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PROSPECTS

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Oral tumors in children: Diagnosis and management

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Abstract

Oral tumors are one of important tumors which could be associated with serious problems in infant and children. It has been showed that a variety of cellular and molecular pathways including genetics and epigenetics mechanisms (eg, chromosomal alterations, and microRNA) involved in pathogenesis events present in oral tumors. Identification of these pathways could contribute to better treatment of oral tumor patients. Early detection is one of key steps in management of oral tumors which could contribute to improve clinical outcomes and better treatment of infant with oral tumors. Despite of easy accession of the oral cavity, oral tumors (malign/benign) are diagnosed in advance stages. Therefore, these tumors indicate a poor survival rate. It has been showed that various approaches including imaging techniques, chemical, genetics, and epigenetic biomarkers could have critical roles in early detection of oral tumors. Treatment of oral tumors is associated with employing of various therapeutic approaches including surgery, chemotherapy, and radiation. Data on effective diagnostic platforms and therapeutic approaches for oral tumors in children and infant are rare. We offer that a variety of biomarkers such as microRNAs which could be used for oral tumors in adults may be good candidates for early detection of oral tumors in children. Here, we summarized various aspects of oral tumors in children such as molecular pathways, diagnosis, and management of them.

KEYWORDS
biomarker, diagnosis, oral tumors

1 | INTRODUCTION

Oral tumors could be associated with serious health problems in children and infant. It has been showed that oral tumors could affect on children and adult in the various ways. Some studies investigated various aspects of oral tumors (ie, molecular pathways, diagnosis, and management of them) in children and infants.[1–3] A various factors including envirmental (eg, viruses, Syphilis, Candida, tobacco, alcohol, and nutritional factors), genetics (eg, tumor suppressor genes, oncogenes, and genomic instability), and epigenetics factors (eg, microRNAs, DNA methylation, and histone modifications) could involve in initiation and progression of oral tumors which could lead to emerging of various cancers.[4,5] Identification of various risk factors involved in oral cancer pathogenesis in infants and adults could provide new insights into biological pathways present in the oral tumors. It could also contribute to better diagnosis and treatment of oral tumors in early stages.[6] Diagnosis and choice of effective therapeutic approach are important dimensions of oral tumors treatment. To date, imaging techniques used as standard diagnosis platform for detection oral tumors in infants and children.[6] Imaging techniques are associated with various limitations which led to emerging new diagnosis platforms such as using of biomarkers. Other important issue is choosing of

effective treatment approaches which provide high effective therapeutic effect for patients with oral tumors.[6] A large number studies indicated that various therapeutic platforms such as chemotherapy, radiation, and surgery could be used as powerful tools in treatment oral tumors in children and adults.[7,8] In the current review, we summarized various aspects of oral tumors including molecular pathways, diagnosis, and therapeutic platforms in infants and children. Moreover, we provide various biomarkers might be used as diagnostic and therapeutic biomarkers for oral tumors in children.

1.1 | Oral tumors in children

Maxillofacial and oral tumors are one of common tumors in adults and show rare incidence in children.[3,9,10] A large number studies indicated that there are a variety of maxillofacial and oral tumors including fibrosarcoma, rhabdomyosarcoma, mesenchymal chondrosarcoma, and melanotic neuroectoderma in infant and children.[3,9,10] For a child with a maxillofacial and oral tumor who being treated, total resection should be undertaken. Monitoring and following up of children with various types of oral tumors should also be considered.[3,9,10]

In a study, Tanaka et al[1] assessed clinical features and management of various types of oral and maxillofacial tumors associated with infants and children. Their results indicated that among of 105 subjects, 102 (97.1%) had benign tumors and only 3 patients (2.9%) had malignant tumors. They showed that hemangioma (25/69; 36.2%) and papillomas (19/69; 27.5%) were the most common types of benign tumors the tongue. odontoma (14/33; 42.4%) ameloblastoma (11/33; 33.3%) were most common tumors in bone. It has been showed that odontogenic tumors (25/28; 89.3%) could develop in children more than 6 years of age and these tumors might develop after dental crown formation. In each subjects with benign tumor, resection recurrence was done on four of these tumors including two hemangiomas, one lymphangioma, and one papilloma. However, after re-resection recurrence has not been observed for more than 4 years. Moreover, in benign jawbone tumors, resection recurrence was done on 3 ameloblastomas recurred after enucleation and after wide resection there has not been observed recurrence for more than 17 years. These results suggested that most oral and maxillofacial tumors in children could be benign. Moreover, minimal surgical treatment option should be the procedure of first choice in benign tumor such as ameloblastoma.[1]

In a study, Trobs et al[11] assessed a variety of oral tumors and tumor like lesions in 95 infant and children. They showed that various tumors and tumor like lesions were located on various sites including lips (22%), tongue (21%), and cheek (19%) and benign lesions found for almost 83 (87%) of the subjects. Among of them, 41 (43%) subjects show benign tumors including hemangiomas (17 subjects), Hamartomas (22 subjects), and 12 subjects were lymphangiomas. They indicated that 14 subjects (15%) were classed mucoceles, ranula and dysontogenetic cysts and 6 subjects (6%) were found as miscellaneous lesions. They results indicated that a simple surgical resection could be an effective tool for treating most benign lesions. In addition, long-term effects of surgical resection as treatment approach could lead to decreasing of the red volume of the lips, scarring following resection of parotid hemangiomas, a forked tongue after wedged resection, and partial facial nerve palsy. Moreover, they assessed 12 (13%) subjects with various types of malignant tumors including 1 osteosarcoma, 2 fibrosarcomas, 5 rhabdomyosarcomas, 2 carcinomas of the parotid, and 2 metastases. They showed that fibrosarcomas and parotid carcinomas could be treated by surgical excision while a multimodal approach should be used for patients with rhabdomyosarcomas. Among of 12 patients, 6 patients with malignant tumors were alive after a median follow-up of 20.5 years. These findings indicated that while most children oral and maxillofacial tumors could be benign, malignant tumors of soft tissue such as salivary glands and bones must be taken into consider.[11]

1.2 | Molecular pathways in oral tumors

It has been showed that there are a various types of oral tumors such as squamous cell carcinoma (accounted for more than 90 percent of oral cancers), verrucous carcinoma, lymphomas, fibroma, keratoacanthoma, and odontogenic tumors which could be associated with cancerous conditions in infants and adults.[5,12] Oral tumors are multifactorial diseases which a variety of genetical and environmental factors could be involved in pathogenesis of them.[1,5]

A large number studies indicated that a various gentical factors including oncogenes, tumor suppressors, epigenetic mechanisms, and chromosomal abnormalities could critical roles in initiation and progression of oral tumors in infants and adults.[13] Identification of them may provide better understanding of biology pathways involved in oral tumors and could contribute to using of better therapeutic platforms for patients with oral tumors.[13] Here, we mention a variety of oncogenes; tumor suppressor genes and chromosal abnormalities which could are associated with imitation and progression of oral tumors (Figure 1).

Epidermal Growth Factor Receptor (EGFR) is one of important oncogenes which have critical roles in the regulation of apoptosis, cell proliferation, angiogenesis, invasion, and metastasis.[14,15] This oncogene exerts its effects via activation/inhibition of tyrosine kinase cascade. It has been showed that these receptors via targeting sequence cellular and molecular pathways including MAPK, Akt, ERK, and Jak/STAT could be associated with cancerous

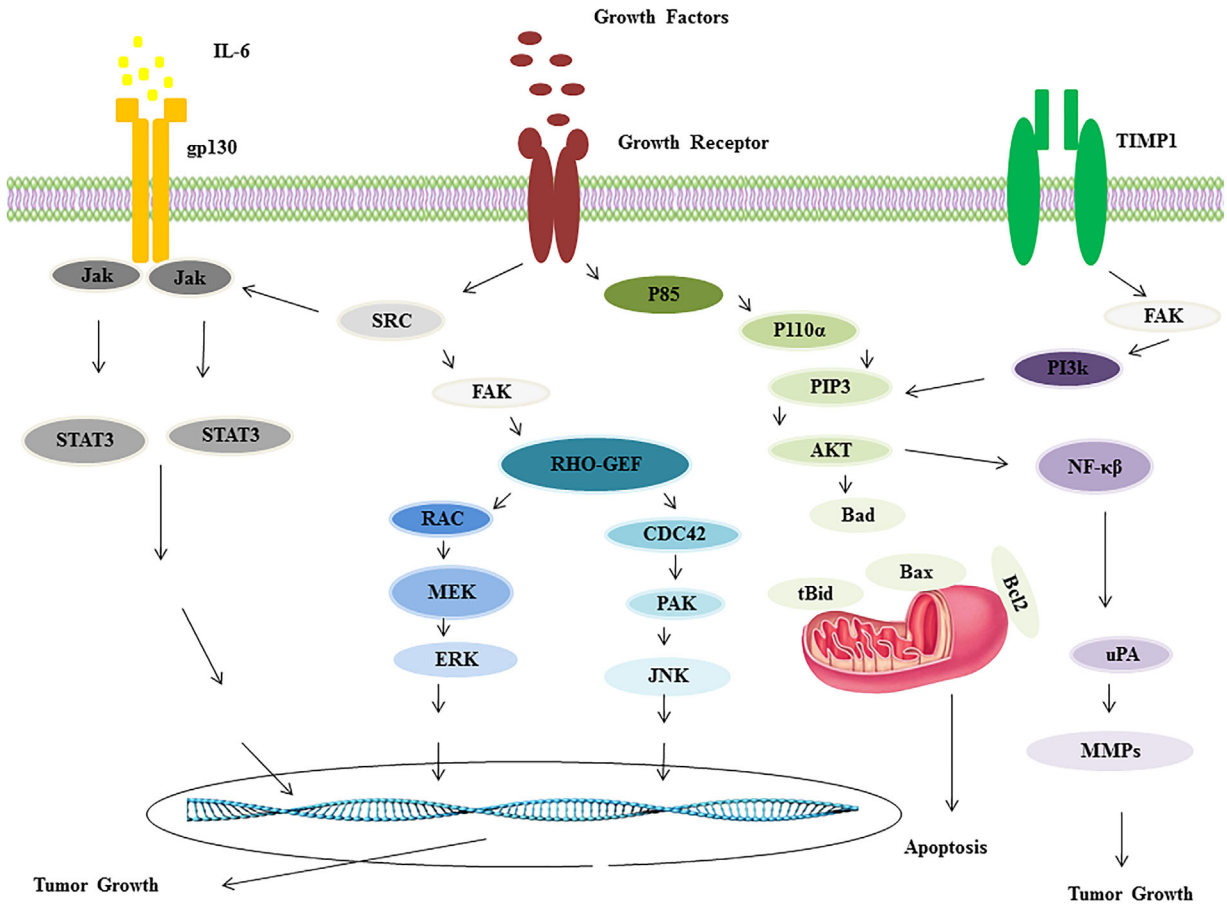

FIGURE 1 Various cellular and molecular pathways involved in oral tumor

conditions in various cancers such as oral cancer.[15,16] Deregulation of EGFR is related with various types of human cancer such as oral tumors.[16,17] It has been showed that an abnormal amplification of the EGFR gene could be related with initiation and progression of oral squamous cell carcinoma. Multiple lines evidence indicated that a low level of gene amplification of EGFR could lead to significant frequency in epithelial dysplasia and carcinoma in situ and also the increasing of EGFR expression could be associated with development of invasive cancer.[16,17]

TGF-α is other gene candidate could be associated with oral cancer progression.[18] It has been showed that the expression of TGF-α is higher than EGFR's in the proliferative pool of the oral epithelium in oral precancer lesions. These findings indicated that up regulation of TGF-α could affect on the adjacent nonproliferative cells via its paracrine effects. These events could lead to increasing of the cell surface receptor expression.[18,19]

PI3K-AKT signal pathway is other important pathways which are associated with various cancerous conditions.[20] Several studies indicated PI3K-AKT signal pathway could play major roles in various cancers such as oral tumors. It has been showed that activation of PI3K-AKT signal pathway could be also closely associated with oral precancerous lesions and a variety of genetic mutations in this pathway could be related with early stage of oral cancer.[21] PTEN is known as dual protein/lipid phosphatase which is important substrate—phosphatidyl-inositol 3,4,5 triphosphate (PIP3)—which produced by PI3 K.[22,23] A large number studies indicated that mutation or epigenetically inactivation of PTEN are associated with in a variety of human tumors such as oral tumors.[22,23] The interaction of PTEN and p53 which both of them are important tumor suppressor proteins in various tumors has been observed.[24] The activation of PTEN could be lost via mutations, deletions, or promoter methylation silencing.[25] Many studies indicated that genetic alterations in PTEN which are located at 10q23.3 could be occurred in 5–10% of oral squamous cell carcinoma lesions. It has been showed that this lack of PTEN expression could be used as diagnostic and prognostic biomarkers in oral cancer patients with poor clinical outcome.[23,26]

Chronic inflammation is other key pathogenesis event which could induce cancerous conditions via increasing of production of reactive oxygen and nitrogen species.[27–29] The increasing of reactive oxygen and nitrogen species could lead to increasing of DNA damage which is known as one of key

steps in initiation of various cancers such as oral tumors.[30] It has been showed that increasing of reactive oxygen and nitrogen species could also induce expression of a variety of cancer associated gens including the tumor necrosis factor gene (TNF), matrix metalloproteinases (MMP) genes, and vascular endothelial growth factor (VEGF) genes. Up regulation of these genes could affect on cell migration and angiogenesis via regulation of Nuclear Factor κB (NFκB).[29,31–33]

1.3 | Diagnosis of oral tumors

One of significant aspects of oral tumors in children and adults is early and fast detection of oral tumors in various subjects.[34] A variety of diagnostic platforms including imaging techniques, and using of chemical, gentical, and epigenetics biomarkers might be used as effective diagnostic approach for early detection of oral tumors in infants and adults.[6] Unfortunately, few studies and guidelines have employed diagnosis approaches for detection of oral tumors in children (Table 1). It seems that a variety of the used diagnosis approaches for adults might be used for infants and children. Here, we have provided few examples of various diagnosis approaches for detection oral tumors in children and also provided various diagnosis approaches employed for diagnosis oral tumors in adults which might be used for infant and children.

Human papillomavirus is one of important infections in oral mucosa which could lead to emerging of various oral tumors in children and infant.[53] Several studies found that a variety of chemical and gentical biomarkers (ie, up regulation of P16, inactivation of P16 and pRb, mutation, and serum antibodies) could be employed for diagnosis human papillomavirus involved in oral tumors in children and adults.[54] Various diagnosis platforms such as IHC, western blot, microarray, and PCR could be employed chemical and gentical biomarkers for diagnosis oral tumors in children and adults. Odontogenic tumors are known as one of oral tumors in children and adults.[30] Multiple line evidence indicated that up/down regulation of a variety of cellular and molecular targets involved in initiation and progression of these tumors.[30]

Ameloblastoma is known as one of important types of dontogenic tumors which is benign but it could be high risk for recurrence.[55] Podoplanin is a lymphatic endothelium marker which has crtical roles in cell migration and invasiveness in ameloblastoma. In a study, Siar et al,[55]

TABLE 1 Various studies on oral tumors for children

Type of oral tumors	Sample	Diagnosis method	Therapy method	Ref.
Ossifying Fibroma	1	CT, MRI	-	35
Condylomata Acuminata	124	Biomarkers (Genetics and chemistry)	-	36
Eosinophilic Granuloma	1	CT, MRI	-	37
Eosinophilic Granuloma	1	MRI	Surgery, Chemotherapy	38
Langerhans cell histiocytosis	30	-	Radiotherapy, Chemotherapy, Surgery	39
Langerhans Cell Histiocytosis	35	IHC) and ISH	-	40
Keratoacanthoma	1	IHC	-	41
Oral Leiomyomas	1	IHC	-	42
Oral Leiomyoma	1	IHC	-	43
Lipoma	1	IHC	-	43
Lipoma	1	IHC		44
Neurofibroma	3	Panoramic radiograph and IHC	-	45
Odontogenic Tumors	48	IHC	-	10
Odontogenic Tumors	31	IHC	-	46
Osteochondroma	1	IHC	-	47
Solitary Oropharyngeal Papilloma	1	X-ray	-	48
Pyogenic Granuloma	1	IHC	Surgery	49
Pyogenic Granuloma	1	IHC	Surgery	50
Rhabdomyoma	1	MRI, IHC	Chemotherapy	51
Schwannoma	1	panoramic radiogeraph, CT, IHC	Surgery	52
Squamous Cell Carcinomas	14	IHC	Chemotherapy, Radiotherapy, Surgery	2
Squamous Cell Carcinomas	10	IHC	Surgery, Radiotherapy	3

CT, Computed tomography; MRI, Magnetic resonance imaging; IHC, immunohistochemistry; ISH, in situ hybridization.

TABLE 2 Various biomarkers in oral tumors

Type of tumors	Biomarker	Expression	Diagnosis methods	Ref.
Ameloblastoma	E-cadherin	Down regulation	IHC	55
	Podoplanin	Up regulation	IHC	55
	β-catenin	Up regulation	IHC	55
	CD44v6	Up regulation	IHC	55
	CCND1	Up regulation	IHC	61
	SMO	Mutation	Western blot, PCR	62
	BRAF	Mutation	Western blot, PCR	62
	TP53	Up regulation	IHC	63
	CDK2	Up regulation	Microarray, RT-PCR, and IHC	64
	AKT1	Down regulation	IHC/ Immunoblotting, Immunofluorescence, ELISA	63
	PCNA	Up regulation	IHC	65
	RB1	Up regulation	PCR	66
	JUN	Up regulation	In situ hybridization	67
	NOTCH1	Down regulation	IHC, PCR Real Time	68
	MTOR	Up regulation	IHC	69
	EGFR	Up regulation	IHC	70
	E2F1	Up regulation	IHC	71
	MDM2	Up regulation	IHC	72
	PTEN	Down regulation	IHC	23
	MMP2	Up regulation	PCR Real Time	73
Keratocysticodontogenic	TP53	Down regulation	IHC	74
	IL6	Up regulation	IHC	75
	VEGFA	Up regulation	IHC	76
	TNFSF11	Up regulation	IHC	77
	TP63	Up regulation	IHC	76
	FHIT	Up regulation	IHC	78
	GLI1	Up regulation	IHC	79
	GLI2	Up regulation	IHC	79
	KRT6B	Up regulation	IHC	80
	MKI67	Up regulation	IHC	81
	BCL2	Up regulation	IHC,qRT-PCR, Western bloting	82
	CALB2	Down regulation	IHC	83
	ALCAM	Down regulation	IHC, qRT-PCR	80
	miR-15a	Down regulation	IHC, qRT-PCR	82
	miR-16-1	Down regulation	IHC, qRT-PCR	82
Schwannomas	miR-7	Down regulation	IHC, qRT-PCR	84
Eosinophilic Granuloma	OKT6	Up regulation	IHC	44
	S-100	Up regulation	IHC	44
Langerhans Cell Histiocytosis	CD1a	Up regulation	IHC	85
	S100	Up regulation	IHC	85
Squamous Cell Carcinomas	miR-9	Up regulation	qRT-PCR	86

(Continues)

TABLE 2 (Continued)

Type of tumors	Biomarker	Expression	Diagnosis methods	Ref.
	miR-7	Down regulation	qRT-PCR	86
	miR-21	Down regulation	qRT-PCR	86
	miR-31	Up regulation	qRT-PCR	86

IHC, immunohistochemistry; PCR, Polymerase chain reaction; RT-PCR, Reverse transcription polymerase chain reaction; QRT-PCR, Quantitative Reverse transcription polymerase chain reaction.

indicated that Podoplanin, β-catenin, and CD44v6 were up regulated in the recurrent ameloblastoma samples. Up regulation of them could be associated with tumor invasive recurrent ameloblastoma. Moreover, they showed that down regulation of E-cadherin could be related with cell adhesion function during tumor progression. These findings indicated that these markers could be used as diagnosis biomarkers for detecting recurrent ameloblastoma.[55]

Imaging techniques are the first lines of diagnosis approaches for a variety of tumors such as breast and oral tumors.[56,57] These techniques could provide various data on condition of tumors in body or distinguishing between normal and cancer tissues.[58]

Multiple lines evidence indicated that some imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI), positron emission tomography (PET), PET-CT could be applied for monitoring oral tumors in various patients.[6] Numerous studies indicated that MRI and CT are as suitable techniques for assessing various types of tumors such as lymph nodes involved with tumor. It has been showed that CT is associated with some limitation such as low resolution of soft tissues and the artifacts generated by X-rays than MRI.[59] In the other hand, MRI is associated with some advantages such as it is useful for distinguishing between the surrounding tissues and the tumor mass, and the absence of radiation exposure.[60] These findings suggested that various imaging techniques could be associated with a variety of advantages and disadvantages which based on various factors such as cost, resolution, and accessible, could choice the best of them.

In study, Lam et al,[37] used CT and MRI for diagnosis sosinophilic granuloma and langerhans cell histiocytosis in two cases. Their results indicated that non-contrast computed CT scan of the neck and MRI with contrast could show an osteolytic contrast-improving lesion primarily involving the C2 posterior elements, with a compressive circumferential epidural component extending from C2 to C5. These results indicated that CT and MRI could be used for diagnosis of sosinophilic granuloma and langerhans cell histiocytosis in children.[37]

Ossifying fibroma is a rare benign fibro-osseous neoplasm of the jaw which could be observed in children. In the a case report, Khan et al[35] used CT, MRI, and IHC for detection of Ossifying fibroma. Their results indicated that these diagnosis techniques are able to detect this oral tumor in children.[35]

The utilization of various types of biomarkers could be other option for early detection of various types of oral tumors in different subjects (Table 2).[6] Circulating biomarkers present in saliva, serum, urine, and plasma have been found as effective tools in the diagnosis of many systemic conditions and for patient monitoring.[87,88] It has been showed that more understanding of oral tumors could lead to identification of new molecular/cellular markers for early detection of oral tumors. Oral tumors are known as a fatal diseases and these have been showed that early diagnosis could contribute to better treat of these tumors.[89–91]There are various targets and molecules which could be used for diagnosis several diseases such as various tumors. These molecules observed in different levels (genomics, transcpripomics, and proteomics).[91]

MicroRNAs (miRNAs) are small non-coding RNAs which are involved in a variety of cellular and molecular pathways.[92–98] A large number studies indicated that deregulation of miRNAs are associated with various types of diseases such as stroke, cardiovascular diseases, inflammatory diseases, and cancer.[99–107] Many studies indicated that deregulation of a variety of miRNAs such as miR-9, miR-7, miR-21, and miR-31 could be involved in pathogenesis of oral tumors.[6] Hence, it seems that these molecules could be used as diagnostic, prognostic, and therapeutic biomarkers for various types of tumor such as oral tumors.[6,108–111]

In a study, Diniz et al[82] indicated that miR-15a and miR-16-1 could affect on expression of Bcl2 in keratocystic odontogenic tumors (KOTs). Their results showed that there were up regulation of miR-15a and miR-16-1 in the KOTs samples than healthy subjects. Up regulation of miR-15a miR-16-1 could lead to decreasing of Bcl2 expression in the human KCOT-1 cell line. Hence, miR-15a and miR-16-1 exert their effects via targeting Bcl2. These results indicated that miR-15a and miR-16-1 could be used as diagnostic and therapeutic biomarkers in KOTs therapy.[82]

In other study, Saydam et al[84] indicated that up regulation of miR-7 could inhibit schwannoma cell growth both in culture and in xenograft tumor models in vivo. Down regulation of miR-7 are associated with inducing tumor growth via activation various signaling pathways. They showed that miR-7 exerts its effect via targeting a variety of cellular and molecular oncogenes such as EGFR, Pak1, and

Ack1. These results indicated that miR-7 play critical roles in growth tumor and it could be used as diagnosis biomarkers for schwannoma therapy.[84] Moreover, several studies indicated that a variety of saliva biomarkers such as, DNAs, RNAs, proteins, and chemical components could be utilized for diagnosis, prognosis and therapeutic markers in various oral tumors (Table 2). It seems that utilization of various chemical and gentical biomarkers could be effective options for early detection of various types of oral tumors. Hence, future studies in this horizon could lead to identification of suitable biomarkers for oral tumors in infants and children.

2 | CONCLUSION

Oral tumors are one of important public health problems worldwide. Although, the incidence of these tumors are rare in children and infant, but, detection and management of them are necessary. Multiple line evidence indicated that a variety of factors including environmental, genetical, and epigenetics factors associated with initiation and progression of oral tumors in children and adults. These factors exert their effects via targeting a sequence of cellular and molecular pathways which led to alteration of cell behavior and emerging of disease conditions. Hence, understanding of various cellular and molecular pathways could contribute to better detection and management of oral tumors in adults and children. Early detection is other important factor which could help to better monitoring and management of oral tumors. Numerous studies used various approaches such as imaging techniques, chemical, and genetical biomarkers for detection of oral tumors in adults. It seems that utilization of them could be utilization as suitable diagnosis platform for detection of oral tumors in children and infant. The future studies in this area, could provide better data and might contribute to better management of patients with oral tumors.

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