypopharynx cancer, larynx cancer, along with synchronous sNL and sSPML. We constructed the following combinations of Medical Subject Headings (MeSH terms) and Boolean operators:

Head and neck neoplasms [MeSH] AND squamous AND (lung OR pulmonary) AND (synchron* OR metachron* OR nodule* OR metasta* OR tumor OR tumour OR malignan*)

Previously published articles such as systematic reviews, *meta*-analyses, prospective and retrospective cohort studies, as well as case studies and narrative reviews were initially included in our database search. The search was restricted to English, Spanish, German, French and Chinese language, published or in-press. All relevant papers, including the case studies and narrative reviews were screened, and a hand search of papers cited in the eligible articles, using their references, and using Scopus for cross-referencing was performed. Extracted papers and additional reports through personal communication were further analysed.

All studies involving humans were included in this review, with no limitations to sex, age, ethnicity, subtypes of HNSCC histology or smoking history. Our emphasis was on HNSCC that originated from the oral cavity, oropharynx, hypopharynx and larynx, along with sNL detected within the period of HNSCC diagnosis, staging and follow-up. Studies including HNSCC of unknown primaries were also retained. All abstracts were screened by two independent investigators (MM and JL).

We excluded all studies that examined only metachronous nodules of the lung or only metachronous SPML and studies, where metachronous/synchronous nodules of the lung and SPML were not analyzed separately. Articles were excluded, if they were related to tumours originating from the head and neck subsites like nasopharynx, sino-nasal cavities, skin, oesophagus, or thyroid; and if the suspicious synchronous lesions were of other anatomic sites than the lungs. We also excluded studies that did not provide data regarding sNL along with head and neck index cancer. The full text was screened for eligibility by two

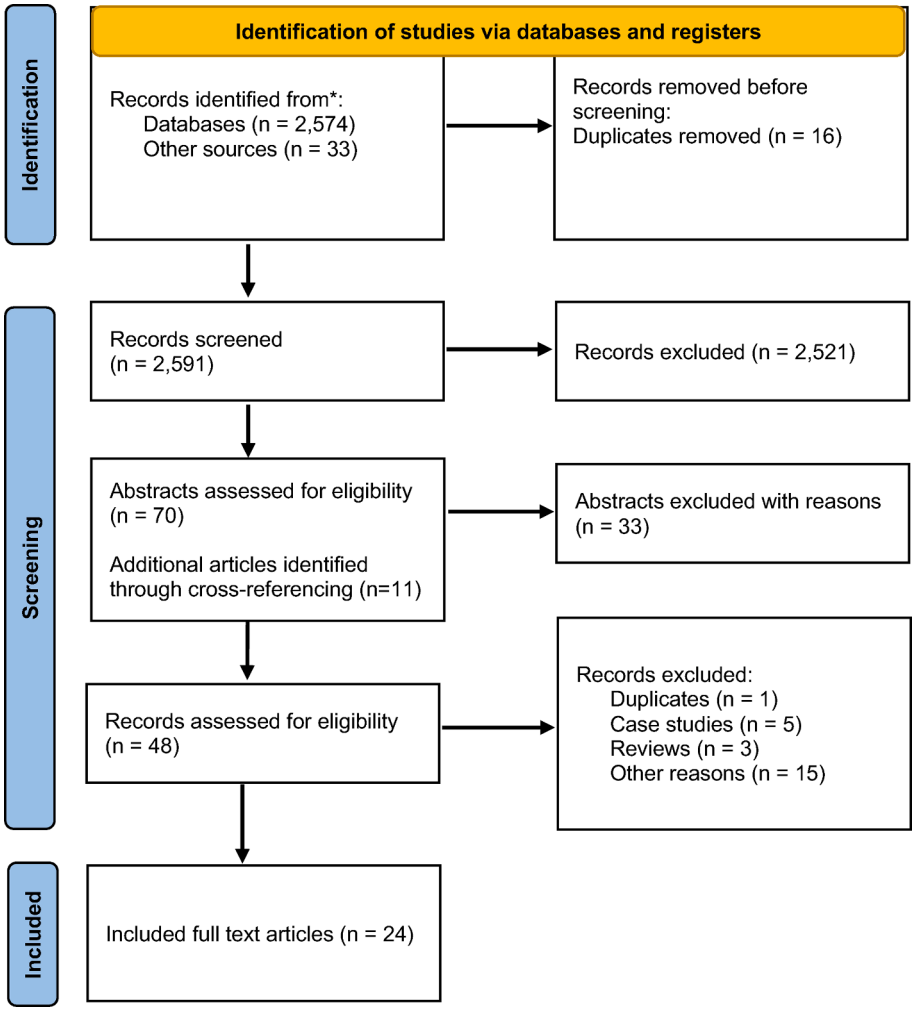

Figure 1. PRISMA Flow Chart, Abbreviations not standard in this field: OCEBM: Oxford Centre for Evidence-Based Medicine; sNL: synchronous nodules of the lung; SPM: second primary malignancies; sSPML: synchronous second primary malignancies of the lung.

independent investigators (MM and JL) and verified by a third (OE), addressing any disagreements regarding article eligibility.

This review was conducted following PRISMA-Guidelines [15]. In accordance with the flow process, our search and selection was conducted in four steps: identification, screening, assessment of eligibility and inclusion. The database search and screening of other sources resulted in 2,607 articles. After removing duplicates, the title and abstracts of the remaining articles were screened to identify relevant studies. Seventy articles were found to be consistent with the scope of the review and their full text was reviewed for eligibility. Papers not fulfilling the above mentioned search criteria were excluded. Available data from systematic reviews, *meta*-analysis and narrative reviews were not considered for analysis. Finally, 24 articles were selected for further analysis in this review (Figure 1).

A set of predefined questions were listed, and the data were filled in a spreadsheet. Information abstracted from each article included its publication year; study type; study period; sample size; incidence of sNL, sSPML and HNSCC metastases. Information about smoking habits; HPV DNA and/or p16 expression status of HNSCC were also extracted. The "take home message" of each article; its emphasis on diagnostics and/or treatment modalities; data regarding survival; number of sSPML identifications from bronchoscopy, chest x-ray, chest CT and ^{18}FDG-PET-CT scan and data about their sensitivity, specificity, positive and negative predictive value were listed. Data extraction was performed independently by two investigators (MM and JL), and differences were resolved by consensus with input from two additional authors (OE and RG). Descriptive statistics were calculated. We classified the included studies by level of evidence according to stipulations of Oxford Centre for Evidence-Based Medicine (OCEBM) [16].

Results

Study characteristics and methodological quality (Table 1)

In total, data of 24 original studies were listed for analysis. The included articles had been published from 1987 to 2019.(See Table 1).

The reviewed articles included 18 retrospective and 6 prospective studies. The OCEBM level of evidence was 2a in 7 and 2b in 17 publications. Twenty of the studies were mainly aimed at investigating the methods to identify sNL and five focused on the treatment and survival (one overlapping [17]).

Smoking habits (Table 1)

Data on the smoking history in the cohorts were provided by seven studies [18–24]. Five of these studies [18–21,24] showed the data in percentage: 100% of the subjects were smokers in two studies and 99.5%, 98%, and 53% in one study each. In one of the studies [19], the patients were classified on the basis of pack-years: 46.5% of the subjects had a history of less than 20 pack-years (with all of them being smokers) and 53.5% have had smoked more than 20 pack-years. In another study [20], the patients had a median of 50 pack-years of smoking history.

HPV status (Table 1)

Five studies provided data on HPV status [22,25–28]. The highest rate of p16 positivity among HNSCC patients reported was 21% (76/307); however, the differentiation between sSPML and metastasis was not done in that study [28]. Moreover, the differentiation of anatomical subsites, especially concerning oropharyngeal primaries in regard to HPV association was not provided. In one study, 6% of the sSPML were found to be HPV/p16 positive, while 20% of the HNSCC were HPV/p16

Table 1
Study period, level of evidence, and design.

First Author	Year	Country	Study Period	LoE	N	Study Focus	Design	Other Data
Metzger[18]	2019	Germany	2010–2018	2b	484	Diagnosis	Retrospective	Smoking
Kim[19]	2019	Korea	2010–2015	2a	740	Diagnosis	Prospective	Smoking
Melchardt[25]	2018	Austria	NR	2a	386	Diagnosis	Retrospective	HPV/DNA
Daher[26]	2017	Germany	NR	2a	NR	Diagnosis	Retrospective	HPV/DNA
Ishibashi-Kannon[27]	2017	Japan	2010–2015	2b	190	Diagnosis	Retrospective	HPV
Tamjid[20]	2017	Australia	2000–2018	2b	597	Treatment/ Survival	Retrospective	Smoking
Rohde[28]	2017	Denmark	2013–2016	2b	307	Diagnosis	Prospective	HPV
Zammit-Maempel[29]	2016	UK	2001–2003	2a	148	Diagnosis	Retrospective	None
Louie[39]	2016	Netherlands	1997–2011	2b	616	Diagnosis	Retrospective	None
Griffioen[21]	2015	Netherlands	NR	2b	NR	Diagnosis	Retrospective	Smoking
Bishop[22]	2012	USA	NR	2b	NR	Diagnosis	Retrospective	Smoking/ HPV
Graff[30]	2011	France	1997–2001	2b	2574	Treatment/ Survival	Retrospective	None
Beech[31]	2010	UK	1994–2005	2b	219	Diagnosis	Retrospective	None
Dequanter[32]	2010	Belgium	2000–2008	2b	412	Treatment/ Survival	Retrospective	None
Ohba[23]	2010	Japan	1977–2008	2b	17	Diagnosis	Retrospective	Smoking/ (CK 8, CK 18,19)
Ghosh[33]	2009	UK	NR	2b	1688	Diagnosis	Retrospective	None
Strobel[40]	2009	Switzerland	2001–2007	2b	589	Diagnosis	Retrospective	None
Krabbe[35]	2008	Netherlands	1999–2007	2b	149	Diagnosis	Retrospective	None
Loh[38]	2005	Canada	NR	2a	102	Diagnosis	Prospective	None
Kuriakose[34]	2002	USA	1974–1997	2b	2964	Treatment/ Survival	Retrospective	None
Wax[36]	2002	USA	1994–1996	2b	115	Diagnosis	Prospective	None
Arunacha-lam[37]	2002	UK	2000	2a	44	Diagnosis	Prospective	None
Shaha[24]	1988	USA	1982–1986	2a	200	Diagnosis	Prospective	Smoking
Atabek[17]	1987	USA	NR	2b	1430	Diagnosis, Treatment/ Survival	Retrospective	None

CK: cytokeratin; HPV: Human papilloma virus; LoE: Level of evidence per Oxford Centre for Evidence-Based Medicine (2009); NR: Not reported.

positive; this study demonstrated that a combination of HPV typing and TP53 mutational profiling can help to differentiate between head and neck and the lung as the origin of the malignant tumour [26]. In another study, HPV/p16 positivity was detected in the lung tissue samples in 5% (11/220) of the cases [22]. Yet another article reported HPV/p16 positivity in 1 of 26 sSPML detected in 386 patients [25].

*Calculation of the incidence of the pulmonary findings (Table 2 **and** Table 3)*

The sample sizes in the included studies ranged from 17 to 2964 (mean: 665; median: 386); three studies did not report the sample size. Nineteen studies reported a total 828 cases of sNL, with 23 studies reporting 331 cases of sSPML and 22 studies reporting 398 cases of malignant sNL. Five, two, and one study did not report the number of sNL, malignant sNL (including pulmonary metastases), and sSPML, respectively. Fifteen studies provided data on the sample size as well as the number of sNL; from these data, the incidence of sNL was determined to be 1.3–27% (mean: 11.4%; median: 7.4%). Nineteen studies [17–20,23–25,27–38] provided sufficient data to calculate the incidence of sSPML in their cohorts, which was determined to be 0.4–7.4% (median: 2.5%; mean: 2.95%). Ten studies provided specified data that distiguished sNL and sSPML [20,24,25,29–31,34,36–38]. The mean percentage of sSPML amongst sNL was 35.2% (range: 5–80%). Seven studies [24–26,31,32,37,38] with a mean of 227 patients (range: 44–412), provided data that allowed determination of the mean number of synchronous metastases, which was calculated to be 12.8 (range: 1–26). From the six studies that provided sufficient data to allow calculation [24–26,31,32,38], the incidence of pulmonary metastases was determined to be 0.003–10.9%. (See Table 2 **and** Table 3).

Workflow to address the synchronous nodules (Table 4)

Eight studies were either reviewing histopathological results or did not exactly define how the sNL were further classified as benign, metastases of the HNSCC or sSPML [20,22,23,25,26,32,39] Fifteen studies mentioned the diagnostic methods addressing the sNL [19,24,27–29,36–38]. A single specific diagnosic modality like CRX, Chest CT and ^{18}F-FDG-PET/CT was examined in 5 of these studies [21,24,29,31,36], while the remaining 10 studies pursued a multimodal approach. In one study [21] the final diagnosis was based on the expert opinion in a interdisciplinary tumour board, two studies also confirmed this approach by further observation [29,35] and 10 studies by the use of supplementary diagnostic modalities. In two studies, a combination of observation and implementing other modalities was utilized to confirm the final diagnosis [31,33]. Therfore, most of the reviewed studies described various heterogeneous approaches. (See Table 4).

Characteristics of diagnostic modalities (Table 5)

Twenty-one studies provided data on the diagnostic modalities used for the evaluation and detection of sSPML in cases of HNSCC with sNL. The mean percentage of sSPML detected with ^{18}F-FDG-PET/CT scan was 3.8% of the total samples (mean: 386.6; range: 115–866) in 7 studies [19,27,28,35,36,39,40], those detected with chest CT scan was 2.4% of the total samples (mean: 440; range: 44–1688) in six studies

Table 3
Diagnosed synchronous second primary malignancies amongst detected synchronous nodules of the lung.

First Author	Year	Detected sNL (N)	Diagnosed sSPML (N)	Percentage (%) sSPML/sNL
Melchardt[25]	2018	26	6	23.1
Tamjid[20]	2017	41	15	36.6
Zammit-Maempel[29]	2016	73	6	8.2
Graff[30]	2011	43	26	63
Beech[31]	2010	36	6	16.7
Kuriakose[34]	2002	42	27	62
Wax[36]	2002	10	8	80
Arunachalam[37]	2002	5	1	20
Shaha[24]	1988	24	9	37.5
Loh[38]	2005	20	1	5

sNL: synchronous nodules of the lung, sSPML: synchronous second primary malignancy of the lung.

Table 2
Sample size and incidence of pulmonary findings.

First Author	Year	Sample Size	N (%*) of sNL	N of malignant sNL	N (%*) of HNSCC metastases	N (%*) of sSPML
Metzger[18]	2019	484	NR	2	NR	2 (0.4)
Kim[19]	2019	740	NR	36	NR	36 (4.9)
Melchardt[25]	2018	386	26 (6.7)	7	1 (0.003)	6 (1.6)
Daher[26]	2017	NR	32	29	26 (NR)	3 (NR)
IsIhibashi-Kannon[27]	2017	190	NR	3	NR	3 (1.6)
Tamjid[20]	2017	597	41 (6.9)	15	NR	15 (2.5)
Rohde[28]	2017	307	NR	NR	NR	4 (1.3)
Zammit-Maempel[29]	2016	148	73 (49)	6	NR	6 (4.1)
Louie[39]	2016	616	167 (27.1)	NR	NR	NR
Griffioen[21]	2015	NR	181	40	NR	40 (NR)
Bishop[22]	2012	NR	22	1	NR	1 (NR)
Graff[30]	2011	2574	43 (1.7)	26	NR	26 (1)
Beech[31]	2010	219	36 (16.4)	30	24 (10.9)	6 (2.7)
Dequanter[32]	2010	412	NR	39	25 (6.1)	14 (3.4)
Ohba[23]	2010	17	17 (NA)	17	NR	4 (NR)
Ghosh[33]	2009	1688	32 (1.8)	30	NR	62 (3.7)
Strobel[40]	2009	589	26 (4.4)	26	NR	26 (4.4)
Krabbe[35]	2008	149	11 (7.4)	11	NR	11 (7.4)
Loh[38]	2005	102	20 (19.6)	11	10 (9.9)	1 (1)
Kuriakose[34]	2002	2964	42 (1.4)	27	NR	27 (0.9)
Wax[36]	2002	115	10 (8.7)	8	NR	8 (6.9)
Arunacha-lam[37]	2002	44	5 (11.4)	3	2 (2.3)	1 (2.3)
Shaha[24]	1988	200	24 (12)	11	2 (1)	9 (4.5)
Atabek[17]	1987	1430	20 (1.3)	20	NR	20 (1.4)

HNSCC: head and neck squamous cell carcinoma; NA: not applicable; NR: not reported; sNL: Synchronous pulmonary nodules; sSPML: synchronous second primary malignancies of the lung.
*Expressed as percentage of sample population in the respective study.

Table 4
Workflow to address the synchronous nodules.

First author	Patient selection	Method to identify sNL	Procedure for the final diagnosis / decision	Further examination
Ishibashi-Kannon [27]	retrospective	^{18}F-FDG-PET/CT, MRI, CCT and others	When oesophago-gastro-duodenoscopy, ^{18}F-FDG-PET/CT, or another diagnostic modality (MRI, CCT, etc.) suggested the presence of other cancers, the patient was examined further to confirm the diagnosis	yes
Zammit-Maempel [29]	prospective	CCT and Biopsies	The benign-looking and equivocal lesions that resolved or did not show any significant radiological change on subsequent CCTs were all grouped as benign. Lesions were considered malignant based on biopsy results or progression detected on subsequent imaging.	follow-up
Griffioen[21]	retrospective	^{18}F-FDG-PET/CT for high risk	multidisciplinary tumour board	no
Graff[30]	retrospective	CCT and pan-endoscopy	CCT/ pan-endoscopy/ multidisciplinary discussion/ additional radiology	yes
Beech[31]	CCT-image database	CCT	depending on nodule size: follow-up CCT, >8 mm ^{18}F-FDG-PET/CT / biopsy	yes/follow-up
Ghosh[33]	retrospective	CRX, CCT, and combination of both	>10 mm: biopsy or CCT interpretation and serial CCT / 3 monthly	yes/follow-up
Strobel[44]	prospective	CCT/ ^{18}F-FDG-PET/CT	uptake / morphology (e.g., scattered pattern) additional pan-endoscopy; second primary suspected: flexible bronchoscopy with biopsy	yes
Kuriakose[34]	retrospective	pan-endoscopy/CRX/CCT/ US/ histopathology	histopathology/ absence of cervical nodules and singularity of pulmonary nodules	yes
Krabbe[35]	retrospective	protocol: ^{18}F-FDG-PET/CT/ CRX/CCT	6-months follow-up with CCT, MRI, CRX, biopsy and cytology	follow-up
Wax[36]	prospective	^{18}F-FDG-PET/CT	suspicious findings verified with CCT and flex bronchoscopy and biopsy	yes
Loh[38]	prospective	CXR/CCT	Repeated CCT/CCT-guided biopsy	yes
Rohde[28]	prospective	CXR, CCT, ^{18}F-FDG-PET/CT	biopsy	yes
Kim[19]	prospective	CXR, CCT, ^{18}F-FDG-PET/CT	biopsy	yes
Arunachalam [37]	prospective	^{18}F-FDG-PET/CT / CCT	biopsy	yes
Shaha[24]	prospective	CXR	bronchoscopy, mediastinoscopy and thoracotomy	yes

CCT: Chest computed tomography; ^{18}F-FDG-PET/CT: Positron-emission tomography/computed tomography; CRX: Chest radiography; MRI: magnetic resonance imaging; sNL: Synchronous pulmonary nodules; US: Ultrasound.

[21,29,31,33,37,38], and those detected with histologic and molecular/genetic examination was 1.5% of the total biopsies (mean: 611; range: 17–1430) in 6 studies [17,22,23,25,26,41]. sSPML were detected in 4.5% of 200 chest x-rays in one study [24], and in 0.4% of 484 bronchoscopies in another [18]. Seven papers [24–26,31,32,37,38] allowed to calculate the number of detected pulmonary metastases and six [24–26,31,37,38] of them could be distributed into the different diagnostic modalities as follows: three studies [31,37,38] that emphasized on chest CT with mean 12 metastases (range: 2–24), two studies [25,26] investigating histologic and molecular/genetic determination with mean 13.5 (range: 1–26) and one study [24] looking at chest X-ray findings reported 2 metastases, respectively. (See Table 5).

Five studies presented data regarding the use of molecular/genetic methods to check for the presence of severe HPV infection [22,23,25,26,40,42], and four of them provided data on p16^{INK4A} immunohistochemistry and DNA analysis [22,23,25,26]. Daher et al. (2018) [26] used HPV sub-typing and targeted next-generation sequencing of all coding exons of TP53 on 55 samples and identified 20% p16 positive and 5% HPV DNA positive cases. With their method, 6% (2/32) of pulmonary nodules could be identified as sSPML. Melchardt et al. (2018) [25] analysed options to distinguish metastasis from primary tumour on the basis of detecting clonal and mutated gene sequences. In this study, 8.6% of the initially stated metastases were subsequently identified as sSPML, because the sequence was not matching. Bishop et al. (2012) [22] performed immunohistochemistry to assess HPV status by evaluating the activity of HPV E7 oncoprotein. Thus, they were able to confirm pairing of the HNSCC and the pulmonary metastases in 95% of their samples. Ohba et al. (2010) [23] evaluated the expression of the antibody CAM5.2. as a distinguishing parameter for primary lung squamous cell carcinoma, which was positive in 6 out of 17 equivocal cases.

Performance of radiologic modalities (Table 6)

Data on the performance of different diagnostic modalities in terms of sensitivity, specificity and predictive values could be extracted from six articles [29,31,33,35–37]. Four of these studies [29,31,33,37] evaluated the performance of chest CT, which was compared with chest

Table 5
Diagnostic procedures evaluated in studies.

Diagnostic Modality	No. of Studies	Mean N (range)	Mean N of sNL (range)	Mean N of Malignant sNL (range)	Mean N of sSPML (range)	Mean % of sSPML* (range)
^{18}F-FDG-PET/CT	7 [19,27,28,35,36,39,40]	386.6 (115–866)	53.5 (10–178)	16.8 (8–90)	14.7 (4–39)	3.8 (1.3–7.4)
BIO	6[17,22,23,25,26,41]	611 (17–1430)	23.4 (17–32)	14.8 (1–29)	6.8 (1–20)	1.5 (1.4–1.55)
CCT	6[21,29,31,33,37,38]	440.2 (44–1688)	57.8 (5–181)	20 (3–40)	19.3 (1–62)	2.4 (0.98–4.05)
CRX	1[24]	200 (NA)	24 (NA)	11 (NA)	9 (NA)	4.5 (NA)
BS	1[18]	484 (NA)	0 (NA)	2 (NA)	2 (NA)	0.4 (NA)

BIO: Biological markers; BS: Bronchoscopy; CCT: Chest computed tomography; CRX: Chest radiography; ^{18}F-FDG-PET/CT: Positron-emission tomography/computed tomography; NA: Not applicable; sNL: Synchronous pulmonary nodules; sSPML: Synchronous second primary malignancy of the lung.
*Expressed as percentage of sample.

x-ray imaging in two studies [33,37]. The two remaining studies [35,36] compared the performance data of chest x-ray with those of ^{18}F-FDG-PET/CT. In one study [36], ^{18}F-FDG-PET/CT yielded a PPV of 80% in superior to chest-CT scan (mean: 77.9%), which in turn was better than chest x-ray (mean: 66.7%). Moreover, the sensitivity of ^{18}F-FDG-PET/CT (mean: 95%) was higher than that of chest-CT scan (mean: 93.1%) and chest x-ray (mean: 55%). (See Table 6).

Zammit-Maempel et al. (2016) [29] investigated the long-term outcomes of a mixed series of synchronous and metachronous lung nodules on chest CTs with HNSCC and found a high sensitivity, specificity and accuracy to predict malignancy. Beech et al. (2010) [31] assessed whether chest CT as initial staging is a robust method in identifying metastases or sSPML, whereas Gosh et al. (2009) [33] and Arunachalam et al. (2002) [37] compared chest CT with chest x-ray. All these studies found that chest CT was a favourable screening method to detect sSPML. Krabbe et al. (2008) [35] assessed the value of whole-body ^{18}FDG-PET/CT in detecting distant metastases below the clavicula in HNSCC and found that this method had higher sensitivity and specificity than chest x-ray and chest CT. Wax et al. (2002) [36] found that ^{18}F-FDG-PET/CT was significantly superior to bronchoscopy, chest x-ray and chest CT in sensitivity, specificity and accuracy in the detection of sSPML.

Survival (Table 7)

Data on survival endpoints were provided in 10 studies [17,20,21,25,27,29,30,32,34,39]. Five studies reported survival data focused on the diagnosis and the remaining five on treatment approaches. Seven of them supported their data with Kaplan-Meier plots [17,25,29,30,32,34,39], some as adjusted and others as proportional overall survival (OS) curves. The mean and median sample sizes of these 10 studies were 1035 and 597 patients, respectively (range: 148–2964). The mean incidence of sSPML in these studies was 2%, with a median of 1.6% (range: 0.9–4.1%). (See Table 7).

Seven studies reported the OS of HNSCC patients with sSPML as median time [17,20,21,30,32,34,39]. We calculated the mean and median OS 25 and 19.1 months, respectively (range: 12–45 months).

Five studies [17,27,30,34,39] provided the 5-year OS for sSPML cases in percentage. The median 5-year OS was 40% and the mean 45.2%, respectively (range: 34–65%).

Five studies reported survival data related to the diagnosis of sSPML [21,25,27,29,39]. All of them, except Griffioen et al. (2015) [21], reported the sample size ranging from 148 to 616 with a mean of 335 patients. Provided data allowed calculating the incidence of sSPML in three studies [25,27,29] with a range of 1.6–4.1% and a mean of 2.4%. While Zammit-Maempel et al. (2016) [29] and Ishibashi-Kanno et al. (2017) [27] either illustrated a Kaplan-Meier curve or described individual survivals anecdotically, the other three studies [21,25,39] reported a median survival with a mean of 30.3 months (range: 19.27–45 months).

Treatment approaches and related survival data in HNSCC patients with sSPML were reported in five studies (mean and median sample sizes: 1595 and 1430 cases, respectively) [17,20,30,32,34]. The mean incidence of sSPML in these studies was 1.84%, with two of these studies [30,34] having sample sizes of more than 2500 patients reporting incidences of 0.9% and 1.0%. Additionally, the incidence was 1.4% in one study that had a cohort of 1430 patients [17,20,32] and 2.5% to 3.4% in two studies [20,32] with sample size of less than 1000 cases.

Atabek et al. (1987) [17] reported a 5-year OS rate of 34%, with a median OS of 19 months; patients with stage I-II lung cancer (n = 17) underwent surgery or radiotherapy +/- chemotherapy, while those with stage III and non-staged (numbers not reported) lung cancer received radiotherapy +/- chemotherapy or palliative treatment. In the study by Kuriakose et al. (2002) [34], the 5-year OS rate was 47% and median OS was 24 months in the surgically treated group; however, no survivors beyond 1 year remained in the palliatively treated group. Graff et al. (2011) [30] reported a median OS of 12 months and a 5-year OS rate of 20% for their entire cohort, which included cases with multiple synchronous malignancies; treatment approaches employed were surgery and/or radiotherapy +/- chemotherapy or brachytherapy (25 cases; for both HNSCC and lung cancer in 2 cases). Among the 34 patients in the study by Tamjid et al. (2017) [20], 13 of the 15 patients with sSPML underwent surgery of the index HNSCC first. Five of their patients with sSPML died, while 10 survived, of which 6 had partial or complete response after curative treatment. The treatment approaches used in their study were primary surgery plus radio +/- chemotherapy and primary radiotherapy +/- chemotherapy. Resumed, all the reviewed papers recommend initiation of the primary treatment for HNSCC, seamlessly followed by the curatively intended treatment for sSPML.

Apart from the treatment modality used, another aspect to be considered is the timing of the curative treatment with regard to the occurrence of the sSPML. Dequanter et al. (2010) [32] and Tamjid et al. (2017) [20] reported median OS of 15.7 and 16 months for synchronous SPML versus 92.6 and 66 months for metachronous SPML, respectively. Dequanter et al. (2010) [32] found that metachronous SPML had a better prognosis than synchronous ones if calculated from the time of detection of HNSCC. Tamjid et al. (2017) [20] reported a 5-year OS of 67% (10 of 15 patients) for patients with SPML, at the time of the last follow-up (median follow-up 39 months; range: 4–279 months). The mean OS for the entire cohort in their study was 13 months compared to 11 months for synchronous and 15 months for metachronous SPML, respectively.

Discussion

Incidence and diagnosis of synchronous nodules and second primary malignancies of the lung

sNL were found in mean 11.4% and sSPML in mean 2.95% of patients with HNSCC, respectively. Incidental detection of sSPML was the highest in the case of ^{18}FDG-PET/CT, at about 4%, and this modality afforded high sensitivity (mean: 95%) as well as specificity (mean: 96%). Wax et al. (2002) [36] reported a PPV of 80% with ^{18}FDG-PET/CT. The mean percentage of sSPML detected amongst SNL was calculated 35.2%. Despite its wide range (range: 5–80%), the mean of 35.2% is expected on the basis of sNL and sSPML incidences being 11.4% and 2.95%, respectively. In the *meta*-analysis by Xi et al. (2014) [43], which

Table 6
Performance of diagnostic methods in detection of synchronous second primary malignancies of the lung.

Diagnostic Procedure	N of Studies	Median Sample	Mean Sample (range)	Mean Sensitivity (range%)	Mean Specificity (range%)	Mean PPV (range%)	Mean NPV (range%)
CRX	4[33,35–37]	132	499 (44–1688)	55% (33–65.3)	96.7% (92–100)	66.7% (50–100)	78.1% (40–95.4)
CCT	4 [29,31,33,37]	148	524.8 (44–1688)	93.1% (87–100)	97% (95–99.1)	77.9% (60–96.9)	97.8% (93.1–100)
^{18}F-FDG-PET/CT	3[28,35,36]	132	132 (115–149)	95% (85–100)	96% (93–98)	80%	NR

[18] F-FDG-PET/CT: Positron-emission tomography/computed tomography; CCT: Chest computed tomography; CRX: Chest radiography; PPV: Positive predictive value; NPV: Negative predictive value.

Table 7
Survival rates associated with diagnosis and/or treatment of synchronous primary malignancies of the lung.

First Author	Year	Focus	N	sSPML*	Median Survival	Details
Studies that focused only on Diagnosis						
Melchardt[25]	2018	Diagnosis	386	1.6%	27 months	Median survival rate at 27 months versus 8 months, depending on the genetic classification
Ishibashi-Kanno[27]	2017	Diagnosis	190	1.6%	NR	OS with sSPML, 15 months; one patient was cancer-free, one patient died 8 months after thoracic surgery, and one survived at 73 months with oral HNSCC and colon carcinoma and sSPML.
Zammit-Maempel [29]	2016	Diagnosis	148	4.1%	NR	
Louie[39]	2016	Diagnosis	616	NR	45 months	Significantly longer OS for surgery and radiation in sSPML cases in 5 years > 40%.
Griffioen[21]	2015	Diagnosis	NR	NR	19 months	
Studies that focused on Treatment						
Tamjid[20]	2017	Treatment, Survival	597	2.5%	13 months	64–70% for HNSCC for the whole HNSCC and 80% for HPV-associated oropharyngeal primaries. Median survival 11 months for metachronous SPML and 15 months for sSPML; 5 died, 4 had survived, and 6 were in CR at the end of the follow-up period
Graff[30]	2011	Treatment, survival	2574	1.0%	12 months	5-year OS: 20%
Dequanter[32]	2010	Treatment, survival	412	3.4%	15.7 months	
Kuriakose[34]	2001	Treatment, survival	2964	0.9%	24 months	5-year OS: 47% after surgery
Atabek[17]	1987	Diagnosis, Incidence, Treatment, Survival	1430	1.4%	19 months	5-year OS: 34% for sSPML

CR: complete remission; HNSCC: Head and neck squamous cell carcinoma; NR: Not reported; OS: Overall survival; SPML: second primary malignancy of the lung; sSPML: synchronous second primary of the lung.
*Expressed as percentage of the sample population.

analysed 12 articles regarding the accuracy of ^{18}F-FDG-PET/CT, they showed a mean sensitivity of 85%, remarkably lower than our results (95%). However, the authors addressed their concerns about the interpretation of their pooled data [43]. On the other hand, chest radiography was found to be useful for the detection of pulmonary malignancies in a large number of cases, but showed lower sensitivity, which was reflected in a mean PPV of 66.7% [33,37]. However, chest CT was reported to have the highest specificity (mean: 97%) and NPV (mean: 97.8%), with a mean PPV of 77.9%. Additionally, it has a mean reported sensitivity of 93.1%, which is comparable to that of ^{18}FDG-PET/CT (95%) [31,33,35–37]. Therefore, chest CT may be recommended as a rapid, relatively cost-effective, and adequate diagnostic method. However, using chest CT, the incidental detection of sSPML was at a mean of 2.4% when compared to the 3.8% achieved with ^{18}FDG-PET/CT.

Genetic typing and molecular markers such as HPV DNA or p16 immunohistochemistry may facilitate the diagnosis of sSPMLs in cases of HPV-associated HNSCC. Melchardt et al. (2018) [25] compared HPV status of primary tumour samples, and metastases targeted massively parallel sequencing. Additionally, DNA fingerprint genotyping was performed to confirm the identity of tumour and matched individual germline DNA samples, along with target resequencing of previously detected TP53 mutation. The designation could be determined from an either branched evolution, or a stable mutational pattern of punctuated evolution as indicator for the survival. Daher et al. (2017) [26] used HPV typing and targeted next-generation sequencing of all coding exons of TP53 and define HPV infection status. For HPV-negative cases, mutational profiling of all coding exons of the TP53 gene was performed which revealed mutations in tumours and enabled the classification of lung tumours as HNSCC metastases or SPM of the lung. Ohba et al. (2010) [23] evaluated the expression of the antibody CAM5.2 with immunostaining. CAM5.2 reacts with Cytokeratin CK 5,6,7 and 8. Keratins are expressed in squamous epithelium.

Thus, ^{18}F-FDG-PET/CT appears to be the contemporary imaging modality that can detect sSPML with the highest sensitivity and specificity at means of 95% and 96%, and chest CT can partially serve as a substitute, particularly in low- and middle-income environments. If the results of imaging studies are equivocal, genetic and molecular analyses of the sNL tissue are encouraged. Nevertheless, there is a lack of a consensus in terms of a standardized workflow to address the sNL. Also, no trend favouring any diagnostic algorithm could be identified in literature.

Smoking history

All the studies that provided data on tobacco habits reported smoking of at least 10 pack-years in 100% of their subjects with HNSCC and sNL. Therefore, it is important for physicians to bear in mind the possibility of synchronous SPML when planning the diagnostic protocol for HNSCC patients with sNL and a history of smoking. On the other hand, the diagnoses of the patients included in the evaluated studies date back to 1974, and the declining trends in smoking can be expected to change the incidence of sNL and SPM of the lung in the future.

Survival, treatment and outcome

Patients diagnosed with HNSCC and sSPML were found to have mean 5-year OS rate of 45.2% (range: 20–47%) and a mean OS of 25 months (range: 12–47 months). Survival (mean: 19.1 months) was the least (12 months) in the study by Graff et al. (2011) [30] and the highest (45 months) in the study by Louie et al. (2016) [39]. HNSCC with metachronous SPML are reported with longer OS compared to their synchronous counterparts. (Tamjid et al. 2017) [20]. However, the longer survival of metachronous SPM of the lung is the obvious result of including the period from the diagnosis of the index tumour to the detection of the metachronous tumour (i.e. lead time bias).

To prolong the survival, most authors recommend early initiation of a standard curative treatment if possible. The mean OS for sSPML was determined to be 35%. Early-stage HNSCC, without metastasis and sNL have been reported to have OS of 64%-70%, which increases to 80% when HPV status was positive [20]. Louie et al. (2016) [39] reported the highest mean OS of 45 months and advocated surgery plus radiotherapy for sSPML. Because patients with HNSCC and sSPML have a worse overall outcome than patients with either of them alone (5-years survival of 15–53% for lung cancer and 49–90% for HNSCC) [11,44,45]. However, Tamjid et al. (2017) [20] argued that curative treatment for sSPML may not always be justified. Although survival was better in the case of synchronous lesions, some patients show a poor prognosis with

aggressive curative surgical treatment. Others suggest annual chest CTs with workup of chest nodules if chest metastasis or sSPML are suspected. Differentiation of synchronous SPM of the lung from metastases and successful curative treatment depends on the proper staging of the sSPML. However, the process for confirmation of the presence/absence of sSPML and the subsequent staging may lead to delayed initiation of primary treatment of the HNSCC [46]. Nevertheless, all authores unanimously acknowledged that the outcome of patients with sSPML would be improved, if curative treatment can be initiated.

The timely detection of sSPML would allow for early initiation of curative treatment [20,30,39]. Depending on the tumour stage, early detection of sNL and subsequently sSPML or pulmonary HNSCC metastases may be associated favourable survival rates in case of proper treatment decision. The mean value of the reported median survival times acquired from 10 publications [17,20,21,25,27,29,30,32,34,39] was 21.5 months (range: 12–45 months) while the mean 5-year OS was 34% (range: 20–47%) [34].

Up-front curative treatment without delay (i.e. concomitant or sequential with a minimal break between the treatment of the primary HNSCC and the sSPML) appears to improve survival. A 5-year OS of up to 47% has been reported for patients with HNSCC and sSPML who benefitted from a curative treatment approach for both tumours (i.e. surgery or radiotherapy with risk-adapted adjuvant therapy if indicated) [34,47]. However, the clinical benefit of early detection and treatment of sSPML warrants further investigation with proper methodology. Future studies with more advanced diagnostics and therapeutic modalities may provide further insight.

Conclusion

Our systematic review of the literature reveals some notable findings. First, sNL occured in mean 11.4% and sSPML in mean 2.95% of HNSCC patients, respectively. The possibility of a sNL to be a sSPML cannot be ignored (mean: 35.2%). Second, ^{18}F-FDG-PET/CT and chest CT are the most important imaging tools for the early detection and differentiation between sNL and sSPML. Histopathology as well as molecular and DNA analyses enhance diagnostic accuracy. Third, once sSPML is diagnosed, a curative treatment provides the best prognosis, with 5-year OS of up to 47% described in the literature, depending the stage of disease.

In the whole review of the literature, we did not encounter any arguing or antithetic positions on this topic that would warrant a debate. In the context of the therapeutic approach, as some authors [20] remarked, that although a curative approach may raise hope for longer survival rates in patients with early detected SPML, the patients often “do poor” due to their specific history (smoking habit). Therefore a carefully evaluated individualized approach should be considered from the beginning. We believe that the incidence of sNL and sSPML are significant enough not to be ignored and that these entities should be systematically addressed in daily practice. On the other hand, further evidence based justification is needed to establish, if early differentiation of such findings really provide an advantage impacting the pathway and outcome of HNSCC treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We are very grateful to Dr. Sneha Nambiar, ELS, for editing the manuscript and formatting the tables.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Ferlay J, Shin H-R, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893–917. https://doi.org/10.1002/ijc.25516.
[2] Johnson N. Tobacco use and oral cancer: a global perspective. J Dent Educ 2001;65:328–39.
[3] Carbone D. Smoking and cancer. Am J Med 1992;93:13S–7S. https://doi.org/10.1016/0002-9343(92)90621-h.
[4] Sasco AJ, Secretan MB, Straif K. Tobacco smoking and cancer: a brief review of recent epidemiological evidence. Lung Cancer 2004;45(Suppl 2):S3–9. https://doi.org/10.1016/j.lungcan.2004.07.998.
[5] Xu Z, Qi F, Wang Y, Jia X, Lin P, Geng M, et al. Cancer mortality attributable to cigarette smoking in 2005, 2010 and 2015 in Qingdao. China PLoS One 2018;13:e0204221.
[6] Praud D, Rota M, Pelucchi C, Bertuccio P, Rosso T, Galeone C, et al. Cigarette smoking and gastric cancer in the Stomach Cancer Pooling (StoP) Project. Eur J Cancer Prev 2018;27:124–33. https://doi.org/10.1097/CEJ.0000000000000290.
[7] Ben Q-W, Liu J, Sun Y-W, Wang L-F, Zou D-W, Yuan Y-Z. Cigarette Smoking and Mortality in Patients With Pancreatic Cancer: A Systematic Review and Meta-analysis. Pancreas 2019;48:985–95. https://doi.org/10.1097/MPA.0000000000001383.
[8] Adjei Boakye E, Wang M, Sharma A, Jenkins WD, Osazuwa-Peters N, Chen B, et al. Risk of second primary cancers in individuals diagnosed with index smoking- and non-smoking- related cancers. J Cancer Res Clin Oncol 2020;146:1765–79. https://doi.org/10.1007/s00432-020-03232-8.
[9] Cooper JS, Pajak TF, Rubin P, Tupchong L, Brady LW, Leibel SA, et al. Second malignancies in patients who have head and neck cancer: incidence, effect on survival and implications based on the RTOG experience. Int J Radiat Oncol Biol Phys 1989;17:449–56. https://doi.org/10.1016/0360-3016(89)90094-1.
[10] Grégoire V, Lefebvre J-L, Licitra L, Felip E, EHNS-ESMO-ESTRO Guidelines Working Group. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21 Suppl 5:v184-6. https://doi.org/10.1093/annonc/mdq185.
[11] Yamamoto E, Shibuya H, Yoshimura R, Miura M. Site specific dependency of second primary cancer in early stage head and neck squamous cell carcinoma. Cancer 2002;94:2007–14. https://doi.org/10.1002/cncr.10444.
[12] Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35. https://doi.org/10.1056/NEJMoa0912217.
[13] Green R, King M, Reid H, Murchison JT, Evans A, Nixon IJ. Management of pulmonary nodules in head and neck cancer patients - Our experience and interpretation of the British Thoracic Society Guidelines. Surgeon 2017;15:227–30. https://doi.org/10.1016/j.surge.2016.10.002.
[14] Kwon M, Lee SH, Lee YS, Lee CW, Roh J, Choi S, et al. Clinical implications of nonspecific pulmonary nodules identified during the initial evaluation of patients with head and neck squamous cell carcinoma. Eur Radiol 2017;27:3725–32. https://doi.org/10.1007/s00330-017-4750-y.
[15] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. statement: An updated guideline for reporting systematic reviews. The BMJ 2020;2021:372. https://doi.org/10.1136/bmj.n71.
[16] Center for Evidence-Based Medicine. Oxford Centre for Evidence-Based Medicine: Levels of Evidence. accessed February 1, 2022 Updated March 2009 n.d.. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009.
[17] Atabek U, Mohit-Tabatabai MA, Raina S, Rush BF, Dasmahapatra KS. Lung cancer in patients with head and neck cancer. Incidence and long-term survival. Am J Surg 1987;154:434–8. https://doi.org/10.1016/0002-9610(89)90019-6.
[18] Metzger K, Horn D, Pfeiffer T, Moratin J, Kansy K, Ristow O, et al. Is panendoscopy a necessary staging procedure in patients with lacking risk factors and oral squamous cell carcinoma? J Craniomaxillofac Surg 2019;47:1968–72. https://doi.org/10.1016/j.jcms.2019.11.009.
[19] Kim Y, Roh JL, Kim JS, Lee JH, Choi SH, Nam SY, et al. Chest radiography or chest CT plus head and neck CT versus 18F-FDG PET/CT for detection of distant metastasis and synchronous cancer in patients with head and neck cancer. Oral Oncol 2019;88:109–14. https://doi.org/10.1016/j.oraloncology.2018.11.026.
[20] Tamjid B, Phan P, John T, Mitchell P, Gan H. Outcomes for patients with synchronous and metachronous primary lung cancer after diagnosis of head and neck cancer. Head Neck 2017;39:1544–9. https://doi.org/10.1002/hed.24751.
[21] Griffioen GHMJ, Louie A, v, de Bree R, Smit EF, Paul MA, Slotman BJ,, et al. Second primary lung cancers following a diagnosis of primary head and neck cancer. Lung Cancer 2015;88:94–9. https://doi.org/10.1016/j.lungcan.2015.01.011.
[22] Bishop JA, Ogawa T, Chang X, Illei PB, Gabrielson E, Pai SI, et al. HPV analysis in distinguishing second primary tumors from lung metastases in patients with head and neck squamous cell carcinoma. Am J Surg Pathol 2012;36:142–8. https://doi.org/10.1097/PAS.0b013e3182395c7b.
[23] Ohba T, Motoi N, Kimura Y, Okumura S, Kawabata K, Yoshizawa Y, et al. Cytokeratin expression profiling is useful for distinguishing between primary squamous cell carcinoma of the lung and pulmonary metastases from tongue

cancer. Pathol Int 2010;60:575–80. https://doi.org/10.1111/j.1440-1827.2010.02565.x.
[24] Shaha AR, Hoover EL, Mitrani M, Marti JR, Krespi YP. Synchronicity, multicentricity, and metachronicity of head and neck cancer. Head Neck Surg 1988;10:225–8. https://doi.org/10.1002/j.1930-2398.1988.tb00003.x.
[25] Melchardt T, Magnes T, Hufnagl C, Thorner AR, Ducar M, Neureiter D, et al. Clonal evolution and heterogeneity in metastatic head and neck cancer-An analysis of the Austrian Study Group of Medical Tumour Therapy study group. Eur J Cancer 2018;93:69–78. https://doi.org/10.1016/j.ejca.2018.01.064.
[26] Daher T, Tur MK, Brobeil A, Etschmann B, Witte B, Engenhart-Cabillic R, et al. Combined human papillomavirus typing and TP53 mutation analysis in distinguishing second primary tumors from lung metastases in patients with head and neck squamous cell carcinoma. Head Neck 2018;40:1109–19. https://doi.org/10.1002/hed.25041.
[27] Ishibashi-Kanno N, Yamagata K, Uchida F, Hasegawa S, Yanagawa T, Bukawa H. Usefulness of esophagogastroduodenoscopy and 18F-fluorodeoxyglucose positron-emission tomography in detecting synchronous multiple primary cancers with oral cancer. Oral Maxillofac Surg 2017;21:391–6. https://doi.org/10.1007/s10006-017-0644-z.
[28] Rohde M, Nielsen AL, Johansen J, Sørensen JA, Nguyen N, Diaz A, et al. Head-to-Head Comparison of Chest X-Ray/Head and Neck MRI, Chest CT/Head and Neck MRI, and ^{18} F-FDG PET/CT for Detection of Distant Metastases and Synchronous Cancer in Oral, Pharyngeal, and Laryngeal Cancer. J Nucl Med 2017;58:1919–24. https://doi.org/10.2967/jnumed.117.189704.
[29] Zammit-Maempel I, Kurien R, Paleri V. Outcomes of synchronous pulmonary nodules detected on computed tomography in head and neck cancer patients: 12-year retrospective review of a consecutive cohort. J Laryngol Otol 2016;130:575–80. https://doi.org/10.1017/S0022215116000736.
[30] Graff P, Schipman B, Desandes E, Mecellem H, Toussaint B, Cortese S, et al. Management of patients with head and neck tumours presenting at diagnosis with a synchronous second cancer at another anatomic site. Clin Oncol (R Coll Radiol) 2011;23:174–81. https://doi.org/10.1016/j.clon.2010.10.008.
[31] Beech TJ, Coulson C, Najran P, Olliff J, Jennings C. How good is a chest CT scan at predicting the risk of pulmonary metastatic disease in patients with head and neck cancer? A retrospective observational study Clin Otolaryngol 2010;35:474–8. https://doi.org/10.1111/j.1749-4486.2010.02198.x.
[32] Dequanter D, Shahla M, Lardinois I, Gilbert O, Hanquet O, Tragas G, et al. Second primary lung malignancy in head and neck cancer patients. Eur Ann Otorhinolaryngol Head Neck Dis 2011;128:11–3. https://doi.org/10.1016/j.anorl.2010.06.004.
[33] Ghosh SK, Roland NJ, Kumar A, Tandon S, Lancaster JL, Jackson SR, et al. Detection of synchronous lung tumors in patients presenting with squamous cell carcinoma of the head and neck. Head Neck 2009;31:1563–70. https://doi.org/10.1002/hed.21124.
[34] Kuriakose MA, Loree TR, Rubenfeld A, Anderson TM, Datta R, v, Hill H,, et al. Simultaneously presenting head and neck and lung cancer: a diagnostic and treatment dilemma. Laryngoscope 2002;112:120–3. https://doi.org/10.1097/00005537-200201000-00021.
[35] Krabbe CA, Pruim J, van der Laan BFAM, Rödiger LA, Roodenburg JLN. FDG-PET and detection of distant metastases and simultaneous tumors in head and neck squamous cell carcinoma: a comparison with chest radiography and chest CT. Oral Oncol 2009;45:234–40. https://doi.org/10.1016/j.oraloncology.2008.05.024.
[36] Wax MK, Myers LL, Gabalski EC, Husain S, Gona JM, Nabi H. Positron emission tomography in the evaluation of synchronous lung lesions in patients with untreated head and neck cancer. Arch Otolaryngol Head Neck Surg 2002;128:703–7. https://doi.org/10.1001/archotol.128.6.703.
[37] Arunachalam PS, Putnam G, Jennings P, Messersmith R, Robson AK. Role of computerized tomography (CT) scan of the chest in patients with newly diagnosed head and neck cancers. Clin Otolaryngol Allied Sci 2002;27:409–11. https://doi.org/10.1046/j.1365-2273.2002.00605.x.
[38] Loh KS, Brown DH, Baker JT, Gilbert RW, Gullane PJ, Irish JC. A rational approach to pulmonary screening in newly diagnosed head and neck cancer. Head Neck 2005;27:990–4. https://doi.org/10.1002/hed.20261.
[39] Louie A v, Damhuis RA, Haasbeek CJ, Warner A, Rodin D, Slotman BJ, et al. Treatment and survival of second primary early-stage lung cancer, following treatment of head and neck cancer in the Netherlands. Lung Cancer 2016;94:54–60. https://doi.org/10.1016/j.lungcan.2016.01.022.
[40] Strobel K, Haerle SK, Stoeckli SJ, Schrank M, Soyka JD, Veit-Haibach P, et al. Head and neck squamous cell carcinoma (HNSCC) – detection of synchronous primaries with 18F-FDG-PET/CT. Eur J Nucl Med Mol Imaging 2009;36:919–27. https://doi.org/10.1007/s00259-009-1064-6.
[41] Ichinose J, Shinozaki-Ushiku A, Takai D, Fukayama M, Nakajima J. Differential diagnosis between primary lung squamous cell carcinoma and pulmonary metastasis of head and neck squamous cell carcinoma. Expert Rev Anticancer Ther 2016;16:403–10. https://doi.org/10.1586/14737140.2016.1147352.
[42] Haerle SK, Strobel K, Hany TF, Sidler D, Stoeckli SJ. 18 F-FDG-PET/CT versus panendoscopy for the detection of synchronous second primary tumors in patients with head and neck squamous cell carcinoma. Head Neck 2009:NA-NA. https://doi.org/10.1002/hed.21184.
[43] Xi K, Xie X, Xi S. Meta-analysis of ^{18} fluorodeoxyglucose positron emission tomography-CT for diagnosis of lung malignancies in patients with head and neck squamous cell carcinomas. Head Neck 2015;37:1680–4. https://doi.org/10.1002/hed.23774.
[44] Groome PA, Bolejack V, Crowley JC, Kennedy C, Krasnik M, Sobin LH, et al. The IASLC Lung Cancer Staging Project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2007 Aug;2(8):694–705. https://doi.org/10.1097/JTO.0b013e31812d05d5.
[45] Rose BS, Jeong J-H, Nath SK, Lu SM, Mell LK. Population-based study of competing mortality in head and neck cancer. J Clin Oncol 2011 Sep 10;29(26):3503–9. https://doi.org/10.1200/JCO.2011.35.7301.
[46] Leto CJ, Sharbel D, Wang CW, Bone TM, Liebman RM, Byrd JK, et al. Workup of Suspected Chest Metastases on 18F-FDG-PET/CT in Head and Neck Cancer: Worth the Wait? Ear Nose Throat J 2019;98:158–64. https://doi.org/10.1177/0145561319828315.
[47] Douglas WG, Rigual NR, Loree TR, Wiseman SM, Al-Rawi S, Hicks WL. Current concepts in the management of a second malignancy of the lung in patients with head and neck cancer. Curr Opin Otolaryngol Head Neck Surg 2003;11:85–8. https://doi.org/10.1097/00020840-200304000-00004.