Oral verrucous carcinoma: From multifactorial etiology to diverse treatment regimens (Review)

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Abstract. Oral verrucous carcinoma (OVC) is a verrucous variant of oral squamous cell carcinoma (OSCC), which accounts for 2-12% of all oral carcinomas with a 5-year survival rate of only approximately 50%. Enormous effort has been dedicated to this cancer, and the past decades have witnessed significant advances in relevant diagnostic and therapeutic approaches. Currently, there exist three challenges from primary sub-fields of research and clinical practice of the cancer, namely multifactorial etiology, complex molecular mechanism, and deficient treatment. This study reviews the existing literature on the cancer, encompassing its etiology, clinical manifestations and pathology, molecular mechanism, diagnosis and differential diagnosis, and treatment. For improved treatment of OVC, multifactorial etiology analysis, incorporation of effective biomarkers for mechanism illustration, and integration of multidisciplinary modalities are expounded, in an attempt to resolve the challenges and to provide a useful guide for future research in the field.

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1. Introduction

Head and neck malignant carcinoma is the world's fifth most common cancer with incidence exceeding half a million annually (1,2). Oral squamous cell carcinoma (OSCC) represents 95% of head and neck malignant carcinoma (3). As a low-grade and well-differentiated verrucous variant of OSCC, oral verrucous carcinoma (OVC) accounts for 2-12% of all oral carcinomas with a 5-year survival rate of only approximately 50%, and is receiving increasing attention (4).

OVC is a malignant tumor characterized by slow exophytic growth, usually presenting cauliflower-like and pebbly mamillated warty lesions (5). It shows a typical 'pushing border' (light and electron) microscopic feature with a local invasive pattern and rare regional and distant metastases (6). The history of OVC can be traced back to as early as 1948 when it was first described by Lauren V. Ackermann (also referred to as 'Ackermann's tumor' or 'verrucous carcinoma of Ackermann') (7). Its pathology was not studied independently until mid-1980s (8). Although ensuing research on diagnosis and treatment of OVC was largely triggered at the beginning of this century (9), the research progress is still far from satisfactory. For instance, the differentiation of OVC from OSCC is important regarding their different molecular mechanisms and prognoses. However, it is currently difficult to differentiate them by simply observing clinical and pathological features because OVC has similar biological behavior to OSCC, including tendency to local invasion, insidious lymph node metastasis and occurrence of malignant lesions (10). These similarities usually cause clinical misdiagnosis and mistreatment (11). Undoubtedly, it is critical to seek reliable molecular markers of OVC to resolve such challenges.

Over the past several decades, there have been numerous studies concerning precise diagnosis and effective treatment of OVC (12-14). The authors' research group has been investigating this type of cancer since 1992 (14). As a timely and detailed review about OVC is still lacking at present, this paper aims to deliver an overview of OVC with emphasis on recent research developments. It covers almost all subfields of OVC, including its etiology, clinical manifestations and pathology, molecular mechanism, diagnosis and differential diagnosis, and treatments, followed by a detailed discussion on main challenges confronted in the field and promising measures for resolving them. This review is expected to offer a useful guide for research development and clinical practice of OVC.

2. Etiology

OVC has complex etiology which depends on a variety of factors (15,16). There exist strong associations between OVC and alcohol consumption, smoking, areca nut chewing and oral microbiota (17-21). These factors may act individually or synergistically in oral carcinogenesis. OVC also has a relationship with undesirable prosthesis, earlier injuries and scars, and chronic inflammation. Moreover, it may occur as a result of deterioration of premalignant lesions, including oral verrucous leukoplakia, oral lichen planus, oral submucous fibrosis (OSF), odontogenic keratocyst (22).

Alcohol and smoking related carcinogens are two main well-established risk factors for oral cancers including OVC (18). Excessive alcohol consumption can increase incidence of OVC because alcohol may act as a solvent that promotes movement of carcinogens via oral cellular membranes, as the consumption has the capability to change intracellular metabolism of the epithelial cells, causing impairment of cellular function (e.g., reduced mitochondrial function and enhanced DNA alkylation) in the initial phase of oral carcinogenesis (23,24). Similar to alcohol consumption, smoking is another potential factor that may induce OVC (19). In fact, there exist over 300 carcinogens, i.e., aromatic hydrocarbon benz-pyrene and the tobacco specific nitrosamines (TSNs), in tobacco smoke or its water-soluble components that will leach into saliva. These carcinogens interfere with DNA replication by generating DNA adducts, primarily 06 methyl Guanine, damaging replicating cells of the immune response (25,26).

Areca nut extracts contain various carcinogens, such as N-nitroso amines. These carcinogens cause DNA single-strand breaks and mutations, facilitating tumor formation and growth. Furthermore, arecoline in areca nut extracts has genetic toxicity and teratogenicity on a variety of cells, playing an important role in oral carcinogenesis (20).

Oral microbiota may present a non-ignorable role in oral carcinogenesis through their impacts on local metabolism of alcohol and smoking-related carcinogens. It was found that five bacterial phyla, including Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria, and Fusobacteria, are associated with oral cancer (21). They activate alcohol and smoking related carcinogens locally. Oral bacteria can convert ethanol to acetaldehyde, an *in vitro* and *in vivo* genotoxin, exposing the oral and gastrointestinal tract directly to carcinogenic acetaldehyde after alcohol use (27). The bacteria may function in enhanced activation of carcinogenic nitrosamines from tobacco smoking because *in vitro* common oral microbes activate nitrosodiethylamine (NDEA, a tobacco smoke nitrosamine) to its carcinogenic (IARC, Group 2A) adduct-forming hydroxylated product (28).

Among other potential causes of OVC, of interest is the controversial and inconclusive pathogenic role of human papillomavirus (HPV) (29-31). Some researchers considered that HPV was a possible pathogeny of OVC (32-35). Noble-Topham *et al* reported the detection of HPV DNA in 12 (48%) of 25 OVC patients. Specifically, HPV 6b/11 DNA, HPV 16 DNA, HPV 18 DNA, and HPV 16 DNA plus HPV 18 DNA were detected in one (4%), one (4%), nine (36%), and one (4%) cases, respectively. The detection of HPV 18 DNA in 40% of OVCs reveals an association between HPV and OVC although the potential etiologic and prognostic significance of HPV in OVC deserves further exploration (34). On the contrary, other scholars argued that the role of HPV might be occasional as there was no verified correlation between OVC and HPV in their work (36-38). For instance, de Spíndula-Filho *et al* examined the role of HPV in cellular proliferation in OVC based on quantitative analyses of 39 OSCCs, 8 OVCs and 9 normal mucosa samples. No correlation between HPV and OVC was established in this study because all samples tested were negative for HPV (36). Evidently, there is conflicting research regarding the role of HPV. Further studies on determination of appropriate sample size and use of highly sensitive molecular biology techniques (e.g., polymerase chain reaction) are expected to produce new information in order to gain further understanding on the topic.

3. Clinical manifestations and pathology

Clinical manifestations. OVC often occurs in buccal mucosa, tongue, lip, gingiva, alveolar ridge and mouth floor (39), exhibiting a predilection for elderly males, especially those over the age of sixty (40,41). Its predominant clinical manifestations are exophytic mass and papillary appearance. Due to its slow growth which contributes to long medical history (up to several years) and to the local aggression that leads to rare regional or distant metastasis, OVC has a relatively good prognosis (42). According to clinical manifestations and prognosis, Tang *et al* first divided OVC into three types: exogenic type, cystoid type, and infiltrative type (14,43). The exogenic type of OVC is characterized by exophytic growth, cauliflower-like warty lesion and slow tumor growth. However, the other two types of OVC grow rapidly, forming bean dreg-like white dry keratosis, accompanying poor prognosis compared to the exogenic type of OVC.

Pathology

Pathological features in optical microscopy. OVC epithelial cells are well differentiated with weak cell atypia. In optical microscopy, the squamous epithelium of OVC shows highly proliferative, papillary appearance and excess aceratosis. The highly proliferative epithelial pegs show swelling and blunt ends in the shape of liquid droplets. All epithelial pegs are infiltrated to the connective tissue in the same depth, forming pushing borders (44). Many lymphocytes and plasma cells are also infiltrated into the connective tissue in which cancer cells may degenerate or become necrosis or be swallowed by phagocytic cells, resulting in carcinoma cell destruction. Between squamous epithelium and connective tissue, the majority of components of epithelial basement membrane (BM) of OVC remains integrated.

Pathological features in electron microscopy. The pathological features of OVC can be reflected by its stereology in the electron microscopy. The stereology of OVC observed under a transmission electron microscope usually shows thick and intact basement membrane of the cancer with obviously thicker substrate than the normal cells in local areas. With increased inflammatory cells (e.g., lymphocytes and plasma cells), the basement membrane is disrupted in some cases. The ultrastructural pathological features of the exogenic type of OVC in the electron microscopy are well differentiated

epithelial cells with keratocyst, large and regular nucleus with obvious nucleolus, no pseudopodia on the membrane and no cytoplasmic vacuolation. However, for the cystoid type and infiltrative type of OVC, they have poorly-differentiated epithelial cell with obvious heteromorphism, large, irregular and lobulated nucleus, clear pseudopodia on the membrane and obvious cytoplasmic vacuolation (43).

4. Molecular mechanisms

The development of OVC is a multistep process involving the accumulation of multiple genetic alterations modulated by genetic predisposition and environmental influences such as tobacco use, alcohol consumption, microbial infections, and chronic inflammation. All of these factors can result in a wide range of genetic alterations and epigenetic modifications that can be detected in a range of molecular studies. Exploration of molecular mechanism is important for reducing the morbidity and mortality and for improving long-term survival rate of OVC. It mainly focuses on seeking definitive and effective molecular biomarkers which are widely used to identify the evolution of dysplasia lesions to cancer. Up to now, a large number of studies have been carried out to reveal the molecular mechanism of OVC from perspectives of genetics and epigenetics (45,46).

Genetics. The molecular mechanism of OVC is closely associated with its genetics. Genetic alterations are involved in polymorphism, point mutation, deletion, and other alterations. Previous investigation mainly focused on gene profiling (47,48).

As a special type of OSCC, OVC has its own specific clinical manifestations and pathological features. Further understanding of the molecular mechanisms of OVC requires gene expression differentiation between OVC and OSCC. In fact, many genes express differentially between OVC and OSCC, and some of them are closely related to cancer progression of OVC. To identify key genes that regulate and control the biological behavior of OVC, Wang *et al* differentiated gene expression profiles between OVC and OSCC (49). The cancer tissues and the matched normal oral mucosa tissues from 5 OVC patients and 6 OSCC patients were analyzed using the Affymetrix HG-U133 Plus 2.0. The function and biological pathways of gene were profiled with the Ingenuity Systems IPA software. It was found that 167 genes expressed differentially between OVC and OSCC. Among them, 108 genes were upregulation and 59 genes were downregulation. Compared with their matched normal mucosa tissues, 39 common genes were expressed differentially (22 upregulation, 17 downregulation) between OVC and OSCC. Some of these 39 genes were related to the networking functions including cellular movement, genetic disorder, inflammatory response and immune cell trafficking. Between OVC and OSCC, 8 of the 39 genes, namely ADAMTS12 (a disintegrin and metalloproteinase with thrombospondin motifs), COL4A1 (α1 type IV collagen), COL4A2 (α2 type IV collagen), INHBA (inhibin, βA), MMP1 (matrix metalloproteinase 1), SERPINE1 (serpin peptidase inhibitor, clade E, member 1), TGFBI (transforming growth factor, β-induced), and HLF (human lactoferrin), were expressed differentially and considered effective biomarkers in differentiating OVC and OSCC.

Epigenetics. The cellular and physiological trait variations of OVC may not involve changes in DNA sequence. Carcinogenesis is a multistep process modulated by a number of epigenetics modifications (50). Prior research devoted much effort to identification of molecular mechanism of OVC from epigenetics perspective according to number and percentages of molecules in each functional category, including tumor growth (cell cycle acceleration and proliferation), tumor suppression (antitumor defense and apoptosis), angiogenesis and tumor invasion and metastasis. The corresponding biomarkers for diagnosis of OVC are summarized in Table I.

Tumor growth (cell cycle acceleration and proliferation) markers. Cell cycle refers to eukaryotic cells with continued division from the end of mitotic cycle growing to the end of next mitotic cycle. Cancer cells often have an abnormal mitotic cycle. Cell proliferation, differentiation, senescence and apoptosis are closely related to the cell cycle regulatory machinery (51). The markers associated with the dysregulation of the cell cycle machinery usually indicate cancer progression. As shown in Table I, the most intensively investigated tumor growth markers for OVC diagnosis are cyclins including cyclin-B1 (36) and cyclin-D1 (52), proliferating cell nuclear antigen (PCNA) (53), Ki67 (54), αB-crystallin (55), S-phase kinase-interacting protein 2 (SKp2) (56), mutant p53 (57) and p63 (58). Most of these markers express in a decreasing order from OSCC through OVC to normal mucosal tissue. Note that the expression levels of some tumor growth markers, (e.g., Cyclin-D1 and PCNA in Table I) remain controversial in well-differentiated OSCC and a part of OVC with strong tendency to local invasion.

Tumor suppressor markers (antitumor defense and apoptosis). During the cell cycle, cyclins control the progression of cancer cells by activating cyclin-dependent kinase (CDK). The progression of OVC may be restrained by a series of CDK inhibitors, e.g., INK4 (Inhibitor of CDK4, including p15, p16, p18 and p19) and Kip (Kinase inhibition protein, such as p21, p27, and p57) (59,60). Other tumor suppression markers include proteins phosphatase and tensin homologue (PTEN) (61), quinone oxidoreductase 1 (NQO1), superoxide dismutase (SOD) (62), and inducible nitric oxide synthase (iNOS) (63). As presented in Table I, the majority of the markers have a declining expression order from oral premalignant lesions, such as dysplastic epithelium, OVH, OSF and oral epithelial dysplasia (OED), through OVC to OSCC. It is worth noting that the typical tumor suppressor protein, wild-type p53, is absent in Table I because its role as a marker for OVC is still unconfirmed.

Angiogenesis markers. Angiogenesis is crucial in the occurrence, development and prognosis of tumor. Angiogenesis markers may have the potential for diagnosis and prevention of carcinomas (64). The markers of angiogenesis may be used for the prognosis and treatment of OVC. As shown in Table I, the vascular endothelial growth factor (VEGF) family is thought to be one of the strongest angiogenesis simulators that induce blood vessel growth. It also induces formation of vascular cavity and increases vascular permeability. Hence, VEGF is regarded as a marker of metabolism and transformation of OVC (62).

Table I. Potential markers for OVC (in previous studies).

Classification	Marker	Function	Expression in OVC compared to normal tissues (NT) or OSCC	Effects	Refs.
Tumor growth	Cyclin B1	Regulating cell cycle (G2-M phase)	OSCC>OVC>NT	Differentiation of OVC from OSCC and prognosis of OVC	36
	Cyclin-D1	Regulating cell cycle (G1-S phase)	Poorly-differentiated OSCC>moderately-differentiated OSCC>OVC>well-differentiated OSCC	Histological grading of OSCC and differentiation of OVC from OSCC	52
	PCNA	Regulating cell cycle (late G1-S phase)	Well-differentiated OSCC>OVC>OVH>NT	Prognosis of OVC	53
	Ki67	Regulating cell cycle (G1-S-G2 phase)	OSCC>OVC	Prognosis of OVC within which OSCC arises	54
	αB-crystallin	Anti-apoptosis	OSCC>OVC>NT	Carcinogenesis by controlling activation of caspase-3	55
	SKp2	Regulating cell cycle (G1 phase)	OVC, OSCC>NT	Prognosis of OVC	56
	Mutant p53	Contributing to oncogenesis instead of suppressing tumor	OSCC>OVC>NT	Differentiation of OVC from OSCC and histological grading of OSCC at invasive front regions	57
	p63	Maintaining epithelial cell regeneration and homeostasis	OSCC>OVC	Diagnosis of OVC	58
Tumor suppression	p16	Preventing cells from going through G1-S phase, inhibiting DNA synthesis and cell proliferation	OVC>OSCC; OVC>dysplastic epithelium	Pathogenesis of OVC with overexpression of p16 caused by inactivation of pRb	59
	p21	Mediating growth arrest (G1 and S phases) and inhibiting DNA synthesis	OVH>OVC	Pathogenesis of OVC	60
	p27	Stopping/reducing the cell division cycle (G1 phase)	Dysplastic lesions>OVC>OSCC	Pathogenesis of OVC	59
	PTEN	Restraining cell growth in the G1 phase, apoptosis and impeding cell invasion and metastasis	NT>OVC, OSCC	Diagnosis of OVC	61
	NQO1 and SOD	Antioxidation, anti-aging, and detoxification	OVC>OSCC	Differentiation of OVC from OSCC	62
	iNOS	Overproduction of iNOS suppressing tumor growth and inducing apoptosis	OVH=OSF>OVC	(Pre)malignant carcinogenesis and prognosis of OVC	63

Table I. Continued.

Classification	Marker	Function	Expression in OVC compared to normal tissues (NT) or OSCC	Effects	Refs.
Angiogenesis	VEGF	Inducing blood vessel growth and formation of vascular cavity	OSCC>OVC	Differentiation of OVC from OSCC	62
Tumor invasion and metastasis	MMPs	Degrading extracellular matrix and basement membrane	Absence of MMP-7, -9 and -12 in OVC rather than OSCC	Differentiation, diagnosis and prognosis of OVC	71
			MMP-2, MMP-9: high-grade OSCC>low-grade OSCC>OVC>NT	Differentiation of OVC and OSCC and histological grading of OSCC at invasive front regions	57
			MMP-10: OSCC>OVC>NT	Differentiation of OVC and OSCC at invasive front regions	72
	Basement membrane (BM) proteins	A supporting pad for epithelial cells, connecting epithelial tissues and connective tissues	Laminin: OED>OVC>OSCC; collagen IV: OVC>OED; discontinuities of laminin, collagen IV and fibronectin: OED>OVC	Tumor invasion indicated by BM loss. Differentiation of OVC from OSCC and OED	73
	Moesin	Cross-linkers affecting cell-cell recognition and signaling and cell movement	Well-differentiated OSCC>OED>OVC> moderately-differentiated OSCC>poorly-differentiated OSCC	Differentiation of OVC from OED and OSCC	74
	Laminin-332 γ2	A component of BM associated with cell migration and tumor invasion	Well-differentiated OSCC>OVC	Differentiation of OVC from well-differentiated OSCC	75

Tumor invasion and metastasis markers. Tumor cells break through the extracellular matrix and basement membrane, which is an important step during the process of tumor invasion and metastasis (65). Many matrix metalloproteinases (MMPs) play significant roles in this process, including MMP-1, -2, -7, -9, -10, -12, -13, -14, -19, and -26 (66-68). Moreover, basement membrane, composed of laminin, collagen IV and fibronectin (69), is a continuous, insoluble but flexible structure located between the basal surface of epithelium and connective tissue. As a selective barrier for molecules, basement membrane is closely related to cell differentiation, cell migration, and tumorigenesis (70). Table I shows different expression levels of tumor invasion and metastatic potential markers (71-75) for OVC.

5. Diagnosis and differential diagnosis

Diagnosis. The diagnosis of OVC includes two aspects: clinical and pathological diagnosis. In the clinical aspect, OVC usually has a characteristic exophytic mass, cauliflower-like warty lesion and slow growth. On the pathological examination, the most important and typical pathological features of OVC are infiltration of all rete pegs to the connective tissue in the same depth which forms pushing borders. These features can be used to diagnose some OVC cases with acceptable accuracy. However, for accurate diagnosis, multiple factors except for clinical and pathological features should be considered to eliminate the influence of other lesions on discrimination, such as OSCC within hybrid VC. First, as pathological diagnosis is subjective, different explanations may occur for the same phenomenon. Second, collection of remarkable characteristic CT and MRI images of OVC may substantially improve the diagnosis. Third, reliable genes and proteins may be sought as diagnostic markers for OVC. Lastly, the medical history and clinical manifestations can serve as good references for the diagnosis.

Differential diagnosis. Although much effort has been spent on differential diagnosis of OVC, gold diagnosis standards or specific diagnostic markers are still lacking. The main reasons are as follows: First, OVC is similar to many diseases in clinical and pathological aspects. Different OVC cases may

show different biological behaviors. Second, for the same OVC, it may be diagnosed differently when pathological examination is performed on different sites. Third, hybrid verrucous carcinoma, composed of OVC and differently-differentiated OSCC, may exist. This type of carcinoma has more aggressive invasion nature with incidence rate up to 20% (76). Obviously, it is crucial to make a differential diagnosis between OVC and other similar diseases for improving treatment and prognosis.

OVC and oral verrucous hyperplasia (OVH). OVC and OVH are two distinctive oral verrucous lesions in the clinicopathology in spite of their similar morphologies in the clinical and histopathological aspects (77,78). From the clinical aspect, both of them have a thick, extensive, white plaque, or exophytic verrucous appearance. The most common sites for the two lesions are buccal mucosa, tongue and lip. However, to differentiate them effectively, some histopathological features may be used because OVC has the explicit 'pushing broader' feature with destructive extrapolation edges at the junction of lower connective tissues, whereas OVH does not show invasion of the hyperplastic epithelium into the lamina propria compared with adjacent normal mucosal epithelium. Further differentiation can also be achieved with the assistance of biomarkers. For instance, CD34, α-smooth muscle actin and HuR protein have the capability to diagnose OVC and OVH (79,80).

OVC and oral squamous papilloma (OSP). Oral squamous papilloma (OSP) shares similar morphology to OVC. OSP and OVC are often clinically present as exophytic, cauliflower and papillary forms. From the histopathological point of view, it is possible to differentiate OSP from OVC. For OVC, all rete pegs of the epithelium tend to project into the underlying connective tissue, at more or less the same level, forming 'pushing border.' OSP often presents as many long, thin and finger-like projections which extend above the mucosal surface. Each finger-like projection, which contains a central connective tissue, is lined by stratified squamous epithelium. The upper epithelial cells of OSP have pyknotic and crenated nuclei, which are often surrounded by edematous or optically clear zone, known as 'koilocytic' cell (81). The differentiation can also be achieved by using some proteins as markers. These proteins include the cytokeratins (CKs) family (e.g., CK 10, 13, 14 and 16), whose expression relates to the biological behavior of both lesions (82).

OVC and OSCC. As aforementioned, OVC has a strong tendency to local invasion whereas metastasis is rarely seen (83). OVC has some pathological similarities to OSCC, especially for well-differentiated OSCC and OVC. Aiming at assessing and validating biomarkers for better understanding of the genesis and molecular mechanisms of OVC and OSCC, Pentenero *et al* (84) found OVC and OSCC could be differently characterized using chromosomal instability biomarkers. The difference in aggressiveness and prognosis of OVC and OSCC was reflected by DNA index characteristics. Some tumor genes and molecular markers including Cyclin-D1, laminin-332 γ2, PCNA, moesin, MMP-2, MMP-9 can also be used for comparative evaluation of OVC and OSCC, especially for OVC and well-differentiated OSCC, guiding clinicians to make an accurate diagnosis (52,53,57,74,75).

OVC and oral hybrid verrucous carcinoma. Oral hybrid verrucous carcinoma (VC) is a neoplasm composed of OVC and differently-differentiated OSCC (85). For example, well-differentiated OSCC was identified within OVC and invaded the underlying connective tissue and bone (76). Unlike OVC, oral hybrid VC is staged and graded similar to OSCC. However, the proportion of conventional OVC component may vary and the prognosis of hybrid VC with high proportion of OVC may have better prognosis than OSCC. Due to high similarity in staging and grading, incision biopsy is extremely unreliable to diagnose and differentiate oral hybrid VC from OVC (86). For diagnosis of this hybrid tumor, it is necessary to examine an adequate biopsy sample extending to the underlying bone for examination of the periosteum and the mucosa-connective tissue interface.

6. Treatment

The general treatment principles of OVC are consistent with OSCC, but the treatment of OVC has its own characteristics. Since the first report of OVC there have been debates regarding the treatment of choice for this tumor. The treatment regimens mainly include surgery, chemotherapy, radiotherapy or combinations, cryotherapy, and shave excision. However, surgery for wide lesion area usually results in uncosmetic appearance and dysfunction. Chemotherapy or radiotherapy may have poor response and anaplastic transformation, and thus questionable effectiveness. Regarding these issues, unconventional treatment modalities have been put forward in recent years. They include photodynamic therapy and CO_2 laser therapy. The details of these treatment regimens for OVC are summarized in Table II.

Surgery. Surgery has been considered the preferred treatment for OVC (87,88). The aim of surgery is to eradicate the tumor without disabling function. For the exogenic type of OVC, surgical excision is the first-line method due to its controlled size, rare tumor recurrence, and good prognosis. However, for the hybrid type of OVC, the surgical excision should be progressive. The excision boundary needs careful estimation because the excision sizes for the hybrid type of OVC are usually much broader. Incomplete or excessive resection often accelerates tumor growth, leading to anaplastic transformation, poor function and difficult reconstruction. In this case, surgery (e.g., primary tumor resection and neck dissection) combined with radiotherapy and chemotherapy may be appropriate to minimize tumor recurrence and undesired prognosis (88-90). Table II shows the uses of surgery for OVC since mid-1980s, clearly demonstrating its effectiveness after treatment (91-94).

Radiotherapy. OVC was initially thought to be somewhat radioresistant in the oral cavity or the larynx (95). It was reported the local recurrence rate could reach as high as 57% by following radiotherapy, resulting from the high incidence rate of multiple primary tumors. The anaplastic transformation may also occur in >10% of OVC cases (96). In fact, the treatment policy mainly depends on the extension of the primary tumor and on the regional nodal involvement. The patients who undergo surgery are usually in Stage I or II, whereas radiotherapy (or combined with surgery) appears more suit-

Table II. Treatment regimens for OVC (in previous studies).

Treatment regimen	Number of patients/gender	Time/age	Specific treatment modalities and additional information	Results (recurrence rate, RR; disease-free survival, DFS; overall survival rate, OSR)	Refs.
Surgery	101/M: 79, F: 22	1990 to 2000/53.9 (average)	Surgery for patients with no history of head and neck treatment	RR: 68% (first-time surgery), salvage rate for recurrent tumors: 66.7%, DFS: 77.6% (5 years)	91
Surgery	38/M: 36, F: 2	1996 to 2002/51 (median)	Staging work-up and preoperative evaluation (e.g., computed tomography of head and neck area and blood chemistry) before surgery	RR: 0, OSR: 94.7% (3 years)	92
Surgery	40/M: 38, F: 2	1991 to 2002/53.8 (average)	/	Control rate: 94.9% (first-time surgery); OSR: 89.9% (5 years)	93
Surgery	86/M: 52, F: 34	1990 to 2012/64.1 (average)	Enlarged resection of pure lesions performed in 1.0 cm to 1.5 cm outside the mass edge	RR: 3.5% (first-time surgery); 0 (second-time surgery) (5 years)	94
Surgery/ surgery + radiation/ radiation	2350 head and neck VC (1314 OVC)/M: 1410, F: 940	1985 to 1996/69 (median)	Early stage: surgery (85.8%); advanced stage: surgery (56.9%), surgery + radiation (16.3%), radiation (12.5%)	SR: 73.7% (5 years); for localized oral cavity tumors, SR: surgery: 85.7%, surgery + radiation: 68.4% radiation: 41.8% (5 years)	12
Radiotherapy	53/M: 29, F: 24	1985 to 1987/<35 (1.9%); 36-59 (47.2%); >60 (50.9%)	Radiotherapy given either as external beam radiotherapy or interstitial implantation, or as a combination of the two	RR: 30.2%; DFS: 66%, OSR: 86% (5 years); No anaplastic transformation in recurrence cases	97
Radiotherapy	107/M: 75, F: 32	1977 to 1987/50-59 (37.3%); 60-69 (27.1%)	Different stage tumors receiving different dosage, fractions, time, and equipment	SR: 100% (stage I), 68% (stage I1), 35% (stage 111), 26% (stage IV) (5 years); RR: 48.6%	98
High-dose-rate (HDR) brachytherapy	1/M	/85	A dose of 48 Gy in 12 fractions three times per week	Tumor disappeared without lymphadenopathy after 5 months	99
Chemotherapy (methotrexate)	12/M: 3, F: 9	1972 to 2010/79 (median)	Different stage tumors receiving different dosages by using various routes (intra-arterial injection, intramuscular injection and intravenous injection)	7 patients: good responses; 4 patients: partial responses; 1 patient: no response. Additional treatments needed for patients with no response after one or two cycles	44
Chemotherapy (capecitabine)	2/F	1990/71; 2002/75	Two times a day for one cycle, namely 2 weeks on and 1 week off, at a dose of 1000 mg	Both lesions achieving nearly complete resolution within 3 weeks (dramatic response); time for a durable partial response: first patient: 1 year, second patient: 6 months	103

Table II. Continued.

Treatment regimen	Number of patients/gender	Time/age	Specific treatment modalities and additional information	Results (recurrence rate, RR; disease-free survival, DFS; overall survival rate, OSR)	Refs.
Intra-arterial chemotherapy (methotrexate)	15/M	/55	50 mg per day for a mean period of 7.5 days, followed by 25 mg per week for 10 weeks	Tumor markedly regressed and finally entirely disappeared after 2.5 months, RR: 0 (43 months)	104
Intra-arterial chemotherapy (methotrexate)	1/M	/68	25 mg per day for 11 days, folinic acid given intramuscularly 6 mg every 6 h during the period	Tumor disappeared after 1.5 months; an ulcer recurred after 5 years and restored by surgical intervention with a nasolabial flap	105
Radiochemotherapy	5/M: 2, F: 3	/74 (median)	Radiotherapy (median, 56 Gy) + chemotherapy (vinblastine 2 mg (day 1); methotrexate 50 mg (day 2); bleomycin 15 mg (days 2 and 3), and repetition at 2-3 week intervals)	5 patients cured and 1 patient died (within a median 2.92 years)	106
Surgery/surgery + radiochemotherapy	15/M: 5, F: 10	1981 to 1997/ 76.9 (average)	One group (A): surgery; the other group (B): surgery + radiochemotherapy	DSF: A: 78%, B: 33% (5 years); A: 52%, B: 33% (10 years); anaplastic transformation occasionally occurred during treatments of OVC	107
Surgery/surgery + chemotherapy, radiotherapy, or both	12/M: 5, F: 7	1980 to 2000/ 67.8±3.7 (average)	One group (A): surgery; the other group (B): surgery + chemotherapy, radiotherapy, or both	Local control rate: A: 86.6%, B: 82.1%, SR: A: 91.3%, B: 92.3% (5 years)	108
Cryotherapy and shave excision	20 (26 lesions: 17 OVH, 9 OVC)/ M: 12, F: 8	/45-91	Shave excision + spraying liquid nitrogen (40-50 sec)+ thawing (30-60 sec)+ repeated freeze-thaw cycle 3 times	Tumors disappeared and lesions healed after 3-4 weeks; RR: 33.3% (23 month); Recurrence cases cured with the same technique	112
Photodynamic therapy (PDT)	1/M	/56	Multiple 3-min fractionated irradiations (1000 sec) with a light emitting diode red light at 635±5 nm +20% 5-aminolevulinic acid (1.5 or 2 h)	Extraoral tumor disappeared after 6 cycles; intraoral tumor disappeared after 22 cycles; no recurrence within 6 months	115
CO_2 laser therapy	1/F	/76	One session of CO_2 laser SmartXide DEKA (Firenze-Italy) (wave length: 10.600 nm, power: 8 W, repetition rate: 80 Hz, pulse width: 1000 msec)	No recurrence and metastasis within the 2-year follow-up	116
CO_2 laser therapy	2/F	2002/72; 2003/70	A focused laser beam (wave length: 10.6 μm, power: 6W) + a defocused beam	Tumor and lesion disappeared after 11 months; no recurrence within 3 years	117

able for patients in Stage III or IV, the advanced tumor stages which are not an indication for surgery (97). It was shown that the 5-year actuarial survival of patients with OVC treated by primary radiotherapy did not show any significant difference when compared to that of patients treated by surgery (98). In this regard, the role of radiation in promoting anaplastic transformation, a risk which is certainly over-emphasized, seems questionable and warrants further verification. Table II shows representative satisfactory results obtained by using radiotherapy for OVC treatment (97-99). Overall, radiotherapy was deemed less effective but an acceptable alternative treatment regimen for OVC.

Chemotherapy. Up to now, few reports have focused on the efficiency of chemotherapy schemes applied to OVC (100). Surgery and radiation are the major treatments for the exogenic type of OVC. However, for some OVC with strong tendency to local invasion, chemotherapy may be another cost-effective alternative treatment for patients, which usually improves the quality of life considerably. For instance, intra-arterial chemotherapy, featured by convenient dosing, excellent drug activity and acceptable toxicity profile, is effective in some OVC patients. Chemotherapeutic drugs have the capacity to evoke rapid and clinically significant sustained response which can be well tolerated in the patients. Moreover, the persistent and greater exposure of the tumor region to the drugs may induce rapid tumor shrinkage and achieve alleviation in a short time with reduced systemic toxicity (101,102). As shown in Table II, methotrexate and capecitabine are the desirable drugs for OVC treatments (103-105).

Radiochemotherapy. There is a controversy over the outcomes of clinical treatments by radiochemotherapy. For example, Strojan *et al* reported that the simultaneous intensification of chemotherapy was useful for reducing the radiotherapy dose, which is of benefit to minimization of toxic side effects induced by the treatment (106). Yoshimura *et al* compared different treatment approaches for 15 patients having OVC at the Shimane Medical University Hospital (107). The results showed that the disease-free survival rates of surgery alone and surgery combined with radiotherapy and chemotherapy were superior to radiotherapy, chemotherapy or their combinations. Surgery was considered the first choice of treatment for OVC, and radiotherapy combined with chemotherapy was regarded as the second most preferable treatment when the patient does not fit for surgery, refuses surgery, or has inoperable tumor. Overall, radiochemotherapy has acceptable therapeutic results (108).

Cryotherapy and shave excision. Cryotherapy is an effective and acceptable treatment method for oral precancerous and cancerous lesions including oral leukoplakia (OL), OVH, OVC and OSCC (109,110). It destroys lesional tissues mainly by disrupting cell membrane and by damaging protein, enzyme and vasculature, resulting in cells swelling, rupturing, or dehydrating. Cryotherapy is capable of reducing blood, scar and pain, and decreasing the occurrence of secondary infections (111). However, cryotherapy does not involve tissue excision and thus lacks precision. It is difficult to judge the final volume of tissue necrosis. Furthermore, OVC lesions are usually bulky and fungating. To obtain complete lesion regression, combined use of cryotherapy and shave excision is demanded (112). In practice, cryotherapy is not the predominant treatment method for OVC, but it is easy, safe, and conservative in OVC treatment.

Photodynamic therapy. Photodynamic therapy (PDT), also known as photochemotherapy (PCT), or phototherapy, was first introduced into oral cancer treatment in the mid-1980s (113). It is a minimally invasive and negligibly toxic technique that has shown great potential in recent years in the treatment of oral precancerous and cancerous lesions, oral premalignant and malignant disorders, including OL, oral erythroleukoplakia (OEL), OVH, OVC, OSCC, and bacterial and fungal infections (114). In general, PDT mediates tumor destruction by three mechanisms. Firstly, the free radicals and singlet oxygen kill tumor cells directly. Secondly, PDT can damage the tumor-associated vasculature, causing thrombus formation and subsequent tumor infarction. Thirdly, PDT-destroyed tumor tissues release tumor specific antigens that activate an immune response against the residual tumor cells. Since PDT has simple procedure with minimal pre-treatment, high efficacy, little or no scar formation, high patient compliance, low invasiveness, and slight side effects, it has played a significant role in the management of OVC (Table II) (115).

CO_2 laser therapy. Since the early 1970s, carbon dioxide (CO_2) laser therapy has been introduced to treat patients having oral lesions. The advantages of this treatment include short surgical time, effective wound sterilization, fast hemostasis and healing process, little pain, sealing of adjacent lymphatic vessels, reduced spread of malignant cells and anti-metastasis. These advantages have been partially confirmed by reported studies in Table II (116,117).

7. Discussion

OVC has received increasing attention in the past decades, which has been demonstrated by much effort spent on its etiology, clinical manifestations, pathology, diagnosis and treatment. There were evident advancements in this field, covering from etiological analysis to effective treatment. In particular, exploration of molecular mechanism and diagnosis of OVC have been largely promoted by employing multiple biomarkers. With advancement of understanding of the mechanism and diagnosis, various treatment regimens have been developed for OVC patients. The most notable ones include surgery, radiotherapy, and chemotherapy, which have already showed desired results in many cases. Other unconventional modalities such as cryotherapy and shave excision, photodynamic therapy, laser and immune therapies further enhanced the treatment effectiveness although they were often recognized as a means of auxiliary approach. Without doubt, these progresses will warrant effective prevention and better treatment of OVC. However, it should be noted that this field is still facing three challenges from primary sub-fields of the research and clinical practice of OVC, namely multifactorial etiology, complex molecular mechanism, and deficient treatment (Fig. 1). To resolve these challenges, more effort on the multifactorial etiology analysis, incorporation of effective biomarkers for mechanism illustra-

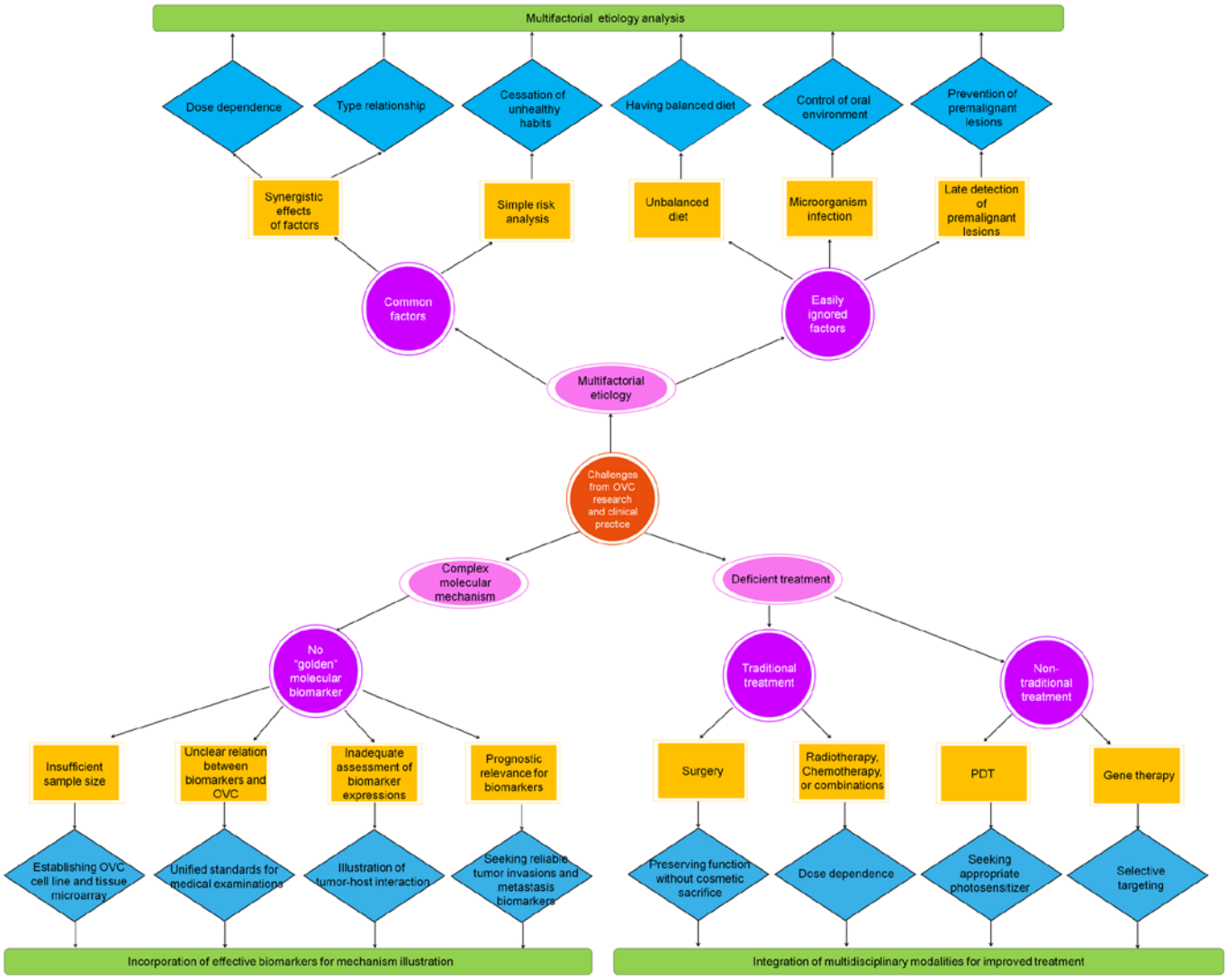

Figure 1. Challenges and potential solutions for research and clinical practice of OVC.

tion, and integration of multidisciplinary modalities for improved treatment is desired.

Multifactorial etiology analysis. As aforementioned, the etiology of OVC is multifactorial. The most important etiological factors are excess consumption of alcohol, tobacco, and areca nut usage. However, it was difficult to explain the increasing incidence of OVC with those common risk factors alone. This is because, on the one hand, these factors often act synergistically and therefore, their dose-dependence and type relationship are hard to determine. On the other hand, there is a lack of detailed risk analysis of these habits. The cessation of these habits may prevent the development of second primary tumors that arise independently, but it is useless for multiple primary tumors that are caused by migration of already transformed clone of cells (118).

Apart from the above risk factors, other factors that predispose towards the development of OVC involve unbalanced diet, i.e., an antioxidant-deficient diet. This finding can be demonstrated by the advantages of consumption of fruit and vegetables. Another easily ignored factor in association with OVC, as discussed in the etiology section, is microorganism infection, which requires control of oral environment. Microbes have the potential of being used as a diagnostic indicator although the relationship between microflora and oral malignancy, and how microorganisms interact with the oral mucosa at a cellular level deserve further investigation. Finally, late detection of premalignant oral lesions has evolved into another important etiological factor. Successful inhibition of development of premalignant oral lesions toward OVC would considerably reduce the risk of OVC. This can be achieved by combining commercial diagnostic aids and adjunctive techniques besides conventional oral examination for screening of patients for signs of oral cancer and precancerous lesions. A large number of oral cancer screening and case-finding aids or adjuncts (e.g., toluidine blue, brush cytology, tissue reflectance and autofluorescence) have already been developed and used to assist in the screening of healthy patients for evidence of occult cancerous change or to assess the biologic potential of clinically abnormal mucosal lesions (119,120). Altogether, it is necessary to enforce multifactorial etiology analysis to reduce the morbidity and even mortality of OVC.

Incorporation of effective biomarkers for mechanism illustration. There is no doubt that the molecular mechanism of OVC remains the focus of attention. To further the understanding of the mechanism, reliable molecular markers associated with the occurrence, progression and prognosis of OVC should be sought regarding the complexity of oral carcinogenesis. For this goal, various molecular markers have been proposed for use. However, clear molecular markers as a golden diagnostic standard are still absent. This fact is attributed to several reasons. Firstly, due to insufficient sample size, some markers showed low predictive values which fail to reach significance. It is thus necessary to establish an OVC cell line and tissue microarray. Secondly, incomplete knowledge for the relation between biomarkers and OVC may cause 'superficial' understanding of their roles, which are often questionable (121). Taking VEGF as an example, there is no identified close correlation between its expression and microvessel density (MVD) (122). Prior work showed the oral carcinomas did not react to experimental anti-angiogenetic therapy and the mean MVD revealed no relationship with the survival rate (123). Thirdly, the assessment of role of expressions of biomarkers like proteins is inadequate. The expressions appear to be more important than the markers themselves. A good example is p53, whose molecules up- or downstream on the apoptotic pathway were found to be more important. It indicates that further exploration of the field has to consider the tumor-host interaction. Fourthly, the prognostic relevance, usually evaluated based on a long-term follow-up, has not been provided for evaluation of markers of the tumor invasion and metastasis (e.g., MMPs). Since the relevance may illustrate another area of local interaction between oral cancer and its host in utilizing proteolytic enzymes for peritumoral matrix degradation and tumor spread, it actually indicates another direction for seeking reliable biomarkers. Overall, more attention should be directed at the role of molecular markers for deep understanding of the molecular mechanism of OVC, which essentially requires good incorporation of effective biomarkers in association with histopathology, molecular profiling with well-established clinical parameters, and prognostic analysis.

Integration of multidisciplinary modalities for improved treatment. In principle, the choice of treatment for OVC depends on many factors. Current clinical applications involve use of a variety of treatment modes. The most extensively used regimens are surgery, radiotherapy, chemotherapy and radiochemotherapy, which, as discussed before, have already showed desired results. Specifically, surgery represents the first choice of treatment for OVC. It aims at preserving functions without cosmetic sacrifice and its efficacy relies on multiple factors including primary site, location, size, proximity to bone, and depth of infiltration. For example, the use of marginal mandibulectomy and mandibulotomy for tumors that approach or involve the mandible requires special attention to the mechanism of bone involvement. The success of surgery also depends on the role of the surgeon which represents an unnegligible factor throughout the life history of an OVC patient and on the techniques involved during surgery. Advanced technologies, such as rapid prototyping combined with X-ray tomography, are expected to remedy the disadvantages of surgery (124-126). For radiotherapy, chemotherapy, and radiochemotherapy, they are usually regarded as the next most preferable treatment when surgery is inappropriate. Employment of either or both of them will contribute to the increase of the overall survival of patients with OVC once dose dependencies of radiation and drugs associated with the drug delivery system are established (127).

Despite considerable advances in the above traditional modalities, the survival of patients with OVC still needs improvement. Unconventional approaches provide alternative ways for treatment of OVC. Among them, PDT is especially promising because of its better prognosis than radiotherapy and chemoradiotherapy (128). For application of PDT, an ideal photosensitizer should be administered easily and safely, targeted appropriately, illuminated and activated at clinically useful wavelengths, pain-free, and obtained easily to achieve apoptosis and tumor necrosis with vascular cessation for clinical operation. The success of PDT also requires accurate dosimetry and suitable illumination devices and sufficiently defined treatment parameters. Thus, interactions between clinical applications and technological innovations and interdisciplinary research approaches should be pursued to overcome the difficulties and challenges for PDT.

Gene therapy is another very promising method as it introduces new genetic material into targeted cells without poisoning non-targeted tissues for treatment (129). The general strategies utilized in a gene therapy approach for cancer include gene addition therapy, gene excision therapy, antisense RNA technique, immunotherapy, 'suicide' gene therapy. For OVC, gene therapy is currently under investigation in clinical trials (130). Although it has a rather high requirement for selective targeting of tumor cells associated with multiple etiological factors, exploitation of the principle and selective targeting of tumor cells are feasible as our understanding of the molecular mechanisms of OVC progresses. Also, regarding that OVC is an attractive tumor target due to its frequent genetic mutations and accessibility for intratumoral administration, the safety and efficacy of gene therapy for prevention and treatment of OVC can be further enhanced by phase clinical studies and trials.

Overall, as OVC is characterized by multifactorial etiology and incomplete understanding of molecular mechanism, a variety of treatment modalities exist and may complement one another well. Integration of multidisciplinary modalities, such as surgery, chemotherapy, radiotherapy and/or unconventional methods, either sequentially or concurrently is highly recommended for OVC treatment.

8. Conclusions

As a verrucous variant of OSCC, OVC has received increasing attention recently. This paper offers a systematic review on its etiology, clinical manifestations and pathology, molecular mechanism, diagnosis and differential diagnosis and treatment. It clearly shows that the enormous effort spent in the past decades has contributed to significant advancements in this field, ranging from etiological analysis to development of various regimens for treatment. Nevertheless, this field also faces three great challenges from primary sub-fields of the research and clinical practice of OVC, namely multifactorial etiology, complex molecular mechanism, and deficient treatment.

From the point of view of etiology, common risk factors alone cannot adequately account for the increasing incidence of OVC. Instead, other factors that predispose towards the development of OVC, namely unbalanced diet, microorganism infection, and late detection of premalignant oral lesions, warrant further analysis. From the perspective of the molecular mechanism of OVC, incorporation of effective biomarkers in association with histopathology and molecular profiling with well-established clinical parameters, and prognostic analysis of OVC deserves more attention for deep understanding of the mechanism. Lastly, to promote effectiveness and efficacy of OVC treatment, it is necessary to integrate multidisciplinary modalities, such as surgery, chemotherapy, radiotherapy and/or unconventional methods (e.g., PDT), either sequentially or concurrently considering their potential complements to each other. In brief, continuous effort on the multifactorial etiology analysis and molecular mechanism through pursuing effective biomarkers will offer key insights into OVC pathogenesis which leads the treatment with integration of multidisciplinary modalities.

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