Annals of Medicine and Surgery 80 (2022) 104224

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

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

Cross-sectional Study

Multiple primary squamous cell carcinomas of the oral cavity: A cross-sectional study in vietnam

Dang Nguyen Van [a,b,*], Quang Le Van [a], Nhung Nguyen Thi Thu [b], Giang Bui Van [c], To Ta Van [d]

[a] Department of Oncology, Hanoi Medical University, Hanoi, Viet Nam
[b] Department of Head and Neck Radiation Oncology, Vietnam National Cancer Hospital, Hanoi, Viet Nam
[c] Radiology Center, Vietnam National Cancer Hospital, Hanoi, Viet Nam
[d] Center of Pathology and Molecular Biology, Vietnam National Cancer Hospital, Hanoi, Viet Nam

ARTICLE INFO

Keywords:
Oral cavity cancer
Multiple primary cancers
Synchronous cancer
Squamous cell carcinoma
Definitive concurrent chemoradiotherapy

ABSTRACT

Background: Multiple primary squamous cell carcinomas (MPSCs) of the oral cavity are very uncommon in clinical practice. This study describes the clinical features, imaging, and treatment characteristics of the oral cavity with MPSCs at the same time of diagnosis in our center. Besides, we review the literature and prior studies on MPSCs.

Study design: A retrospective, descriptive study from January 2019 to December 2021 was conducted on seven patients with MPSCs of the oral cavity at the time of their first diagnosis. Evaluation of the patient's characteristics, the treatment plan, the response to treatment, and the overall survival (OS).

Results: Seven male patients ranging in age from 43 to 70 years (Mean: 53.5). Positron Emission Tomography/Computed Tomography (PET/CT) revealed a significantly increased standardized uptake value (SUV) in the index tumor (SUVi = 15.76 ± 1.96). The index tumor is often staged T3, T4; whereas the synchronous tumor is typically staged T1, T2. All patients had concurrent chemoradiotherapy (CCRT) and achieved a partial response in all cases. Mean OS was 14.71 ± 11.85 months.

Conclusions: MPSCs of the oral cavity at the time of diagnosis are uncommon and associated with a poor prognosis for patients. Comprehensive clinical examination, combined imaging diagnostics, with PET/CT being critical for detecting the second lesion, particularly in patients with an advanced index tumor.

1. Introduction

Oral cavity cancer accounts for between 30% and 40% of head and neck malignancies. Despite breakthroughs in diagnosis and multimodality care, improved local control, and decreased recurrence rates, gains in overall survival were not statistically significant. This might be because MPSCs are associated with a higher risk of oral cavity cancer, even at an early stage. This rate steadily increases over time, reaching a maximum of 10%–24%. Warren and Gates devised the MPSCs in 1932, which had three major components: 1, two or more lesions that were histopathologically verified to be malignant; 2, a distance of at least 1.5 cm between two tumors from the normal epithelial surface; and 3, the absence of metastasis from one lesion to another [1,2]. If the second lesion develops within six months of the first, the condition is called synchronous multiple primary carcinomas. If the second lesion manifests six months after the first, it is classified as metachronous. The distance between lesions is determined directly from the new onset lesion to the prior one, using the patient's medical records and diagnostic imaging as a reference. When it was unclear whether the distance was within 1.5 cm due to a surgical scar or an uneven margin, the lesion was categorized as a recurrent lesion (defined as new lesions appearing within 1.5 cm of the original tumor site) [2]. Around one-third of MPSCs are found in the oral cavity, presumably as a result of long-term continuous exposure to carcinogens, particularly alcohol and cigarettes, on the oral mucosal epithelium. Numerous ideas have been advanced to explain why head and neck cancer therapy has been unsuccessful. The clinical, imaging, and therapeutic results of oral cavity cancer with synchronous MPSCs at the time of initial diagnosis at our facility are described in this study. Additionally, review the literature research to acquire insight on MPSCs in the oral cavity.

* Corresponding author. Department of Oncology, Hanoi Medical University, 01 Ton That Tung Street, Dong Da District, Hanoi, 10000, Viet Nam.;
E-mail addresses: nguyenvandang@hmu.edu.vn, drdangnguyen@gmail.com (D. Nguyen Van), quangledhy@gmail.com (Q. Le Van), thunhung.hmu@gmail.com (N. Nguyen Thi Thu), buivangiang@hmu.edu.vn (G. Bui Van), tavanto.bvk@gmail.com (T. Ta Van).

https://doi.org/10.1016/j.amsu.2022.104224
Received 8 June 2022; Received in revised form 18 July 2022; Accepted 20 July 2022
Available online 6 August 2022

List of abbreviations

MPSCs	multiple primary squamous cell carcinomas
CCRT	concurrent chemoradiotherapy
PET/CT	positron emission tomography/computed tomography
MRI	magnetic resonance imaging
SCC	squamous cell carcinoma
OS	overall survival
SUV	standardized uptake values
HPV	Human papilloma Virus
PR	Partial Response
VMAT	Volumetric Modulated Arc Therapy

2. Materials and methods

2.1. Registration

In accordance with the Declaration of Helsinki, our study has been registered with **Researchregistry. com.** Unique Identifying number or registration ID: **researchregistry7973** [3].

Ethical approval

The study was approved by the Ethics Council for Biomedical Research, and informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the Helsinki declaration as revised in 2013 and its later amendments.

2.2. Study design

The retrospective, descriptive study from January 2019 to December 2021 enrolled individuals who had synchronous MPSCs in the oral cavity at the time of their initial diagnosis.

Inclusion criteria:

- The patient was diagnosed with squamous cell carcinoma of the oral cavity cancer, confirmed by histopathological results.
- At the time of initial diagnosis, at least two lesion sites in the oral cavity, confirmed by histopathological findings, met the criteria for MPSCs.
- The patient had no distant metastatic lesions and had not been previously treated.

Exclusion criteria:

- The patient did not complete the entire course of treatment
- The patient lost or incomplete information during the study

2.3. Procedure of study

Prior to therapy, all patients had a clinical assessment, an ENT endoscopic examination, and histopathological confirmation by needle biopsy of all suspicious lesions. Lesions at separate locations in the oral cavity were verified using a combination of MRI and 18FDG PET/CT. We classified cancers into two groups in this study: index tumors (bigger tumors believed to be the first tumors) and synchronous tumors (early stage tumors thought to be the second tumors).

Following a conclusive diagnosis of MPSCs, the patients received CCRT. The CCRT regimen is chosen individually after consultation with a head and neck radiation oncologist, chemotherapist, surgeon, radiologist, and pathologist.

Target volume delineation: GTV = GTVi + GTVs + GTVn, as determined by ENT endoscopy, head and neck MRI, and 18FDG PET/CT. CTV70 = GTV +0.5–1 cm. PTV70 = CTV70 + 0.5 cm.

Follow-up every 3 months after treatment by head and neck MRI, CT, 18FDG PET/CT, head and neck ultrasound, ENT endoscopy, and additional imaging if there were any abnormalities or complaints. The last follow up period is December 2021.

3. Objective

Primary objective:

Describe the clinical and para-clinical characteristics of the study group of patients: Analysis of variables such as age, gender, smoking status, alcohol use, TNM stage (as defined by UICC 8th), tumor features as determined by 18FDG PET/CT.

Secondary objective.

Evaluation of treatment results of the study group of patients: Variables like response to CCRT, and overall survival were analyzed. In which the response to CCRT is assessed at 8-week post-treatment using ENT" endoscopy, head and neck MRI, or 18FDG PET/CT, in accordance with the RECIST v1.1 criteria.

3.1. Data analysis

Using SPSS software version 20.0. Means with standard deviations were calculated for continuous variables, and medians with interquartile range were calculated for non-normal continuous variables. Categorical variables are presented as counts and proportions.

Our work has been reported in line with the STROCSS criteria [4].

4. Results

4.1. Clinical and para-clinical characteristics

Analysis of variables: age, gender, smoking status, alcohol use, TNM stage, tumor features.

Seven male patients with a mean age of 53.3 years [43–70] were included in the research. 7/7 patient smokes pipe tobacco and consumes an average of 30 packs per year. 5/7 patient have a history of binge drinking. At the time of initial diagnosis, 100% of patients had two tumors. Squamous cell carcinomas were verified histopathologically. SUVi = 15.76 ± 1.96, SUVs = 9.41 ± 1.24, and SUVn = 5.9 ± 1.01. There is considerably more SUV in the index tumor than in the synchronous tumor. (See Table 1).

The index tumor is predominantly T3, T4, whereas the synchronous tumors are T1, T2. 6/7 individuals had N2, N3 stage tumors; due to the tumor's enormous size, numerous primary tumors imply an extended period of tumor growth. (See Fig. 1).

4.2. Treatment results

Analysis of variables: response to CCRT, overall survival.

CCRT with Cisplatin or Cetuximab was used to treat all patients. All patients in this study received radiation sing volumetric modulated arc therapy (VMAT) technique. Three patients received bolus Cisplatin (100 mg/m^2) every three weeks, three patients received weekly Cisplatin (40 mg/m^2), and one patient received Cetuximab with a loading dose and a weekly dosage owing to renal insufficiency. All patients achieved a partial response (PR) and then required palliative care when the illness recurred or progressed. OS on average: 14.71 ± 1.85 months. (See Table 2). (See Fig. 2).

5. Discussion

Head and neck cancers account for 5–6% of all malignancies, with SCC accounting for more than 90% of cases. According to GLOBOCAN 2020, oral cavity cancer accounts for 1.2% of all cancers in Viet Nam and

Table 1
Tumor staging and metabolism characteristics in 18FDG PET/CT.

No	Index tumor	Ti	SUVi	Synchronous tumor	Ts	SUVs	N	SUVn
1	Mobile tongue (R)	4	11.7	Floor of mouth (L)	1	8.2	0	2.1
2	Mobile tongue (R)	3	18.2	Mobile tongue (L)	2	7	2c	4
3	Retromolar trigone (L)	2	10.2	Retromolar trigone (R)	1	5.5	3	8.5
4	Buccal mucosa (R)	3	13.5	Mobile tongue (L)	1	14.8	2b	8.6
5	Floor of mouth (L)	3	20.9	Hard palate	2	10.7	2c	8.7
6	Upper gingival (L)	4	23.7	Hard palate	2	12.2	2b	4.9
7	Mobile tongue (R)	2	12.1	Floor of mouth (R)	1	7.5	2b	4.5
	$x \pm SD$	15.76 ± 1.96			9.41 ± 1.24		5.9 ± 1.01	

Ti: Tumor stage of index tumor.
Ts: Tumor stage of synchronus tumor.
SUVi, SUVs, SUVn: Standardized uptake value of index tumor, synchronous tumor, and cervical lymph node, respectively.
(R: Right; L: Left).

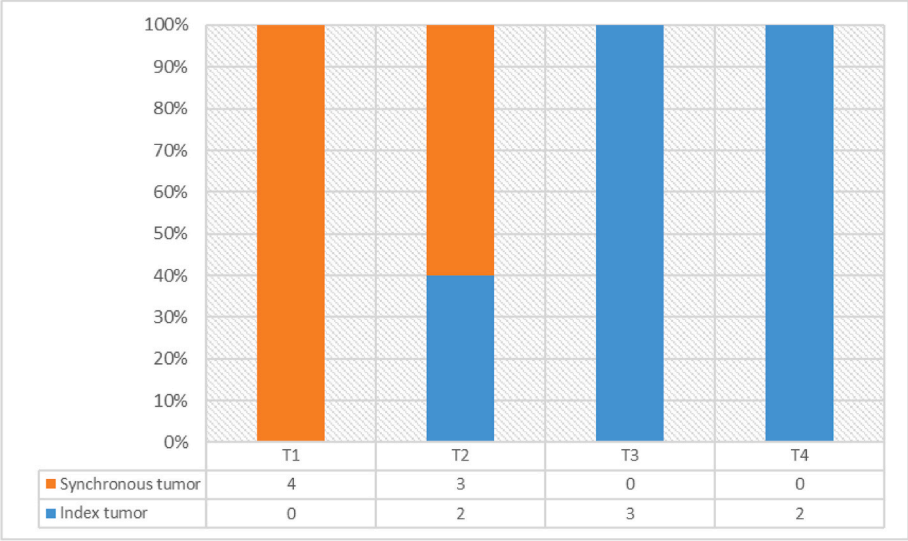

Fig. 1. T stage of synchronous tumor and index tumor.

Table 2
Treatment, response, and overall survival of patients.

No.	Treatment	Response	OS (month)
1	CCRT, 70Gy (VMAT) with Cetuximab	PR	9
2	CCRT, 70Gy (VMAT) with Cisplatin 100 mg/m^2 every 3 weeks × 3 cycles	PR	21
3	CCRT, 70Gy (VMAT) with Cisplatin 40 mg/m^2 every week x 6 cycles	PR	21
4	CCRT, 70Gy (VMAT) with Cisplatin 100 mg/m^2 every 3 weeks × 3 cycles	PR	7
5	CCRT, 70Gy (VMAT) with Cisplatin 40 mg/m^2 every week x 6 cycles	PR	5
6	CCRT, 70Gy (VMAT) with Cisplatin 100 mg/m^2 every 3 weeks × 3 cycles	PR	10
7	CCRT, 70Gy (VMAT) with Cisplatin 40 mg/m^2 every week x 6 cycles	PR	14

CCRT: concurrent chemoradiotherapy; PR: Partial Response; VMAT: Volumetric Modulated Arc Therapy.

ranks 18th in terms of new cases and mortality rate, accounting for 2152 new cases and 1099 deaths, accounting for 0.9% [2]. Surgery is the most critical therapy. However, with a large number of patients at a loco-regional advanced stage, around 30%–40%, and a complex oral cavity anatomy with numerous blood arteries and a lymphatic drainage system, the treatment plan must strike a balance between cancer benefits, function, and aesthetics. Because obtaining a negative margin is more difficult in instances with MPSCs, definitive CCRT is regarded as a suitable alternate therapeutic option.

From 2000 to 2012, Sweeting Ping Ng evaluated 1512 patients who had definitive radiation [5]. The study discovered that the chance of developing a second primary malignancy rose with time, with rates of 4, 10, and 25% after 5, 10, and 15 years, respectively. This risk was considerably greater ($p < 0.001$) among current smokers, with cumulative rates of 1, 6, 18, and 32% in the 2, 5, 10, and 15-year time periods, respectively.

From 1993 to 2011, an analysis of 790 patients from an Australian head and neck oncology department found that 29 patients (3.7%) had synchronous MPCs, 18 patients (2.3%) had metachronous tumors, and 37.8% of primary tumors occurred in the lip and oral cavity, which had a significant second tumor. This region may have been exposed to carcinogens directly, chronically, and cumulatively, therefore beginning carcinogenesis. Additionally, this investigation established a link between smoking and second cancer, and progression to synchronous or metachronous malignancy was linked with a worse overall survival rate [6].

Through the generation and accumulation of genetic mutations, loss of heterozygosity, microsatellite alterations, and a variety of other genetic variations, the oral cavity exposed to carcinogens frequently induces the appearance of precancerous lesions [7]. Slaughter first mentioned the field cancerization theory in 1953, when he examined 783 SCCs in head and neck cancer, esophagus, lung, stomach, colon, anus, cervix, and skin [8]. He noted the appearance of one or more independent malignant lesions on the entire mucosa adjacent to the tumor. Oral field cancerization can occur as a result of cells migrating

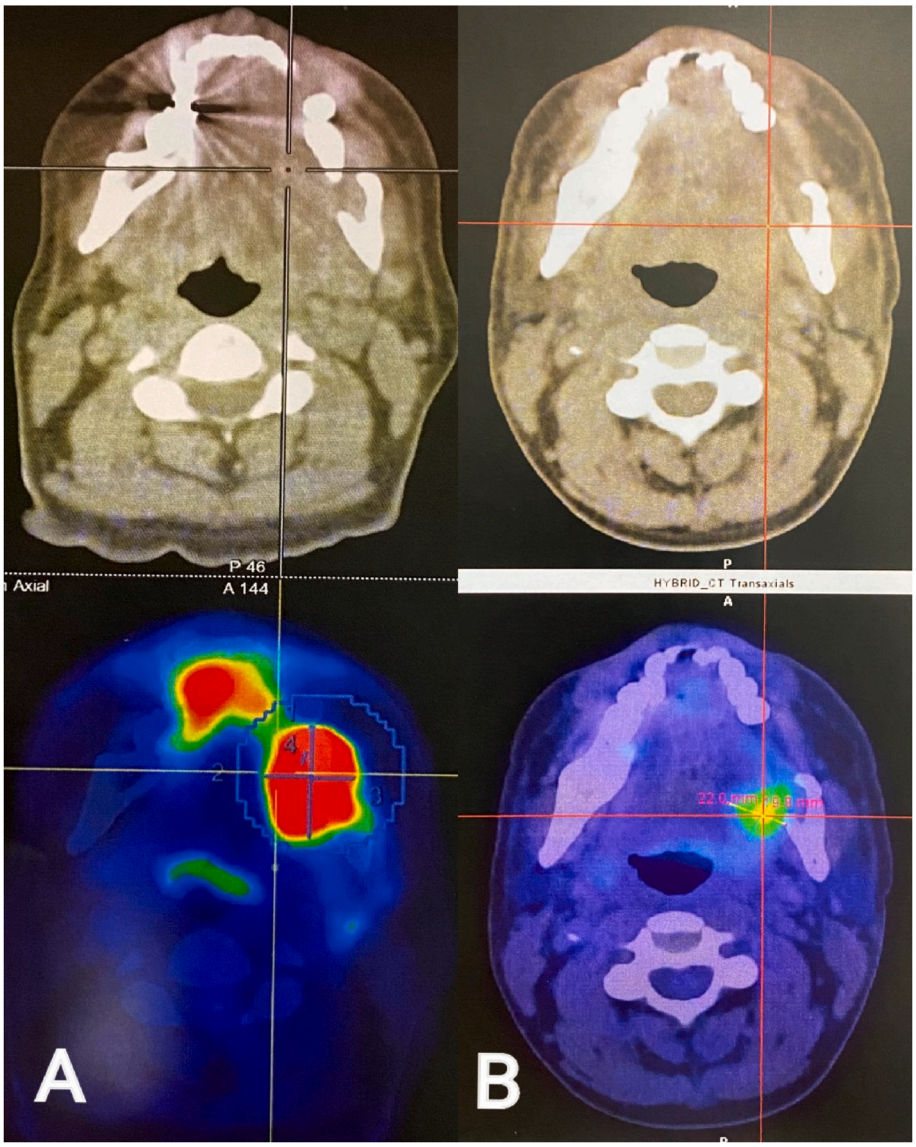

Fig. 2. A. Pre-treatment 18-FDG PET/CT result: There are two tumors in Upper gingival (L) (SUVmax 23,7) and hard plate (SUVmax 12,2)
B. Post-treatment 18-FDG PET/CT result: partial response, there is still a mass (SUVmax 6,4).

from the tumor to adjacent healthy tissues (one or a group of cells migrating through the submucosa to a nearby site, or transplantation into another organ and proliferation), or it can occur as a result of cells migrating from another independent site and proliferating, or it can occur as a result of cells migrating from another independent site and proliferating. In these instances, analysis of variable mutations or specific markers associated with tumors can be distinguished. As a result, the carcinogenic model we propose is monoclonal in origin and consists of three major steps: 1, patch formation: transformation of a single stem cell (patch) into a group of cells (clone) that carry the genetic alterations without a growth control pattern; 2, clonal expansion: additional genetic alterations develop and the patch proliferates, forming a field that dispenses with the normal epithelium; 3, transition to tumor: the clone or field eventually turns into an overt carcinoma with invasive growth and metastasis [8].

Even with Warren and Gate's criteria for MPSCs, diagnostic difficulties persist in clinical practice [1]. For instance, when evaluating two tumors 1.5 cm apart with normal mucosal surfaces, how should the mucosa be evaluated visually, using narrow-band imaging, or by staining with fluorescence? Numerous cases of precancerous lesions or abnormal cell proliferation have been reported, but none have been observed with the naked eye. Tumors that have spread submucosally will be identified using MRI or 18FDG PET/CT. However, there are still artifacts that cause confusion. The most accurate diagnosis is made through histopathology analysis, which is difficult to perform due to inoperable synchronous MPSCs. Additionally, determining whether the synchronous tumor is a metastasis from the index tumor is difficult. Despite extensive research into various genes and markers, there has been little change in the basis for diagnosis and application in clinical practice. These issues require further investigation in order to ascertain the nature of tumors and to provide an accurate prognosis and treatment strategy.

Smoking and alcohol consumption are strongly associated with the risk of developing synchronous and metachronous MPSCs. Leon (2009) demonstrated that continuing to smoke and drink alcohol after treatment increased the risk of developing a second malignancy by approximately three to five times, not only for oral cavity tumors but also for tumors affecting the entire upper gastrointestinal tract [9]. As a result, it is recommended that long-term follow-up of patients with oral cavity cancer who have undergone radical treatment and have abstained from alcohol and tobacco completely can improve survival [10].

Huang (2012) discovered that approximately 30% of oral cavity

cancers were caused by HPV, particularly HPV-16 and HPV-18, with HPV-18 increasing the risk of subsequent cancers ($p = 0.033$) [11]. However, some studies have demonstrated that HPV is not associated with an increased risk of oral cavity cancer and that there is no correlation between HPV and prognosis [12,13] Between 2000 and 2014, Adjei Boakye examined SEER data on 109,512 patients with head and neck cancer. The study found that those with a first potentially HPV-associated SCC head and neck cancer (SIR, 1.98; EAR, 114 excess cases per 10,000 PYR) had a lower risk of developing second primary malignant neoplasms than those with a first non-HPV-associated HNSCC (SIR, 1.98; EAR, 114 excess cases per 10,000 PYR) (SIR, 2.28; EAR, 188 cases per 10,000 PYR). For cancers of the head and neck, lung, and esophagus, the largest SIRs and EARs were observed [14].

The majority of patients in our study had a history of smoking and binge drinking, which is a very common bad habit in Vietnam. As a result, the incidence of associated diseases such as head and neck cancer, esophageal cancer, lung cancer, and liver cancer remains high, increasing the national cancer burden. Which includes lung and liver cancers, which are the most prevalent and have the highest mortality rates [15].

Concerning the stage of the disease, there is no clear classification of the TNM stage of synchronous MPSCs in oral cavity cancers according to the UICC/AJCC classification version 8, 2017. As a result, we classify tumors as Ti (index tumor) for large, advanced lesions that are considered the primary tumor, and Ts (synchronous tumor) for smaller lesions that are considered a secondary tumor.

When treating patients with head and neck cancer, particularly oral cavity cancer, it is critical to carefully evaluate the patient's medical history, clinical examination, ENT endoscopy, narrowband light imaging, or fluorescence staining for early mucosal changes. Regrettably, modern techniques have not been routinely used in our hospital. PET/CT is extremely useful in diagnosing MPSCs because it is capable of accurately distinguishing distinct lesions and identifying predictors via SUVmax, metabolizing tumor volume (MTV). SUVmax values greater than 7.5 were associated with a lower survival rate than SUVmax values less than 7.5, and MTV values greater than 7.78 cm^3 were associated with a worse prognosis [16]. Not only index tumors, but also synchronous tumors had a high SUVmax and large volume sites of increasing metabolic activity, which contributed to overall survival being decreased.

Regarding the treatment strategy for head and neck cancer with MPSCs, particularly in the chewing and swallowing functions of the oral cavity, definitive surgery must have been considered. To improve cure rates and balance functional outcomes, early stage tumors should be removed with a negative margin of 1 cm surrounding lesions in an experienced head and neck surgery center. Combination modality functional organ preservation approaches have been used to treat patients with incurable cancers and those with operable cancers for whom a nonsurgical technique is either equivalent to or preferable in terms of oncological benefit. All of our patients were in a locally advanced stage and had large tumors. Concurrent definitive chemoradiotherapy with Cisplatin bolus (100 mg/m^2 every three weeks) or weekly (40 mg/m^2 weekly) is preferred. Numerous studies have established the target regimen's efficacy. However, our center is inexperienced. After CCRT, our patients had a partial response with an enhanced lesion in post-treatment MRI.

From 2003 to 2017, Kawasaki reported on 261 patients with oral cavity SCC, including 241 patients with a single primary carcinoma and 20 patients with MPSCs [17]. MPSCs were more prevalent in females and occurred more frequently in the lower gingival than in the tongue ($p < 0.01$). MPSCs had a significantly higher rate of recurrence ($p < 0.01$). Metachronous MPSCs had cumulative rates of 3.45% and 5.36% after five and ten years, respectively. The 5-year OS was not significantly different between the two groups (88% and 95%, respectively, $p = 0.54$). The 15-year OS of the MPSCs group was approximately 28%, which was significantly less than that of the single tumor group.

Mochizuki followed 961 patients with oral cavity cancer for 12 years. 54 patients developed new malignant lesions, the majority of which were in the gingival region [18]. MPSCs had a higher rate of local recurrence. At ten years, the disease-specific survival rate was 85.3% for single tumors and 79.6% for multiple tumors, respectively.

Our study had a lower overall survival rate than these studies because our patients were in an advanced loco-regional stage with extensive invasion and metastatic lymph nodes involved; additionally, synchronous MPSCs demonstrate the disease's long progression.

Limitations of this study: Limited of number patients not representative of all cases with synchronous PMCs in the oral cavity and head and neck cancers.

6. Conclusion

In clinical practice, synchronous MPSCs in the oral cavity at the time of initial diagnosis are uncommon, which is a poor prognostic sign. Thorough clinical examination in conjunction with other imaging modalities, including 18FDG PET/CT, is critical for detecting and confirming synchronous lesions, particularly in patients with large index tumors and a history of smoking and drinking. Individualized treatment strategies are used, and definitive CCRT is considered an appropriate course of action. After treatment, careful monitoring is necessary to detect and manage MPSCs early.

Conflict of interest statement

The Authors declare that there is no conflict of interest.

Funding information

Not applicable (There is no funding for this manuscript).

Statement of informed consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

Provenance and peer review

Not commissioned, externally peer reviewed.

Ethical approval

The study was approved by the Ethics Council in Biomedical Research of Vietnam National Cancer Hospital (No 1311/BVK-HĐĐĐ, Code IRB-VN 01034), and informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the Helsinki declaration as revised in 2013 and its later amendments.

Consent

"Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request".

Author contributions

Dang Nguyen Van: Radiation Oncologist, treated the patients and wrote a manuscript.

Quang Le Van: Professor, revised manuscript.

Nhung Nguyen Thi Thu: Radiation Oncologist, wrote a manuscript.

Giang Bui Van: Professor, revised manuscript.

To Ta Van: Professor, revised manuscript.

Registration of research studies

1. Name of the registry: Researchregistry.com
2. Unique Identifying number or registration ID: researchregistry7973
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/629b2f5026b082001e2f317b/

Guarantor

Dang Nguyen Van, MD.
Address
Department of Oncology, Hanoi Medical University
No 1 Ton That Tung, Dong Da District, Hanoi, Vietnam
Zip Postal Code: 10000. Tel: +84 94 2727 899. Email: nguyenvandang@hmu.edu.vn; drdangnguyen@gmail.com

Table 2: The full revised STROCSS 2021 checklist.

STROCSS 2021 Guideline.

Item no.	Item description	Page
TITLE		
1	**Title**	1
	•The word cohort or cross-sectional or case-control is included*	1
	•Temporal design of study is stated (e.g. retrospective or prospective)	1
	•The focus of the research study is mentioned (e.g. population, setting, disease, exposure/intervention, outcome etc.)	
	*STROCSS 2021 guidelines apply to cohort studies as well as other observational studies (e.g. cross-sectional, case-control etc.)	
ABSTRACT		
2a	**Introduction** – briefly describe:	2
	•Background	2
	•Scientific rationale for this study	2
	•Aims and objectives	2
2b	**Methods** - briefly describe:	2
	•Type of study design (e.g. cohort, case-control, cross-sectional etc.)	3
	• Other key elements of study design (e.g. retro-/prospective, single/multi-centred etc.)	3
	• Patient populations and/or groups, including control group, if applicable	3 4
	• Exposure/interventions (e.g. type, operators, recipients, timeframes etc.)	4
	• Outcome measures – state primary and secondary outcome(s)	
2c	**Results** - briefly describe:	4
	• Summary data with qualitative descriptions and statistical relevance, where appropriate	4
2d	**Conclusion** - briefly describe:	9
	• Key conclusions	9
	• Implications for clinical practice	9
	• Need for and direction of future research	
INTRODUCTION		
3	**Introduction** – comprehensively describe:	2
	• Relevant background and scientific rationale for study with reference to key literature	2 2
	• Research question and hypotheses, where appropriate	2
	• Aims and objectives	
METHODS		
4a	**Registration**	2
	• In accordance with the Declaration of Helsinki*, state the research registration number and where it was registered, with a hyperlink to the registry entry (this can be obtained from ResearchRegistry.com, ClinicalTrials.gov, ISRCTN etc.)	2 3
	• All retrospective studies should be registered before submission; it should be stated that the research was retrospectively registered	
	* *"Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject"*	
4b	**Ethical approval**	3
	• Reason(s) why ethical approval was needed	3
	• Name of body giving ethical approval and approval number	3

(*continued on next column*)

(*continued*)

	• Where ethical approval wasn't necessary, reason(s) are provided	
4c	**Protocol**	3
	• Give details of protocol (*a priori* or otherwise) including how to access it (e.g. web address, protocol registration number etc.)	3 3
	• If published in a journal, cite and provide full reference	
4d	**Patient and public involvement in research**	3
	• Declare any patient and public involvement in research	3
	• State the stages of the research process where patients and the public were involved (e.g. patient recruitment, defining research outcomes, dissemination of results etc.) and describe the extent to which they were involved.	3
5a	**Study design**	3
	• State type of study design used (e.g. cohort, cross-sectional, case-control etc.)	3 3
	• Describe other key elements of study design (e.g. retro-/prospective, single/multi-centred etc.)	
5b	**Setting and timeframe of research** – comprehensively describe:	3
	• Geographical location	
	• Nature of institution (e.g. primary/secondary/tertiary care setting, district general hospital/teaching hospital, public/private, low-resource setting etc.)	
	• Dates (e.g. recruitment, exposure, follow-up, data collection etc.)	
5c	**Study groups**	3
	• Total number of participants	
	• Number of groups	
	• Detail exposure/intervention allocated to each group	
	• Number of participants in each group	
5d	**Subgroup analysis** – comprehensively describe:	3
	• Planned subgroup analyses	
	• Methods used to examine subgroups and their interactions	
6a	**Participants** – comprehensively describe:	3
	• Inclusion and exclusion criteria with clear definitions	
	• Sources of recruitment (e.g. physician referral, study website, social media, posters etc.)	
	• Length, frequency and methods of follow-up (e.g. mail, telephone etc.)	
6b	**Recruitment** – comprehensively describe:	3
	• Methods of recruitment to each patient group (e.g. all at once, in batches, continuously till desired sample size is reached etc.)	
	• Any monetary incentivisation of patients for recruitment and retention should be declared; clarify the nature of any incentives provided	
	• Nature of informed consent (e.g. written, verbal etc.)	
	• Period of recruitment	
6c	**Sample size** – comprehensively describe:	3
	• Analysis to determine optimal sample size for study accounting for population/effect size	
	• Power calculations, where appropriate	
	• Margin of error calculation	
METHODS - INTERVENTION AND CONSIDERATIONS		
7a	**Pre-intervention considerations** – comprehensively describe:	3
	• Preoperative patient optimisation (e.g. weight loss, smoking cessation, glycaemic control etc.)	
	• Pre-intervention treatment (e.g. medication review, bowel preparation, correcting hypothermia/-volemia/-tension, mitigating bleeding risk, ICU care etc.)	
7b	**Intervention** – comprehensively describe:	3
	• Type of intervention and reasoning (e.g. pharmacological, surgical, physiotherapy, psychological etc.)	
	• Aim of intervention (preventative/therapeutic)	
	• Concurrent treatments (e.g. antibiotics, analgesia, antiemetics, VTE prophylaxis etc.)	
	• Manufacturer and model details, where applicable	
7c	**Intra-intervention considerations** – comprehensively describe:	3
	• Details pertaining to administration of intervention (e.g. anaesthetic, positioning, location, preparation, equipment needed, devices, sutures, operative techniques, operative time etc.)	
	• Details of pharmacological therapies used, including formulation, dosages, routes, and durations	
	• Figures and other media are used to illustrate	
7d	**Operator details** – comprehensively describe:	3
	• Requirement for additional training	
	• Learning curve for technique	

(*continued on next page*)

(*continued*)

	• Relevant training, specialisation and operator's experience (e.g. average number of the relevant procedures performed annually)	
7e	**Quality control** – comprehensively describe: • Measures taken to reduce inter-operator variability • Measures taken to ensure consistency in other aspects of intervention delivery • Measures taken to ensure quality in intervention delivery	3
7f	**Post-intervention considerations** – comprehensively describe: • Post-operative instructions (e.g. avoid heavy lifting) and care • Follow-up measures • Future surveillance requirements (e.g. blood tests, imaging etc.)	3
8	**Outcomes** – comprehensively describe: • Primary outcomes, including validation, where applicable • Secondary outcomes, where appropriate • Definition of outcomes • If any validated outcome measurement tools are used, give full reference • Follow-up period for outcome assessment, divided by group	4
9	**Statistics** – comprehensively describe: • Statistical tests and statistical package(s)/software used • Confounders and their control, if known • Analysis approach (e.g. intention to treat/per protocol) • Any sub-group analyses • Level of statistical significance	4
RESULTS		
10a	**Participants** – comprehensively describe: • Flow of participants (recruitment, non-participation, cross-over and withdrawal, with reasons). Use figure to illustrate. • Population demographics (e.g. age, gender, relevant socioeconomic features, prognostic features etc.) • Any significant numerical differences should be highlighted	4
10b	**Participant comparison** • Include table comparing baseline characteristics of cohort groups • Give differences, with statistical relevance • Describe any group matching, with methods	4
10c	**Intervention** – comprehensively describe: • Degree of novelty of intervention • Learning required for interventions • Any changes to interventions, with rationale and diagram, if appropriate	4
11a	**Outcomes** – comprehensively describe: • Clinician-assessed and patient-reported outcomes for each group • Relevant photographs and imaging are desirable • Any confounding factors and state which ones are adjusted	4,5
11b	**Tolerance** – comprehensively describe: • Assessment of tolerability of exposure/intervention • Cross-over with explanation • Loss to follow-up (fraction and percentage), with reasons	4,5
11c	**Complications** – comprehensively describe: • Adverse events and classify according to Clavien-Dindo classification* • Timing of adverse events • Mitigation for adverse events (e.g. blood transfusion, wound care, revision surgery etc.) * Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications. A New Proposal with Evaluation in a Cohort of 6336 Patients and Results of a Survey. Ann Surg. 2004; 240(2): 205-213	4,5
12	**Key results** – comprehensively describe: • Key results with relevant raw data • Statistical analyses with significance • Include table showing research findings and statistical analyses with significance	4,5
DISCUSSION		
13	**Discussion** – comprehensively describe: • Conclusions and rationale • Reference to relevant literature • Implications for clinical practice • Comparison to current gold standard of care • Relevant hypothesis generation	5
14	**Strengths and limitations** – comprehensively describe: • Strengths of the study	9

(*continued on next column*)

(*continued*)

	• Weaknesses and limitations of the study and potential impact on results and their interpretation • Assessment and management of bias • Deviations from protocol, with reasons	
15	**Relevance and implications** – comprehensively describe: • Relevance of findings and potential implications for clinical practice • Need for and direction of future research, with optimal study designs mentioned	6
CONCLUSION		
16	**Conclusions** • Summarise key conclusions • Outline key directions for future research	9
DECLARATIONS		
17a	**Conflicts of interest** • Conflicts of interest, if any, are described	9
17b	**Funding** • Sources of funding (e.g. grant details), if any, are clearly stated • Role of funder	9
17c	**Contributorship** • Acknowledge patient and public involvement in research; report the extent of involvement of each contributor	9

Acknowledgements

Not applicable.

References

[1] S. Warren, Multiple primary malignant tumors. A survey of the literature and a statistical study, Am. J. Cancer 16 (1932) 1358–1414.
[2] H. Sung, J. Ferlay, R.L. Siegel, et al., Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, Ca - Cancer J. Clin. 71 (3) (2021) 209–249, https://doi.org/10.3322/caac.21660.
[3] https://www.researchregistry.com/browse-the registry#home/registrationdetails/629b2f5026b082001e2f317b/.
[4] G. Mathew, R. Agha, for the STROCSS Group, Strocss 2021: strengthening the Reporting of cohort, cross-sectional and case-control studies in Surgery, Int. J. Surg. 96 (2021), 106165.
[5] S.P. Ng, C. Pollard, M. Kamal, et al., Risk of second primary malignancies in head and neck cancer patients treated with definitive radiotherapy, Npj Precis Oncol 3 (1) (2019) 1–6, https://doi.org/10.1038/s41698-019-0097-y.
[6] J. Ha, G. Parham, T. Baerg, P. Fisher, Synchronous and metachronous head and neck squamous cell carcinoma in western Australia—a single center experience, Aust. J. Oto Laryngol. 2 (2019), 0, https://www.theajo.com/article/view/4166.
[7] W. Zhang, Z. Zhu, M. Huang, Y.-J. Tang, Y. Tang, X. Liang, Susceptibility of multiple primary cancers in patients with head and neck cancer: nature or nurture? Front. Oncol. 9 (2019) 1275, https://doi.org/10.3389/fonc.2019.01275.
[8] M. Mohan, N. Jagannathan, Oral field cancerization: an update on current concepts, Onco Rev. 8 (1) (2014) 244, https://doi.org/10.4081/oncol.2014.244.
[9] X. León, M. del Prado Venegas, C. Orús, M. López, J. García, M. Quer, Influence of the persistence of tobacco and alcohol use in the appearance of second neoplasm in patients with a head and neck cancer. A case-control study, Cancer Causes Control CCC 20 (5) (2009) 645–652, https://doi.org/10.1007/s10552-008-9277-8.
[10] B. Kuhlin, B. Kramer, V. Nefas, N. Rotter, C. Aderhold, Indicators for secondary carcinoma in head and neck cancer patients following curative therapy: a retrospective clinical study, Mol Clin Oncol 12 (5) (2020) 403–410, https://doi.org/10.3892/mco.2020.2004.
[11] S.F. Huang, H.F. Li, C.T. Liao, et al., Association of HPV infections with second primary tumors in early-staged oral cavity cancer, Oral Dis. 18 (8) (2012) 809–815, https://doi.org/10.1111/j.1601-0825.2012.01950.x.
[12] P.M. de Abreu, A.C.G. Có, P.L. Azevedo, et al., Frequency of HPV in oral cavity squamous cell carcinoma, BMC Cancer 18 (1) (2018) 324, https://doi.org/10.1186/s12885-018-4247-3.
[13] V. Palve, J. Bagwan, N.M. Krishnan, et al., Detection of high-risk human papillomavirus in oral cavity squamous cell carcinoma using multiple analytes and their role in patient survival, J Glob Oncol 4 (2018) 1–33, https://doi.org/10.1200/JGO.18.00058.
[14] E. Adjei Boakye, P. Buchanan, L. Hinyard, N. Osazuwa-Peters, M. Schootman, J. F. Piccirillo, Incidence and risk of second primary malignant neoplasm after a first head and neck squamous cell carcinoma, JAMA Otolaryngol Neck Surg 144 (8) (2018) 727–737, https://doi.org/10.1001/jamaoto.2018.0993.
[15] T.P. Nguyen, H.N. Luu, M.V.T. Nguyen, et al., Attributable causes of cancer in Vietnam, JCO Glob Oncol 6 (2020) 195–204, https://doi.org/10.1200/JGO.19.00239.
[16] M.A. Pasha, C. Marcus, C. Fakhry, H. Kang, A.P. Kiess, R.M. Subramaniam, FDG PET/CT for management and assessing outcomes of squamous cell cancer of the

oral cavity, Am. J. Roentgenol. 205 (2) (2015) W150–W161, https://doi.org/10.2214/AJR.14.13830.

[17] M. Kawasaki, T. Tamura, Y. Harada, N. Fujii, R. Doi, I. Kodani, Clinical features of oral multiple primary carcinomas compared with oral single primary carcinoma, Yonago Acta Med. 63 (4) (2020) 246–254, https://doi.org/10.33160/yam.2020.11.002.

[18] Y. Mochizuki, H. Harada, M. Ikuta, et al., Clinical characteristics of multiple primary carcinomas of the oral cavity, Oral Oncol. 51 (2) (2015) 182–189, https://doi.org/10.1016/j.oraloncology.2014.11.013.