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Contents

Quarterly Volume 2 Number 4 November 20, 2013

EDITORIAL	67	Pharmacogenomics in oral diseases <i>Gokul S, Sapna G</i>
THERAPEUTICS ADVANCES	71	Stomatological management of head and neck cancer patients treated with chemotherapy and radiotherapy <i>Bologna-Molina R, Maglia A, Castañeda-Castaneira RE, Molina-Frechero N</i>
MINIREVIEWS	79	Molecular biomarkers of cell proliferation in ameloblastomas <i>Bologna-Molina R, Bedoya-Borella AM, Soria-Moreira L, Soría-Suárez S</i>
BRIEF ARTICLE	86	Cytotoxicity of a silorane-based dental composite on human gingival fibroblasts <i>Orsini G, Catellani A, Ferretti C, Gesi M, Mattioli-Belmonte M, Putignano A</i>
	91	Accuracy of linear vs spiral tomography: Alveolar crest to sinus/nasal floor height <i>Yoozbashizadeh M, Fatemitabar SA, Sedighara E, Nikgoo A</i>
CASE REPORT	97	Surgical obturator duplicating original tissue-form restores esthetics and function in oral cancer <i>Patil PG</i>
	103	Soft tissue aneurysmal bone cyst of the mandible: Report of a case <i>Jahanbani J, Sadri D, Hassani A, Kavandi F</i>

Contents

World Journal of Stomatology
Volume 2 Number 4 November 20, 2013

APPENDIX I-V Instructions to authors

ABOUT COVER Editorial Board Member of *World Journal of Stomatology*, Sridharan Gokul, MDS, Lecturer, Oral Pathology and Microbiology, YMT Dental College and Hospital, Kharghar, Institutional area, sector-4, Kharghar, Navi Mumbai 410210, Maharashtra, India

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World Journal of Stomatology (*World J Stomatol*, *WJS*, online ISSN 2218-6263, DOI: 10.5321) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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Pharmacogenomics in oral diseases

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Abstract

The availability of newer technologies for identification and characterization of the human genome has enabled our understanding of the genetic variations in a majority of human diseases. Human genomic sequence varies in less than 1% among the different population group and these differences known as gene polymorphisms are the primary reasons for differences in individuals' response to various drug therapy. Also understanding the genetic changes may enable implementation of targeted therapy, thus providing for effective treatment strategies and minimizing the adverse side effects. Pharmacogenomics is a recent development in the field of personalized medicine which focuses on the genetic determinants of drug response at the levels of entire human genome. It primarily deals with tailoring of drug therapy for every individual based on their genetic make-up and identifying new target in various diseases for drug therapy. While the application of pharmacogenomics in systemic illness is well researched, its role in oral diseases needs documentation. Identifying specific targets in periodontitis, head and neck cancer, infections and genetic disorders can be beneficial in discovery of new drugs. This editorial provides an overview of basics of pharmacoge-

nomics, its current role in disease management and its potential role in various head and neck diseases.

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Key words: Pharmacogenomics; Oral Cancer; Periodontal diseases; Genomic variations; Targeted drug therapy

Core tip: Pharmacogenomics mainly focuses on the genetic determinants of drug response at the level of entire human genome. It primarily deals with tailoring of drug therapy among every individual based on their genetic make-up and identifying new targets in various diseases for drug therapy. Identification of gene polymorphisms in humans will aid in modulating drug therapy for individual needs as well as leading to discovery of target drugs. This editorial provides an overview of basic pharmacogenomics and its usefulness in oral diseases.

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INTRODUCTION

Pharmacogenomics is a component of individualized medicine focusing on how genetic factors influence individual responses to different medications that may affect drug efficacy, side effects and adverse events to drug therapy^[1]. The aim of pharmacogenomics is to decrease adverse responses to therapy through determining new therapeutic targets and genetic polymorphisms that affect drug specificity and toxicity^[2]. The term pharmacogenomics, a relatively new term is often used interchangeably with a much older term pharmacogenetics though differences exist between the two terms. While pharmacogenetics refers to the study of how individual genes in-

fluences the response to medications, pharmacogenomics is related to the study of how individuals' genomic composition as a whole affects their response to medicine^[3]. The field of pharmacogenomics uses genetic and genomic information of individuals in order to predict the response of patient groups to drugs and thus guide clinical trial and the drug development process. This can be made possible with the development of human genome project which encodes majority of human genes.

Most of the commonly occurring diseases such as cancer, atherosclerosis and neurodegenerative disorders comprise of a group of genetically discrete entities with separate molecular etiologies and possibly different responses to therapy. Pharmacogenomic therapy has been attempted to treat cystic fibrosis^[4], acquired immune deficiency syndrome (AIDS), cardiovascular diseases, psychiatric illness and targeted therapy towards epidermal growth factor receptor (EGFR) for treatment of pancreatic cancer^[5] and non small cell lung carcinoma^[6]. In addition to the development of new therapeutic agents, pharmacogenomics can also predict outcomes and beneficial therapy regimens. The various targets that are extensively studied are angiotensin converting enzyme regulating cardiovascular functions; analyzing the association between β 2 adrenergic receptor polymorphism and asthma^[7] and use of apolipoprotein polymorphisms to predict the risk of heart disease and response to treatment^[2].

Most of the disorders affecting the head and neck region excluding trauma have genetic implications in various forms. The disorders range from developmental disturbances, microbial infections and bone disorders to various forms of head and neck cancers. An understanding of the genetic changes occurring in these disorders may be helpful in implementation of drug therapy aiming to obtain maximum efficacy with minimum side effects and also to evolve targeted drug therapy for the management of such lesions.

BASICS OF PHARMACOGENOMICS

A gene is defined as a specific sequence of nucleotide bases whose sequences carry the instructions for the constructions of proteins. Hundreds of genes reside on each chromosome and the complete human genome is estimated to contain about 30000 genes^[8]. More than 99% of DNA sequence is the same across the entire human population. The small genetic dissimilarities have a major impact on persons' physical makeup and response to disease as well the effectiveness of the therapy instituted. Pharmacogenomic technologies try to detect these genetic variations in a patient or patient populations to help select drug compounds and doses that are more likely to work.

These genetic variations which account for around 1 million of the 3 billion bases of human genome are termed as polymorphisms. Polymorphisms arise from three fundamental types of DNA sequence variations namely single nucleotide polymorphisms (SNPs) representing nucleotide substitutions, insertions or deletions

and indel of repetitive DNA^[9]. Advances in pharmacogenomics mainly depend on identification of SNPs in the human genome. These arise from mutations affecting a single nucleotide, occurring relatively frequently and must exceed in a population of a frequency of 1% to meet the requirement of genetic polymorphism^[10]. The main research use of a human SNP map would be to determine the contributions of genes to diseases that have a complex multifactorial basis. More than 1.4 million SNPs have been identified in human genome till date^[8]. Majority of the genetic polymorphisms are found in drug metabolizing enzymes, receptors and transport proteins and produce varying effects on drug metabolism^[2]. The use of these genetic variations in order to individualize drug therapy and to identify novel targets to enable the development of new drugs for various diseases are the primary reasons for which pharmacogenomics is employed.

Drugs in the body are metabolized by enzymes and most of the enzymes belong to the members of cytochrome P450 (CYP) system. These enzymes are located in the liver and gastrointestinal tract and include greater than 30 isoforms^[11]. Individual variations in the genes that produce these enzymes causes different people to metabolize the same drug differently; less active or inactive forms of CYP enzymes that are unable to breakdown and efficiently eliminate a drug from the body (slow metabolizers) can cause the drug to build up while very active forms (rapid metabolizers) can cause the body to clear itself of a drug before it has a chance to work^[12]. Understanding an individuals' response to a certain drug can help the clinician to decide the accurate drug dosage required for effective therapy thereby reducing the chances of overdose or insufficient dosage. Of all the types of CYPs, most of the functional genetic polymorphisms reside in only few of them namely CYP3A4, CYP2A6, CYP2C9, CYP2C19 and CYP2D6^[10]. Of these, CYP3A is involved in the oxidative biotransformation of up to 50% of clinically important therapeutic agents that has resulted in the withdrawal of important drugs like Mibefradil (anti-hypertensive drug), Rezulin (oral anti-hyperglycemic agent) and propulsid (for treatment of gastrointestinal disorders).

Other less common polymorphisms can be seen in drug transport proteins and receptors. Transport proteins are proteins that allow compounds to be transported across cell membranes and P-glycoprotein is a drug transport protein known to be involved in the metabolism of many drugs^[13]. Identifying this polymorphism would be a valuable tool in determining therapeutic concentrations required for individual patients. Receptors polymorphisms are helpful for development of new therapeutic agent and to predict outcomes and beneficial treatment regimens. Some of the common receptor targets that have been targeted by the use of drugs include angiotensin converting enzyme, β 2-adrenergic receptor polymorphism, cystic fibrosis transmembrane conductance regulator and p53 and EGFR for anti-cancer therapy.

APPLICATIONS OF PHARMACOGENOMICS IN ORAL DISEASES

Genetic mutations are a common finding in majority of the human diseases affecting the head and neck region. which may contain one or many genetic polymorphisms. Examples of disorders exhibiting single gene mutations include Treacher-Collins syndrome, Pierr-Robin syndrome, Crouzon syndrome, Ectodermal dysplasia, achondroplasia and Gorlin syndrome while cleft lip and palate, congenitally missing teeth, dental caries, severe malocclusion, head and neck cancer, periodontal diseases and autoimmune disorders are caused by multiple gene mutations^[14].

Chemotherapeutic intervention for cancer therapy is undergoing changes from being an empiric random screening approach to a target directed approach where specific abnormalities in cell functioning are modulated in a drug receptor fashion. The use of small molecules with tyrosine kinase inhibitory activity directed towards the EGFR such as gefitinib and erlotinib are used for treatment of NSCLC, pancreatic and breast cancer^[5]. EGFR is a transmembrane glycoprotein member of erbB family of type I tyrosine kinase which plays a crucial role through downstream signaling pathways in cell cycle progression, survival and proliferation^[15]. Overexpression of EGFR in head and neck cancer are known to be associated with poor prognosis and hence the use of drugs such as tyrosine kinase inhibitors may help in improving the prognosis and survival rate. Adequate understanding of the molecular mechanisms involving various growth factors (such as transforming growth factor, platelet derived growth factor, hepatocyte growth factor), cytokines and genetic mutations occurring in carcinogenesis will aid in the development of chemotherapeutic drugs against specific targets for appropriate management and to reduce patient morbidity and mortality.

Periodontitis is a polymicrobial infection resulting from a complex interaction between oral microbes and host immune response leading to periodontal destruction and alveolar bone resorption. The host response to infection is primarily in the form of inflammatory reaction leading to release of various cytokines, growth factors and matrix metalloproteinases (MMP). Identification of therapeutic targets which are directed towards the specific host alteration may be helpful as an adjuvant treatment for periodontitis. Monoclonal antibody derivatives directed towards MMP are promising as therapeutic agents and mainly involves non-antimicrobial activities of low dose tetracycline and tetracycline analogue doxycycline hyclate via the inhibition of MMP-8 and -13 protease mechanisms. The therapeutic action of these agents is primarily due to the modulation of the host response because the low dose formulations of these drugs have lost their antimicrobial property^[16]. Research in targeted therapy are also underway for treatment of various other microbial infections like candidiasis, birth defects, ortho-

odontic tooth movements but are still at initial stages.

To summarize, decoding the human genome with aim to describe genetic changes in various oral diseases will be beneficial in providing appropriate therapy. The use of pharmacogenomics in determining the functioning of various drugs in individual patients will be a boon for clinicians to decide the appropriate dosage. Research concerning targeted drug therapy has advanced exponentially and could be ideal for treatment of diseases like cancer and AIDS without major side effects and also for management. This has been enhanced by the availability of advanced technologies such as SNPs and DNA microarrays which helps in analyzing genetic changes.

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Stomatological management of head and neck cancer patients treated with chemotherapy and radiotherapy

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regeneration perspectives.

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Key words: Stomatological management; Head and neck; Cancer

Core tip: The aim of the present study was to conduct a review of therapeutic advances in the prevention and management of oral disorders in head and neck cancer patients receiving radio- and chemotherapy. The study focuses on possible risk factors and on the prevention of these disorders.

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Abstract

Treatment of head and neck cancer with radiotherapy and/or chemotherapy can cause oral damage. Long-term treatment can damage the salivary glands, the oral mucosa, and the maxilla, leading to altered production of saliva and to multiple infections. These lesions can be prevented, limited or avoided by thorough evaluation prior to treatment and by therapeutic follow-up and preventive measures. The dentist must have strong medical knowledge of the possible short-, medium-, and long-term oral complications of the cancer treatment, and must have knowledge of the protocols for oral management of cancer patients. The availability of a multidisciplinary medical team together with a dentist to attend to the patient prior to the cancer treatment, as well as close communication between team members during and after treatment, is crucial. The aim of the present study was review the stomatological management of head and neck cancer patients treated with chemotherapy and radiotherapy and summarizing current treatments, therapeutic innovation and tissue

INTRODUCTION

In recent decades, an increase in the prevalence of oral cancer has been observed in several countries. Surgery, radiotherapy and chemotherapy continue to be the treatments of choice for such cancers, and advances have been made in minimizing their adverse effects^[1]. However, treatment of cancer with radiotherapy and/or chemotherapy can cause oral damage. Long-term treatment can damage the salivary glands, the oral mucosa, and the maxilla, leading to altered production of saliva and to multiple infections^[2]. The surgical treatment of oral and maxillofacial neoplasms can lead to sequelae such as limited speech, eating disorders, alterations in the patient's sense of taste and smell, and changes in the patient's physical appearance^[3,4]

Lesions of the oral cavity secondary to head and neck

cancer treatment can be prevented, limited or avoided by thorough evaluation prior to treatment and by therapeutic follow-up and preventive measures^[5].

The dentist must have strong medical knowledge and be continuously updated on common head and neck malignant neoplasms, their clinical manifestations, therapeutic alternatives, and the complications that may occur as a result of their treatment^[6].

The availability of a multidisciplinary medical team consisting of an oncologist, a hematologist, a head and neck surgeon, a radiologist, a physiotherapist, a speech therapist, a social worker, and a psychologist together with a dentist to attend to the patient prior to the cancer treatment, as well as close communication between team members during and after treatment, is crucial^[5,7].

Ideally, cancer centers should provide oral health care. However, because patients are frequently referred to the family dentist, dentists must have basic knowledge of the protocols for oral management of cancer patients and of the relevant National Cancer Institute guidelines^[8].

INITIAL CONTACT WITH THE PATIENT

It is important for the dentist to join the oncology team so that he or she is informed of the type of surgery and radio- and/or chemotherapy the patient will receive^[5,9].

At the patient's first visit, the dentist must perform a complete oral health evaluation to establish an integral oral and maxillofacial management plan before the cancer treatment is initiated^[5].

The possible short-, medium- and long-term oral complications of the cancer treatment must be explained to the patient and to his or her close relatives^[10] in a simple and didactical way, preferably through the use of images, so that they will be able to identify problems such as xerostomia and mucositis. Patients must be instructed in the importance of dental follow-up care before, during, and after chemo- and radiotherapy as a means of preventing radiation-associated dental caries and osteonecrosis. The dentist must provide the patient and the patient's relatives with an instructional manual on oral hygiene, diet, and measures to be followed before, during, and after cancer treatment^[11-14].

The primary objective of providing information to the patient and of diagnosing and treating the patient prior to cancer treatment is to eliminate or stabilize any oral lesions that are present and to minimize the possibility of the occurrence of local or systemic infections during or after cancer treatment^[14-16].

Patients often show tumor-related symptoms or dental conditions related to an incisional biopsy or pre-surgical therapy. These symptoms must be evaluated and correctly diagnosed so as to differentiate tumor symptoms from previous oral manifestations of dental caries, periodontal disease, pulpal diseases and soft tissue conditions^[13,17].

A detailed exploration of the head and neck region must be performed following a preset order from external to internal, and abnormal growth, asymmetries, and cutaneous lesions must be identified and evaluated. Salivary

glands, muscles, and the temporomandibular joint must be inspected. Palpation of submental, submandibular, and cervical lymph nodes is important and must be followed by an intraoral examination starting with the soft tissues, buccal mucosa, tongue, floor of the mouth, and the hard and soft palates. Any lesion, irritation, erosion, ulceration, or hemorrhage must be identified, and the patient's general periodontal state must be evaluated as well^[18].

It is essential to note the presence of caries, damaged restorations, pulpal lesions, necrotic teeth, or apical lesions suggestive of a cyst or granuloma.

The clinical diagnosis is complemented by X-ray imaging with a full set of periapical radiographs and by orthopantomography.

PREVIOUS DENTAL TREATMENT

The essential steps of dental pre-treatment prior to anticancer therapy are focused on the elimination or stabilization of oral lesions and are aimed at minimizing the presence of potential sites of infection during or after treatment^[19,20].

The important goals of such pre-treatment are as follows: (1) To eliminate any deep carious processes that may compromise pulp vitality during cancer treatment; (2) To control pulp and periapical infections two weeks before therapy to ensure tissue healing; (3) To restore or extract any tooth that shows a periapical lesion because such teeth can become infection sites in patients receiving chemo- and radiotherapy and these treatments affect the immune response; (4) To extract teeth with poor periodontal or pulpal prognosis, such as teeth with deep caries or deep periodontal pockets and non-vital teeth with an expectancy of less than one year in the mouth. The extraction should be performed as soon as possible and at least three weeks before cancer therapy begins to ensure that the healing process is completed before the onset of therapy; (5) To assess the need for extraction of teeth associated with the tumor or radiation site; (6) To eliminate or restore sharp edges of fractured teeth to reduce mucosal friction or trauma that could aggravate mucositis; (7) To assess the need for extraction of retained teeth and impacted third molars that can cause pericoronitis; (8) The use of pit and fissure plaque sealants on recently erupted teeth is recommended; (9) To perform dental hygiene and scaling to completely eliminate dental and supra- and infra gingival tartar; (10) To inform the patient of the need to change a cariogenic diet^[7] and to suspend the consumption of alcohol, tobacco, and any foods or substances that can damage oral structures; (11) To evaluate the need for adjustment or removal of partial or complete dentures or orthodontic appliances that can cause irritation or trauma. During the cancer treatment, dentures must be used by the patient only when eating; and (12) To encourage the patient to maintain proper oral hygiene and to emphasize a preventive treatment aiming on remineralization to minimize caries formation. The patient must be advised to: use fluoride toothpaste; brush his/her teeth four times a day, including after every meal;

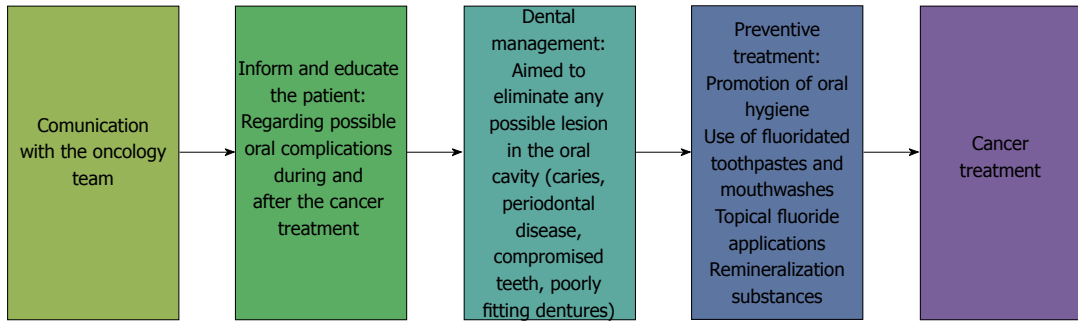


Figure 1 Steps the dentist should follow before cancer treatment is initiated.

use topical fluoride gel daily for 5 min at bedtime; use a calcium phosphopeptide remineralization cream; use alcohol-free fluoride mouthwash.

The diagnostic, preventive, and therapeutic steps that should be followed prior to cancer treatment are shown in Figure 1.

PATIENTS UNDERGOING RADIOTHERAPY

Conventional radiotherapy is very useful in the treatment of oral carcinoma; however, it acts on both tumor cells and healthy cells, producing tissue damage. Approximately 50% of malignant head and neck neoplasms are treated with radiotherapy alone or with chemotherapy and surgery. Radiotherapy involves the use of ionizing radiation, which produces morphological and functional changes in tissues and has chemical effects, included the hydrolysis of intracellular constituents and the rupture of DNA strands^[20].

The response of tissue to radiation depends on a variety of factors, including the received dose, the fractionation dose, the nature of the radiation, the previous condition of the irradiated tissue, the degree of cell differentiation, cellular kinetics, cell temperature, and the tumor's sensitivity to radiation, location and oxygenation^[21].

ORAL COMPLICATIONS OF RADIOTHERAPY

Complications are classified depending on their time of appearance (immediate, medium and late side effects), their intensity, and as reversible or irreversible. Immediate complications appear within 1 wk of treatment and may include erythema, mucositis, dysgeusia, glossodynia, infections (candidiasis, herpes), xerostomia, periodontal disease, severe necrosis, and alopecia. Medium-term complications appear after the third month of treatment and may include trismus, caries, dysphagia, and dental hypersensitivity. Late side effects appear months after the treatment and may include osteoradionecrosis, alterations in tooth development (agenesis, coronal hypocalcification such as enamel hypoplasia, and root alterations such as root shortening, early canal closure, and dilaceration),

pulpal necrosis, and pain. Table 1 shows the most frequent complications of radiotherapy classified by time of appearance and prognosis^[22].

Preventive measures and management of oral complications of radiotherapy

The occurrence of oral complications of radiotherapy (Figure 2) can be minimized by taking the following preventive actions: Educating the patient about the importance of oral hygiene and emphasizing the cessation of toxic habits such as alcohol and tobacco consumption. Performing professional dental cleaning including tartar removal, root scaling and planing. Eliminating areas of trauma resulting from ill-fitting dentures and sharp edges. Suspending the use of mucosa-supported dentures for 15 d after radiotherapy begins; if possible, suspending their use indefinitely or using them moderately to avoid trauma. Protecting salivary glands and the mucosa of areas that do not require irradiation. Performing quantitative sialometry to evaluate the production of saliva after radiation doses. Extracting compromised or severely damaged teeth (severe periodontal disease, mobility, fractures, caries). Performing conservative dental treatments that include restorations and root canal therapy. Applying topical fluoride before, during, and after radiation treatment. Recommending the use of 0.12% chlorhexidine mouthwashes. Applying pit and fissure sealants to recently erupted premolars and molars in pediatric patients. Modifying the cariogenic diet. The first side effects of a cariogenic diet may become obvious after radiotherapy.

PATIENTS UNDERGOING CHEMOTHERAPY

Chemotherapy in cancer treatment consists of the use of cytotoxic drugs that are intended to destroy or avoid the proliferation of tumor cells. This therapy is not selective; it affects both tumor cells and normal cells, especially cells that undergo rapid cell cycling for continuous replacement. Such cells include bone marrow cells, cells of hair follicles, and gastrointestinal epithelial cells, including oral mucosal cells^[23].

Cisplatin, cyclophosphamide, methotrexate, bleomycin, 5-fluorouracil, and vinblastine are used most frequently in the treatment of head and neck neoplasms^[24]. The use of

Table 1 Common complications of the head and neck region following radiotherapy

Complication	Characteristics	Time of appearance	Prognosis
Erythema/radiodermatitis	Redness/ decreased skin thickness; skin dryness due to epidermal basal cell damage	Immediate	Reversible
Mucositis	Generalized inflammation of the oral mucosa due to basal cell damage; scaling, mucosal ulcerations	Immediate	Reversible
Dysgeusia	Altered taste (especially to sour and acid tastes) due to taste bud damage	Immediate	Reversible
Glossodynia	Pain and burning sensation in the tongue due to taste bud damage and inflammation	Immediate	Reversible
Candidiasis and Herpes simplex	Secondary infections resulting from loss of mucosal protection caused by mucositis and xerostomia	Immediate	Reversible
Xerostomia	Decrease in salivary flow and dryness of the mouth caused by alterations in salivary glands	Immediate	Irreversible at high radiation doses (more than 60 Gy)
Periodontal disease	Inflammation of the periodontium due to augmented plaque from decreased salivary flow	Immediate	Reversible
Alopecia	Hair loss from hair follicle atrophy	Immediate	Reversible
Severe necrosis	Loss of tissue, scurvy and malodorous ulcerations	Immediate	Irreversible
Trismus	Reduced mouth opening caused by fibrosis of the muscles of mastication or of the temporomandibular joint	Medium-term	Reversible/irreversible
Caries	Damage to the cement-enamel junction, incisal edges and cusps caused by decreased salivation	Medium-term	Irreversible
Dysphagia	Difficulty swallowing food caused by oropharyngeal alterations; may be evidenced by malnutrition	Medium-term	Reversible
Dental hypersensitivity	Dental sensitivity caused by radiation	Medium-term	Reversible
Osteoradionecrosis	Aseptic necrosis of the irradiated bone	Late	Irreversible
Tooth germ alterations	Alteration in odontogenesis in pediatric patients	Late	Irreversible
Pulp necrosis and pain	Pulp necrosis and pain	Late	Irreversible

these drugs may affect the basal epithelial cells that make up the oral mucosal epithelium. When these cells are damaged, the replacement of the epithelium is compromised and scaling and ulcerations of the mucosa occur. Furthermore, xerostomia caused by salivary gland damage may occur, with resulting alterations in the levels of saliva protectors and ageusia. A high percentage of patients present oral infections, bleeding, or a combination of both, and more than 50% of patients also present complications from surgery and head and neck radiotherapy. Most patients who receive high doses of chemotherapy for head and neck cancer develop severe mucositis^[24-26].

Bone marrow suppression is one of the most common side effects of chemotherapy. It is often evident in peripheral blood after 10-14 d of treatment; typical signs are leukopenia, neutropenia, thrombocytopenia and anemia. Hair loss, nausea, vomiting, and palmoplantar erythrodysesthesia syndrome are common. The latter is a palmoplantar erythema with erosions, burning sensation, and local pain^[27].

PATIENTS UNDERGOING BISPHOSPHONATE TREATMENT

Bisphosphonates are a group of drugs used for the prevention and treatment of bone resorption diseases such as maxillofacial cancer, bone metastasis, malignant hypercalcemia, osteoporosis, Paget's disease, and multiple myeloma. Their structure is based on that of pyrophosphate, a metabolite that regulates the precipitation and extraction of bone minerals; similar to pyrophosphate,

they are sensitive to hydrolysis by phosphatases^[28-30].

When bisphosphonates are incorporated into bone, osteoclast-mediated bone resorption is prevented, and osteoclast apoptosis is stimulated. These drugs have affinity for active bone replacement sites and growth plates^[30,31].

Bone resorption does not occur in patients undergoing bisphosphonate treatment due to inhibition by bisphosphonates of the osteoclastic activity that normally causes decreased bone replacement and a lack of new bone formation. In these patients, the bone is present for a longer period without replacement, making it prone to chronic infections and necrosis. Bisphosphonates also inhibit angiogenesis, leading to diminished bone vascularization and induction of bone cell apoptosis^[27,32-34].

Osteonecrosis of the jaw is one of the complications of treatment with bisphosphonates in cancer patients. It most often occurs in the mandible and is associated with 53% of dental interventions; 48% of affected patients show a response to treatment when the drug has been used for a period of over eight weeks^[35-37].

DIAGNOSTIC CRITERIA FOR BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW

Treatment with bisphosphonates must be considered in the medical history of patients with ulcerated lesions within the jaw with bone exposure for over eight weeks, necrotic bone, or lesions that do not heal spontaneously.

Mucositis	<ul style="list-style-type: none"> • Preserve excellent oral hygiene • Avoid irritating foods (spices, coffee, acids, alcohol, tobacco, <i>etc.</i>) • 0.12% chlorhexidine mouthwashes • 2% lidocaine or 1% dyclonine hydrochloride topical anesthetics in an aqueous or viscous solution or mucoadhesive benzocaine hydrochloride to reduce pain • Use of epithelial protective drugs such as kaolin, magnesium hydrochloride, aluminum hydrochloride • Conventional strong analgesics and antiinflammatory drugs • Soft diet • Hydration • If secondary infection occurs, a culture and a cytological test must be performed, and broad-spectrum antibiotics must be used <p>In cases of <i>Candida albicans</i> superinfection, Nystatin oral suspension should be used 4 times daily for 4 min for 4 wk in addition to 200 mg of ketoconazole per day or 100 mg of fluconazole. A cyclovir is prescribed for <i>Herpes simplex</i></p>
Dysgeusia	<ul style="list-style-type: none"> • Zinc supplements: 110-120 mg of zinc sulfate 2 times per day • Diet modification
Xerostomia	<ul style="list-style-type: none"> • Increase hydration • Use of carboxymethyl cellulose saliva substitutes, sorbitol synthetic saliva, artificial saliva • Sialogogues with xylitol, such as gum • 5 mg pilocarpine in the morning and at night • 2% pilocarpine droplets applied to the floor of the mouth
Osteoradionecrosis	<ul style="list-style-type: none"> • Preventive measures • Avoid mucosal trauma • Avoid dental extractions • Irrigation with physiological solution, antibiotics • Chlorhexidine mouthwashes and irrigations • Use of hyperbaric oxygen • Avoid the use of regional or intraligamentary anesthesia, maintain low vasoconstriction
Trismus	<ul style="list-style-type: none"> • Physiotherapy • Muscle relaxant drugs
Caries from radiation	<ul style="list-style-type: none"> • Daily application of topical fluoride and fluoride mouthwash • Chlorhexidine mouthwash • Meticulous oral hygiene with use of a soft toothbrush • Eliminating cariogenic diet • Frequent dental check-ups to evaluate oral health
Pain	<ul style="list-style-type: none"> • Depending on the degree of pain: acetylsalicylic acid, codeine, dihydrocodeine, Tramadol

Figure 2 Treatment steps the dentist must follow in cases of oral complications in radiotherapy patients.

Additional tests such as orthopantomography and computerized tomography scanning are recommended to evaluate the extent of the lesion.

PREVENTIVE MEASURES IN PATIENTS UNDERGOING BISPHOSPHONATE TREATMENT

Once oral or intravenous treatment with bisphosphonates has been decided upon, preventive measures must

be taken before and after treatment to avoid or minimize osteonecrosis^[38,39].

Basic preventive measures prior to treatment focus on eliminating potential sites of infection and extracting teeth with poor prognoses to minimize the risk during therapy^[40]. Once treatment has begun, meticulous control of the patient must be maintained so as to detect any sign of osteonecrosis. Good oral hygiene with plaque control and dental cleaning, tartar removal, and periodontal pocket treatment must also be included. Surgical procedures must be minimally invasive, performed only when

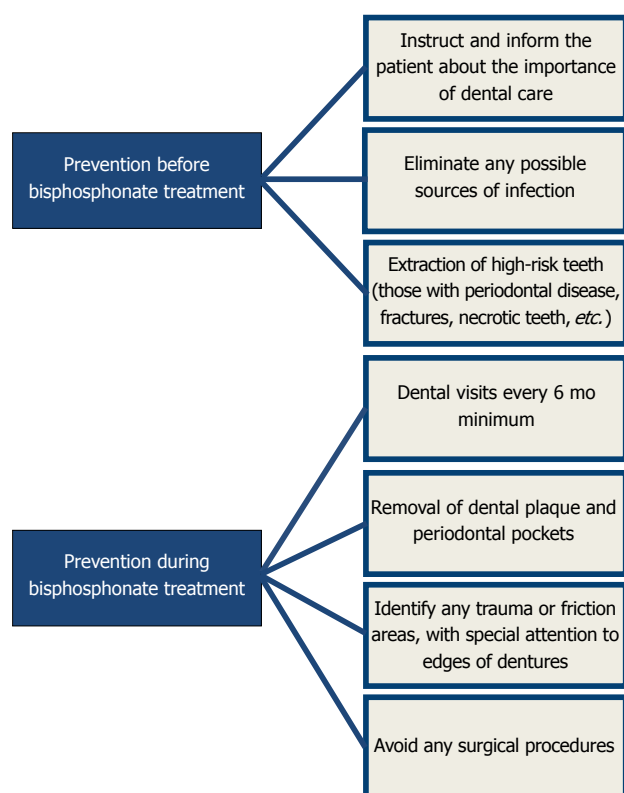


Figure 3 Preventive measures for bisphosphonate-related osteonecrosis of the jaw.

necessary, and include prophylactic antibiotic treatment and the use of chlorhexidine mouthwashes.

The Figure 3 outlines the preventive measures that must be followed before and after bisphosphonate treatment.

TREATMENT OF OSTEONECROSIS

The treatment of osteonecrosis consists of eliminating pain, controlling bone and soft tissue infections, reducing the progression of bone necrosis, decreasing or eliminating possible risk factors, improving oral hygiene, and following a specific antibiotic therapy protocol that is based on a previous culture growth and antibiogram of the exposed bone. If possible, bisphosphonate treatment should be suspended for 6 to 12 mo, which will allow improvement and possible resolution of the condition. Suspension of corticosteroid treatment is recommended when such agents are used as adjuvants in the maintenance treatment. When conservative management fails, surgical debridement of necrotic bone tissue with a primary tension-free closure is an option, all with coadjuvant antibiotic prophylactic therapy^[10,41-43].

Treatment depends on the size and extent of the lesion. Figure 4 outlines the treatment protocol depending on the extent of the lesion.

THERAPEUTIC INNOVATION AND TISSUE REGENERATION PERSPECTIVES

Tissues injured by chemo- and radiotherapy require

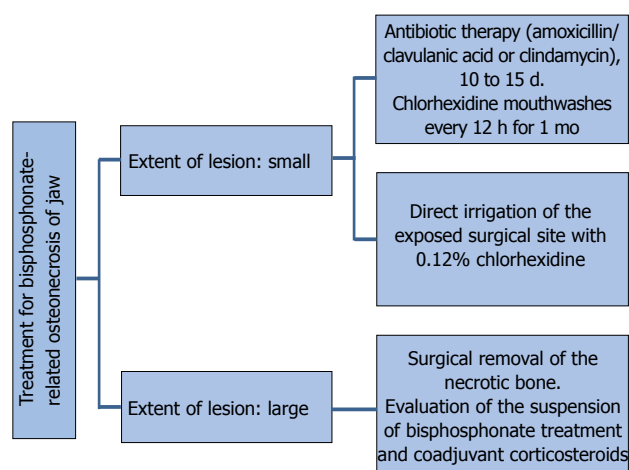


Figure 4 Therapeutic steps to be followed by the dentist in cases of bisphosphonate-related osteonecrosis of the jaw.

preventive measures to minimize damage. Furthermore, severe lesions with no possible repair require additional therapy. In this regard, the stem cell transplant described above is undergoing further development with the goal of achieving the regeneration of tissue damaged by radio- or chemotherapy.

Tissue and organ regeneration requires cells that can regenerate and that are similar to the cells that have been damaged, often irreversibly, by chemo- and radiotherapy. The possibility of restoring these cells allows consideration of tissue regeneration as a therapeutic option.

As the backbone of regenerative medicine, stem cells have acquired a decisive importance; scientific research in the field of stem cell biology has proven to be essential for allowing a transfer from basic to therapeutic research and generating new perspectives for clinical treatment.

Stem cells are defined as “cells that have both the capacity to self-renew (make more stem cells by cell division) and to differentiate into mature, specialized cells”^[43]. Therefore, these cells provide a source of cells that can both generate other stem cells and form specific tissues and organs. Their absence limits or prevents regeneration.

Stem cell migration to the damaged site, as well as stem cell transplantation, are being considered as options in therapeutic regeneration, and currently, there are similar initiatives in radiotherapy^[44,45]. Although at an experimental stage, the use of stem cells in such regeneration is potentially a viable therapeutic alternative. As indicated above, this approach could potentially be used to repair lesions caused by chemotherapy.

One of the therapeutic advantages of stem cell transplantation is the possibility of autologous transplantation; this would prevent the occurrence of graft versus host disease.

While research is progressing in this field, it must presently be considered an experimental field that, as such, does not permit the formation of any definitive conclusions.

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Molecular biomarkers of cell proliferation in ameloblastomas

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Abstract

Cell proliferation is a vital biological process that is important for all living organisms because of its role in growth and the maintenance of tissue homeostasis. The control of this important process differs greatly among benign and malignant neoplasms, and the evaluation of cell proliferation in neoplasms has become a common tool used by pathologists to provide useful information pertaining to diagnosis, clinical behavior, and treatment. The usefulness of information regarding cell proliferation has led to numerous studies on the value of these methods for diagnosing different types of tumors and for clinical decision making. Ameloblastomas are no exception. This review discusses the use of several classical molecular proliferation markers, including Ki-67, proliferating cell nuclear antigen, cyclin D1 and DNA topoisomerase II alpha, to characterize ameloblastomas and proposes the use of new proliferation markers used previously to characterize other neoplasms. The use of these biomark-

ers offers valuable opportunities to evaluate the biological behavior of this type of odontogenic tumor.

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Key words: Ameloblastoma; Ki-67; Proliferating cell nuclear antigen; cyclin D1; DNA topoisomerase

Core tip: Specific molecular markers are characteristic of particular cellular events such as proliferation, and in this context, "proliferation markers" refer to specific proteins or other factors in actively growing and dividing cells, whose presence serves as an indicator for such cells. In this mini-review, we aim to provide an overview of the methods currently available for the assessment of proliferation, and we review the different cell proliferation markers used to assess the biological behavior of ameloblastomas. In addition, we propose a new marker.

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INTRODUCTION

New cells are generated from pre-existing cells through an ordered sequence of events that is repeated. These events constitute the cell cycle. Traditionally, the cell cycle is divided into stages, the duration of which varies depending on the cell type.

The division of an original cell into daughter cells requires prior DNA replication and the synthesis of various proteins associated with this replication step, as well as the production of structures and organelles for the new cells. These processes occur at the interphase of the cycle, which itself is divided into phases: G1 (Gap 1), S

(Synthesis) and G2 (Gap 2).

When all the conditions necessary for division are met, M stage (or division) starts, which results in the separation of the chromosomes and then the division of the cytoplasm, known as cytokinesis. Some cells can remain in a state of active metabolism for a very long time without replicating their DNA or dividing. These cells are in G0 phase or the quiescent state. G0 is also considered a post-mitotic state^[1].

The different cell types divide in a regulated manner. Certain environmental changes, such as temperature variations, changes in pH, nutrient scarcity and contact with neighboring cells, can slow down the cell cycle. Additionally, the presence of growth factors and hormones can trigger a series of intracellular processes that stimulate cell division. Cell proliferation can be defined as an increase in the number of cells as a result of cell growth and cell division.

In neoplastic processes, the abnormal and uncontrolled proliferation of cells is observed, and the cell cycle is altered. The assessment of cell proliferation activity in tumors has become a common tool used by histopathologists to provide useful information for assessing and predicting the behavior of tumors—that is, their likelihood of local recurrence, their metastatic potential, and the growth of metastases, and thus the likely duration of disease-free survival and survival to death^[2]. Today, the most common method for evaluating proliferative activity is the use of immunohistochemical techniques.

Immunohistochemical staining is widely used in the identification of abnormal cells such as those found in cancerous tumors. This technique is also widely used in basic research to understand the distribution and localization of biomarkers and differentially expressed proteins in different parts of a biological specimen.

Specific molecular markers are characteristic of particular cellular events such as proliferation, and in this context, “proliferation markers” refer to specific proteins or other factors in actively growing and dividing cells, whose presence serves as an indicator for such cells^[3].

Two requirements have been postulated for this type of marker: (1) the antigen should be continuously present during the cell cycle of all cell types; and (2) the transition to a nonproliferative state from any step of the cell cycle should be followed by a rapid disappearance of the antigen^[4].

Odontogenic tumors constitute a group of heterogeneous lesions that range from hamartomatous or non-neoplastic tissue proliferations to benign and malignant neoplasms with variable aggressiveness.

Odontoma is the most common odontogenic tumor, but it is considered a non-neoplastic lesion. Ameloblastoma is the most common odontogenic neoplasm. According to the 2005 Histological Classification of Tumors of the World Health Organization, ameloblastomas are divided into four variants: solid/multicystic, extrasosseous/peripheral, desmoplastic and unicystic. There exist several histological subtypes: follicular, plexiform, acanthomatous, granular and basal cell. Although ameloblastomas are classified as benign neoplasms, they can be locally invasive and destructive tumors of the jawbone. The molecular

mechanisms that regulate cell growth and invasion in ameloblastomas are unknown. Determining the proliferative activity of ameloblastomas may provide important information regarding the appropriate treatment strategy.

In this mini-review, we aim to provide an overview of the methods currently available for the assessment of proliferation, and we review the different cell proliferation markers used to assess the biological behavior of ameloblastomas.

There are many methods for determining the level of proliferative activity in different types of tumors, including the analysis of the mitotic index, flow cytometry, silver staining (AgNOR), and immunohistochemistry techniques. The last two are the most widely used techniques to study ameloblastomas.

It is important to clarify that there are more specific and sensitive techniques for determining the presence of these proliferation markers such proteomics techniques which allow to know what proteins are present or absent in these tumors. Another technique quantitative, sensitive and highly specific is the real-time polymerase chain reaction that allows determining the expression levels of genes in the ameloblastoma.

Both techniques are more expensive and more laborious than the immunohistochemistry technique that despite having less specificity and sensitivity has the advantage of being able to display “*in situ*” the presence of proteins, important data for understanding how the tumor proliferates.

MOLECULAR MARKERS

Silver binding nucleolar organizer region

Several methods have been used for the identification of proliferating cells in tissue sections with the aim of using them as markers of impending malignancy. One among of these methods is the silver binding nucleolar organizer region (AgNOR) technique.

Nucleolar organizer regions (NORs) are segments of DNA that are closely associated with nucleoli, which contain the ribosomal DNA. These regions therefore contribute strongly to the regulation of protein synthesis. NORs are argyrophilic and can therefore be visualized using a silver staining technique, what has led to the use of the term AgNOR^[2]. AgNOR staining is a simple one-step staining technique that overcomes the disadvantages of other techniques, such as the requirements for sophisticated equipment and technical expertise, high cost and long run-time^[3,5]. The amount of AgNOR protein, estimated during interphase, can be used as a marker of cell proliferation and has prognostic value for several human cancers.

In the study by Seifi *et al.*^[6], the number of AgNOR dots in solid/multicystic ameloblastomas was found to be higher than that in unicystic ameloblastomas.

Coleman *et al.*^[7] reported that unicystic ameloblastomas lined with characteristic epithelium had a significantly lower AgNOR count than solid ameloblastomas, residual dentigerous cysts and keratocystic odontogenic tumors, and these authors concluded that AgNOR counts are not

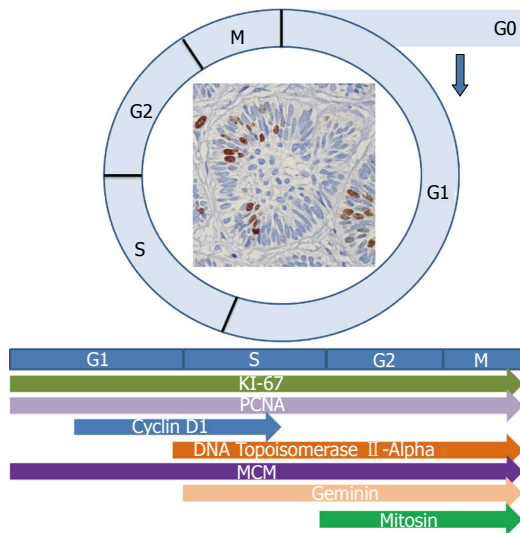


Figure 1 Presence of proliferation markers proteins during the cell cycle phases. The figure illustrates the presence of each marker of cell proliferation at different phases of the cell cycle. G1: Gap 1; G2: Gap 2; S: Synthesis; M: M-phase; PCNA: Proliferating cell nuclear antigen; MCM: Minichromosome maintenance complex.

of diagnostic significance and cannot be used to distinguish the various types of odontogenic cysts from one another or from unicystic ameloblastomas.

In terms of histological patterns, a significant difference has been found only between the follicular and plexiform types^[8]. A significantly higher number of Ag-NOR dots per nucleus was found in follicular ameloblastoma cells than in plexiform ameloblastoma cells^[9].

IMMUNOHISTOCHEMISTRY OF PROLIFERATION-ASSOCIATED ANTIGENS

Ki-67

The monoclonal antibody Ki-67 was first described in 1983 by Gerdes *et al.*^[10], who suggested that it might be used as a marker for proliferating cells. The Ki-67 antigen (Ki-67) is a classic marker of cellular proliferation and has been widely applied in the diagnostic, research and drug-discovery fields. The Ki-67 antigen was originally defined by the monoclonal antibody Ki-67, the name of which was derived from the city of origin (Kiel) and the number of the original clone in the 96-well plate^[10]. The expression of Ki-67 occurs during all phases of the cell cycle except the G0 phase and the early G1 phase (Figure 1), and the expression level increases as cell proliferation progresses, especially in the S phase, with peaks in the G2 and M phases. This protein is then degraded rapidly after mitosis^[3]. The standard antibody for the detection of Ki-67 is MIB-1. The fraction of MIB-1-positive tumor cells (the MIB-1/Ki-67 labeling index) is often correlated with the clinical course of the cancer, and Ki-67 is of prognostic value for many types of malignant tumors^[11]. There have been numerous studies that have aimed to determine the

Table 1 Cell proliferative activity measured using Ki-67 and/or proliferating cell nuclear antigen antibodies in ameloblastomas

Ref.	n	Type (n)	Ki-67	PCNA
Kim <i>et al.</i> ^[40]	38	Unicystic (13)		+
		Solid/Multicystic (25)		+
		Follicular		+
		Plexiform		
		Acanthomatous		
		Granular		
		Basal Cell		
		Ameloblastic Carcinoma		+
Fonaoka <i>et al.</i> ^[41]	23	Plexiform (15)		++
		Follicular (5)		+++
		Unicystic (3)		+
Ong'uti <i>et al.</i> ^[18]	54	Plexiform (30)	+	
		Follicular (24)	++	
Piatelli <i>et al.</i> ^[42]	22	Unicystic (5)		+
		Solid/Multicystic (13)		
		Plexiform (5)		++++
		Follicular (4)		++
		Acanthomatous (4)		+++
Nagao <i>et al.</i> ^[43]	30	Plexiform (15)	++	
		Follicular (15)	+	
Sandra <i>et al.</i> ^[12]	32	Plexiform (9)	++++	++++
		Follicular (9)	+++++	+++++
		Acanthomatous (3)	+++	+++
		Basal Cell (3)	+++++	+++++
		Desmoplastic (3)	+	++
		Unicystic (5)	++	+
Han <i>et al.</i> ^[19]	70	Follicular (ND)	+++	
		Plexiform (ND)	++	
		Unicystic (ND)	+	
Meer <i>et al.</i> ^[15]	20	Solid/Multicystic (10)	+	+
		Unicystic (10)	++	++
Galvão <i>et al.</i> ^[44]	16	Follicular (7)		++++
		Plexiform (4)		++
		Acanthomatous (3)		+++
		Basal Cell (2)		+
Bologna-Molina <i>et al.</i> ^[3,13,45]	120	Solid/Multicystic (66)	+++	+++
	10	Unicystic (87)	++++	++++
	161	Peripheral (3)	++	++
		Desmoplastic (5)	+	+
		Ameloblastic Carcinoma (4)	+++++	+++++
Rizzardi <i>et al.</i> ^[14]	15	Peripheral (2)	+++	
		Unicystic (2)	++	
		Solid/Multicystic (11)	+	
Salehinejad ^[46]	30	Plexiform (15)		+
		Follicular (12)		+
		Acanthomatous (3)		++
Yoon <i>et al.</i> ^[47]	17	Ameloblastomas (10)	+	
		Ameloblastic Carcinoma (7)	++	
Maya <i>et al.</i> ^[21]	15	Plexiform		+++
		Follicular		++
		Unicystic		+

The table describes the immunohistochemical studies performed with markers proliferating cell nuclear antigen and Ki-67 from the year 1994 to date. PCNA: Proliferating cell nuclear antigen.

proliferative capacity of ameloblastomas using the Ki-67 marker (Table 1). However, the comparisons of solid or multicystic tumors with unicystic tumors have yielded conflicting results. Some authors found a higher rate of positivity for Ki-67 in the solid/multicystic type^[12], but other authors obtained different results, finding that the unicystic type had greater Ki-67 positivity^[13-15]. Given that

several clinicopathological studies have found that solid ameloblastomas are more aggressive than unicystic ameloblastomas^[16-19], the higher index of cell proliferation in unicystic ameloblastomas (determined using the Ki-67 antibody) found in some studies appears contradictory. This finding could be explained by the fact that unicystic ameloblastomas contain fewer stellate reticulum-like cells than solid/multicystic ameloblastomas, and consequently, most of the cells counted corresponded to basal or suprabasal layers, which are more likely to be positive. In other words, the proportions of the diverse types of epithelial cells, as well as the different mechanisms of growth in unicystic ameloblastoma and solid/multicystic ameloblastoma, may influence the results of the proliferation index^[13].

When histological subtypes were studied Ong'uti *et al.*^[18] in a study of 54 cases of ameloblastoma in Kenya, these researchers found that follicular ameloblastomas had a higher proliferation index than the plexiform variant. These results are similar to those of Han *et al.*^[19], who studied a Chinese population and found a slight predominance of a higher proliferation index in the follicular variant. Sandra and colleagues included the basal cell variant in their study, and this variant was found to have greater positivity for Ki-67 than the follicular variant^[12]. In our previous study, we found similar results, with the follicular variant having a higher proliferation index^[13].

Proliferating cell nuclear antigen

Proliferating cell nuclear antigen (PCNA) is a nuclear nonhistone protein that is necessary for DNA synthesis and is an accessory protein for DNA polymerase alpha, the expression of PCNA occurs during all phases of the cell cycle and the level of this protein is elevated during the G1/S phase of the cell cycle (Figure 1). PCNA expression can be used as a marker of cell proliferation because cells remain in the G1/S phase for a longer time when proliferating. Furthermore, this protein has an essential role in nucleic acid metabolism as a component of the DNA replication and repair machinery^[20,21].

Multiple studies using PCNA have been performed to determine the rates of cell proliferation in various types of ameloblastomas, but the results are contradictory (Table 1). Some authors did not find any relevant differences between the different types and subtypes of ameloblastomas^[3,11,22]. This result is most likely because PCNA is also involved in DNA repair. Because there is active ongoing DNA repair in many tumors, PCNA may also be upregulated in non-proliferating cells. Indeed, in some tumors, 100% of cells show positive staining. Therefore, after an initial period of popularity, PCNA is no longer considered a reliable proliferation marker in tumors^[2]. Despite this conclusion, there are still numerous studies using PCNA as the first-choice marker of cell proliferation in ameloblastomas (Table 1).

Cyclin D1

The cyclins, together with cyclin-dependent kinases (CDKs), are the proteins responsible for the orderly

progression of cells through the cell cycle. Cyclin D1 is amplified and/or overexpressed in a substantial proportion of different human tumors. Increased cyclin D1 expression occurs relatively early during tumorigenesis^[23]. Changes in the genes encoding these proteins as well as changes in the expression levels of these proteins are found during the process of carcinogenesis. The overexpression of this protein leads to uncontrolled cell proliferation and tumor development^[23]. Cyclin D1 is the regulatory subunit of the holoenzyme that phosphorylates and, together with sequential phosphorylation by cyclin E/CDK2, inactivates the cell-cycle inhibiting function of the retinoblastoma protein (pRb). pRb serves as a gatekeeper for the G1 phase, and passage through this restriction point leads to DNA synthesis. Thus, cyclin D1 promotes progression through the G1/S phase of the cell cycle (Figure 1)^[24,25].

Follicular and plexiform ameloblastomas express cyclin D1 in many peripheral columnar or cuboidal cells and in some central polyhedral cells. No distinct difference in the reaction was detected between these two main tumor types^[26]. Kumam *et al.*^[27] found that 19/25 follicular ameloblastomas were positive for staining with the cyclin D1 antibody, as were 9/10 plexiform ameloblastomas and 3/4 unicystic ameloblastomas.

DNA topoisomerase II alpha

DNA topoisomerases are enzymes that disentangle the topological problems that arise from double-stranded DNA. Many of these problems can be solved by generating either single- or double-strand breaks. However, when it is necessary to alter the DNA topology by introducing transient double-strand breaks, only DNA topoisomerase II (Top2) can fix the problem^[28]. Type II topoisomerases change the DNA topology by generating transient DNA double-strand breaks. The DNA topoisomerase II alpha (TOP2α) is one of the major nuclear proteins, with peak expression in the S to G2/M phase. It is involved in nearly every aspect of DNA metabolism, playing an important role in chromosome organization and segregation^[28].

Kumamoto *et al.*^[26] studied the presence of this protein in tooth germs and ameloblastomas, finding lower expression than that reported for Ki-67.

New cell proliferation markers

The usefulness of a marker for tumor diagnosis must be tested for each tumor type and application. Only those markers that have proven to be useful in practice should be considered. These three new cell proliferation markers have been studied in various types of cancer, although there are not currently any reports demonstrating their usefulness in ameloblastomas.

Geminin and minichromosome maintenance complex

Minichromosome maintenance complex (MCM2-7) and geminin have important roles in the prevention of DNA re-replication during the cell cycle. MCM proteins are

expressed cells in all phases of the cell cycle, including cells that exit the G0 and enter the G1 phase^[29]. Geminin is present from the G1/S transition to the early M phase. Thus, MCM is a G0/G1/S/G2/M-phase marker, and geminin is an S/G2/M-phase marker (Figure 1)^[30]. MCM proteins are known to contribute to the regulation of transcription, chromatin remodeling and checkpoint responses. The activated MCM complex appears to play a key role in DNA unwinding, acting as a DNA helicase^[31]. Following the initiation of DNA replication during the cell cycle, geminin inhibits the reloading of the MCM complex onto chromatin and prevents DNA re-replication during the same cell cycle^[32,33].

In recent years, these two proteins have been studied in various types of malignant neoplasms and have been shown to be very useful prognostic markers^[34,35].

Mitotin

Mitotin, also termed centromere protein F (CENP-F), is a member of the human centromeric protein family. This protein is associated with the centromere/kinetochore complex and is expressed in all active phases of the cell cycle, with a maximum in G2 and M phases^[36]. At the end of mitosis, CENP-F is rapidly proteolyzed by the proteasome. Accumulating evidence suggests that CENP-F is an important protein involved in chromosome alignment and kinetochore-microtubule interactions.

The cell cycle-specific expression of CENP-F makes it a potential marker of proliferation. Indeed, CENP-F is correlated with tumor proliferation in a variety of human tumors, including lung cancer^[37], non-Hodgkin lymphoma^[38] and salivary gland tumors^[39].

CONCLUSION

The evaluation of cell proliferation activity in tumors provides useful information related to diagnosis, clinical behavior, treatment and research.

Note that the use of these biomarkers alone are not useful for the diagnosis of ameloblastoma, the diagnosis is based on clinical and histopathologic features, but yet proliferation molecular biomarkers provide important information when predicting the prognosis of patients with ameloblastoma, so the histopathological types together with proliferation marker expression could be useful tools for evaluating the biological behavior of ameloblastomas.

Over the past several decades, various cell proliferation biomarkers have been demonstrated to be useful in the study of various types of neoplasms, and these markers have been studied in some odontogenic tumors and ameloblastomas. The Ki-67 protein remains an excellent operational marker for determining the growth fraction of a given cell population and is considered the gold standard method for the evaluation of proliferation activity.

Despite the abundance of research, the results regarding which type of ameloblastoma has the highest rate of cell proliferation remain controversial. One problem is the lack of standardization regarding how to determine

the cell count among many studies. In addition, ameloblastomas are polymorphic odontogenic tumors, with various types and variants, and the specific histomorphology of each type and the different mechanisms of growth may influence the observed proliferation index counting.

In recent years there have been found some new molecular biomarkers directly involved in the proliferation biology of tumors. Today new monoclonal antibodies are being tested in different tumors, hence the importance of new research using these new markers in ameloblastomas.

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Cytotoxicity of a silorane-based dental composite on human gingival fibroblasts

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Abstract

AIM: To evaluate the direct and indirect biocompatibility of Filtek Silorane on human gingival fibroblastic cells.

METHODS: Sixty-three standardized cylindrical specimens (8 mm diameter and 2 mm thickness) of restorative material were prepared using a light emitting diode-curing unit. The sample were built up in one increment and divided in 2 groups. In the first group, 21 samples (unpolished samples) were left without a specific polishing procedure; in the second one, 42 samples (polished samples) were polished with 4 different grains of discs. Fibroblast cultures, obtained from gingiva of 2 subjects without systemic and oral disease, were used to assess the direct and indirect biocompatibility. Cells cultured for 48 h in normal culture medium were used as a control.

RESULTS: The scanning electron microscope observations of fibroblasts cultured on the silorane samples, either polished or unpolished, confirmed the good biocompatibility of the material, favouring the cellular spreading. 3-dimethylthiazol-2, 5-diphenyltetrazolium bromide tests showed a significant reduction ($P < 0.01$) of gingival fibroblasts viability cultured both in polished samples ($90.05\% \pm 19.00\%$) and unpolished samples ($78.15\% \pm 11.00\%$) compared with the control. Cells growth in medium conditioned with the samples for 1 wk showed a significant viability reduction ($P < 0.01$) compared to the control. A reduction of cell viability was observed even in the groups containing the material for 3 wk (polished: $89.45\% \pm 10.00\%$; unpolished: $65.97\% \pm 10.00\%$), even if the cytotoxicity was reduced after this long time exposure.

CONCLUSION: Although the poor chromatic availability of this material remains a big limit that restricts its use to posterior sectors, the silorane-based material can be considered an option to perform restorations when aesthetic demands are not the priority, such as the class II restorations

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Key words: Silorane; Cytotoxicity; Resin composite; Fibroblasts

Core tip: The behaviour of silorane-based materials seems to be comparable to the one observed for conventional composite material, thus decreasing the cytotoxicity after long time exposure. Further studies are still needed to characterize the biological response of these methacrylate-free composite formulations, in order to definitely demonstrate their safe use in restorative dentistry.

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INTRODUCTION

Recently, the use of composite materials for restoring dental elements has significantly increased due to the growing aesthetic demand of patients^[1].

Despite extensive improvements in mechanical and aesthetic properties of dental composites, volumetric shrinkage and contraction stress during polymerization are still a problem^[1]. Contraction stress transferred to the tooth may lead to cusp deflection or enamel micro cracks; additionally, contraction stress of tooth-composite interface can determinate post-operative sensitivity, microleakage, marginal discoloration and recurrent caries^[2].

In several studies different techniques have been investigated in order to minimize polymerization shrinkage and contraction stress^[3-7]. At the same purpose low-shrinkage materials have been proposed, but none of them offered significant improvement to Bis-GMA-based composites^[8].

In 2007, a low shrinkage dental composite based on silorane monomers has been introduced. This material contains traditional filler particles (quartz) and monomers based on a silane or a siloxane core bonded with several oxirane functional groups. The silorane monomers polymerize by a ring-opening polymerization process of the oxirane groups. According to its composition, this resin has two advantages: low polymerization shrinkage, due to the ring-opening oxirane monomer, and increased hydrophobicity, due to the presence of the siloxanes^[9].

The release of substances from dental composite materials after polymerization and their possible toxicity have been widely examined during previous years^[10-12]. Several *in vitro* studies have shown cytotoxic, genotoxic, mutagenic, or estrogenic effects of some monomers released by composite materials^[13-17].

Limited information is available about the substance eluted from silorane composite and its cell or tissue compatibility. Kopperud *et al*^[18] found no substance eluted from Filtek silorane in water, while silorane were found in ethanol solution. Krifka *et al*^[19] revealed no significant signs of cytotoxicity on human pulp-derived cells caused by silorane-based materials, while a slight increase in reactive oxygen species was detected.

The aim of present study was to evaluate the biocompatibility of Filtek silorane. The maintaining of surface architecture after finishing was also investigated. These properties were investigated in polished and unpolished silorane polymerized samples.

As regards biocompatibility, we studied the viability of human fibroblastic cells both after direct contact with silorane composite and after cells conditioning using a medium exposed to silorane.

MATERIALS AND METHODS

Sixty-three standardized cylindrical specimens (8 mm in diameter and 2 mm in thickness) were prepared using a transparent plastic molds. The molds were positioned on a glass plate and filled with Filtek silorane (3 mol/L ESPE, Seefeld, Germany). The samples were built up in one increment. The specimens were polymerized using a diode unit with a power of 1100 Mw/cm² for 60 s (LE Demetron I; Kerr, Bioggio, Switzerland). Forty two of these samples were polished using a slow speed hand-piece using 4 polishing discs of different grains (Sof-Lex discs, 3 mol/L ESPE; Seefeld, Germany), from the most (2382 C) to the least (2382 SF) abrasive. The remaining samples were left unpolished. All the samples were processed for observation under a scanning electron microscope (SEM: Philips XL20; FEI, Milano, Italy).

Cell culture

Cultured fibroblasts were obtained from subjects without systemic and oral disease, after signing informed consent. Biopsies (2 cm × 2 cm) were taken from the gingiva of 2 subjects (40 years old), rinsed twice with phosphate buffered saline (PBS) at pH 7.4, containing penicillin (100 U/mL), streptomycin (100 µg/mL) and amphotericin B (2.5 µg/mL; all from Sigma Aldrich, Milan, Italy) and cut in small pieces with a sterile blazer. The tissue fragments were placed in culture flasks of 25 cm² with Dulbecco Modified Essential Medium (DMEM), containing 1 mg/mL of collagenase (all from Sigma Aldrich), and incubated for 3 h at 37 °C. Afterwards, fragments were incubated at 37 °C (5% CO₂) in Petri plates of 35 mm containing DMEM supplemented with 10% of fetal bovine serum (FBS, Life Technologies, Monza, Italy), 4.5 g/L of glucose, penicillin (100 U/mL) and streptomycin (100 µg/mL) all from Sigma Aldrich. The first fibroblast cells were visible after 3-4 d. Culture medium was changed twice a week until cells confluence (2 wk). Using a trypsin/EDTA treatment (0.25% trypsin, 0.02% EDTA; Sigma Aldrich), the cells were detached and cultured in flasks of 75 cm² until a new confluence was achieved. Cells between the 2nd and the 4th passage of subculture have been used.

For direct toxicity test, silorane samples have been disinfected with alcohol at 70% for 3 h and washed with PBS for 24 h after the alcohol removing. After a conditioning treatment in DMEM containing 10% FBS and penicillin (100 U/mL) and streptomycin (100 µg/mL) for 24 h, the medium was discarded and samples considered suitable for cell seeding. Specimens were placed in ultra-low attachment 24/well plates (Corning, Tewksbury, MA, United States) and seeded with 1 × 10⁴ cells/cm².

To assess indirect toxicity assay, samples disinfected as previously described were placed in agitation in DMEM containing 10% FBS and penicillin (100 U/mL) and streptomycin (100 µg/mL) for 1 and 3 wk. The conditioned medium was placed in contact with fibroblasts (1 × 10⁴ cells/cm²) seeded in 24/well polystyrene plates for 48 h. Cells cultured for 48 h in normal culture medium were used as a control.

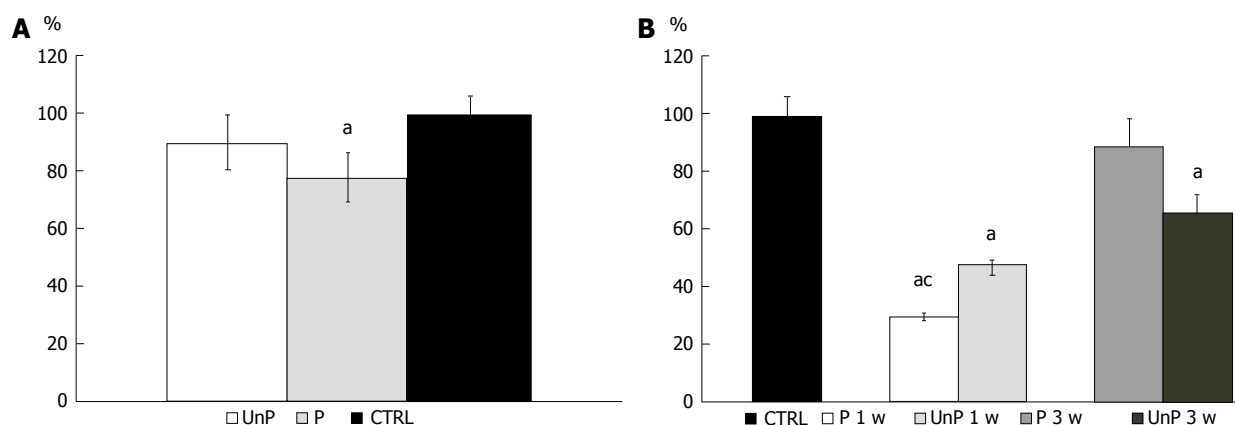


Figure 1 Histogram of cell viability. A: Cell viability of fibroblast cultured directly on unpolished samples (UnP), polished samples (P: finished surface using polishing discs) and control (CTRL); B: Cell viability of fibroblasts in CTRL, polished samples at 1 wk (P 1 w), unpolished samples at 1 wk (UnP 1 w), polished samples at 3 wk (P 3 w), unpolished samples at 3 wk (UnP 3 w); ^a $P < 0.05$ vs CTRL; ^c $P < 0.05$ P 1 w vs P 3 w.

Cell culture processing for SEM analysis

The obtained monolayer cells were fixed in 2% glutaraldehyde in cacodylate buffer for one hour at 4 °C. After fixation, cells were rinsed in cacodylate buffer 0.1 mol/L, pH 7.4 and 7% sucrose; cells were then post-fixed using 0.1% OsO₄ in cacodylate buffer 0.1 mol/L, at 7.4 pH (1 h in dark at 4 °C). After a second rinse in cacodylate buffer for 10 min, samples were dehydrated using a growing grade of ethanol (from 25% to 100%) at 4 °C with Critical Point Drying at 31.3 °C and 72.9 Atm. The samples were placed on aluminium stubs with a graphite-based glue, covered with gold, using an Edwards sputtering device, and observed with a SEM operating at 20 kV.

Cell culture processing for 3-dimethylthiazol-2, 5-diphenyltetrazolium bromide test

After 48 h of culture, medium was removed and 200 µL of a solution (5 mg/mL in medium without phenol red) containing 3-dimethylthiazol-2, 5-diphenyltetrazolium bromide (MTT; Aldrich, Sigma) and 1.8 mL of medium was added to the monolayer cells. The plates were incubated at 37 °C for 4 h. The supernatant was removed, the blue-violet formazan crystals were dissolved adding 2 mL of solvent (HCL 4% in isopropanol) and quantified with the spectrophotometer (Secoman; Anthelie light, 3.8 version, Contardi, Italia) at 570 and 690 nm. The results have been reported as viability percentage compared with the control culture.

Statistical analysis

Statistical analysis of the data was performed using two-ways analysis of variance. In detail, cell viability was evaluated on fibroblasts: (1) directly cultured on polished samples (P), unpolished samples (UnP) and control (CTRL); and (2) in contact with the eluates of P, UnP and CTRL samples at 1 and 3 wk.

Levels of $P < 0.05$ were considered to be statistically significant. The results were also evaluated in accordance with ISO standard 10993-5^[20] which describes less than 25% inhibition as non-cytotoxic, 25% to 50% inhibition as slightly

cytotoxic, 50% to 75% inhibition as moderately cytotoxic and more than 75% inhibition as highly cytotoxic^[21].

RESULTS

Biocompatibility

MTT tests showed a significant reduction ($P < 0.01$) of gingival fibroblasts viability cultured both in P (90.05% ± 19.03%) and in UnP (78.15% ± 11.01%) compared with the CTRL (100.00% ± 6.00%), as shown in Figure 1A.

As regards to indirect toxicity, the viability of fibroblastic cells incubated in a medium conditioned with both P and UnP, for 1 or 3 wk, respectively, was studied using MTT test.

Cells growth in medium conditioned for 1 wk showed a significant viability reduction ($P < 0.01$) compared to the CTRL: the group conditioned with P showed a viability of 29.83% ± 1.92%, the one with UnP: 47.06% ± 1.87% (Figure 1B).

A reduction of cell viability was also observed in both groups conditioned for 3 wk (P: 89.45% ± 10.11%; UnP: 65.97% ± 9.89%), but only in the second group this reduction was statistically significant (Figure 1B).

SEM evaluation

As shown in Figure 2, SEM observations of fibroblasts cultured on the silorane samples, either P or UnP, confirmed the good biocompatibility of this material, which favoured cell spreading. These observations showed that the surface of the silorane-based material is able to absorb a big quantity of the serum component from the culture medium.

DISCUSSION

Silorane-based composite is a candidate for use in conservative dentistry due to its low polymerization shrinkage. However, it cannot be excluded that the potential release of remaining monomer substances may exert harmful effects on cells of periodontal tissues^[22]. The current

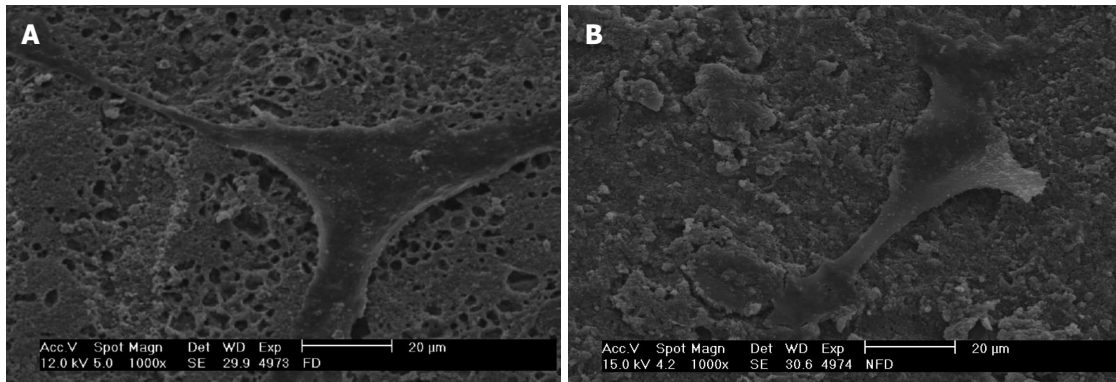


Figure 2 Scanning electron micrograph (x 2000, magnification). A: Gingival fibroblasts cultured directly on polished sample; B: Gingival fibroblasts cultured directly on unpolished sample.

limited literature indicates that silorane-based composite has a low toxicity presumably due to the low rate of free monomers released after polymerization^[18]. In order to ensure a safe use of silorane-based materials, studies on the biocompatibility of this material are still needed.

Biocompatibility of a dental material can be studied exposing tissue directly to the material (direct toxicity) or placing it in a medium (conditioning), which will be used for additional tests (indirect toxicity)^[23].

The results obtained in our study show a low direct cytotoxicity of both samples: P and UnP. The percentage of survival is lower in UnP than in P probably due to the larger surface contact area between composite and fibroblasts. Furthermore, the presence of oxygen inhibits the polymerization, resulting in a higher percentage of unreacted composite on the composite surface. Incomplete polymerization not only causes a decrease in the mechanical properties, but it can cause tissue reaction, as shown by Spangberg *et al.*^[24]. Composite finishing and polishing may indeed decrease the toxicity, as hypothesized in the study of Mohsen and Vankerhoven^[25,26]. A moderate (with a few peaks of high toxicity) indirect cytotoxicity was observed in the samples placed in culture medium conditioned for 1 wk with silorane eluates (being the UnP slightly less cytotoxic than the P ones). Slight indirect cytotoxicity values were obtained for the samples placed in culture with medium conditioned for 3 wk. Under this condition, the fibroblast cultures show a different behaviour, since cell viability was slightly greater in case of contact with P than with UnP ones. These findings are in agreement with Sheridan *et al.*^[27], reporting that the cytotoxic effect of acrylic resin was greater after polymerization and decreased with time for many resins. The authors concluded that the longer a prosthesis is soaked, the less cytotoxic effects it is likely to have regardless of the denture base resin it is manufactured from^[27]. Due to the not univocal data among P and UnP, the surface roughness does not seem to be a determining factor in the study of indirect toxicity. Indirect toxicity can be determined by release of substances from silorane as widely described in scientific literature^[22].

Scanning electron micrographs allow observing the

characteristic fibroblastic spreading. This is consistent with a study of Balcells *et al.*^[28], which states that the adsorption of serum proteins present in the culture medium is the first event that occurs when cells are seeded on a material and the adsorbed protein layer influences cell adhesion, spreading and proliferation.

In conclusion, although the poor chromatic availability of this material remains a big limit that restricts its use to posterior sectors, the silorane-based material can be considered an option to perform restorations when aesthetic demands are not the priority, such as the class II restorations^[29]. The behaviour of silorane-based materials seems to be comparable to the one observed for conventional composite material^[30], thus decreasing the cytotoxicity after long time exposure. Further studies are still needed to characterize the biological response of these methacrylate-free composite formulations, in order to definitely demonstrate their safe use in restorative dentistry.

ACKNOWLEDGEMENTS

Dr. Marcantoni, Dr. Morici and Dr. Kyriakidou are kindly acknowledged for technical assistance.

COMMENTS

Background

Despite extensive improvements in mechanical and aesthetic properties of dental composites, volumetric shrinkage and contraction stress during polymerization are still a problem.

Research frontiers

In several studies different techniques have been investigated in order to minimize polymerization shrinkage and contraction stress at the same purpose low-shrinkage materials have been proposed but none of them offered significant improvement to Bis-GMA-based composites.

Innovations and breakthroughs

The behaviour of silorane-based materials seems to be comparable to the one observed for conventional composite material, thus decreasing the cytotoxicity after long time exposure.

Applications

Further studies are still needed to characterize the biological response of these methacrylate-free composite formulations, in order to definitely demonstrate their safe use in restorative dentistry.

Peer review

The authors considered and concluded that the materials are biocompatible.

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Accuracy of linear vs spiral tomography: Alveolar crest to sinus/nasal floor height

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shown to be 0.455 ± 0.838 mm ($P = 0.029$) and 0.17 ± 0.78 mm ($P = 0.347$), respectively. There was a statistically significant difference between the linear tomography values and actual values ($P = 0.029$). This difference was representative of underestimation. McNamara's test was used to assess the ± 1 mm error; 73.7% of the linear values and 84.2% of the spiral values were within the ± 1 mm error limit. McNamara's test did not show any significant differences between the 2 methods in this regard ($P = 0.625$). The linear values were significantly different to the actual values ($P = 0.029$) but not to the spiral values ($P = 0.185$).

CONCLUSION: Spiral tomography has enough accuracy for the measurement of alveolar ridge height. Although linear tomography somewhat underestimates the actual values it provides satisfactory accuracy.

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Key words: Linear tomography; Spiral tomography; Maxillary sinus; Dental implants

Abstract

AIM: To determine the accuracy of tomography in the linear measurement of alveolar bone at maxillary sinus/nose location.

METHODS: Two dry skulls each marked with 10 pairs of guttaperchas placed on buccal and lingual sides of the maxillary ridge were used in this *in vitro* study. The distance between the alveolar crest and the sinus/nasal floor was measured on tomographic views, prepared by linear and spiral techniques. The ridges were then sectioned so that each section would include one pair of buccal and lingual guttaperchas. The actual distances directly measured on the sections were compared to those of the equivalent tomographic sections (the magnification co-efficient was applied). Paired *t*-test was used to statistically analyze the data.

RESULTS: The measurement error with the application of linear tomography and spiral tomography was

Core tip: Maxillary partial or complete edentulism represent some challenging conditions in implant dentistry. The position of sinus/nasal floor in partial/complete edentulous maxilla determines the alveolar bone height and consequently the length of the implants that can be used. Although cone beam computed tomography and conventional computed tomography are widely used for pre-operative implant treatment planning, they are expensive and can expose patients to relatively high dose of radiation. We demonstrated that tomography can be a good substitute for conventional and cone beam computed tomography for alveolar length measurement at maxilla, although spiral tomography is more accurate than linear tomography.

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Accuracy of linear vs spiral tomography: Alveolar crest to sinus/nasal floor height. *World J Stomatol* 2013; 2(4): 91-96 Available from: URL: <http://www.wjgnet.com/2218-6263/full/v2/i4/91.htm> DOI: <http://dx.doi.org/10.5321/wjs.v2.i4.91>

INTRODUCTION

Although computed tomography (CT) and cone beam computed tomography (CBCT) are frequently used for pre-operative implant planning, their use in the post-operative assessments is limited due to metallic streak artifacts^[1,2]. Also CBCT is associated with artifacts such as truncated view and beam hardening artifacts^[3,4]. Another disadvantage of computed tomography is its relatively high radiation risk compared to conventional tomography^[5-7].

The position of the maxillary sinus floor influences the height of the alveolar bone and consequently the implant length to be placed. Tomographic views are considered as the most reliable projections in the assessment of potential implant sites prior to surgery since they provide the clinician with the buccolingual information of the anatomic structures^[1,5].

The measurement accuracy of most recent tomographic techniques in the assessment of mandibular landmarks has been thoroughly discussed through the literature^[8-14]. A recent systematic review has concluded that each landmark possesses a unique error pattern and contributes independently to the measurement inaccuracy^[15]. Since the alveolar crest height meaning the distance between the maxillary sinus floor and the alveolar crest serves as an important factor in the placement of dental implants, The present study aimed to compare the measurement accuracy of two tomography techniques, linear and spiral, in the maxilla of dry human skull.

MATERIALS AND METHODS

In this *in vitro* study, two dry skulls with intact maxillary sinus, nasal floor and foramen magnum, one completely and the other partially edentulous, were used. Each skull was then marked in 10 regions posteroanteriorly. Panoramic scout views were prepared to measure the alveolar ridge height. Each skull was then marked in five regions on each side with 70 guttapercha using glue every 1 cm and perpendicular to the ridge. The most distal guttapercha was placed in the third molar region and the most anterior one was placed in the lateral incisor region. A total of 20 areas (4×5) were marked (Figure 1). Each area was marked with two guttaperchas one on the lingual and the other on the buccal aspects of the alveolar ridge.

To prepare tomographic views, skulls were fixed on a wooden jig. Tomographic views were obtained twice, first using multitask Cranex TOME device (Orion Corporation Sordex, Helsinki, Finland) and then using Planmeca Promax (Helsinki, Finland). Kodak X-Omat cas-

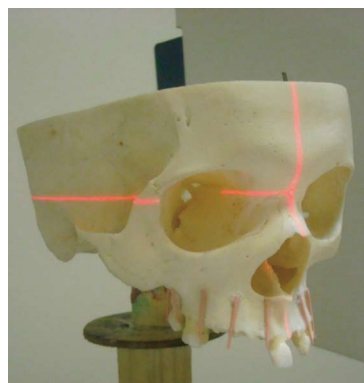


Figure 1 One of the two dry skulls marked with guttaperchas.



Figure 2 The measurement approach for bone height on film.

sette (Ektavision) and Agfa Single Emulsion (CP-VB) (15 cm \times 30 cm) film were used. For spiral tomography, the dental tomo program for the upper jaw was selected at 57 kV, 2.5 mA and 56 s. Slice thickness was set to be 2 mm and the aperture number was 4. For linear tomography, the minimum adjustments, 54 kV and 0.5 mA, were set. Slice thickness was set to be 3 mm (Table 1). In all cases skulls were placed so that the maxillary occlusal plane would be parallel to the horizon. A total number of 20 cross-sections were prepared on each X-ray unit.

The films were processed in an automatic processing machine (OPTIMAX 2010; PROTEK Medizintechnik, oberstenfeld, Germany). Measurements were done on a negatoscope in a semi-dark room using a digital sliding caliper. The view with the clearest gutta-percha was selected for measurement on each radiograph. The alveolar crest and the maxillary/nasal floor were then outlined on tracing papers which were superimposed on the radiographic views. Bone height was measured in an oblique direction along the medial axis of the alveolar process, similar to the direction of implant placement^[5]. The distance between the sinus floor to the alveolar ridge traced on this line was considered as the ridge height (Figure 2). Measurements were done twice by an oral radiologist and an oral radiology senior resident each with a time interval of 2 wk.

The whole alveolar process was cut with electric saw first and then hand jig saw was used to separate the



Figure 3 Sectioned specimen using a hand jig saw.

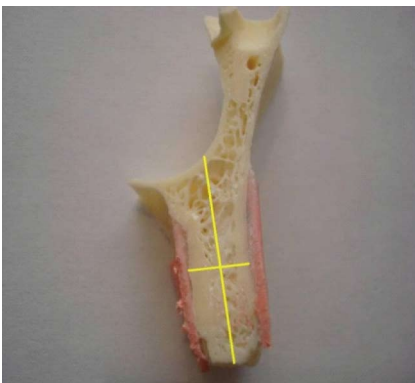


Figure 4 The measurement approach on the sectioned specimen.

Table 1 Summary of image protocols

Machine type	Promax	Cranex Tome
Manufacturer	Planmeca, Helsinki, Finland	Sordex, Helsinki, Finland
Tube voltage (kV)	54	57
Tube current (mA)	0.5	2.5
Slice thickness (mm)	3	2

marked sections (Figure 3). Bone height on the sections was measured similar to the films using a digital sliding caliper with a nominal resolution of 0.01 mm (Figure 4). To determine the magnification factor, a pilot study was designed and performed through which the actual length of the guttaperchas and their length on the radiographic view was measured. The magnification was calculated dividing the mean radiographic values to the actual values. The magnification factors were similar to the ones defined by the manufacturer (1.5 for both devices). The actual values measured on the bone sections were considered as the gold standard.

Statistical analysis

Data were inserted in SPSS v. 15, and then were analyzed by Paired *t*-test and McNemar's test. Linear regression model was used to assess the relation between the actual values and tomogram values. Mean values and standard deviation

were used to describe quantitative values and percent. Proportions and bar charts were used to describe qualitative data. A 0.05 level of significance was considered.

RESULTS

Twenty specimens were primarily used in the present study, from which one specimen was excluded due to the displacement of guttapercha. The extent of maxillary sinus floor and nasal floor was recognizable on all tomographic views. Measurements were, however, more challenging in the posterior areas and also in dentate skull. Paired *t*-test was used to compare the measurement differences between the linear and spiral tomography to the actual values multiplied by the magnification coefficient. The mean error for linear and spiral tomographic views were 0.455 ± 0.838 mm ($P = 0.029$) and 0.174 ± 0.787 mm ($P = 0.347$), respectively. There was a statistically significant difference between the linear tomography values and actual values ($P = 0.029$). This difference was representative of underestimation. Non-parametric Wilcoxon signed rank test (a non-parametric equivalent to paired *t*-test) also revealed a statistically significant difference for linear tomography ($P = 0.035$) and a statistically not significant difference for spiral tomography ($P = 0.587$).

Paired *t*-test also showed a significantly higher deviation from the actual values in linear tomography compared to spiral tomography ($P = 0.017$). This was confirmed by Wilcoxon test ($P = 0.026$). However, neither *t*-test ($P = 0.185$) nor Wilcoxon test ($P = 0.199$) revealed a significant difference between the linear and spiral values after they were multiplied by the magnification factor. McNemar's test was used to assess the ± 1 mm error. Error values in linear and spiral tomographies were within ± 1 mm respectively in 73.68% and 84.2% of the cases. McNemar's test did not show any significant differences between the two methods in this regard ($P = 0.625$).

After the application of magnification factors to the values obtained by linear tomography, overestimation and underestimation were respectively seen in 21.01% and 78.99% of the cases. Overestimation and underestimation were respectively seen in 47.3% and 52.7% cases of spiral tomography. All the overestimation cases of

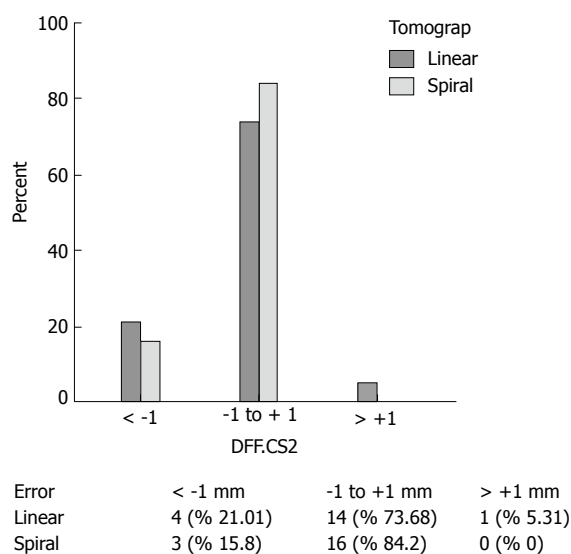


Figure 5 Frequency percent of the measurement errors after the application of magnification factors.

spiral tomography were within the error limit of ± 1 mm. Mean spiral overestimation was within 0.02 to 0.91 mm. Mean linear overestimation was within 0.38 to 1.5 mm. Mean underestimation values of linear and spiral tomographies were respectively within the ranges of 0.04 to 1.8 mm and 0.03 to 1.4 mm (except for one case of spiral tomography which showed an underestimation of 2.19 mm). Figure 5 represent the distribution of errors within the ± 1 mm range.

DISCUSSION

Linear and spiral tomography techniques were compared in the present study in terms of accuracy in the pre-operative assessment of the maxillary bone height. To the best of our knowledge, the literature lacks enough studies on the localization of maxilla, maxillary sinus and nasal floor and most studies have addressed the localization of mandibular canal.

It is generally accepted that more complex tomographic movements are associated with higher blurring of the background images and less streaking artifacts^[1]. Spiral and hypocycloidal movements will reduce the incidence of streaking artifacts^[16,17]. In the studies of Lindh *et al*^[18] spiral tomography provided more accurate views of the mandibular canal compared to hypocycloidal tomography. In the present study, the actual values measured directly on the skull sections and the values obtained from linear tomograms were significantly different ($P = 0.029$). The mean difference was measured 0.455 ± 0.83 mm for linear tomography and 0.174 ± 0.78 mm in spiral tomography. This difference was not significant for spiral tomography ($P = 0.347$). The significant difference in linear tomography may be partly due to the quality of images. In spiral tomography the quality of images especially in the anterior area was better and the outlines could be more easily detected. Due to the insufficient number of specimens,

however, this comparison between the anterior and the posterior areas was not statistically implacable.

Naitoh *et al*^[19] compared the measurement accuracy of direct laser positioning and reformatted CT. They suggested that other factors including tomographic angle and the placement angle of the object to be projected also influence the measurement accuracy in addition to the motion pattern. They did not find any significant differences between the two methods in mandible measurements ($P = 0.526$). They believed the significant lower accuracy of the linear tomography found through other studies is due to the difficulties in the adjustment of the projection plan of the object and not due to the image quality.

The main purpose of the present study was to compare two types of tomography in terms of linear measurements rather than image quality. Statistical analysis failed to reveal any significant differences between the two methods in the measurement of the distance between the alveolar crest and the sinus/nasal floor ($P = 0.185$). Spiral tomography values obtained through the present study are consistent to the findings of Bou Serhal *et al*^[5] who assessed the measurement accuracy of the spiral tomography in upper jaw. They reported a mean error of 0.24 ± 0.19 mm which was not significantly different to the actual values ($P > 0.05$). They stated some quality impairment in the images obtained from the most distal slices and though it was attributed to the placement of more bony structures in the area. Similarly, Kim *et al*^[20] experienced quality impairment in mandibular posterior areas projected by Scanora spiral tomography. Higher image quality in the study of Bou Serhal *et al*^[5] may be attributed to the complete edentulousness of the studied skulls, which may have eliminated the artifacts commonly created by the presence of restorations and natural teeth. Similarly, the quality of images obtained from the anterior areas was higher compared to those of posterior areas in the present study both with spiral and linear tomographies. Also spiral projections were associated with higher image quality in anterior areas compared to linear tomography.

Bou Serhal *et al*^[21] also evaluated the accuracy of conventional spiral tomography [Cranex TOME multifunctional unit (Orion Corporation Sordex; Helsinki, Finland)] for the localization of the mandibular canal on human fresh cadavers and reported higher mean error values compared to their previous study. They concluded that the information provided by spiral tomography of the posterior mandible using the studied unit is reliable and sufficient for preoperative planning of implant placement. They attributed the different results of the two studies to the fact that the absence of overlying soft tissue provides the observer with a higher resolution of the bony mandible and also more precise adjustments of skull compared to the patient or cadaver in the latter study.

Butterfield *et al*^[17] examined linear tomography in terms of accuracy and validity in the pre-surgical evaluation of potential implant sites in mandible. They claimed that linear tomography suffers from prominent dimensional instability, which significantly limits its role in

preoperative assessment of implant sites. Seven observers traced eight anatomic landmarks including the mandibular cortical bone and inferior alveolar canal on linear tomographic images. Statistically significant differences were found between the perceived and actual anatomic values ($P < 0.05$). They suggested that since the source to image receptor distance, source to object distance and object to image receptor distance change with a constant proportion to each other during the tomographic movements, linear tomography does not hold a constant magnification factor. Consistently, linear tomography in the present study was associated with a significant underestimation of the measurement values of alveolar crest height ($P = 0.029$). On the other hand, the pilot linear tomography of guttaperchas conducted by the author of the present study revealed a magnification factor (1.498) which closely approximated the manufacturers (1.5).

Bou Serhal *et al*^[21] measured an actual magnification factor of 1.49 for the Cranex TOME spiral tomography unit both in vertical and horizontal planes. Closely similar, the magnification factor measured in the present study for the same device was equal to 1.518.

In the present study, spiral tomograms showed underestimation and overestimation respectively in 52.7% and 47.3% of the cases. The overestimation in the present study was higher than that of Bou Serhal study in 2000 (33.3%). Also the linear tomograms of our study presented with underestimation and overestimation in 78.99% and 21.01% of the cases, respectively. Based on these findings, it may be suggested that overestimation occurs more frequently in spiral tomography and underestimation occurs more frequently in linear tomography. Underestimation would seemingly be preferable in the implant placement especially when the mandibular body above the mandibular canal is considered as a potential implantation site^[18]. Loubele *et al*^[3] comparatively assessed the measurement accuracy of multi-slice spiral CT, spiral tomography and cone-beam tomography. They measured an overestimation of 1 mm for the spiral tomography. CBCT in their study (except for one case) was only associated with approximate overestimation of 0.5 mm. In the present study, spiral tomography was associated with an overestimation of less than 1 mm (maximum of 0.91 mm). This value was measured to be maximally 1.5 mm with the application of linear tomography especially in the anterior areas of dentate skulls. However, since the significant difference tended towards underestimation with the application of linear tomography in the present study, and also due to the higher safety of underestimation compared to overestimation, the measurement accuracy of the linear tomography seems to be within the satisfactory clinical range. On the other hand, underestimation may result in the application of a shorter implant, which may impair the long term prognosis survival of the implant and success of the overlying prosthetic restoration^[18].

Spiral tomography in the study of Bou Serhal *et al*^[5] was associated with a accuracy of ± 1 mm in the measurement of alveolar crest to maxillary sinus distance.

Klinge *et al*^[22] measured the distance between the alveolar crest to the inferior border of the mandibular canal by means of hypocycloidal tomography and reported that only 39% of the cases were associated with a accuracy of within ± 1 mm. Hanazawa *et al*^[23] measured the same distance by spiral tomography and reported that 47.9% of the cases are within the ± 1 mm accuracy. In the present study, spiral tomography and linear tomography were associated with ± 1 mm accuracy respectively in 84.2% and 73.68% of the cases after the magnification factors were applied.

McNemar's test did not reveal any significant differences between the two tomographies in terms of the percent of the cases within the ± 1 mm accuracy ($P = 0.625$). Clinically the value of underestimation and overestimation is more important than the absolute difference of the perceived and actual values^[21].

The values measured on the linear tomograms obtained by Promax unit significantly differ to actual values ($P < 0.029$). This difference tends toward underestimation. There is, however, a significant correlation between the linear and spiral tomographies. Therefore it seems that both linear (Promax) and spiral (Cranex Tome) tomography are associated with sufficiently accuracy in the pre-surgical assessment of potential implant sites in dry skull. Also the magnification factor introduced by the manufacturer is seemingly reliable for both devices. Linear and spiral tomography did not show any significant differences in the present study. This may not be the case in clinical situation where the soft tissue and dentition are present. Therefore, studies on human cadaver or *in vivo* trials are highly recommended to further assess the reliability of the two methods.

COMMENTS

Background

Maxillary Partial or complete edentulism is a common condition in dentistry and insufficient bone can be a challenge for a clinician who wants to place implants at edentulous Maxilla. The loss of maxillary teeth result in decrease in bone height (and width). The position of the maxillary sinus floor/nasal floor influences the height of the available alveolar bone and consequently the implant length to be placed. Different imaging modalities are used for determining the height of available bone at maxillary sinus area.

Research frontiers

The imaging modality should be chosen that yields the necessary diagnostic information and results in less radiologic risk. Periapical radiography is of limited value in determining bone quantity due to its magnification, distortion, lack of third dimension and size limitation. Nowadays computed tomography and cone beam computed tomography are frequently used for pre-operative implant planning. Although they can provide us with invaluable information (3D images with high accuracy), they have their own disadvantages such as exposing the patient to the relatively high radiation, beam hardening artifacts and high costs. The hot spot is how to employ a modality which produces 3D images but wouldn't expose patients to a high radiation dose. The answer can be tomography.

Innovation and breakthrough

To the best knowledge of the authors of this article, the literature lacks enough studies on the localization of maxillary sinus and nasal floor and most studies have addressed the localization of mandibular canal. Linear and spiral tomography techniques were compared in the present study in terms of accuracy in the pre-operative assessment of the maxillary bone height. In this study, the actual values measured directly on the skull sections and the values obtained from linear

tomograms were significantly different. This difference was not significant for spiral tomography. The significant difference in linear tomography may be partly due to the quality of images. In spiral tomography the quality of images especially in the anterior area was better and the outlines could be more easily detected. Due to the insufficient number of specimens, however, this comparison between the anterior and the posterior areas was not statistically implacable.

Application

The study result suggests that spiral tomography has enough accuracy for the measurement of alveolar ridge height. Although linear tomography underestimates the actual values, it seems to provide satisfactory accuracy.

Terminology

Tomography is generic term for describing sectional radiography. X-ray source and film move in opposite direction during exposure in this technique. Consequently, structures in the section of interest are sharp while the above and below sections appears blurred.

Peer review

This is an interesting study in which authors tested the accuracy of the measurements of linear and spiral tomography in maxilla. The results were intriguing and demonstrated that spiral tomography is an accurate imaging modality for pre-operative treatment plan. Although, linear tomography is not perceived as accurate as spiral tomography, it appears to be accurate enough to be utilized for a pre-surgical treatment plan.

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Surgical obturator duplicating original tissue-form restores esthetics and function in oral cancer

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Abstract

Oral cancer treatment primarily focused on the surgical removal of cancer tissues followed by surgical/prosthetic reconstruction. Restoration of the missing structures immediately after surgery shortens recovery time and allows patient to return to community as a functioning member. The most practiced surgical obturators are simple resin prosthetic bases without incorporation of the teeth. This article highlights a technique to fabricate a surgical obturator that duplicates patient's original tissue form including teeth, alveolus and palatal tissues. The obturator is placed immediately after surgery and make patient feel unaware of surgical deformity. The obturator prosthesis fabricated with this technique supports soft tissues and minimizes the scar contracture. We have clinically tried this technique in 11 patients. Patients' satisfaction level was recorded on visual analogue scale (VAS) and it ranges between 74% and 94% (with average of 87%). Four different prosthodontists have visually evaluated facial asymmetry of patients at 6 mo recall and their average perception on VAS varies between 71% and 93% (with average of 84%).

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Key words: Maxillofacial prosthesis; Maxillectomy; Ob-

turator prosthesis

Core tip: This article highlights a technique to fabricate a surgical obturator that duplicates patient's original tissue form including teeth, alveolus and palatal tissues. Make patient feel unaware of surgical deformity. The obturator prosthesis fabricated with this technique supports soft tissues and minimizes the scar contracture. We have clinically tried this technique in 11 patients. Patients' satisfaction level was recorded on visual analogue scale (VAS) and it ranges between 74% and 94% (with average of 87%). Four different prosthodontists have visually evaluated facial asymmetry of patients at 6 months recall and their average perception on VAS varies between 71% and 93% (with average of 84%).

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INTRODUCTION

Treatment of oral cancer necessitates surgical removal of the affected maxillofacial hard and soft tissues^[1]. Loss of structural continuity affects esthetic appearance and functional performance like mastication and swallowing^[2]. Esthetic disfigurement significantly affects patients' social and psychological wellbeing^[3]. In addition to local and general health psychological, social and economic aspects determine final treatment outcome of the prosthetic rehabilitation^[2]. Patient may get disease free after resection of the cancer tissues but can become a permanent handicap if not rehabilitated in a proper manner. Plastic surgeons face great challenges to reconstruct oral and maxillofacial defects to maintain the functional integrity and esthetic appearance especially in large sized defects and trismus. In

case of malignancies, radiotherapy is a vital parameter in controlling neck metastasis. Though surgical reconstruction restores the defect, replacement of teeth and facial tissue support can only be achieved by prosthodontic reconstruction. Obturators are given to maintain an artificial barrier between nasopharynx and oropharynx so that oral intake of food should not be regurgitated from the nose and sufficient negative pressure develops in the oral cavity to facilitate deglutition^[1]. Depending upon the time of prosthesis given they are classified as immediate surgical (immediate), delayed surgical (7-10 d), interim (4-6 wk) and definitive (After 4-6 mo) obturators^[1,4].

Immediate or delayed surgical obturator minimizes scar contracture and disfigurement thereby making a positive effect on the patients' psychology. Various designs have been proposed for fabrication of the surgical obturator. The design ranges from acrylic resin record base bearing no teeth^[5]. With or without wrought-wire clasps^[6], to a clasped acrylic resin prosthesis that restores the dental arch form^[7]. Dentate patients are relatively easier to treat than edentulous patients as maximum retention and stability can be achieved from remaining teeth. The most practiced surgical obturator is a simple resin prosthetic base without incorporation of teeth. Addition of teeth in initial healing phase may cause constant source of irritation and hamper healing process according to many authors. However only anterior teeth can be restored until surgical wound is healed in some clinical situations^[1,8]. In case of radiotherapy, the tissues become more friable and vulnerable hence the simplest form of prosthesis is advocated in most of the clinical situations^[3].

This article highlights a treatment concept which restores resected maxillofacial tissues with a surgical obturator that duplicates patient's original tissue form^[9,10]. The technique is developed in our hospital and total 11 cancer patients were treated in last 2 years. Patients were evaluated for patients' satisfaction level and clinicians' perception for bilateral facial symmetry on visual analogue scale (VAS) at 6 mo recall visit.

Technique

Prior to surgery maxillofacial prosthodontist should examine patient and discuss the plan of treatment with surgeons about a proposed line of incision and amount of resection (Figure 1A).

A pre-surgical impression of the maxillary arch is made with irreversible hydrocolloid and poured to obtain a working cast. An anticipated line of resection is drawn with a marking pencil on the cast following discussion with maxillofacial and plastic surgeons.

The area (of the lesion) on the cast is modified to obtain normal anatomical contours (Figure 1B). For example, swollen areas of the lesion on the cast can be scraped-out and defect (ulcer/breach) areas can be built-up with dental stone in order to create the normal anatomical tissue form on the cast.

Labial/lingual infrabulge retentive areas of the remaining healthy teeth are engaged with the retentive clasp

arms. A processed prosthetic base is fabricated in heat polymerizing acrylic resin by incorporating the clasps (Figure 1C).

The processed prosthetic base is resealed on the maxillary cast and an over-impression of the whole cast (along with the seated processed prosthetic base) is made with polyvinyl-siloxane putty in perforated stock metal tray to form putty impression index (P II) (Figure 1D). Facial surface on the defect side of the cast should be completely recorded in the over-impression till border areas.

The P II and the cast are separated from each other. The prosthetic base is resealed on the P II (Figure 1E).

The separated cast is sectioned according to the anticipated line of resection. The planned defect section of the cast is separated from the remaining normal portion (Figure 1F). This remaining portion (of normal structures) of the cast is used to fabricate the prosthesis.

The P II (along with the processed prosthetic base) is resealed onto the remaining portion of the cast (Figure 1G).

Prosthetic teeth are created with sprinkle-on technique by incrementally adding tooth-colored autopolymerizing acrylic resin into the impression areas of teeth in the P II. The facial flange can also be created by adding the pink colored autopolymerizing acrylic resin uniformly 2-3 mm in width (Figure 1H).

After setting the P II along with the prosthesis is separated from the cast (Figure 1I) and then P II is separated from the prosthesis carefully. The excess resin is removed and the flange and teeth areas are finished and polished in a conventional manner (Figure 2)^[11,12]. Note that the smooth borders and polished surfaces are critical parameters to avoid any tissue injury. Occlusal surfaces of the posterior teeth can be trimmed off by approximately 2 mm to make them out of occlusion^[1,8].

The prosthesis must be disinfected before using it in the mouth with any suitable disinfectant like 2% glutaraldehyde solution.

Routine minor adjustments are carried out and the prosthesis can be seated in position immediately after surgery. A surgical pack can be placed in the defect area before placement of the obturator if necessary.

CASE REPORT

We have treated 11 patients undergone maxillary partial or subtotal resection with the immediate surgical obturator in last 2 years (Table 1). Out of 11 patients, 6 had Armanny's Class I defect, 4 had class II defect (Figure 3) and 1 had Class IV defect^[13]. All 11 patients were assessed at the interval of 1, 2, 6 and 12 mo follow up visits for evaluation of healing process and evaluated for patients' own satisfaction level and clinicians' perception level for bilateral facial symmetry on VAS. Patients' satisfaction level was recorded on VAS (with 0 indicating no satisfaction and 100 indicating complete satisfaction) and it ranges between 74% and 94% (with average of 87%) (Table 1). Four different prosthodontists have visually evaluated facial asym-

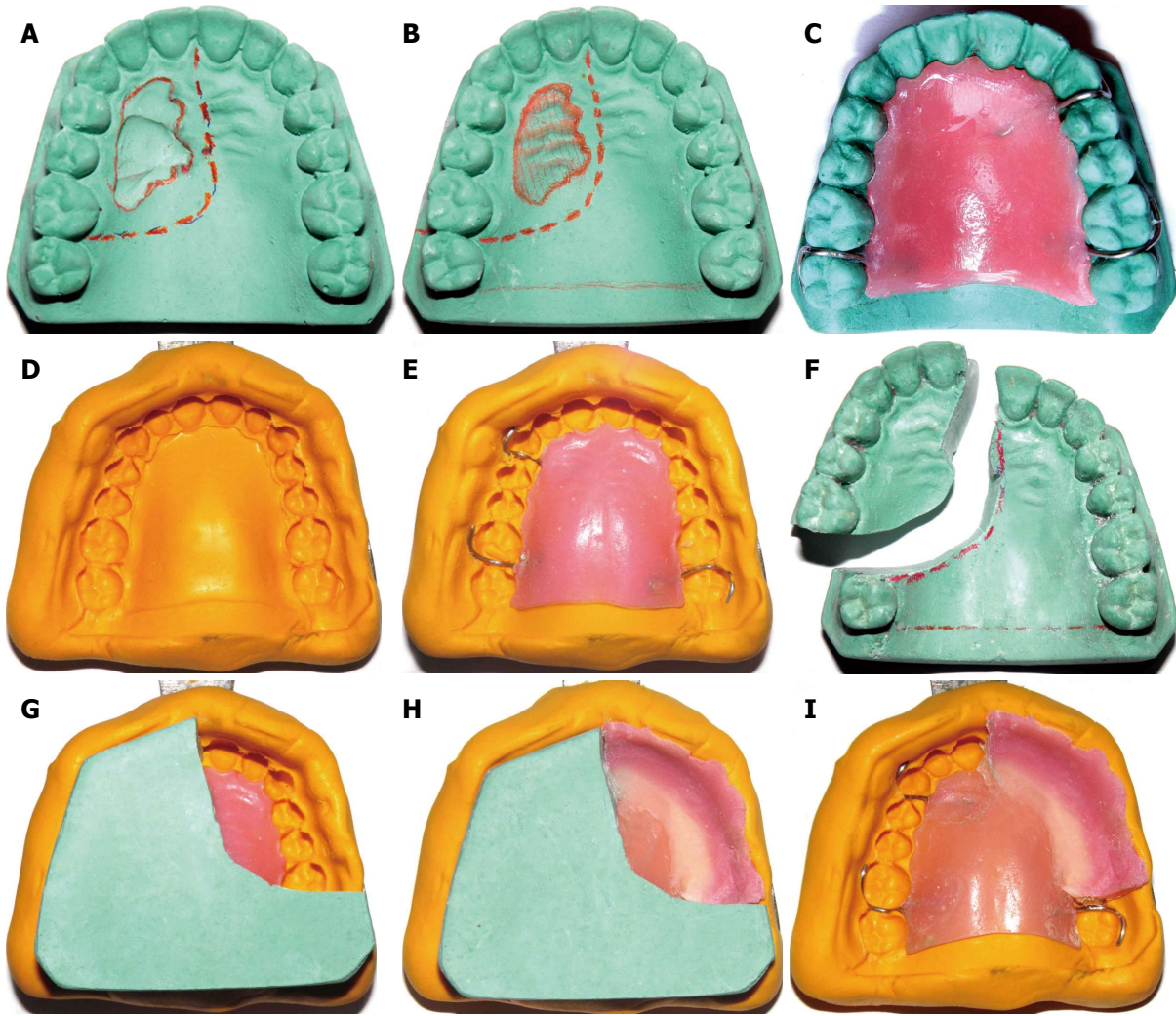


Figure 1 Technique to fabricate surgical obturator duplicating original tissue-form. A: Working cast; B: Modification of cast; C: Prosthetic base; D: Putty impression index; E: Prosthetic base transferred onto putty index; F: Maxillary cast sectioned; G: Reseating of putty index onto sectioned cast; H: Creation of the prosthetic teeth in tooth-colored and facial surface in pink-colored resin; I: Removal of cast from index.

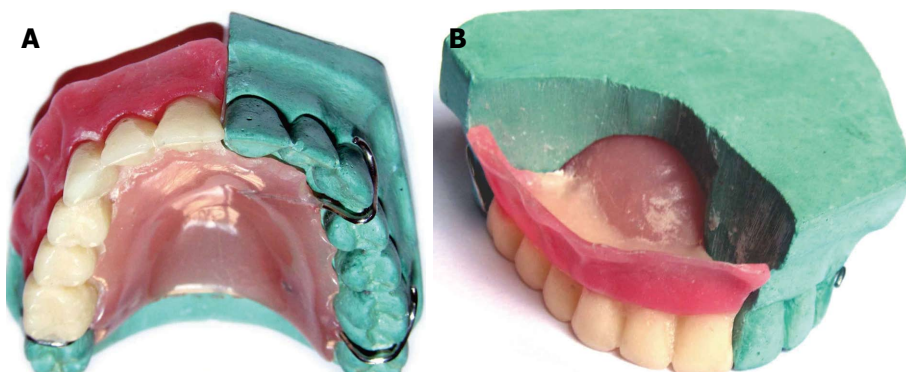


Figure 2 Completed obturator. A: Palatal view; B: Obturator in relation with remaining normal structures on cast.

metry of patients at 6 mo recall visit and indicated their visual perception for symmetry of the face on VAS (with 0 indicating completely asymmetric face and 100 indicating completely symmetric face). The average VAS scores of 4 clinicians' readings were calculated and presented in Table 1. Clinician perception VAS scores vary between

71% and 93% (with average of 84%).

DISCUSSION

Neglecting timely prosthodontic rehabilitation may lead to inappropriate facial contour which is difficult to correct^[14-16].

Table 1 Details of the patients enrolled and visual analogue scale scores for patients' satisfaction level and clinicians' observation for facial asymmetry at 6 mo recall visits

Sr. No	Patient's surgical defect-type (Armany Classification)	Age (yr)	Sex (M/F)	Diagnosis	Post-surgical radiotherapy (Y/N)	Patient's satisfaction level (VAS at 6 mo)	Clinicians' observation for facial asymmetry (Average VAS scores of 4 clinicians at 6 mo)
1	Class II	47	F	Squamous cell carcinoma of right maxilla	Y	86%	84%
2	Class I	45	M	Adenocarcinoma of left maxillary sinus	Y	78%	86%
3	Class II	50	F	Squamous cell carcinoma of maxillary sinus	Y	92%	80%
4	Class IV	63	M	Ameloblastoma of palate	N	93%	88%
5	Class I	50	F	Squamous cell carcinoma of right maxilla	Y	88%	74%
6	Class I	65	F	Squamous cell carcinoma of left maxilla	Y	94%	93%
7	Class I	65	F	Squamous cell carcinoma of right maxilla	Y	83%	71%
8	Class II	40	F	Squamous cell carcinoma of hard palate	Y	94%	93%
9	Class I	36	M	Squamous cell carcinoma of Maxillary sinus	Y	81%	86%
10	Class I	35	F	Squamous cell carcinoma of right maxilla	Y	74%	73%
11	Class II	48	M	Ameloblastoma of left maxilla	N	94%	92%

M: Male; F: Female; VAS: Visual analogue scale.

The significance of immediate surgical obturators has been well documented. Immediate obturators resist tissue contracture of the soft tissues that are not supported by the underlying osseous structures. During healing phase, surgical wound is protected from external irritants, contaminants, food debris and trauma^[17,18].

Advantages of adding flange and teeth

The borders of the defect are more prone to collapse due to lack of underlying support. Addition of teeth and labial/buccal flanges provide maximum support to the borders. Facial contours of the immediate obturator described in this article support overlying skin and skin grafts with optimum pressure providing their close adaptation to the cavity walls without getting contracted. After the operation, patients are able to swallow food more readily and to resume a normal diet at an earlier stage which leads to shorter recovery period^[4]. Addition of teeth to the obturator allows mastication of semisolid food in initial phase and solid food several days later^[4,14]. Speech is minimally altered and in many instances remains nearly unchanged^[19,20]. Also the awareness of the surgical defect by the tongue is prevented and the patient remains unaware of the size of the defect giving the patient a positive psychological boost. By maintaining facial contour and aesthetics, patients are psychologically better equipped to face rehabilitation^[21].

Purpose of replacing teeth immediately

Immediate restoration of the resected tissues by means the obturator that restores every missing portion of the tissues helps patients undergo unnoticed to the surgery.

This gives patient positive psychological boost during the initial vulnerable period of healing. According to many authors, the posterior teeth should not be added to surgical obturator as they may exert unnecessary stress on the open wound and delay the healing process^[3]. This technique describes replacement of dentition that would be missing followed by grinding occlusal contacts of posterior teeth (at least 2 mm) to position them out of occlusion. The facial surfaces must be kept intact to serve the purpose of facial soft tissue support as well as esthetics without disturbing the healing process. Anterior teeth should not be altered unless the incisal contacts hinder the healing tissues. The purpose of adding missing teeth (anterior or posterior) may prevent significant psychological trauma to the patient and helps to prevent scar contracture and subsequent disfigurement. The developed facial flange also helps to support the facial soft tissues which can maintain the patient's original facial esthetic appearance.

Catch at early healing stage

Contracture of the wound and scar formation leave very serious facial deformities after cancer surgeries^[22]. Even slight depression in either side will also cause major deformity due to face value and patient's vulnerability towards esthetic appearance. If the radiotherapy follows the surgery the tissues become even more friable and are difficult to manage due to loss of natural laxity. Maximum wound contracture happens in initial stages within 4-6 wk. This is the period in which the losses of intraoral structures also cause difficulty in mastication and deglutition. Thus in initial stages of healing, patients may

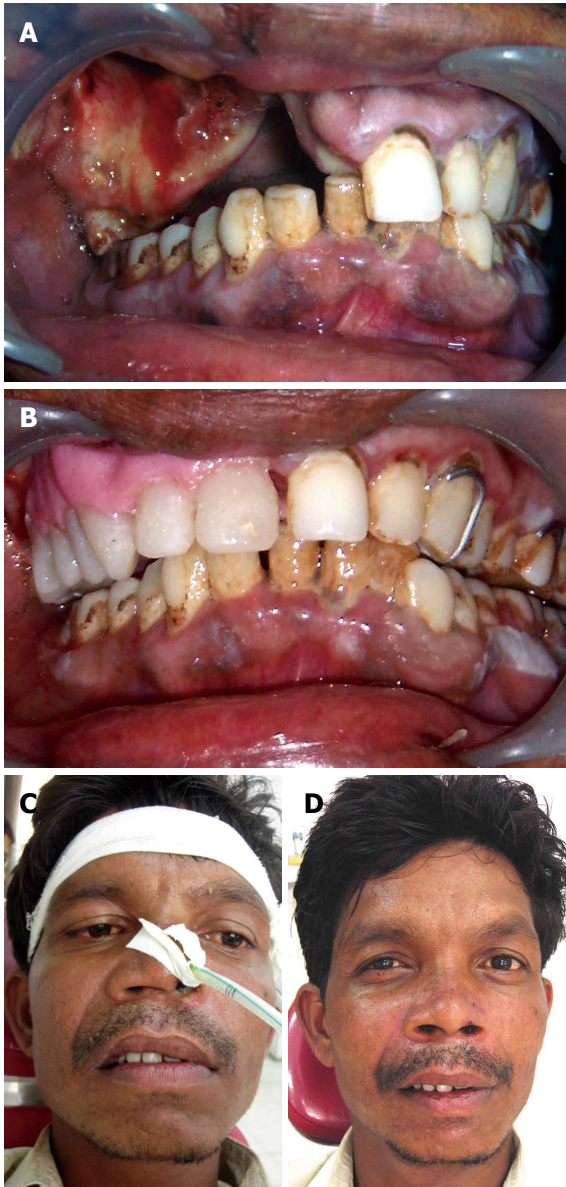


Figure 3 Post-treatment view immediate and after 6 mo. A: Immediate post-surgical view; B: Obturator in place; C: Immediate post treatment extraoral view; D: Six month post treatment extraoral view.

undergo severe psychological depression due to multiple problems. Immediate obturation can create a positive effect on the patients' psychology.

Works as Interim obturator

Interim obturators with teeth may be made using several methods, using a celluloid matrix^[2], modifying a surgical obturator^[7], using a denture duplicator^[23], or using light^[11,24] or heat-polymerized acrylic resin^[25]. The obturator fabricated with this technique utilizes the PII of patient's original tissue form and duplicated mostly in heat and slightly in autopolymerizing acrylic resin.

Time and cost effective

Same surgical obturator can later (for 4-6 mo) serve as an interim obturator following modification of the tissue

surfaces thus it saves time and cost.

Housing for placement of surgical pack

The space automatically formed between intaglio surfaces of facial flange and palatal plate can easily be utilized for placement of the surgical pack immediately after the surgery. Thus the obturator can provide supporting and stabilizing medium for the surgical pack.

Future dental implant planning

The same surgical obturator can be an effective tool for implant retained definitive fixed or removable prosthesis. Most of the acquired defects are surgically covered with thin mucosa which is not able to support denture bases. In such situations dental implants are indicated, leaving the vulnerable and/or non keratinized mucosa unloaded^[26]. The use of dental implants is an alternative option to achieve better function and self confidence due to improved retention and stability^[27]. Edentulous patients undergoing partial maxillectomy must be treated with implant supported ball and socket attachments to achieve retention to the surgical obturator. Same obturator can be used to prepare the diagnostic as well as surgical template for dental implant placement.

Limitations

As the teeth and facial flanges of the obturator are created in auto polymerizing acrylic resin, the free residual monomer may irritate the supporting tissues and hamper the healing process. The light polymerizing acrylic resin can be used alternatively to solve this problem provided the combinations of the light polymerizing acrylic resins and the methylmethacrylate based denture base resins were selected carefully to ensure sufficient bond strength^[11,23,24,28].

Future scope

Future prospective clinical trials with large sample size should be promoted to treat cancer patients with better esthetics and function.

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Soft tissue aneurysmal bone cyst of the mandible: Report of a case

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Key words: Bone cysts; Aneurysmal; Mandible; Neoplasm; Soft tissue

Core tip: A case of soft tissue aneurysmal bone cyst (STABC) of the mandible is presented in a male teenager. STABC is a rare entity with histological and radiological features that are identical to those of aneurysmal bone cyst, except for that STABC is of extra osseous location. The differential diagnosis of STABC in this location, includes giant cell tumor of soft tissue and extra skeletal osteosarcoma making it quite a challenge in the process of diagnosis.

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Abstract

We report the case of a 17-year-old boy with a soft tissue aneurysmal bone cyst (STABC) located in the posterior aspect of the right mandible. Conventional radiography revealed no positive findings. On the computed tomography scan, the lesion appeared to have a non-uniform intralesional density. Magnetic resonance imaging revealed an abnormal soft tissue masses with cystic component in the superficial part of right mandibular body and angle with intact cortex. Following histopathological examination, fibro-histiocytic proliferation, blood-filled spaces and multinucleated giant cells were seen and the lesion was diagnosed as a STABC. The mass together with underlying bone and periosteum on its periphery was surgically resected under general anesthesia. Thirty-six months after surgery the patient was assessed at outpatient clinic and found no sign of recurrence. This may be only the first reported case of the mandible in the English literature of this extremely rare benign tumor occurring in soft tissue.

INTRODUCTION

Aneurysmal bone cyst (ABC) is a benign cystic lesion of bone, composed of blood filled spaces separated by connective tissue septa containing fibroblasts, osteoclast-type giant cells and reactive woven bone^[1]. Previously, ABC was believed to occur exclusively in bone^[1,2], but in recent years a few cases of soft tissue ABC (STABC) have been reported^[3,4]. The first cases of soft tissue ABC were reported by Salm *et al*^[5]. These cases were categorized as "vascular cystic tumors of soft tissues". Recent literature review of well-documented cases shows that STABC is a recognized lesion and extremely rare^[6]. To the best of our knowledge the reported cases of STABC have been located in thigh, cervical spine, shoulder and upper extremities^[7,8] and STABCs in the jaws have not been reported in the English language literature.



Figure 1 Clinical view. Facial asymmetry was apparent with, a firm, non fluctuant and non tender mass covered by normal skin on the right mandibular angle.

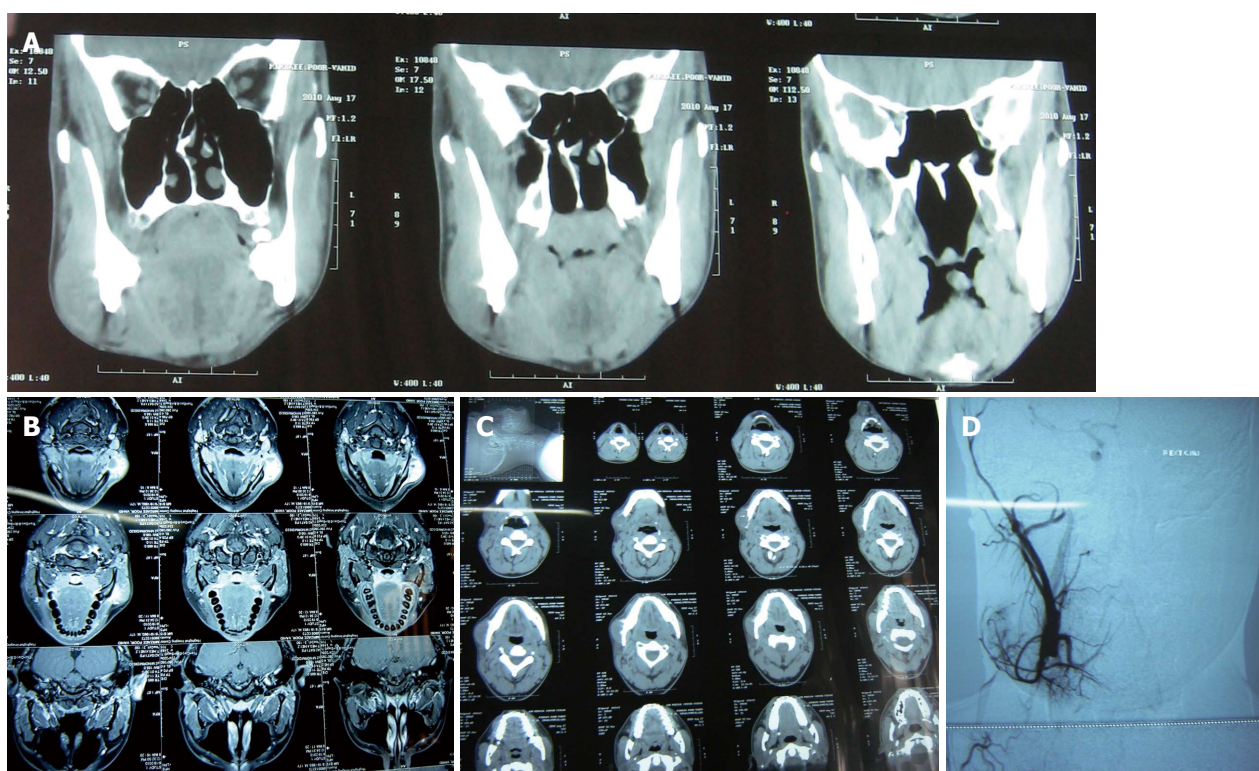


Figure 2 Computed tomography, magnetic resonance imaging and angiography. A: Coronal-axial computed tomography scan showed a lesion appeared to have a non-uniform intra lesional; B: Magnetic resonance imaging (MRI), T1 post contrast view demonstrated a well defined lesion with high signal intensity in the superficial part of right mandibular body and angle; C: MRI, T2 post contrast view demonstrated a well defined lesion with high signal intensity in the superficial part of right mandibular body and angle; D: Angiography of right carotid artery showed a lesion with only mild to moderate vascularity and ruled out arteriovenous malformation and hemangioma.

To increase our understanding of ABC arising in soft tissue, we report here a very rare case of soft tissue aneurysmal bone cyst of mandible. This case report was conducted in accordance with the principles of the Declaration of Helsinki.

CASE REPORT

In August 2009, a 17-year-old man was referred to a dentist complaining of a small swelling in his lower right angle of mandible beginning 4 mo ago. The patient was otherwise healthy, with no significant past medical history. He also did not have any previous history of trauma to head and neck region. The dentist suspected an inflammatory lesion and prescribed antibiotics. The patient continued

the antibiotic use for one month but the size of the lesion did not change and began to increase. The patient was referred to Oral and Maxillofacial Surgery, Department of Buali Hospital in Tehran. On physical extra oral examination, facial asymmetry was apparent with, a firm, non fluctuant and non tender mass covered by normal skin on the right mandibular angle (Figure 1). On intra oral examination a firm swelling was found on the right mandibular angle without any fistula or suppuration. There were no positive findings in panoramic radiography. On magnetic resonance imaging (MRI), an abnormal soft tissue mass with cystic component in the superficial part of right mandibular body and angle with intact cortex (Figure 2A-C). In fine-needle aspiration, blood was detected and angiography was requested to rule out vascular lesions.

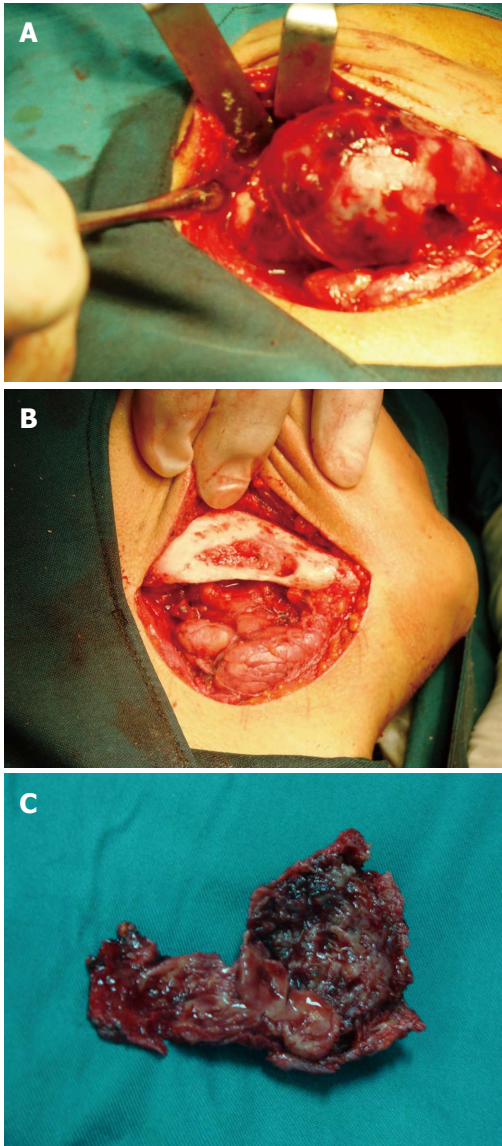


Figure 3 Clinical features at the surgery time. A: The mass was seen without involving adjacent bones; B: Periosteal reaction was seen in underlying bone; C: Gross view of excised lesion showed a solid lesion with eggshell-like rim of bone on its periphery and hemorrhagic cystic space.

The angiography report showed a lesion with only mild to moderate vascularity and ruled out arteriovenous malformation and hemangioma (Figure 2D). An incisional biopsy through an intraoral approach was performed under general anesthesia. The specimen consisted of 5 pieces of brownish-creamy fragmented tissues with rubbery consistency and solid on cut surface totally measuring 3.0 cm × 2.0 cm × 0.4 cm, sent for histopathological examination. The microscopic evaluation showed spindle cell proliferation, many multi-nucleated giant cells, osteoid formation and pools of blood without any epithelium linings. Three weeks after the incisional biopsy, the patient was hospitalized and decortication of the lesion was surgically carried out under general anesthesia (Figure 3A and B). During the operation, frozen sections were requested and revealed no malignancy. Grossly, the mass was totally measured

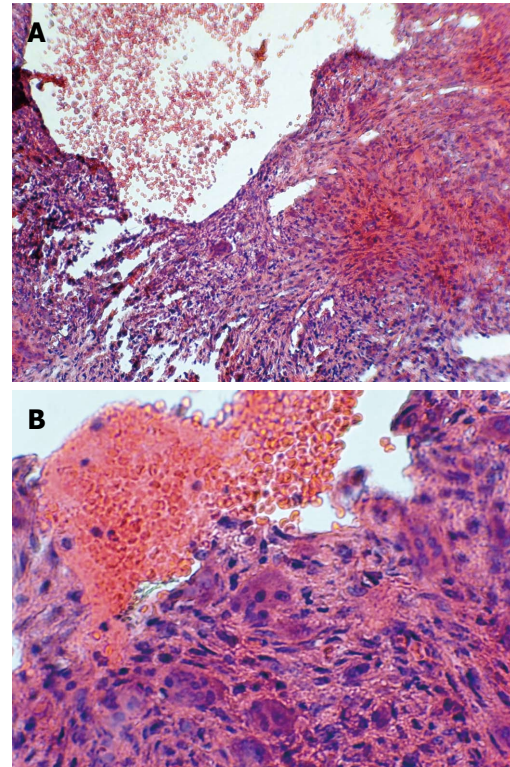


Figure 4 Pathological findings. A: Blood-filled space, fibro histiocytic stroma and multinucleated giant cells (HE × 100); B: Blood-filled space and multinucleated giant cells (HE × 400).



Figure 5 Coronal-axial computed tomography scan showed the patient is free of any lesion, 12 mo after surgery.

6.5 cm × 4.2 cm × 1.2 cm and showed a soft tissue lesion with hemorrhagic cystic spaces (Figure 3C).

Histopathological examination of the main lesion and the underlying bone and periosteum revealed fibro-histiocytic proliferation, blood-filled spaces and multinucleated giant cells (Figure 4). On reviewing all histopathological sections and paraclinical tests, the definitive diagnosis of STABC was confirmed. After 36 mo of follow up examination, the patient is well and free of any lesion (Figure 5).

DISCUSSION

STABC is a rare entity with histological and radiological

features that are identical to those of ABC, except for that STABC is of extra osseous location^[4,5,7,8].

To the best of our knowledge the reported cases of STABC have been located in thigh, cervical spine, shoulder and upper extremities^[3,8] and STABCs in the jaws have not been reported in the English language literature.

Our reported patient was male and a teenager, the age of the patient is in agreement with Nielsen *et al*^[3] reporting five cases of soft tissue aneurysmal bone cyst in three females and two males who ranged from 8 to 37 years (median 28 years). Their reported cases arose in the soft tissues of upper extremities, thigh and groin region as a rapidly growing mass. Clinical evaluation of our patient revealed rapidly growing non fluctuant and non tender mass on the right angle of mandible. Rapidly growing feature of ABC is a result of pathogenesis of this lesion and abnormal hemodynamics that leads to enlarging and hemorrhagic extravasation^[3,6]. The maximal diameter of the lesion was 6 cm and macroscopically, the soft tissue mass was consisted of blood-filled cavities separated by septa of various thickness which is similar to the findings in other reported STABC^[3,6,7].

Radiographically, the lesion had no positive findings in panoramic radiography. On the computed tomography scan, the lesion appeared to have a non-uniform intra lesional density.

MRI revealed an abnormal soft tissue mass with cystic component in the superficial part of right mandibular body and angle with intact cortex which is similar to the findings in other soft tissue ABC reports^[7,8].

The changes seen in MRI appearance of aneurysmal cyst of soft tissue depends on its stage ranging from a primarily solid tumor to a predominantly multicystic lesion^[9].

Histologically our reported case revealed fibro-histiocytic proliferation, blood-filled spaces and multinucleated giant cells, which is similar to other reports^[3,4,6].

The differential diagnosis of STABC in this location, includes giant cell tumor of soft tissue and extra skeletal osteosarcoma^[10].

Soft tissue giant cell tumor can be confused with STABC because of the presence of osteoclast- type giant cells in both lesions, but cystic change is the prominent view of STABC in histopathological evaluation^[11,12].

Follow up information of our reported patient after 36 mo revealed no tumor recurrence, a similar finding compared to other reported cases^[3,8]. On the contrary, local recurrence in soft tissue giant cell tumors are very common^[12] and it may be considered as another factor differentiating STABC from soft tissue giant cell tumor.

Extraskelatal telangiectatic osteosarcomas, which are very rare, have gross features similar to those of STABC^[10]. However, histologic examination of the STABC shows cells without cytologic atypia that are seen in extra skeletal telangiectatic osteosarcoma^[3,10].

The etiology of STABC is unclear. Several investigators have proposed trauma and vascular malformation as

etiological factors^[1,2]. However recent cytogenetic studies have provided evidence that STABC may be neoplastic in origin^[13,14].

Follow-up showed that the patient has been free of any lesion 36 mo after the surgery, a good point to indicate that this lesion can be treated by simple excision and this treatment modality was in agreement with the report of Nielsen *et al*^[3].

In conclusion, based on our experience STABC is an extremely rare type of benign soft tissue tumor especially in the head and neck area. Morphologically, it may be confused with a variety of soft tissue tumors. STABC infrequently recurs and complete excision is an appropriate treatment.

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- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

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- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; **(401)**: 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

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- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

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- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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- 12 **Breedlove GK**, Schorffheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis* serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

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- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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