

C A S E R E P O R T

Second primary carcinoma arising on a flap: a new primary or a relapse?

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Abstract. *Background and aim:* Free flaps or pedicle flaps are the mainstay of cancer surgery in the head and neck area. However, their long-term sequelae are still poorly understood. Among these, the development of a secondary primary tumor on a flap is a rare and uncertain reported event. *Methods:* A computer-aided systematic literature search was performed by using the PubMed, EMBASE and Cochrane Library databases. A systematic review of the literature, following the PRISMA checklist, was carried out with the aim of analyzing all the citations reporting this second primary, with attention to risk factors, behavior, etiological causes. *Results:* Overall, 27 cases of second primary squamous cell carcinoma arising on a pedicle or free flap were identified. In addition, other three cases were discussed. *Conclusions:* Persistent exposure to oral stimuli such saliva, oral microbiome, smoke or a colonization by the adjacent mucosa were considered as a possible cause of second primary carcinoma. Although rare, a new neoplasm onset should know and considered as a new concept in the follow-up of patients undergoing reconstruction with free or pedicle flaps. (www.actabiomedica.it)

Key words: free flap, reconstructive surgery, second primary, squamous cell carcinoma, mucosalization, relapse

Introduction

Head and neck squamous cell carcinoma (HNSCC) are the fifth most prevalent disease worldwide, with an estimated incidence of 600.000 new cases every year and an annual global mortality rate of around 300.000 patients (1). Survival in advanced HNSCC has remained alarmingly unchanged over the last 60 years, despite the great advances in medicine. The causes of this related to numerous factors: locally advanced stage at diagnosis, relapses in more than 50% of cases after the first treatment (surgery and/or

chemo-radiotherapy), delayed diagnosis due to non-specific symptoms (2).

Alcohol consumption, tobacco exposure, human papillomavirus infection and dental trauma are the main causative agents of HNSCC; they often cause widespread field cancerization and a chronic inflammation state with a poor host-vs-disease immune response (1,2). Genetic susceptibility plays an important but undefined etiological role, determining the predisposition and the onset of the tumor or its recurrence (1-4).

Since the 1980s, microsurgical free flaps or pedicled flaps have become the first choice for reconstruction of wide post-surgical defects after tumor

resection in the head and neck area, allowing the preservation of the cosmetic and functional status (5-7). The causes and failure rates of flap surgery are widely discussed in literature, describing the early and the late postoperative complications (8,9).

Second primary tumors developing within the flap used for reconstruction are rarely reported. Two hypotheses of late recurrence are possible: A) exposure of the flap to a new environment of the oral cavity which could lead to metaplasia, a phenomenon called “mucosalization”, and possibly to cancer (10); B) skin colonization by residual cells of the adjacent original mucosa: cells chronically exposed to carcinogens possess all genetic alterations that previously predisposed to cancer transformation (field cancerization) (11).

This review aims to analyze all cases reported of second primary tumors that have grown inside the flap applied for head and neck reconstruction and determine causal factors, etiological assumptions and how they affect oncological treatment and follow-up. In addition, three cases of a new squamous HNSCC cavity arising on a flap used in the previous reconstruction are presented.

Methods

The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement and the recommendations of the Meta-Analysis of Observational Studies in Epidemiology group (12). The study was carried out in accordance with the principles of the Helsinki Declaration. This systematic review was conducted according to PICOS acronym: Patients (P), patients suffering from second primary on free or pedicled flap; Intervention (I), primary surgery with flap reconstruction; Comparator (C), none; Outcomes (O), overall survival (OS), disease-free survival (DFS), relapse on the flap; Study design (S), retrospective case reports/series.

Study eligibility criteria

Studies were excluded if they (a) were not in English, (b) were not available in full-text form, (c) reported insufficient data, (d) data were not extractable, (e) the article type was conference abstract, letter to

the editor, or book chapter. No restriction was applied according to the time of publication.

Search strategy

A computer-aided systematic literature search was performed on PubMed, EMBASE and Cochrane Library. MeSH terms were adjusted in various combinations to maximize yield.

Data collection process

Two independent reviewers (GP and TDB) conducted the electronic search. All articles were initially screened by title and abstract. Then, studies that were believed to be relevant to our search were downloaded and the full-text manuscripts reviewed to determine eligibility. The conflict between reviewers was resolved by a third author (VM). Data extraction from the included studies was systematically made using a structured form by two independent reviewers (GP and TDB). Moreover, a manual search was conducted for references from the selected studies. Duplicate abstracts and articles unrelated to our analysis were carefully removed.

The following data were extracted, when available: author and year of publication, country, number of patients, gender (male or female), age (years), duration of follow-up (months), clinical symptoms, risk factors, tumor size and staging, location (site and subsite), primary and adjuvant treatment and type of flap used. Data related to patient's follow-up in terms of survival and adjuvant and secondary treatments in case of recurrences were also extracted.

All SCC arising in the skin of a flap described in literature were included in this review.

Last search was made online on 3 March 2023. The PRISMA 2020 flow chart diagram is shown in Figure 1.

Results

The literature search retrieved 176, 101, and 0 citations from PubMed (Medline), EMBASE, and Cochrane Library databases, respectively (Table 1)..

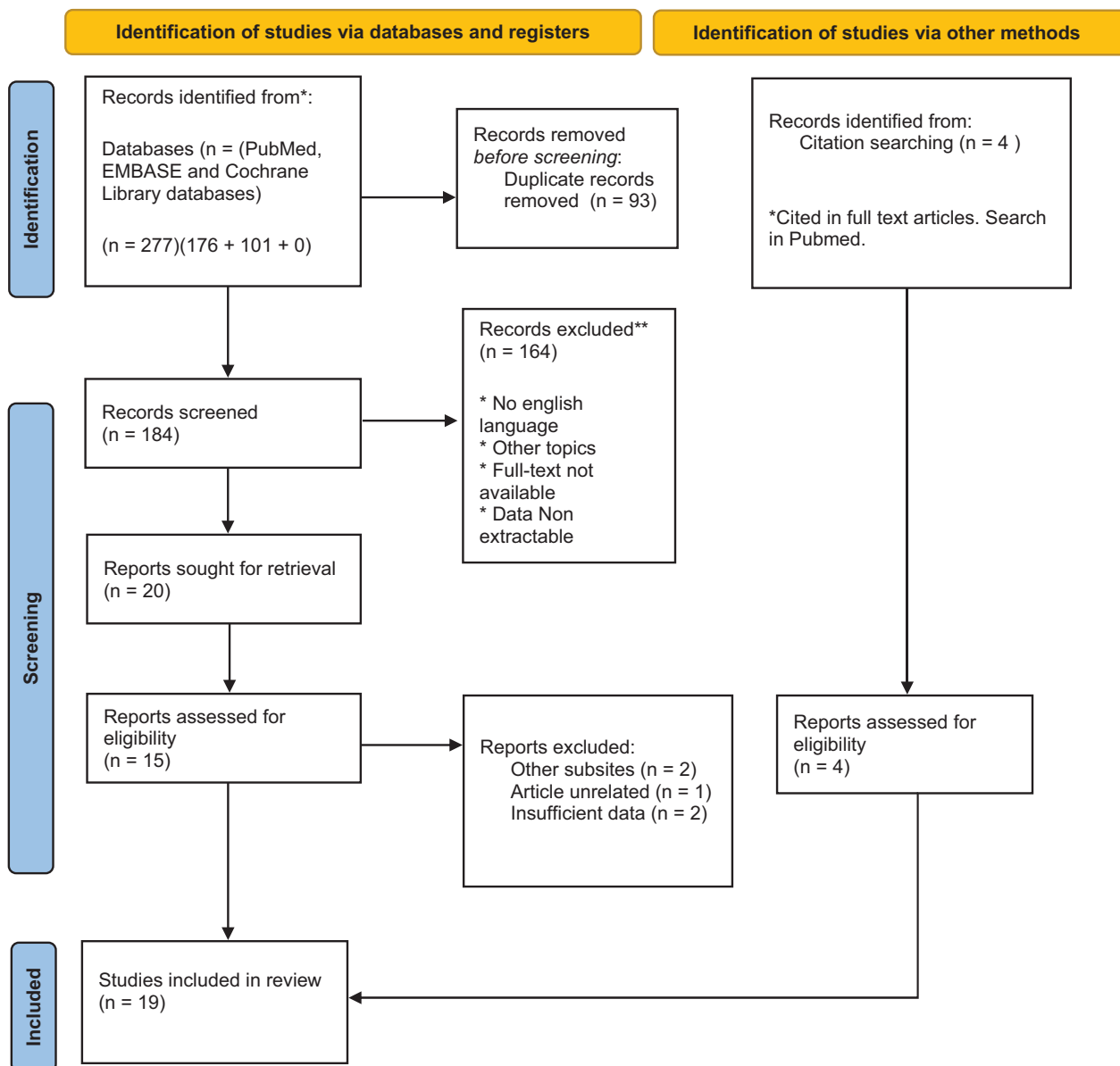


Figure 1. PRISMA 2020 Flow chart.

The articles that fully met the inclusion criteria were 15, identified through the search terms and 4 by reading the bibliography and literature on the subject.

These 192 articles were all case reports or small series conducted between 1983 and 2019, describing 27 cases of second primary squamous cell carcinoma arising in a skin flap.

Moreover, 3 additional cases were herein presented.

Primary lesion site was oral cavity in 19 cases, pharynx/hypopharynx in 9 cases, larynx in 2 cases. As regards the major site involved, the oral cavity, in 6 cases affects the buccal mucosa, in 6 the tongue, in 5 cases the floor of the mouth, 1 retromolar trigone and 1 hard palate. 17 (57%) patients were male and 13 (43%) females. The age of the patients at the time of the first surgical treatment and reconstruction was between 32 and 80 (mean, 55.6 years), while at time

Table 1. Summarizes the demographics and data of the included patients (13-32).

Author	Gender/Age at First treatment	Previous Risk factors	Site of primary lesion	Type of flap reconstruction	Previous Non-Surgical Treatment	Age at Second Primary	Interval (yr)	Follow-up*
1 Riaz, 1996	Male 48	Smoke	Buccal mucosa	Forehead pedicle flap	ChT	59	12	NED at 60 months
2 Deans, 1990	Male 37	Smoke	Hypopharynx	DPF	No	61	24	NED at 36 months
3 Valentini, 2016	Female 41	None	Tongue	RFFF	No	62	21	N/A
4 Cymerman, 2013	Male 49	Smoke and alcohol	Floor of the mouth	RFFF	RT	72	23	NED at 72 months
5 Foschini, 2010 <i>Case 1</i>	Female 61	Smoke	Retromolar trigone	FFF	N/A	63	4	DOD at 24 months
6 <i>Case 2</i>	Female 58	Smoke	Floor of the mouth	RFFF	No	62	4	NED at 12 months
7 <i>Case 3</i>	Male 52	Smoke	Tongue	RFFF	N/A	56	4	NED at 5 months
8 Sakamoto, 1998	Male 63	Smoke and alcohol	Hypopharynx	RFFF	ChT-RT	73	10	NED at 24 months
9 Monnier, 2008 <i>Case 1</i>	Male 58	Smoke and alcohol	Tonsil	RFFF	No	62	4	NED at 24 months
10 <i>Case 2</i>	Male 44	Smoke	Tonsil	DPF	RT	54	10	NED at 24 months
11 Amin, 2019	Male 50	N/A	Supraglottic larynx	PMMF	RT	62	12	NED at 24 months
12 Scott and Klaassen, 1992	Male 32	Smoke and alcohol	Floor of the mouth	Achromiotoric pedicle flap	RT	67	35	NED at 6 months
13 Iseli, 2002	Male 42	Smoke	Glottic larynx	DPF	RT	67	25	NED at 1,5 months
14 Chung-Wai Ho, 2011	Male 41	Smoke and alcohol	Tongue	PMMF	RT	53	12	NED at 36 months
15 Zemann, 2011	Female 32	Candida	Hard Palate	Pedicled jump flap	No	62	30	NED at 120 months

Author	Gender/Age at First treatment	Previous Risk factors	Site of primary lesion	Type of flap reconstruction	Previous Non-Surgical Treatment	Age at Second Primary	Interval (yr)	Follow-up*
16 Tokita, 2013 Case 1	Male 80	HPV, candida, smoke and alcohol	Floor of the mouth	RFFF	No	86	6	NED at 12 months
17 Case 2	Male 57	None	Tongue	PMMF	RT	59	7	N/A
18 Case 3	Female 64	N/A	Buccal mucosa	PMMF	N/A	72	8	N/A
19 Case 4	Female 66	None	Hypopharynx	DPF	No	74	8	N/A
20 Case 5	Female 72	None	Hypopharynx	Skin graft	RT	78	6	N/A
21 Case 6	Female 60	None	Hypopharynx	DPF	RT	76	16	N/A
22 Montgomery, 2015	Male 52	Smoke and alcohol	Floor of the mouth	PMMF	RT	60	8	NED at 36 months
23 Yamasaki, 2011	Male 70	Smoke and alcohol	Hypopharynx	RFFF	RT	75	5	N/A
24 Sado, 1994	Female 51	None	Buccal mucosa	Skin graft	RT	70	19	NED at 48 months
25 Terauchi, 2019	Female 62	None	Buccal mucosa	ALT	RT	66	4	NED at 24 months
26 Nasu, 2012	Male 75	Smoke and alcohol	Tongue	RFFF	N/A	91	16	N/A
27 Johnson, 1983	Female 61	N/A	Pharynx	DPF	RT	67	6	N/A
28 Current	Male 55	Smoke and alcohol Smoke	Tongue	Rectus abdominis flap	Yes	66	11	NED at 27 months
29 Current	Female 72	N/A	Buccal mucosa	TF	No	84	12	NED at 17 months
30 Current	Female 65		Buccal mucosa	TF	ChT-RT	71	6	DOD at 48 months

RFFF = Radial Forearm Free Flap; PMMF = Pectoralis Major Myocutaneous Flap; DPF = Deltpectoral Flap; FFF= Fibular Free Flap ALT = Anterolateral Thigh Flap; TP = Temporal Flap
 NED = no evidence of disease; DOD = died of disease

*Follow-Up = post second primary treatment

of recurrence between 53 and 91 years (means 65.6 years). The mean interval of onset of recurrence was 12.3 years with a range of 4 to 35 years.

Possible risk factors associated with the onset of the second primary carcinoma were assessed. Data on risk factors were available in 26/30 cases. Regarding smoking and drinking, 18/26 patients were frequent users of tobacco or alcohol before primary treatment. Information on neo-adjuvant or adjuvant treatment was available for 26/30 patients: 16/26 patients received adjuvant radiotherapy, 1/26 received concomitant chemo-radiotherapy, 1/26 received chemotherapy alone.

The main type of flap implemented for head and neck reconstruction was the radial forearm free flap in 9 cases. The other flaps were: 6 deltopectoral flaps, 5 pectoralis major myocutaneous flaps, 1 rectus abdominis, 1 forehead pedicle flap, 1 acromiothoracic pedicled flap, 1 pedicle jump abdominal flap, 1 osteocutaneous fibula free flap, 2 skin grafts, 1 anterolateral thigh flap and 2 temporal flaps.

All authors reported recurrent tumors were localized in the center of the transposed flap, with clear margins.

Details on the type of treatment of the secondary neoplasm were available in 26/30 cases. All were treated with surgical resection; 10/26 had a reconstruction with a new flap, 3/26 had an adjuvant RT, while 2/26 underwent treatment with ChT-RT. Only 2/26 had a concomitant neck dissection. However, the authors do not report whether elective or curative. Local resection by CO₂ laser was the treatment in 2/26 cases.

Follow-up data after the treatment of the recurrent tumor on the flap were reported in 21/30 cases. DFS ranged from 1.5 months to 120 months (mean 31 months), 19/21 patients were alive and without evidence of disease (NED) at the time of follow-up, 2/21 of cases died during the follow-up (DOD between 24 and 48 months).

Case report 1

A healthy 55 years-old male with smoking habit came for the first time on visit in October 2009, due to a locally advanced SCC of the tongue classified as

cT3N2cM0 Stage IVA, according to the 8th edition of AJCC TNM.

After Multidisciplinary Team (MDT) evaluation, the patient underwent to a total glossectomy type IVa, with en-bloc bilateral selective neck dissection I-IV (33); the tumor was removed with a “pull-through” approach. Due to the defect size, a reconstruction was carried out by a free rectus abdominis myocutaneous free flap, based on the deep inferior epigastric artery (DIEA). Histological examination of the surgical specimen disclosed a SCC (G2) staged as pT-3pN2cR0 (AJCC 8th edition); adjuvant radiotherapy was performed. The patient’s postoperative course was uneventful. Since 2009, the patient stopped smoking and there was no evidence of recurrent disease during clinical and radiological follow up.

After eleven disease-free years, in June 2020, the patient referred to hospital complaining of a persistent white flat patch growing on the surface of the previously transplanted flap (Figure 2A). The patient denied any complaints of local bleeding or pain. At physical examination, it appeared as a painless 2 cm focal mass with increased consistency on palpation and firmly attached on a deep plane. The patient underwent MRI, which demonstrated a solid exophytic lesion (diameter 22 mm; thickness 9 mm) arising from the flap surface, isointense on T1 images, hyperintense on T2-weighted sequences and positive for radiological signs of malignancy (Figure 2B). No suspicious lymph nodes were found. PET-CT confirmed a solitary lesion affecting the neo-tongue, with increased FDG uptake (SUV max 6.1). Biopsy revealed a SCC (G1).

Neoplasm was staged as rycT2N0M0 (AJCC 8th edition), and a surgical treatment was planned. The aim of surgery was to remove the lesion with curative intent (Figure 2C). No complications occurred after surgery. Postoperative histology revealed a completely excised well-differentiated SCC (Figure 2D). Based on clinic history, the MDT of our institute decided to perform a clinical and radiological follow up. At the last check in September 2022, the patient was NED.

Case report 2

A 72 years-old female without smoking history, came for the first time to the clinic in 2009, due to a

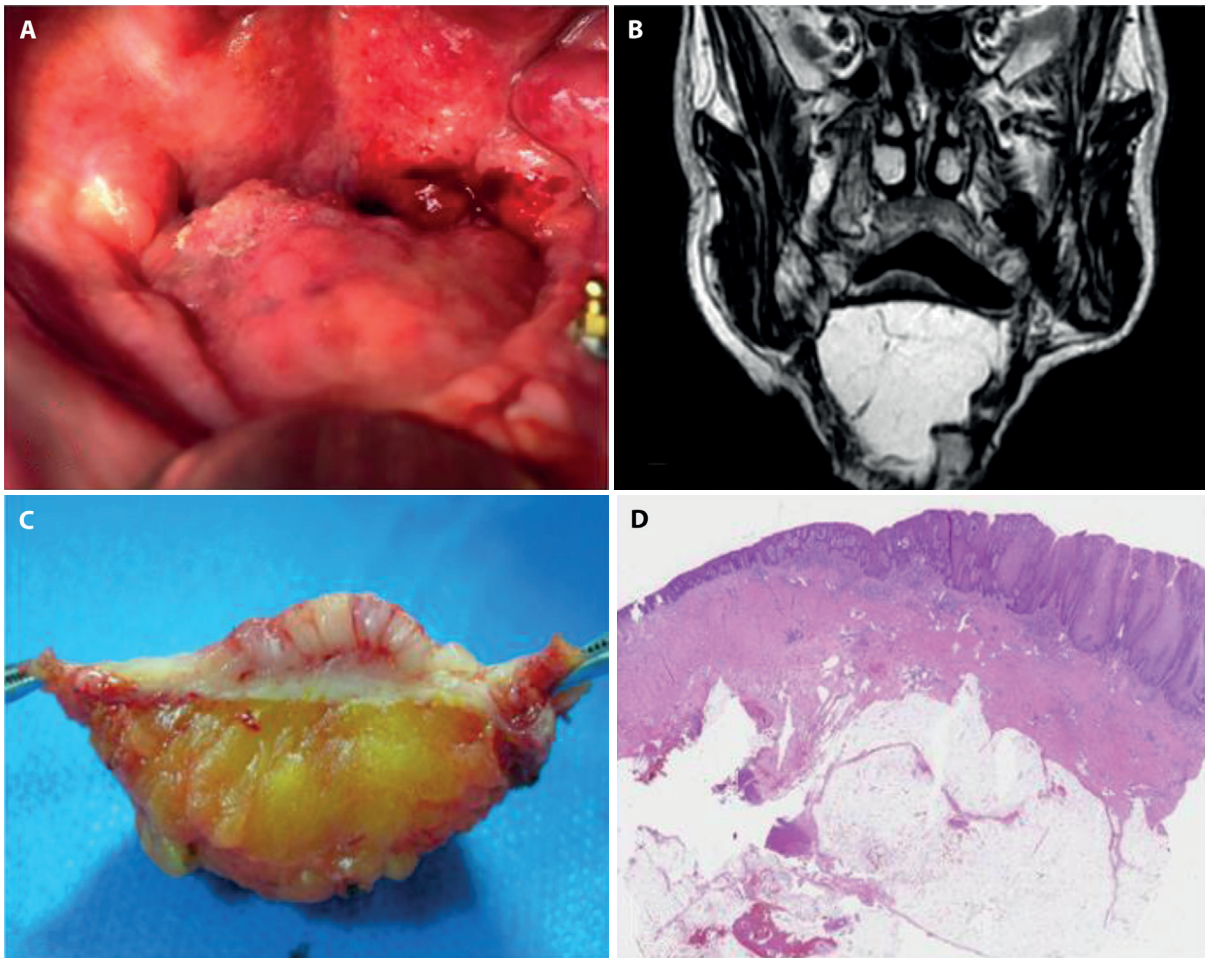


Figure 2. Clinical Case. (A) oral cavity clinical aspect; (B) MRI T2 weighted coronal view. (C) macroscopic aspect of the specimen (the “rising sun” aspect); (D) hematoxylin and eosin staining.

SCC of the right maxilla classified as cT2 N0 M0. After MDT evaluation, the patient underwent surgery, a hemi-maxillectomy with temporal flap reconstruction (34). Histological examination of the surgical specimen disclosed a SCC (G2) staged as pT2cN0 R0; no adjuvant radiotherapy was performed. The patient’s postoperative course was uneventful, fed by mouth independently. Since 2009, the patient remained a non-smoker and there was no evidence of recurrent disease during the follow up.

After eleven years, in June 2021, the patient came to the same clinic complaining of a persistent red patch growing on the surface of the previously rotated flap. At physical examination, it appeared as a painless

1x1 cm exophytic mass with increased consistency on palpation and firmly attached on a deep plane. The patient underwent a CT scan, which demonstrated a solid exophytic lesion (diameter 12 mm; thickness 5 mm) arising from the flap surface. No suspicious lymph nodes were found. PET-CT confirmed a solitary lesion affecting the oral cavity. No distant metastasis was detected. Biopsy revealed a SCC (G1), and a surgical treatment was planned. Postoperative histology revealed a completely excised well-differentiated SCC. Based on clinic history, the MDT of the institute decided to perform a clinical and radiological follow up. At the last check in November 2022, the patient was NED.

Case report 3

A 65-years-old female came to our unit in 2013 for a G2 pT4a N0 squamous cell carcinoma of the mandibular alveolar ridge that was treated with resection and fibula reconstruction followed by concurrent chemoradiotherapy. In February 2016 she had a second SCC in the maxilla that was treated with hemi maxillectomy and reconstruction with temporal flap (34,35).

In March 2019 she came to the same clinic for the persistence of a red patch on the surface of the temporal flap, which a subsequent biopsy showed to be SCC. The lesion was removed but in the following months she had progression of disease and, despite immunotherapy and palliative debulking surgery, died in July 2020.

Discussion

Malignant transformation of the flap tissues used to reconstruct post-oncological defects is a rare event. Despite its infrequency, the recurrence on the reconstructive flap, is one of the possible complications related to reconstructive surgery. The first reported case was presented by Johnson et al. (32) in 1983 in a patient who had undergone pharyngeal resection and reconstruction with transposed deltopectoral flap. In this case, the authors described multiple verrucous tumors developed in the neo-pharynx six years after previous treatment. To date, according to our review, only 27 cases have been reported and it is difficult to answer why new cancers arise on the transplanted flap. Analysis of the results is complicated because many studies present heterogeneous types of flaps and sites.

When the phenomenon of a rapid onset cancerization occurs, four causes have been proposed: 1) carcinoma implantation on the flap during demolition time; 2) lymphatic/hematic dissemination along the neurovascular pedicle of the flap; 3) incomplete resection of primary tumor; 4) a second primary tumor that already exists in the flap before the flap is raised (17,22).

A late onset instead poses the dilemma: the new tumor arises from the skin of the flap exposed to oral stimuli or derives from a colonization by adjacent mucosa?

The first steps to define the new neoplasm closely related to the transposed flap is to define some

peculiarities: 1) carcinoma occurred in the center of the flap far from the skin-mucosa junction, not involving the adjacent oral mucosa; 2) absence of tumor residues after the first surgical exeresis (R0); 3) at least one radiological or clinical check without evidence of neoplasm; 4) absence of other skin malignancies in other parts of the body (13-17, 32, 36).

In patients with a strong history of cutaneous squamous cell carcinoma, a careful examination of the skin is essential.¹⁰ Therefore, during the planning phase, it is always preferable to choose the volar surfaces of the limbs or to take the tissues from the areas less exposed to sunlight or with fewer skin annexes. The first hypothesis of increased risk of neoplastic transformation is based on the exposure of the epidermis to new environmental conditions (32-34).

Historically, the most common risk factors implicated in carcinogenesis are smoking, alcohol consumption, poor hygiene, and chronic trauma, as well as primary cancer. In our cases described above, these risk factors had a low impact on the development of second primary: only 3/27 and 2/27 respectively patients used to smoke and drink from the time of first reconstruction to the time of recurrence. Radiation therapy performed after first surgery was considered. Some authors also suggest anemia (25), candida or HPV infection (21,22) although such exposures, at least as a single trigger, are unlikely.

Furthermore, prolonged exposition to new stressors stimuli, such as saliva, oral flora, a new pH or carcinogenic substances, to which skin is not normally exposed (10), could be considered the "primum movens" of chronic inflammation and adaptive process which are triggers for neoplastic changes. The skin of flap undergoes malignant transformation because of the development of genetically altered keratinocytes that progressively gain further mutations, most probably through the constant and prolonged exposure to oral cavity stressors. The skin flap begins to undergo mucosal-like changes caused by inflammatory facts (37,38). Common histological changes defined as "mucosalization" include loss of keratinization, partial loss of epidermal appendages with low presence of eccrine ducts, sweat glands, erector pillar muscle and hair follicles and progressive desquamation (10). This slow metaplastic transformation that mimics the histological features

of the oral mucosa is like the development of esophageal adenocarcinoma from Barrett's esophagus. However, this frequent macroscopically and microscopically transformation, although plausible, would not alone justify the low incidence of a secondary tumor.

A second mechanism could involve the migration and subsequent replacement of flap cutaneous cells with neighboring oral mucosa cells. This hypothesis would fit with the well-known risk of second primary or synchronous/metachronous SCC development in patients with previous HNSCC (17). Those cells would come from mucosal areas adjacent to the flap that have been chronically exposed to common carcinogens. These cells already possess all the genetic alterations that are predisposing to cancer transformation (11). Starting from a field of genetically altered cells in the oral mucosa, the spread of the clonal cell population to the cutaneous flap could be stimulated by cytokines produced by inflammation of the transposed skin.

In 1953, Slaughter et al. defined this phenomenon by introducing the concept of "field cancerization" (37) as a biological process in which large areas of mucosal cells are affected by carcinogenic alterations. This pathogenetic pathway is related to multiple primary HNSCC arising in different areas in a single patient. This thesis was supported by the work of Foschini et al. in 2010 (17). They evaluated the relationship between primary cancer (oral mucosa) and the secondary neoplastic changes affecting the flap by screening the mitochondrial (mt) DNA D-loop region. Clonal assessment by mtDNA analysis is based on the concept that mitochondrial DNA is presented in high copy numbers in each cell and these copies are identical at birth. Neoplastic cells preserve the high copy number but show a high frequency of mutations in the mtDNA, especially in the D-loop region. Therefore, these acquired mutations may be a reliable marker to assess clonality. In all three cases presented by Foschini, the neoplastic lesions arise in the skin graft 4 years after primary resection, showed a clonal and genetic relationship with the previous HNSCC. Primary SCC and tumors arising in transposed skin could develop from a common genetically altered field. As it is well known, tumor cells can spread through the epidermis, as seen in "Borst-Jadasson phenomenon" (39). From a patch of genetically altered cells, through clonal expansion in a lateral

direction, a field lesion gradually develops and grows, taking over the normal epithelium (40). Within this background it is possible that after a radical resection of the tumor, the genetically altered field is still present in the patient. Therefore, a cellular expansion from the adjacent mucosa can spread over the tissue used to reconstruct the defect and could be the cause of a new cancer.

Regarding the treatment of the second primary tumor arising in a flap, surgical resection was used in all reported cases. The extent of resection would be decided based on the size of the tumor. Some authors have reported endoscopic removal for some pharyngeal lesions which were usually well circumscribed, limited and with clear margins (10,11). In all the cases included in the present systematic review, local recurrence was not accompanied by lymph node metastases, probably because the lymphatic network associated with the flap is mild or underdeveloped.

Considering the indication of the follow-up, the standard of care at 5 years in these cases does not seem to be respected. In fact, if the risk of neoplastic transformation is related to the concept of field cancerization, it lasts for life, eliminating the most common short-term control. Likewise, it makes us understand how high the risk is in a patient with previous head and neck cancer. In our review, the case of Scott and Klaassen (20) was the most striking, with a cancer recurrence on the flap after 35 years (14,21,28).

Conclusion

The late onset of a second tumor on the surface of the flap used for head and neck reconstruction is rarely described in literature, as highlighted by the present systematic review. The possible cause could be colonization of the skin from the adjacent mucosa, or a metaplasia of skin paddle caused by chronic inflammation from the oral area. However, the widespread diffusion of this type of reconstructive surgery and the increase in the overall survival of patients could lead to an increase in the finding of this clinical entity soon. A joint management of these rare cases would therefore be useful, to create a single international database, with genetic studies on histological specimens to better define the pathophysiology of these second primary tumors.

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Ethic Committee: IRCCS Regina Elena National Cancer Institute; The Institutional Review Board and the Ethics Committee of our institution approved the study. (Protocol N° RS 1284/19 2294 IFO, 19/11/2019). The study was carried out in accordance with the principles of the Helsinki Declaration, and an informed consent was obtained from all participants before including them in the study.

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