Journal of Cranio-Maxillo-Facial Surgery 47 (2019) 1968–1972

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Is panendoscopy a necessary staging procedure in patients with lacking risk factors and oral squamous cell carcinoma?

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ARTICLE INFO

Article history:
Paper received 6 June 2019
Accepted 16 November 2019
Available online 27 November 2019

Keywords:
Panendoscopy
Bronchoscopy
Esophagogastroduodenoscopy
Staging
OSCC
Oral squamous cell carcinoma

ABSTRACT

Objectives: Routine panendoscopy is used to detect synchronous malignancies of the upper aerodigestive tract in staging of oral squamous cell carcinoma. The goal of this study was to investigate the occurrence of synchronous malignancies at time of diagnosis using panendoscopy. To challenge the role of panendoscopy as inherent part of routine staging procedures, we were especially interested in low risk patients.

Materials and methods: Retrospectively, a cohort of 484 patients with pathologically confirmed diagnosis of primary oral and oropharyngeal squamous cell carcinoma was investigated. Electronically recorded findings of in-house conducted panendoscopy were retrieved and evaluated for the occurrence of pathological changes of the mucosa. In case of synchronous malignancies, findings were correlated to preoperative radiographic imaging. Patients were classified as high or low risk. Patients with lacking risk factors (no smoking, no drinking in history) were defined as low risk patients.

Results: Overall, we detected three synchronous malignancies of the upper aerodigestive tract (3/484; 0.6%). Two non-small cell lung cancers were detected in patients with a smoking history of 60 pack years. One esophageal carcinoma in situ was detected in a patient with reported alcohol consumption. No synchronous malignancy was detected in patients without risk factors and no malignancy was previously detected by diagnostic imaging.

Conclusion: Pre-treatment panendoscopy can reveal synchronous malignancies of the upper aerodigestive tract in patients with primary oral squamous cell carcinoma. Risk stratification of patients can avoid unnecessarily conducted panendoscopy in patients without risk factors. This may lead to a higher cost-efficacy in public health system, less treatment-related complications and earlier treatment initiation.

1. Introduction

Head and neck squamous cell carcinoma is one of the six most common malignancies worldwide affecting up to 600.000 patients per year and oral squamous cell carcinoma (OSCC) define a major part of this entity (Ferlay et al., 2010; Siegel et al., 2018). Surgery plays a fundamental role in primary treatment and is complemented by radiation and chemotherapy in advanced stages for a better locoregional control (Forastiere et al., 2001). As a result of multi-modal therapy, five-year relative survival rates have increased up to 67% for all stages during the last decades (Forastiere et al., 2001; Jemal et al., 2017). Tobacco smoking, alcohol consumption, betel nut chewing and human papillomavirus (HPV) infection are the main risk factors for the development of head and neck squamous cell carcinoma (Goldenberg et al., 2004; Hashibe et al., 2007; Pelucchi et al., 2006; Sturgis and Cinciripini, 2007).

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https://doi.org/10.1016/j.jcms.2019.11.009
1010-5182/

According to the model of field cancerization, epithelial cells of the upper aerodigestive tract are altered genetically in response to a carcinogenic agent bearing a high risk to develop premalignant and malignant lesions (Mohan and Jagannathan, 2014; Slaughter et al., 1953). Therefore, the mucosa of the upper aerodigestive tract may be more susceptible to develop synchronous or metachronous carcinoma (Mohan and Jagannathan, 2014; Priante et al., 2011).

An increase of esophageal adenocarcinoma in western countries has been reported (Thrift, 2016). Tobacco smoking, alcohol, gastro-esophageal reflux disease and obesity have been identified as the top risk factors accounting for over 70% of all cases in western countries (Thrift, 2016). Also, tobacco smoking has been identified as a major risk factor in the carcinogenesis of lung cancer with more than 80% attributed to lung cancer in western population (Bray et al., 2018). Due to the coincidence of these carcinogenic agents in malignancies of the upper aerodigestive tract and the often reported high risk of these patients to develop another malignancy simultaneously, panendoscopy is a standard procedure in staging of OSCC (Priante et al., 2011; Stoeckli et al., 2001). However, the need for panendoscopy in low-risk groups with a lack of carcinogenic agents has been questioned (Koo et al., 2015). Furthermore cost-efficacy plays a major role in public health systems and a positive effect of panendoscopy on mortality of OSCC has not been reported. Although complication rates of panendoscopy are low, one must take into account severe intrinsic hazards like bleeding, organ perforation and consecutive sepsis. Finally, potentially delayed treatment due to excessive staging in low risk patients may impair patients' outcome.

The objective of this study was to analyze the presence of synchronous malignancies in the upper aerodigestive tract detected by panendoscopy in a cohort of patients with primary OSCC. The investigators hypothesize that the overall detection rate for synchronous malignancies of the upper aerodigestive tract is low, especially when patients lack common risk factors, and challenge panendoscopy in its settled role in OSCC staging. The specific aims of the study were: (i) to measure the occurrence of synchronous malignancies of the upper aerodigestive tract in patients with OSCC; (ii) to analyze patients risk factors in case of synchronous malignancies and (iii) to correlate panendoscopy findings with radiographic imaging.

2. Material and methods

We retrospectively analyzed 484 patients with pathologically confirmed primary oral (442/484; 81%) and oropharyngeal (42/484; 9%) squamous cell carcinoma undergoing surgical treatment at the Department of Oral and Cranio-Maxillofacial Surgery of the Heidelberg University Hospital from January 2010 until October 2018. Patients with history of previously diagnosed malignancies were excluded from this study.

Written informed consent was provided by each patient. The study was approved by the Ethics Committee of Heidelberg University (Ethic vote: S-183/2015). Clinical data and histopathological parameters were assessed using SAP Patient Management research (SAP, Walldorf, Germany). Tobacco and alcohol consumption were defined as risk factors for the development of synchronous malignancies of the upper aerodigestive tract. Patients with lacking risk factors were defined as low risk patients regarding the development of synchronous malignancies.

In house diagnostic findings were recorded in a Microsoft Office Word-based, electronic progress document (Microsoft, Redmont, USA). Staging was conducted consistent with the German national guideline for OSCC (Wolff, 2012). In-house esophagogastroduodenoscopy and bronchial endoscopy were performed in 387 and 376 patients respectively at the interdisciplinary endoscopy center of the Heidelberg University Hospital. Tissue specimen of suspicious lesions were histologically examined by the Institute of Pathology of the Heidelberg University Hospital. Malignant lesions were defined as synchronous lesions when found within six months of diagnosis. After staging was completed, all patients were treated surgically according to German national guidelines. SPSS was used for statistical analysis. Descriptive statistics are given by absolute numbers, percentage and median as appropriate.

3. Results

Patients' clinical characteristics and tumor sites are shown in Table 1. Pathological tumor characteristics are given in Table 2. Bronchial endoscopy and esophagogastroduodenoscopy findings are reported in Tables 3 and 4, respectively. Detailed information about patients with diagnosed synchronous malignancy of the aerodigestive tract are shown in Table 5.

The median patient age at initial diagnosis of primary malignancy was 65 (±11.6) years with a range from 18 to 92 years. Out of 484 patients, 298 were male (62%) and 186 were female (38%). Positive smoking history was recorded in 252 (52%) of patients. According to UICC classification 236 patients (48.9%) had limited (I/II) and 248 patients (51.1%) had advanced (III/IV) disease.

3.1. Bronchial endoscopy findings

Out of 484 patients, 376 (78%) received in-house bronchial endoscopy. Two patients (0.5%) were found to have synchronous lung cancer, including one squamous cell carcinoma (SCC) and one minimal-invasive SCC. Both patients had a smoking history of 60 packyears. One of the two patients had a primary oropharyngeal carcinoma. High-grade dysplasia was found in one patient (0.03%). Mucositis, including bronchitis and tracheitis, was diagnosed in 164 patients out of 376 (44%). None of the two malignancies had been detected previously by radiographic imaging.

Table 1
Descriptive data regarding demographic and clinical features of the investigated cohort.

Parameter	Patients	Patients with synchronous bronchial carcinoma	Patient with synchronous esophageal carcinoma
Number of patients	n = 484	n = 2	n = 1
Gender			
Male	298 (62%)	2	1
Female	186 (38%)	0	0
Median age (range)	65 (18–92)	66,5 (65–68)	65
Smoking history			
Yes	252 (52%)	2	0
No	234 (48%)	0	1
Alcohol history			
Yes	181 (37%)	2	1
No	303 (63%)	0	0
Never drinkers and never smokers	209 (43%)	0	0
Tumour site			
Tongue	109 (23%)	0	0
Buccal mucosa	40 (8%)	0	0
Tongue base, soft palate, tonsil	42 (9%)	1	0
Floor of mouth	121 (25%)	1	1
Alveolar process	125 (26%)	0	0
Lower lip	8 (2%)	0	0
Maxilla	39 (8%)	0	0

Table 2
Descriptive data regarding pathological features of the investigated cohort.

Parameter	Patients	Patients with synchronous bronchial carcinoma	Patient with synchronous esophageal carcinoma
T Stage			
T1	187 (39%)	1	0
T2	135 (28%)	0	0
T3	38 (8%)	0	0
T4	124 (26%)	1	1
N Stage			
N0	309 (64%)	0	1
N1	42 (9%)	0	0
N2	55 (11%)	0	0
N3	71 (15%)	2	0
Nx	7 (1%)	0	0
N+	163 (34%)	2	0
ECS+	71 (15%)	2	0
UICC			
I + II (limited)	236 (49%)	0	0
III + IV (advanced)	248 (51%)	2	1
Grading			
G1	39 (8%)	1	0
G2	337 (70%)	1	0
G3	81 (17%)	0	1
G4	2 (0.4%)	0	0
Gx	25 (5%)	0	0

3.2. Esophagogastroduodenoscopy findings

Out of 484 patients, 386 (80%) received in-house esophagogastroduodenoscopy. Overall, one patient (0.3%) with a positive alcohol history was found to have a synchronous esophageal carcinoma in situ, which had not been detected previously by radiographic imaging. Out of 386 patients undergoing esophagogastroduodenoscopy, 284 (73%) had mucositis, including esophagitis, gastritis and duodenitis. *Helicobacter pylori* was found in 49 patients (13%). 21 patients (5%) were diagnosed with a histologically proven Barrett's esophagus. Intestinal metaplastic mucosa other than Barrett's was found in twelve patients (3%). Eight patients (2%) had peptic ulcer disease and two patients (0.5%) could be diagnosed with esophageal varices.

3.3. Impact on patient's treatment plan

Two of the three patients with synchronous malignant lesions had their treatment changed as shown in Table 5. Interdisciplinary tumor board discussion resulted in radiotherapy of these malignancies without an effect on the treatment of the primary tumor. The patient with esophageal carcinoma in situ received no altered treatment plan as the malignancy had been removed completely by the performed biopsy. All synchronous malignant lesions of the upper aerodigestive tract were related to tobacco and alcohol consumption. No synchronous malignant lesion was found in non-smoking and non-drinking patients. No synchronous malignancy was found in females. According to UICC classification all patients with detected synchronous malignant lesions had advanced stage (III/IV) disease.

Table 3
Bronchial endoscopy findings.

Parameter	Number of patients (n = 376)
Bronchitis/Tracheitis	164
High-grade Dysplasia	1
Minimal-invasive SCC	1
SCC	1
No pathologic findings	209

Table 4
Esophagogastroduodenoscopy findings.

Parameter	Number of patients (n = 386)
Mucositis	284
Helicobacter pylori	49
Barrett mucosa	21
Intestinal metaplastic mucosa other than Barrett	12
Peptic ulcer disease	8
Esophageal varices	2
Papilloma	1
Esophageal SCC	0
Esophageal Carcinoma in situ	1
No pathologic findings	91

4. Discussion

In staging of OSCC and oropharyngeal carcinoma clinical examination, CT scan and panendoscopy of the upper aerodigestive tract are conducted routinely to examine the extend of the primary tumor, the occurrence of lymph node and distant metastasis and to reveal synchronous malignancies (Wolff, 2012). In this retrospective analysis of 484 patients, three synchronous malignant lesions were detected in three different patients. One SCC and one minimal-invasive SCC of the lung were detected in patients with a smoking history of 60 pack years. One esophageal carcinoma in situ was detected in a patient with a history of alcohol consumption. One of the patients with secondary bronchial carcinoma has had an oropharyngeal carcinoma. None of these synchronous malignancies had been detected by radiographic imaging. No synchronous malignant lesion had been found in non-smoking and non-drinking patients. These findings suggest a low risk profile for the development of secondary malignancies in patients without classical risk factors such as alcohol and tobacco consumption.

Focusing on bronchial endoscopy and esophagogastroduodenoscopy in OSCC in Germany, previous studies revealed synchronous malignancy rates from 0 to 8% (Hoffmann et al., 2002; Kesting et al., 2009a, 2009b). Koo et al. investigated a cohort of 119 early stage oral tongue SCC patients, detecting no synchronous malignancy of the upper aerodigestive tract (Koo et al., 2015). No synchronous malignancies were discovered in nonsmoking patients, whereas smokers were diagnosed with synchronous malignancies in 12% of all cases in a cohort with oral cavity and oropharyngeal squamous cell carcinoma (Rodriguez-Bruno et al., 2011). In a study investigating complications of esophagoscopy in head and neck cancer patients no synchronous esophageal carcinoma were found in 546 patients (Tsao and Damrose, 2010). These findings provide evidence for a low risk profile for the development of synchronous malignancies of the upper aerodigestive tract in patients with oral and oropharyngeal carcinoma and lacking risk factors. These observations are also consistent with the model of field cancerization, where carcinogenic agents are required for the presence of genetically altered cells in the mucosa of the whole upper aerodigestive tract.

Patients with a low risk profile for the development of synchronous malignancies may not benefit from panendoscopy in the course of staging. In this cohort a substantial percentage of 43% (209 out of 484 patients) had a low risk profile as they reported neither tobacco nor alcohol consumption. Furthermore, the decision to perform a pre-treatment panendoscopy has to respect the risk of potential complications of the procedure. The reported risks

Table 5
Descriptive data regarding detailed characteristics of patients with synchronous malignancy.

Case Number	Histological findings	Smoking history	Alcohol history	CT scan findings	Treatment of synchronous malignancy
1	SCC of the lung	Yes (60 pack years)	No	not noticeable	Radiotherapy subsequent to OSCC treatment
2	Minimal-invasive SCC of the lung	Yes (60 pack years)	No	not noticeable	Radiotherapy subsequent to OSCC treatment
3	Esophageal carcinoma in situ	No	Yes	not noticeable	Excisional biopsy during Esophagogastroduodenoscopy

in flexible panendoscopy are minimal in general with no associated mortality, though esophageal perforations have been reported (Kim et al., 2001; Pue and Pacht, 1995; Rodriguez-Bruno et al., 2011; Tsao and Damrose, 2010). In contrast, high risk patients with a reported history of tobacco and/or alcohol consumption profit from panendoscopy in routine staging, as synchronous malignancies of the upper aerodigestive may not be detected by radiographic imaging initially. In our cohort, the detected synchronous malignancies had not been described by radiologists previous to panendoscopy.

Financial considerations must be taken into account as public health systems demand cost-efficacy. In our department, panendoscopy mostly is carried out in propofol sedation within an additional in-patient stay combined with a CT scan of head, neck and thorax as well as biopsy of the tumor, if not already conducted. Facing cost-efficacy in public health systems a detailed 5-year cost data analysis for endoscopic procedures in the German diagnosis-related-group system has been published (Rathmayer et al., 2017). Esophagogastroduodenoscopy with or without biopsy of tissue specimen resulted in average costs of 250€ per procedure in a cohort of 21.802 patients. Additional costs may be triggered by bronchoscopy, as it extends examination time, and in-patient stay due to monitoring after sedation. Performing a risk-stratification in staging of OSCC could reduce costs due to lower numbers of panendoscopy and subsequent in-patient stay without an increased risk of undetected synchronous malignancies in patients with lacking risk factors. Furthermore, risk stratification could abbreviate staging procedure resulting in an earlier treatment initiation and therefore improve patients' prognosis.

Our data scrutinizes the common practice of routinely conducted panendoscopy in staging of OSCC without a differential risk stratification relating to the presence of field cancerization or cancerogenic agents.

As the retrospective design of the study is a major limitation, further studies may investigate the occurrence of synchronous malignancies in a prospective manner. This may also improve documentation of panendoscopy findings, as heterogenous documentation is an issue in retrospective analysis.

5. Conclusion

Pre-treatment panendoscopy can reveal synchronous malignant lesions of the upper aerodigestive tract in patients with primary OSCC. Risk stratification of patients can avoid unnecessarily conducted panendoscopy in patients with lacking risk factors. This may also lead to a higher cost-efficacy in public health system, less treatment-related complications and earlier treatment initiation.

Declaration of Competing Interest

None.

Funding

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

Acknowledgements

None.

References

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68: 394–424. https://doi.org/10.3322/caac.21492, 2018

Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127: 2893–2917. https://doi.org/10.1002/ijc.25516, 2010

Forastiere A, Koch W, Trotti A, Sidransky D: Head and neck cancer. N Engl J Med 345: 1890–1900. https://doi.org/10.1056/NEJMra001375, 2001

Goldenberg D, Lee J, Koch WM, Kim MM, Trink B, Sidransky D, et al: Habitual risk factors for head and neck cancer. Otolaryngol Head Neck Surg 131: 986–993. https://doi.org/10.1016/j.otohns.2004.02.035, 2004

Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, et al: Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. J Natl Cancer Inst 99: 777–789. https://doi.org/10.1093/jnci/djk179, 2007

Hoffmann J, Scheiderbauer H, Krimmel M, Grund KE, Reinert S: Value of panendoscopic examinations within the scope of diagnosing the extent of carcinoma of the mouth cavity. Mund Kiefer Gesichtschir 6: 111–116. https://doi.org/10.1007/s10006-002-0366-7, 2002

Jemal A, Ward EM, Johnson CJ, Cronin KA, Ma J, Ryerson B, et al: Annual report to the nation on the status of cancer, 1975-2014, featuring survival. J Natl Cancer Inst 109. https://doi.org/10.1093/jnci/djx030, 2017

Kesting MR, Robitzky L, Al-Benna S, Steinstraesser L, Baurecht H, Wolff KD, et al: Bronchoscopy screening in primary oral squamous cell carcinoma: a 10-year experience. Br J Oral Maxillofac Surg 47: 279–283. https://doi.org/10.1016/j.bjoms.2009.01.009, 2009a

Kesting MR, Schurr C, Robitzky L, Steinstraesser L, Nieberler M, Baurecht H, et al: Results of esophagogastroduodenoscopy in patients with oral squamous cell carcinoma–value of endoscopic screening: 10-year experience. J Oral Maxillofac Surg 67: 1649–1655. https://doi.org/10.1016/j.joms.2009.04.061, 2009b

Kim MK, Deschler DG, Hayden RE: Flexible esophagoscopy as part of routine panendoscopy in ENT resident and fellowship training. Ear Nose Throat J 80: 49–50, 2001

Koo K, Harris R, Wiesenfeld D, Iseli TA: A role for panendoscopy? Second primary tumour in early stage squamous cell carcinoma of the oral tongue. J Laryngol Otol 129(Suppl.1): S27–S31. https://doi.org/10.1017/S0022215114002989, 2015

Mohan M, Jagannathan N: Oral field cancerization: an update on current concepts. Oncol Rev 8: 244. https://doi.org/10.4081/oncol.2014.244, 2014

Pelucchi C, Gallus S, Garavello W, Bosetti C, La Vecchia C: Cancer risk associated with alcohol and tobacco use: focus on upper aero-digestive tract and liver. Alcohol Res Health 29: 193–198, 2006

Priante AV, Castilho EC, Kowalski LP: Second primary tumors in patients with head and neck cancer. Curr Oncol Rep 13: 132–137. https://doi.org/10.1007/s11912-010-0147-7, 2011

Pue CA, Pacht ER: Complications of fiberoptic bronchoscopy at a university hospital. Chest 107: 430–432, 1995

Rathmayer M, Heinlein W, Reiß C, Albert J, Akoglu B, Braun M, et al: Für die DRG-Projektgruppe der DGVS, 2017. Kosten endoskopischer Leistungen der Gastroenterologie im deutschen DRG-System – 5-Jahres-Kostendatenanalyse des DGVS-Projekts. Zeitschrift für Gastroenterologie 55: 1038–1051. https://doi.org/10.1055/s-0043-118350, 2017

Rodriguez-Bruno K, Ali MJ, Wang SJ: Role of panendoscopy to identify synchronous second primary malignancies in patients with oral cavity and oropharyngeal squamous cell carcinoma. Head Neck 33: 949–953. https://doi.org/10.1002/hed.21561, 2011

Siegel RL, Miller KD, Jemal A: Cancer statistics, 2018. CA Cancer J Clin 68: 7–30. https://doi.org/10.3322/caac.21442, 2018

Slaughter DP, Southwick HW, Smejkal W: Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 6: 963–968, 1953

Stoeckli SJ, Zimmermann R, Schmid S: Role of routine panendoscopy in cancer of the upper aerodigestive tract. Otolaryngol Head Neck Surg 124: 208–212. https://doi.org/10.1067/mhn.2001.112311, 2001

Sturgis EM, Cinciripini PM: Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? Cancer 110: 1429–1435. https://doi.org/10.1002/cncr.22963, 2007

Thrift AP: The epidemic of oesophageal carcinoma: where are we now? Cancer Epidemiol 41: 88–95. https://doi.org/10.1016/j.canep.2016.01.013, 2016

Tsao GJ, Damrose EJ: Complications of esophagoscopy in an academic training program. Otolaryngol Head Neck Surg 142: 500–504. https://doi.org/10.1016/j.otohns.2010.01.008, 2010

Wolff KDGerman national guideline for diagnostik and therapy of OSCC, https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Mundhoehlenkarzinom/S3-Mundhoehlenkarzinom-OL-Langversion_.pdf