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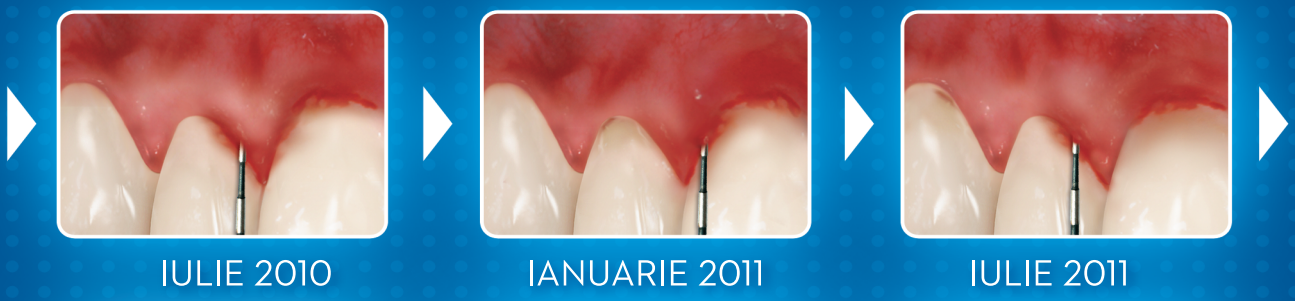

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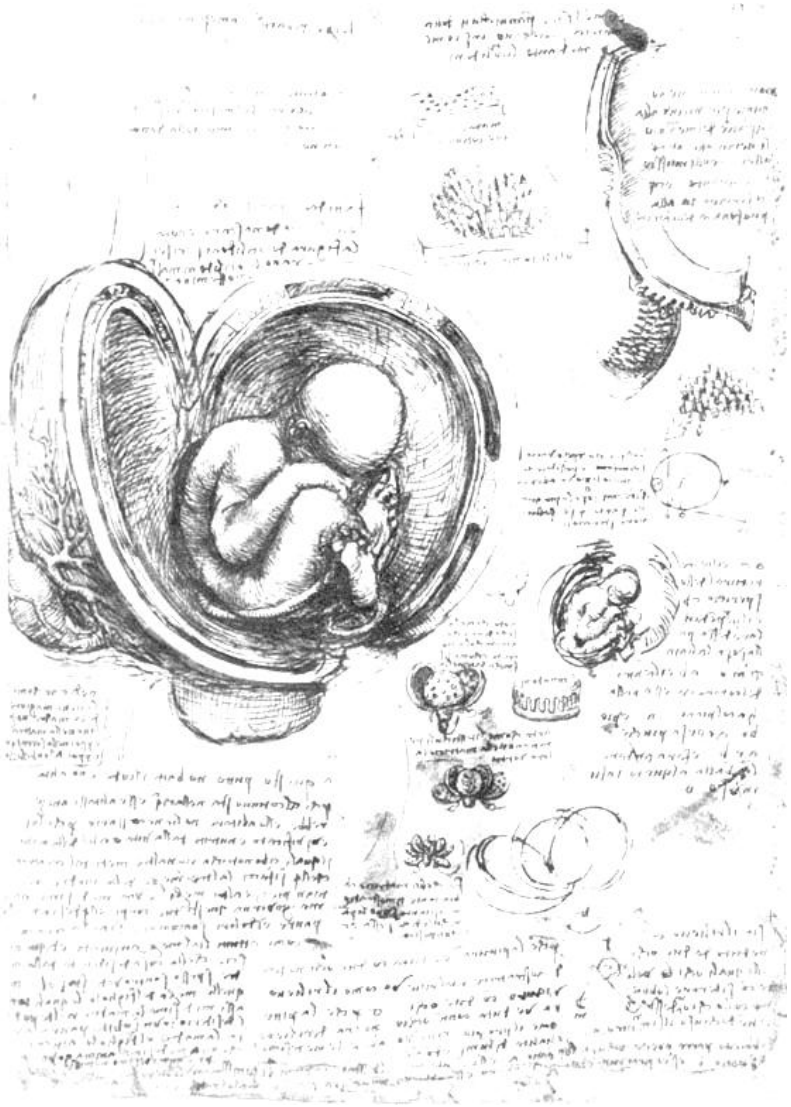

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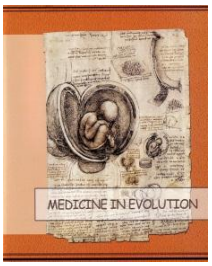
CONTENTS

ARTICLES

THE ROLE OF PRIMARY CYTOREDUCTIVE SURGERY IN ADVANCED OVARIAN CANCER



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ABSTRACT

Objectives: *To determine the value of primary cytoreductive surgery in advanced ovarian cancer.*

Methods: *A retrospective clinical study in which 45 female patients, with epithelial ovarian cancer FIGO stage IIIC, operated in the Surgical Oncology Clinic of the Municipal Hospital Timisoara over a period of six years (2003-2008), were evaluated.*

Results: *The diagnosis was established based on the histopathological examination. The 45 patients were divided into two groups, Group 1 (n = 24) who underwent optimal cytoreductive surgery followed by adjuvant chemotherapy, and Group 2 (n = 21) who followed neoadjuvant chemotherapy, after being performed cytoreductive surgery. Between the studied Groups, there were not significant differences in terms of epidemiological data (area of origin, age at diagnosis and comorbidities) and neoplastic disease characteristics (histopathological type, grading). To achieve the optimal threshold after the cytoreductive surgery, 26 patients requested multiple organ resections. Long term survival was significantly higher for Group 1, 54% at 5 years, compared with only 28.5% for the 2nd Group.*

Conclusions: *Optimal cytoreductive surgery performed as the first therapeutic act and requiring the surgeon to have an aggressive attitude brings clear benefits in terms of long-term survival for patients with advanced ovarian cancer.*

Key words: *Ovarian cancer, optimal citoreductive surgery, survive, tumor residue*

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INTRODUCTION

Ovarian cancer is a major cause of mortality and morbidity, being on the seventh place as the incidence of malignant tumors among females, with a five years survival for all stages of disease between 35-38% (1). Increased mortality is due to the fact that over 60% of patients are diagnosed in advanced stages (FIGO III-IV) (2).

The black prognosis is due to the late detection, the disease being asymptomatic until it develops disseminated peritoneal metastases. Peritoneal cavity is the main place of dissemination of the ovarian neoplasm by direct implantation in various intraperitoneal locations of neoplastic cells, which follows the peritoneal fluid hydrodynamics through the parietocolic spaces to the diaphragm and back towards the pelvis (3).

The basic treatment for patients with advanced ovarian cancer is the surgery that aims an optimal cytoreduction (postoperative tumoral residue with a diameter of maximum 1 cm) and subsequently adjuvant chemotherapy (4, 5). Unfortunately, only a relative low number of patients, between 40-50%, can follow this therapeutic model (6, 7). Patients, who cannot benefit from the beginning from the optimal tumor cytoreduction, will follow neoadjuvant chemotherapy (3-6 cycles) and, subsequently, an "interval" surgery with a cytoreductive purpose will be taken into consideration. The chemotherapy scheme used in recent years has included Cisplatin/Carboplatin and Paclitaxel and had superior results compared to others used in the past. (4, 8).

Cytoreductive surgery is an important prognostic factor in terms of disease-free survival and overall survival.

Aim and objectives:

The aim of the study was to see the the role played by the optimal tumor cytoreduction in the treatment of patients with epithelial ovarian cancer performed as a first therapeutic act, knowing that around 75% of epithelial ovarian neoplasms present chimiosensibility.

METHODS

The clinical study was conducted on a group of 45 female patients, with epithelial ovarian cancer stage IIIC, hospitalized in the General Surgery II and Surgical Oncology Clinic of the Emergency Municipal Hospital Timisoara, between 2003- 2008. Patients were selected from a total of 197 sick subjects with ovarian cancer treated in our clinic during that period of time.

Among the criteria to enter the study as subject, there were: histological diagnosis of epithelial ovarian cancer, FIGO stage IIIC, following optimal cytoreductive surgery as the first therapeutic act or after neoadjuvant systemic chemotherapy, following at least 6 cycles of adjuvant or neoadjuvant chemotherapy. Patients presenting significant comorbidities (other neoplasm diseases associated with kidney failure, liver failure) patients who interrupted the systemic chemotherapy, patients who died before performing a minimum of 6 cycles of chemotherapy, and patients older than 80 years old at the time of diagnosis were excluded from the study.

The patients studied were divided into two groups: patients who underwent optimal cytoreductive surgery as first therapeutic act (n=24) followed by adjuvant chemotherapy and patients who followed neoadjuvant chemotherapy, after being

performed cytoreductive surgery (n = 21).

The correct diagnosis was set for patients of Group 1 using the histopathological result on the excision pieces, and at Group 2, the positive diagnosis was set by staging laparotomy with biopsy at 20 patients and at 1 patient by paracentesis with positive cytological examination, increased tumoral marker CA 125 and tomography which certified the presence of ovarian tumors and of peritoneal carcinomatosis. Patients from Group 2 were considered to have unresectable tumors.

All patients were treated with adjuvant chemotherapy or neoadjuvant chemotherapy from the platinum derivates class (cisplatin/carboplatin) according to the therapeutic guidelines.

The role of primary cytoreductive surgery at patients with advanced ovarian cancer was evaluated after the survival analysis. The study is based on retrospective analysis of the observation sheets, discharge records, consultation records from outpatient facility, surgery protocols, histology reports, and oncology sheets.

RESULTS

Systematic epidemiological data of both groups are presented in Table 1. The entire group recorded an average age of 56.06 years and a rate of 44.44% had presented co morbidities, the most common being: hypertension in 28.88%, chronic ischemic heart disease 35.55%, diabetes type II at 11.11% and obesity (grades II-III) at 17.77%. In most of the cases associated pathologies occurred simultaneously.

Table 1. Epidemiological data

	Group 1 (n=24)	Group 2 (n=21)
Environment (rural area/ urban area)	10/14	8/13
Average age	57.08 (35-79)	56.05 (20-74)
Comorbidities		
Hypertension	8 (33.33%)	5 (23.80%)
Chronic ischemic heart disease	9 (37.50%)	7 (33.33%)
Diabetes type II	3 (12.50%)	2 (9.52%)
Obesity	4 (16.66%)	4 (19.04%)

From the neoplastic disease's characteristics (Table 2), all patients had epithelial ovarian cancer FIGO stage IIIC. In Group 1, the histopathological outcome presented papillary serous adenocarcinoma at 17 (70.83%) patients, adenocarcinoma type endometrioid at 2 patients (8.33%), mucinous adenocarcinoma at 2 patients (8.33%), adenocarcinoma with clear cells at one patient (4.16%), undifferentiated adenocarcinoma at 2 patients (8.33%). For Group 2, 16 patients (76.19%) had papillary serous adenocarcinoma, 2 patients (9.52%) had endometrioid adenocarcinoma, 1 patient (4.76%) had mucinous adenocarcinoma, 2 patients (9.52%) anaplastic carcinoma. Patients of Group 1 had the tumor grading G2/G3 of 15/9 patients; and in Group 2, the G2/G3 ratio was 16/5 patients.

Table 2. The neoplastic disease's hystopatological characteristics

	Group 1 (n=24)	Group 2 (n=21)
Hystipatological Type		
Serous carcinoma	17(70.83%)	16(76.19%)
Endometrioid carcinoma	2(8.33%)	2(9.52%)
Mucinous carcinoma	2(8.33%)	1(4.76%)

Carcinoma with clear cells	1(4.16%)	-
Anaplastic carcinoma	2(8.33%)	2(9.52%)
Tumoral grading		
G2	15(62.50%)	16(76.19%)
G3	9(37.5%)	5(23.80%)
|Neoplastic ascites	21(87.50%)	19(90.47%)

Both, in terms of epidemiological data and neoplastic disease's characteristics, the results reveal a similar structure of the two groups (Table 1 and 2).

The extent of the optimal cytoreductive surgery for the entire group of patients consisted in total hysterectomy with bilateral anexectomy and omentectomy, and it was associated with intestinal resection at 4 patients from Group 1 and 2 patients from Group 2; partial resection of bladder at 1 patient from Group 1; segmental resection of the sigmoid colon at 1 patient from each of the studied Groups. At 10 patients from Group 1 and 7 patients from Group 2, the ablation of tumor formation from the parieto-colic areas, the Douglas space, the gastrocolic, and gastrohepatic ligament, was performed.

From Group 1, after ending the six cycles of adjuvant chemotherapy, 17 patients had complete remission documented, at 6 patients through "second-look" surgery and at 11 patients by CT and CA-125 values normalization. Four patients had presented partial remission through second-look surgery and 3 patients had the disease in evolution.

From Group 2 all patients presented favorable response after the neoadjuvant chemotherapy, 10 patients showing complete remission with pieces of sterile resection and 11 patients had partial remission, being able to perform optimal cytoreductive surgery with residual remnants of tumor of <1 cm postoperatively.

The patients' survival was analyzed over a period of 5 years, from the time of diagnosis (Figure 1) and the results were as follows: after the first year, in Group 1 survived 21 patients (87.5%) and 19 patients (90.46%) in Group 2; after the second year, in Group 1 survived 20 patients (83.33%) and 15 patients (71.42%) in Group 2; at 3 years after the diagnosis, in Group 1 survived 16 patients (66.66%) and 8 patients (38.09%) in Group 2. At five years after the diagnosis in Group 1 survived 13 patients (54.16%) and 6 patients (28.57%) in Group 2, the difference being statistically significant (p = 0.036).

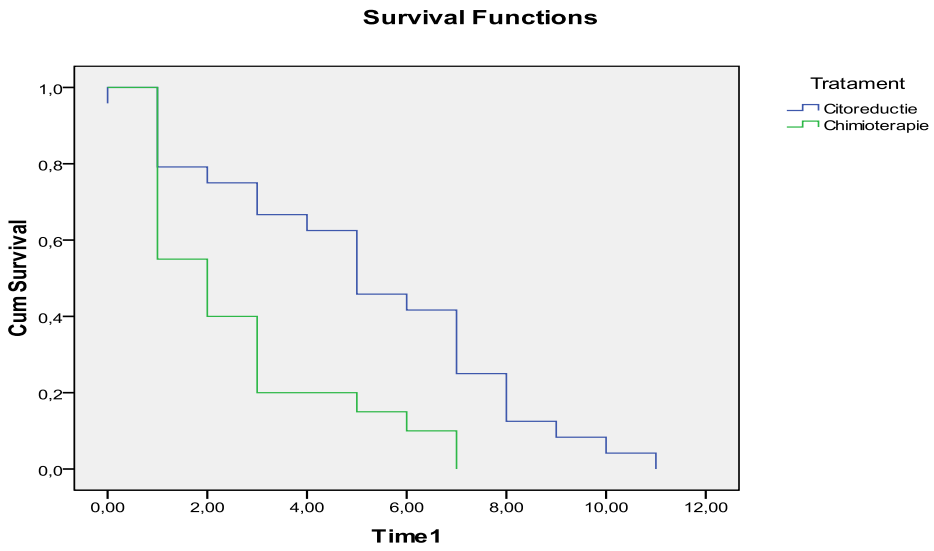

Figure 1. ***The survival curve between the groups***

DISCUSSIONS

Ovarian cancer is an important cause of morbidity and mortality in the diagnosis of malignancies due to the impossibility to put the diagnosis in the early stages of the disease.

Considering that over 60% of the ovarian cancer cases are diagnosed in advanced stages, which requires a multidisciplinary approach, mainly based on the combination of surgery with chemotherapy, the analysis and evaluation of the therapeutic possibilities is necessary in order to implement an onco-surgical protocol with a radical character which has to bring clear benefits for these patients.

The first therapeutic approach for patients diagnosed with ovarian cancer is, generally, the surgery, which aims both to put the exact diagnosis and to reduce the tumoral volume as much as possible, knowing that postoperative tumoral residue is an important factor in terms of the period "free" without disease and the overall survival.

Since the '70s, Griffiths et al (9, 10) have described the relationship between cytoreductive surgery and survival, considering the optimal cytoreductive surgery the one which obtains a postoperative tumoral residue with a maximum diameter of 1.5 cm. During the following years numerous studies confirmed the inverse relationship between residual disease after the primary surgery and the survival (11-14), considering currently tumoral cytoreduction optimal, and getting a residual postoperative tumoral residue with a diameter of maximum 1 cm. In a study on 3126 patients analyzed, du Bois et al (17) achieved an average survival of 99.1 months for patients who underwent complete resection and 36.2 months at patients who had a residue <1 cm. After primary cytoreductive surgery, patients with advanced ovarian cancer will follow adjuvant chemotherapy with regimes associating platinum and taxane derivatives.

For patients who are not candidates for the primary cytoreductive surgery, neoadjuvant chemotherapy and surgery at a certain period of time, with cytoreductive purposes, are taken into consideration. Multiple studies have presented the neoadjuvant chemotherapy's effectiveness, treatment which used platinum derivatives regimes, followed by surgery of "interval", finding an overall survival rate similar to that of patients who received primary tumoral cytoreduction followed by adjuvant chemotherapy (8, 15, 16).

The two studied groups were homogeneous, both in terms of epidemiological data (average age and comorbidities), as from the point of view of the neoplastic disease (stage of disease, histological type, and tumoral grading).

Our study highlights the benefit optimal cytoreductive surgery is brought, surgery leaves a tumoral residue under than 1 cm, performed the first therapeutic sequence. If for a period of up to 24 months after the diagnosis, significant differences weren't found, the optimal primary tumor cytoreduction on long term offers 54% for survival at 5 years, compared with 28.5% for patients who have undergone neoadjuvant chemotherapy despite tumoral chemo-sensitivities present at this.

It is also observed that in order to obtain an optimal tumoral residue, an aggressive surgery is requested, surgery which often involves multiple organ resection. The recurrences appeared later and their responses to treatment were not taken into account in the study, which benefit from the combination of surgery with chemotherapy.

The results in terms of survival of patients in both groups are within the

limits mentioned in the scientific literature.

CONCLUSIONS

The first therapeutic sequence for patients with advanced epithelial ovarian cancer must be the cytoreductive surgery, with the goal of leaving residual tumoral volume as small as possible or even absent macroscopically.

Cytoreductive surgery should be an aggressive one, as very often it requires multiple organ resections to obtain the optimal threshold.

Survival of patients with advanced ovarian cancer is closely related to the therapeutic method applied per received, and optimal tumor cytoreduction is superior in terms of this issue.

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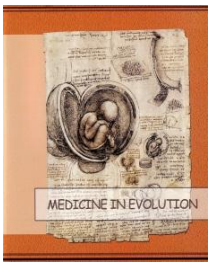
KERATOACANTHOMA: CLASSICAL AND MODERN THERAPEUTIC APPROACHES



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ABSTRACT

Keratoacanthoma is a cutaneous tumor that originates in the pilosebaceous follicle. In most cases it is characterized by an initial rapid evolution followed by a slow involution and healing. In rare cases, keratoacanthomas may progress to invasive and metastatic squamous cell carcinoma, therefore aggressive treatment might be recommended. Although surgery is the first-choice therapy, a number of other destructive and medical treatments are used, depending on tumor features and patient condition. In this article we intend to present the indications and benefits of various keratoacanthoma treatment methods, with emphasis on the most modern techniques.

Key words: *keratoacanthoma, squamous cell carcinoma, treatment.*

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INTRODUCTION

Keratoacanthoma is a low grade, rapidly evolving skin tumor which originates in the pilosebaceous follicle. Although it shows clinical and histopathological similarities with squamous cell carcinoma, its evolution is different. [1] The tumor clinically presents as an exophytic, painless lump with central ulceration filled with keratin; its margins show numerous telangiectasias on the surface (fig. 1). Keratoacanthomas, ehich may be solitary or multiple, are generally characterized by rapid growth, reaching 1-2 cm in diameter in a few weeks, followed by slow regression lasting up to one year, leaving an atrophic scar if not excised.

Keratoacanthoma was first described in 1889 in London by Jonathan Hutchinson as a "crateriform ulcer of the face". [2] However, it is important to emphasize that signals on the existence of these tumors had occurred in several medical centres in the world, including our country, even before the publication of the official recognition from London, 1889.

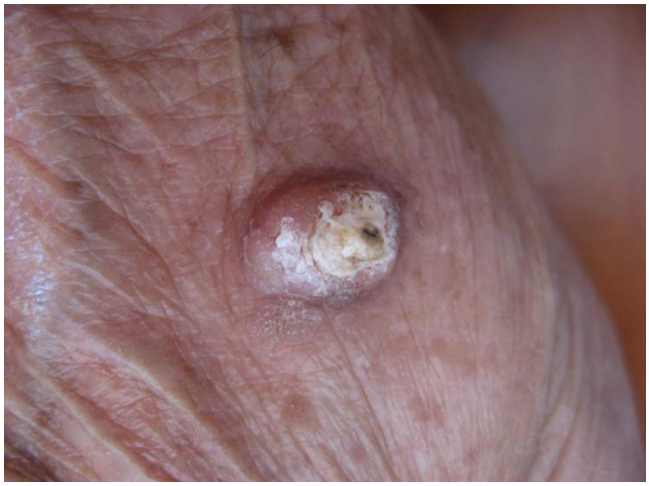

Figure 1. Solitary Keratoacanthoma on sun-damaged skin

THERAPEUTIC APPROACHES IN KERATOACANTHOMA

In this paper we aim to discuss the treatment methods for keratoacanthoma with emphasis on modern therapies and their applicability.

The treatment of keratoacanthoma (KA) is **primarily surgical.** The medical therapy is reserved for exceptional cases where surgery is not possible. For example, medical treatment is suitable for patients with multiple lesions, with lesions that are not amenable to surgery due to the size or location and in patients with comorbidities that discourage surgical procedures.

Surgery involves **surgical excision** of the tumor. In rare cases, keratoacanthomas can progress to metastatic invasive squamous cell carcinomas where aggressive surgical treatment is recommended. [3-6] It is advised that surgical excision should be complete, with safety margins of 3-5 mm and subsequent histopathological examination to rule out an invasive squamous cell carcinoma (SCC); tangential biopsy is not recommended because the changes occurring in the base of the lesion are of great importance in the differentiation from an invasive SCC. [7][8]

Complete surgical excision or deep incisional biopsies are preferred; if the lesion cannot be excised entirely, we recommend taking a spare spindle in the centre of the lesion containing at least one edge. [7] [8] Since one cannot

predict the biological behaviour of individual lesions, many specialists consider that surgical treatment of keratoacanthoma is equivalent to that of SCS. In some patients, smaller lesions may be treated with deep shave excision and curettage or other destructive techniques [7].

Mohs micrographic surgery may be indicated for large or recurrent keratoacanthomas or keratoacanthomas distributed in anatomic areas where wide excisions are not recommended due to cosmetic or functional considerations.[9]

Mohs surgery, also known as chemosurgery, developed in 1938 by Frederic E. Mohs - a general surgeon, is a microscopically controlled surgery used to treat common types of skin cancer.[9] It was initially used for primary basal cell carcinoma, the most common type of skin cancer, with a cure rate between 97% and 99,8%, as shown in most studies. [11][12] Mohs procedure is also used for squamous cell carcinoma, but with a lower cure rate. It has been used in the removal of melanoma-in-situ (cure rate 77% to 98%), as well as other types of melanoma (cure rate 52%).[13][14] However, Mohs surgery should be reserved for the treatment of skin cancers located in anatomic areas where tissue preservation is of utmost importance (face, hands, feet, genitals).

The advantages of this technique as compared with those of other methods for treating cutaneous neoplasms include the following:

- Superior cure rates
- Maximal tissue conservation
- Ability to histologically trace perineural or infiltrating tumors
- Low cost as compared to that of radiation therapy or surgery in hospital operating rooms.

Radiotherapy: Keratoacanthomas are radiosensitive and respond well to low doses of radiation (doses less than 10 Gy). Radiation therapy is used in selected patients presenting with large tumors where surgical resection would result in unacceptable cosmetic outcomes, those who do not have access to Mohs surgery or tumor recurrence after incomplete resection. [7][16] Radiation therapy is not indicated in young patients due to long-term destructive effects in the treated area.

Other destructive methods:

-cryotherapy

-curettage and electrocautery

-Argon laser or NdYAG

Both laser therapy and cryotherapy have been successfully used in small keratoacanthomas, in keratoacanthomas found in difficult to treat areas and as an adjunct to surgical removal.[7]

Medication is used for the treatment of large or multiple tumors or for inoperable tumors due to their anatomic location or patient's poor status. They are also useful for eruptive keratoacanthomas of the lower legs. Topical and systemic antineoplastic agents are available.

Topical agents

- Intralesional injection of methotrexate. Methotrexate is an antimetabolite that inhibits DNA synthesis and proliferation of cancer cells; it can lead to immunological suppression; a satisfactory response occurs within 3-6 weeks after administration. [18]
- Topical or intralesional 5-Fluorouracil (5-FU). 5-FU is an antimetabolite that inhibits thymidylate synthase and interferes with RNA synthesis and function; it is useful for the palliative treatment of patients with progressive disease. [17]
- Intralesional bleomycin injection. Bleomycin is a glycopeptide antibiotic that inhibits DNA synthesis; is used at concentrations of 1mg/ml and then diluted with local anaesthetic. It decreases the size and sebum production of the sebaceous glands. It inhibits sebaceous gland differentiation and

abnormal keratinization. It is an effective drug associated with good cosmetic results. [20]

- Intralesional corticosteroids; [21]
- Intralesional interferon alpha and interferon beta. [22]
- Topical photodynamic therapy with delta aminolevulinic acid or methyl aminolevulinic acid. It is an excellent treatment option for various non-melanoma skin cancers and precancerous lesions, including actinic keratosis, Bowen's disease, and basal cell carcinoma. [23]. The use of PDT has been extended to other non-melanoma skin cancers, inflammatory diseases and skin infections. [24]. Cases of keratoacanthoma successfully treated with photodynamic therapy have also been reported in the literature. [23] [25] [26] The "photodynamic reaction" is the photochemical process involving the absorption of light by a photo-sensitizer and the subsequent generation of reactive oxygen species. These reactive oxygen species damage KA tissue cells, block the microcirculation and induce an immune response and a cellular inflammatory response in the surrounding tissue. [27]

Photodynamic therapy (PDT) has emerged as a new therapeutic modality in dermatology. It is applied to patients who are not eligible for surgical procedures due to age and comorbidities, after histopathological confirmation of the clinical diagnosis and signing an informed consent. Both delta-aminolevulinic acid (ALA) and methylaminolevulinic acid (MAL) can be used. To improve the absorption of the photosensitizing agent the lesions are initially scraped. A thick layer of cream containing the photosensitizing substance is applied on the lesion and 5mm around it and the lesion is covered with an occlusive dressing. After 3-4 hours, the dressing is removed, the wound is cleaned and light is applied according to the local protocol. Local anaesthesia is not required; the patients feel a sensation of heat or burning which can be improved with thermal water sprays. Sun exposure is prohibited and the use of sunscreen creams is recommended.

- Topical Imiquimod 5%. Imiquimod is an immune-response modifier that has the potential to be useful in many dermatological indications.[30] It is capable of enhancing both innate and cell-mediated immune pathways. Topical treatment with imiquimod 5% cream was originally approved by the FDA for external perianal and genital warts in 1997. It was not before 2004 that topical imiquimod has been approved for superficial basal cell carcinoma and non-hypertrophic actinic keratoses.[31]

The specialty literature comprises several cases reporting the successful treatment of keratoacanthomas using imiquimod 5%. In most reported cases the patients were elderly and could not undergo surgery (patients on anticoagulation medication, multimorbid patients, patients with multiple lesions, and patients with recurrent or incompletely excised tumors) and presented with different types and sizes of keratoacanthomas [32][33]

In 2004 Bhatia N. reported a case of large keratoacanthoma that was completely resolved after using a treatment regimen consisting in imiquimod 5% cream topically applied on a daily basis for 5 months.[32]

Two cases of facial KAs (Di Lernia V et all, 2004) treated with topical 5% imiquimod cream with successful clearance of KAs after 8 weeks of treatment were also reported. No recurrences occurred after one year of follow up.[33]

Despite the fact that KAs are characterized by the potential for spontaneous regression, it is possible that a more rapid activation of CD4+ lymphocytes, via interferon release and

cytokine secretion, takes place after imiquimod application, leading to KA regression.[33]

Keratoacanthoma treated with Imiquimod 5% continued to be reported in the literature. In 2011 Chan Jeon Hye et al. report 4 cases of keratoacanthoma treated with 3-4 applications per week; apparent remission was observed after 4-6 weeks of treatment, and the lesions healed with residual scarring after 9-11 weeks. Biopsy is recommended after 5-8 weeks of treatment to assess histological remission and shorten the duration of treatment. [34]

Due to the ability of imiquimod to rapidly and potently stimulate both innate and adaptive arms of the immune system, it has rapidly been recognized as a potential candidate for off-label use in over 60 conditions. This is illustrated in many reported cases, open letters and small clinical trials. [34]

Further study is needed to investigate indication in conditions successfully treated with imiquimod, application frequency, duration of maintenance and treatment success rates.

Systemic treatment

- Retinoids (isotretinoin, acitretin and etretinate) are oral agents used for severe skin conditions in patients with numerous injuries.
- Oral Methotrexate
- 5-fluorouracil intravenously
- Alpha-2 interferon [1]

Patients who develop nonmelanoma skin cancers such as keratoacanthoma, squamous cell carcinoma, basal cell carcinoma are at high risk of developing a second nonmelanoma skin cancer. Therefore regular follow up of the patients and treatment of injuries is required.

CONCLUSIONS

Keratoacanthoma is a squamous cell carcinoma precursor lesion, originating from the hair follicle. Multiple treatment options, both systemic and topical therapies, are available to the physician; knowledge regarding the advantages and disadvantages of each therapeutic method is of paramount importance in the treatment approach of keratoacanthomas.

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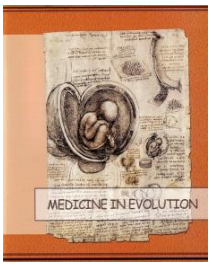
CORRELATIONS BETWEEN HETEROMORPHIC CHROMOSOMAL VARIANTS AND INFERTILITY



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ABSTRACT

Chromosomal heteromorphisms are considered normal chromosomal variants that show variability of the length in some chromosomal regions as well as different degrees of staining intensity for specific segments of certain chromosome. We considered important to present our experience on a large cohort of patients from the Western part of Romania in regards with the reproductive implication of heterochromatic chromosomal variants. Constitutional karyotype was done from peripheral blood lymphocyte, using standard protocol and at least 30 metaphase spreads were analyzed for each patient.

Chromosome heteromorphisms were found in 47 females and 50 males. The heteromorphism 9qh+ was found in 47 cases, pericentric inversions of chromosome 9 in 18 cases, 1qh+ in 12 patients and 16qh+ in 9 patients, abnormal long stalks of acrocentric chromosome in 8 cases, 2 cases of inversion of chromosome 16 and 1 case of Yqh+.

Polymorphic chrosomosonal variants found with a higher frequency in the couple with reproductive disturbances sustain the possible implication of those heteromorphism in cases with infertility.

Key words: *heteromorphism, reproduction failure*

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INTRODUCTION

Polymorphic variants of human chromosomes, a synonym for chromosomal heteremorphisms were observed since when staining techniques allowed the study of chromosome. Chromosomal heteromorphisms were defined as normal variants of human chromosomes showing a variability of the length in some chromosomal regions as well as different degrees of staining intensity for specific segments of certain chromosome. (1)

At the molecular level, these chromosomal variants are mainly due to tandem repeated sequences of DNA. Tandemly repeated DNA sequences are commonly located in the heterochromatic chromosomal regions, in the short arm of acrocentric chromosome and in the long arm of Y chromosome. (2)

Even if heteromorphisms were reported for virtually all human chromosomes, there are a number of chromosomes that exhibit this type of variability often: paracentric long-arm regions of chromosomes 1, 9 and 16, short arms of acrocentric chromosome, long arm of Y chromosome.(2)

Regarding the implication of those chromosomal variants in reproduction failure, until now a consensus was not reached. There are contradictory reports showing no effect of heteromorphisms in reproductive fitness (3,4) but also different study, recently published indicating a possible implication of chromosomal polymorphisms in infertility. (5–7)

We considered important to present our experience in regards with the reproductive implication of heterochromatic chromosomal variants especially because the study is the first study on a large cohort of patients from the western part of Romania on this topic.

MATERIAL AND METHODS

The study lot included 505 couples with reproduction failure evaluated in the Genetic Laboratory from the University of Medicine and Pharmacy ''Victor Babes" Timisoara and in the Genetic Laboratory from the Obstetrics and Gynecology Clinic "Dumitru Popescu" Timisoara. From the total number of those couples 15% present sterility, while the rest of 85% had one or more abortions in antecedents.

The women included in the study were between 17 and 47 years old, the median age was 30,3 ±4,99. The men included in the study were between 20 and 52 years old, the median age was 32,69 ±5,16.

For all the couples the cytogenetic analysis was done. Constitutional karyotype was done from peripheral blood lymphocyte. We used the standard protocol with minor modifications in order to obtain chromosomal spreads for cytogenetic evaluation. The peripheral blood samples were cultured in RPMI culture for 72 hours, then exposed to colchicine, hypotonized with KCl and fixed with a 3:1 mix of methanol and acetic acid. The next day GTG banding and staining was done. At least 30 metaphase spreads were analyzed for each patient.

We recorded the polymorphism of heterochromatic regions of 1, 9, 16 and Y chromosome, pericentric inversion of chromosomes 9 and 16, prominent stalks and satellites of acrocentric chromosome.

RESULTS

Chromosome heteromorphisms were found in 47 females and 50 males (Table 1).

The most frequent heteromorphisms recorded were 9qh+ (figure 1) and pericentric inversions of chromosome 9 (figure 2). Variable length of the heterochromatic region on the long arm of chromosome 9 was found in 47 cases, while the pericentromeric inversion of the chromosome 9 was recorded in 18 patients.

Table 1. Polymorphisms found in the study lot

	9qh+	Inv(9)	1q+	16qh+	D group cenh+/s+	D group cenh+/s+	Inv(16)	yqh+
female	23	9	6	4	3	1	1	0
Males	24	9	6	5	2	2	1	1

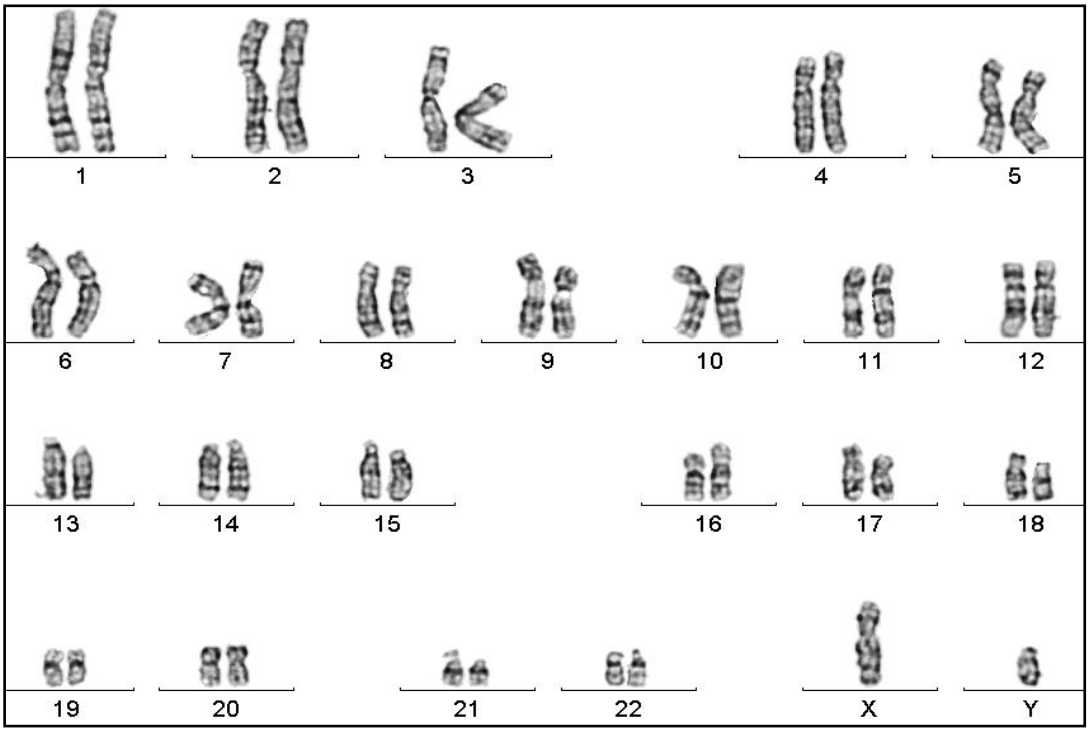


Figure 1. Constitutional karyotype: 46,XY,9qh+

Variable length of heterochromatic regions of chromosome 1q and 16q were found in 12 patients and 9 patients respectively.

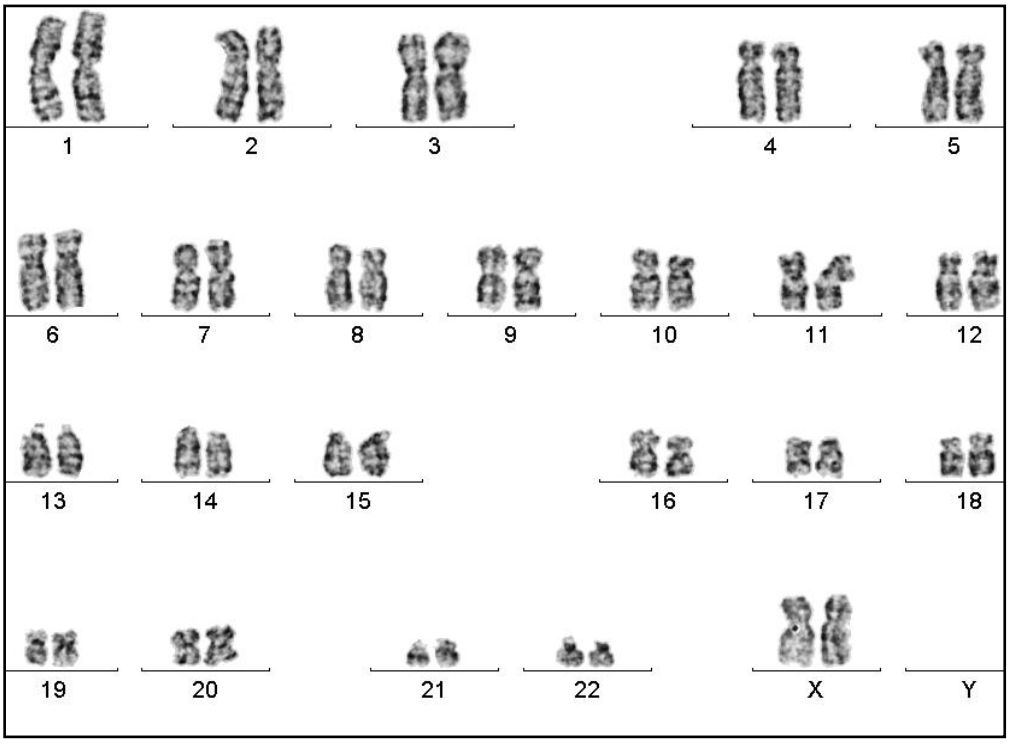


Figure 2. Constitutional karyotype: 46,XX,inv9(p13q13)

Other polymorphism found were abnormal long stalks of acrocentric chromosome (figure 3) -8 cases and 1 case with inversion of chromosome 16 and enlarged heterochromatic region on the Y chromosome respectively.

The distribution of the results is presented in Graphic 1.

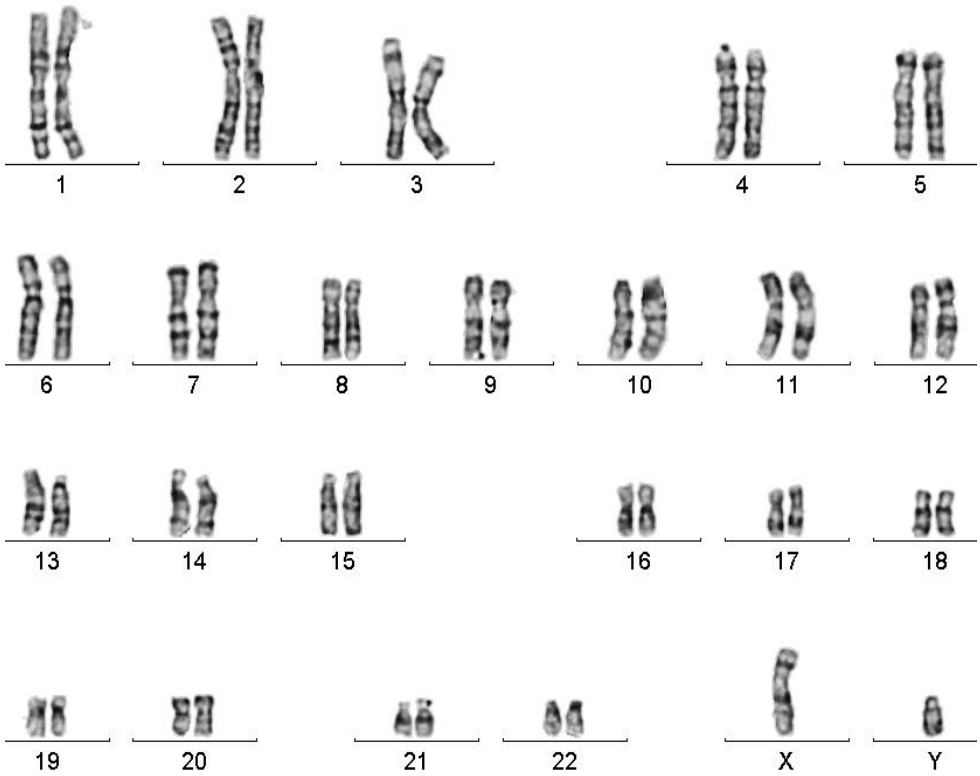
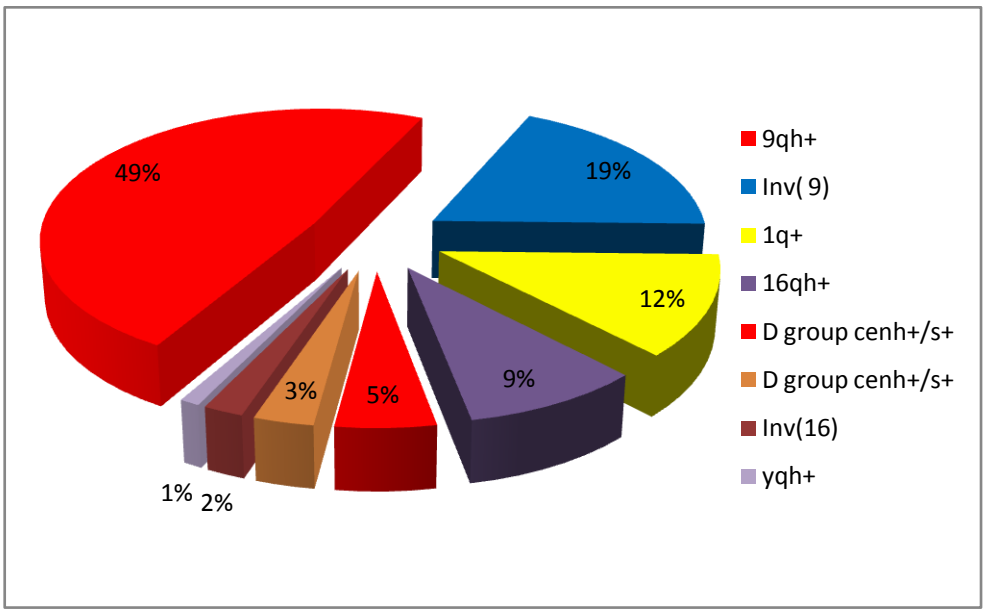


Figure 3. Constitutional karyotype: 46,XY,14pstk+



Graphic 1. Distribution of the heteromorphisms found in the study lot

DISCUSSIONS

Reproduction failures are becoming an important problem of public health due to the increased number of the infertile couples and the impact on the natality rate. In many cases the cause of infertility is difficult to be established, because of the complexity of possible etiologies.(8)

Among the major causes of reproduction failure are genetic defects including chromosomal anomalies, gene defects as well as multifactorial disorders.(6) The implication of chromosomal defects was established in the early period of cytogenetic era and many studies are available as regard of these aspects.

Apart from the numerical anomalies and structural aberrations generally accepted as cause for reproduction failure, there are some studies that raised the hypothesis of heteromorphism as cause of miscarriages, abortions or sterility. The hypothesis was based on the observation that in infertile couples the incidence of those chromosomal variants is higher than in normal population. (9,10)

The mechanism that can explain the role of heteromorphisms in reproduction failure can be the fact that these polymorphic regions alter the synapsis established in the process of crossing over during gametogenesis.(6) Because those regions are late replicative, a possible alteration of the timing of meiosis might lead to gametogenesis defects and possible aberrant gametes.(5)

Our results show that chromosome 9 polymorphisms were the most frequent (65 cases). Different variations of the heterochromatic region on the long arm of chromosome 9 were found in 47 couples from the study lot. The correlation between this polymorphism and reproduction failure is still unknown. The variation of that region length is due to highly repetitive DNA sequences. These heteromorphisms might be involved in epigenetic regulation of different genes and in silencing genes when it is transferred near the heterochromatic pericentric region. (11)

In general population chromosome 9 inversions were reported with a frequency between 1 to 3%. (12) The association of chromosome 9 inversions with reproduction failure and also in cases of children with dysmorphic features was reported by different researchers.

(6,10,12) These were explained by the events during inversions when at the breakpoints a loss or suppression of several genes can occur. Another interesting aspects regarding chromosome 9 is that it seems that relative frequently presents structural aberrations in sperm. (13)

Frequent gaps and splits were also reported for chromosomal regions 1 qh and 16qh. These gaps and splits were associated with an alteration of timing of synapsis that can be explained by the size and molecular aspects of the specific region.(14)

Polymorphic variants of chromosome 16 were found with a higher frequency in the couples with reproductive failure. The rate of miscarriages in the cases with one parent carrier of a chromosomal 16 anomaly was of 100% sustaining the role of those polymorphisms in reproduction failure. (15)

Heteromorphisms of the acrocentric chromosome of groups D and G were represented by large heterochromatic telomere regions, long p arm and additional satellites. These variants affects centromere and kinetochore function as well as the crossing over process, leading to formation of aberrant gametes. (16)

We compared this result with the results of a study conducted by us on 528 amniotic and chorionic villus samples, based on the assumption that this lot represents a sample of normal population. From the study lot of prenatal diagnosis, only 7 polymorphic variants were recorded: 4 cases of abnormal long p arm of acrocentric chromosome, 2 cases with inversions of chromosome 9 and one case with enlarged heterochromatic region of chromosome 9. (17) For all the cases in which the fetuses presented polymorphic chromosomal variants, cytogenetic investigation of the parents established that the chromosomal anomaly was inherited from one of the genitors. These finding allowed us to conclude that in couples with reproduction failure there is a higher frequency of polymorphisms of chromosome 9, and to sustain a possible implication of those chromosomal variants in infertility. As polymorphisms of chromosome 1 q, 16q were not found in the prenatal cases we consider that they may be responsible for reproduction failure.

CONCLUSIONS

Cytogenetic investigation in couples with reproductive failure remains a useful tool for detection of the major cause of those cases with abnormal reproductive fitness. Polymorphic chromosomal variants found with a higher frequency in the couple with reproductive disturbances sustain the possible implication of those heteromorphism in cases with infertility. Cytogenetic investigations permit a correct evaluation and appropriate counseling for the couples with infertility allowing patients to acknowledge further reproductive options.

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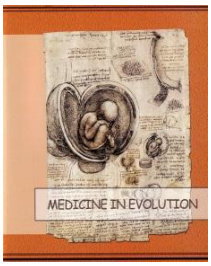
KAPLAN-MEIER ESTIMATE FOR THE CLINICIANS – SURVIVAL CURVES IN A NUTSHELL



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ABSTRACT

Survival analysis is a very important tool for medical research and is widely used in nowadays clinical studies. Kaplan-Meier survival curves (Kaplan-Meier estimate) represent a statistical method suitable for calculating the cumulative probability of an event occurrence in a sample of patients, in a given length of time. One advantage of Kaplan-Meier curves is that they can compute the estimated probability of the event occurrence even if the subjects entered the study at different time moments or if a certain number of subjects have been lost for follow-up or left the study; another advantage of Kaplan-Meier survival curves is that they are able to deal with variable intervals of time, as intervals are measured from one event to another. The present paper aims to 1). introduce the fundaments of designing the Kaplan-Meier curves from any given data sample and 2). to present the main statistic apparatus to be employed in order analyse and assess the differences between various survival curves.

Key words: *Kaplan-Meier curves, survival curves, medical statistics, log-rank test*

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INTRODUCTION

Kaplan-Meier estimate (Kaplan-Meier curve) is a method of the calculating the probability of an event occurrence in a sample of patients, in a given length of time. Widely known as "survival curves" in statistical/medical literature, Kaplan-Meier curves can actually measure not only the probability of death in a given time period, but also the probability of any event occurring, be it death of patients, disease relapse, tumor recurrence, infection occurrence, child conception, etc (1,2). Kaplan-Meier curves are widely used in medical literature; they represent an important instrument in evaluating results in clinical studies and are employed in analysisng data in various medical field. (3-6)

One advantage of Kaplan-Meier curves is that they can compute the estimated probability of the event occurrence even if the subjects entered the study at different time moments or if a certain number of subjects have been lost for follow-up or left the study. For instance, if patients have entered the study at different moments, the chronological times of event occurrences overlap (i.e. one event may occur in a patient, while another patient has just entered the study); this aspect makes the analysis more difficult; one way to go round the problem is to calculate the time for event occurrence from the moment of study enrollment as a refference as *time zero* (not from the start of the study *per se*). If patients are lost for follow-up at a certain point in the study, the data can also be utilised, even if partial (e.g. a patient has been observed at a few visits, but was lost aftewards). This last situation is nominated as 'censored' and is still used in Kaplan-Meier analysis. Moreover, the patients still alive (i.e. no event occurred) at the end of the study are also considered censored, as information about moment of event occurrence *after* the end of the study misses (7). Another advantage of K-M survival curves is that they deal with variable intervals of time, as intervals are measured from one event to another (2,7).

Kaplan-Meier curves use in medical statistics implies respecting several assumptions, as follows: censored patients' survival prospects are similar to those of the followed patients, survival prospects of early enrolled subjects are similar to those of the late patients entering the study, the subjects in the study must be independent (i.e. each participant belongs only once in their group, and not in any other group) and the probability of censoring is not related to the probability of the event (1,8).

CALCULATING KAPLAN-MEIER CURVES

The calculation behind Kaplan-Meier curves is quite simple, and consists obtaining cumulative probability at a certain point in time by multiplying probabilities up to that certain point in time. For each interval, the cumulative probability of surviving the anterior event equals the cumulative probability of the anterior interval times the probability to survive past the anterior event. This last probability is calculated by dividing the number of patients surving the anterior event divided the number of patients at risk for the event in the antetior interval. To notice, the number of patients at risk for the event in an interval equals the number of patients at start of the interval minus the number of censored patients; an interval is situated between 2 succesive events; censored patients do not terminate an interval; if a censored patient is lost at a similar point in time

as an event occurring in another patient, the censored patient is considered to have occurred after that event. Also to note, the first interval probability is 1.0 (100%) (1,2,7).

Patients at risk (PR)=patients at start of the interval (PS)– censored patients (C)

$$PR = PS - C \quad [1]$$

Patients surviving *after* the interval (PA)= patients at risk in that interval (PR)– number of events (E)

$$PA = PR - E = PS - C - E \quad [2]$$

Cumulative Probability to survive an interval (CP)= cumulative probability of surviving *until* that interval (PC_i) X patients surviving *after* the interval (PA)/ patients at risk in that interval (PR)

$$CP = CP_i \text{ X } PA / PR \quad [3]$$

The following adnotations were used: PR= patients at risk in that interval; PS=patients at start of the interval; C= censored; E= number of events; PA= patiens surviving after the interval; CP_i=cumulative probability of surviving *until* that interval; CP= cumulative probability to survive *after* that interval

For example, a number of 12 patients are enrolled in a study for calculating melanoma mortality in patients following a certain treatment (denominated as "treatment A"/ "group A") (Table 1). At time 2 months one event (death) occurs in one patient. Initial probability is 1.00 (100%). The cumulative probability to survive *that event/past first interval* (the next level of Kaplan-Meier curve) equals 1 (the cumulative probability to survive until that interval) X 11 (the number of patients surviving that interval)/12 (the number of patients at risk in the interval) = 0.917 (91.7%); cumulative probabilities and calculations are listed in table 2. For the next interval, at time 3 months, one event occurs in a patient; the cumulative probability for the next interval is calculated as follows: 0.917 (probability of surviving to that interval) X 10 (patients surviving that interval)/11 (patients at risk in that interval)=0.833. In the next interval, we notice a censored patient (a patient that has been seen alive at a follow-up visit at 5 months, but was lost afterwards). At time 8, one event occurs again; the interval is 3-8 months, because as stated above, a censored patient does not cease an interval. So the probability in that interval equals 0.833 X 8 (patients surviving the interval)/9 (patients at risk in the interval, i.e. 10 at start of interval minus 1 censored through the interval)= 0.741. The calculations follow the same pattern until the moment of the end of the study; therefore, the curve may terminate either in a censored patient (not the case in our example, but may happen if a certain number of subjects survive *past* the end of the study) or at probability zero, if all patients die (i.e. event occurs in all patients) *until* the end of the study.

Table 1. Patients in hypothetical group A, consisting in 12 patients, each characterised by patient identifier, time and event occurrence (1=event occurred at that time, 0=censored patient)

Patient identifier	Time (weeks)	event
D	2	1
B	3	1
G	5	0
I	8	1
K	12	1
C	15	0
E	18	0
J	24	1

Patient identifier	Time (weeks)	event
A	28	0
H	29	1
F	33	0
L	36	1

Table 2. Calculations of cumulative probability to survive after a certain event (interval)

Interval	time to end interval	PS	C	E	PA	PR	CP_i	CP=Cpi x PA/PR	CP value
1	2	12	0	1	11	12	1.000	=1 x 11/12	0.917
2	3	11	0	1	10	11	0.917	=0.917 x 10/11	0.833
3	8	10	1	1	8	9	0.833	=0.833 x 8/9	0.741
4	12	8	0	1	7	8	0.741	=.741 x 7/8	0.648
5	24	7	2	1	4	5	0.648	=.648 x 4/5	0.519
6	29	4	1	1	2	3	0.519	=.519 x 2/3	0.346
7	36	2	1	1	0	1	0.346	=.346 x 0/1	0.000

The ***graphical representation of Kaplan-Meier survival function*** consists in a multiple step curve; each interval is depicted by a horizontal line; each interval is terminated by an event; censored patients are depicted with short vertical lines *within* intervals; they do not terminate the intervals (see *Figure 1*).

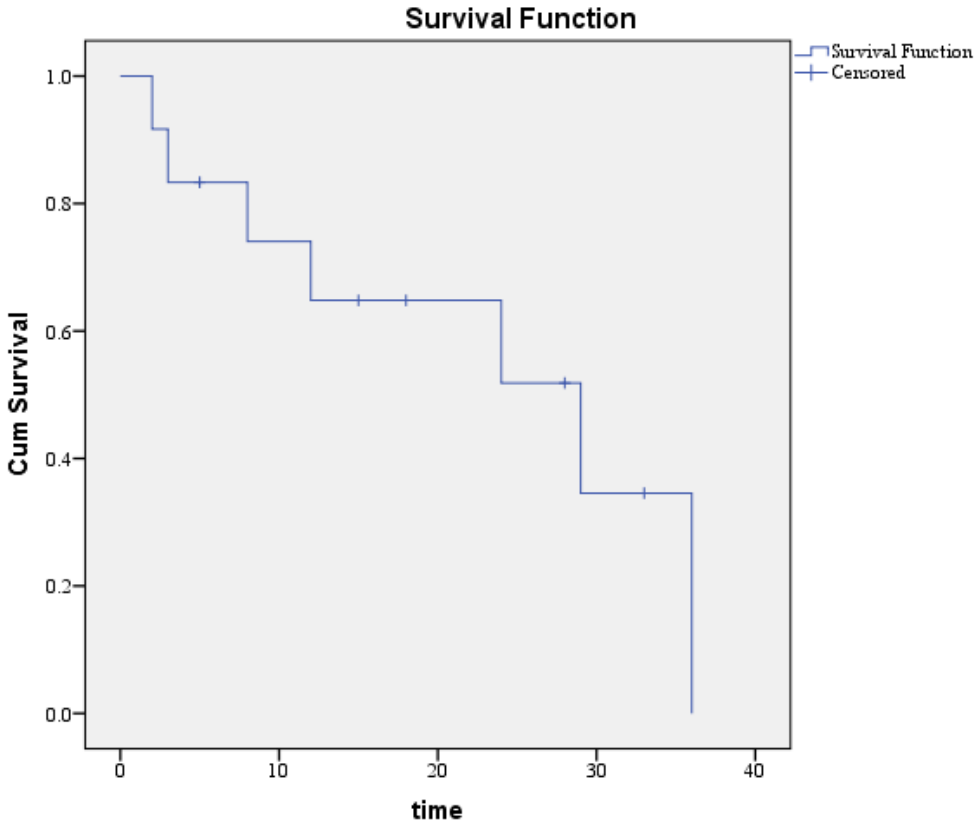

Figure 1. Kaplan-Meier survival curve for group A

COMPARING KAPLAN-MEIER CURVES

Very often clinical studies compare various survival curves, for example a survival curve for group A treated with drug A and the survival

curve of group B treated with drug B. Kaplan-Meier curves of survival appear in 40% of publications from randomised controlled trials including a survival plot (8). Although survival curves may look alike, i.e. both start from cumulative probability of 1 and go down to null or almost null (depending of number of events occurred until end of study), the curves may differ statistically. For example, the curves in the following image (*Figure 2*) may look dissimilar, but in order to assess the difference in statistical terms, a test statistic is needed.

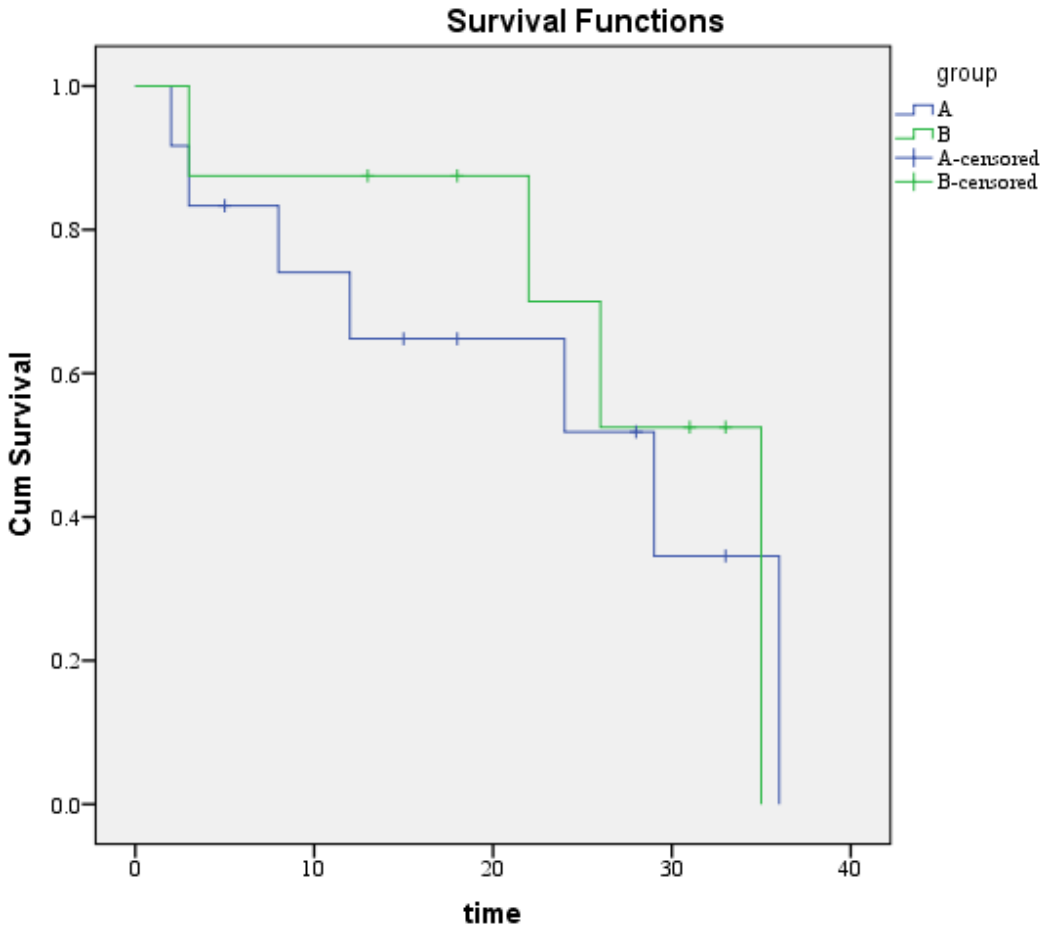

Figure 2. Survival curves for patients in group A and group B (treatment A and B, respectively)

For a practical example, we may use group A, previously described (melanoma patients treated with drug A) and a second group, denominated as group B, with similar patients (in terms of known factors that may influence survival, such as: age, sex, diagnosis, etc) treated with drug B.

Grouping the patients in the same table, we get the following data (table 4).

Table 3. Group B of patients, characterised by an identifier, time for an event occurrence, an event status (1= event, 0=censored patient).

Patient identifier	Time (weeks)	Event
Z	3	1
T	13	0
X	18	0
U	22	1
Y	26	1
W	31	0
S	33	0
V	35	1

Table 4. Grouping patients in both group A *and* B in ascending order for the time-to-event

Time (weeks)	Event	Group
2	1	A
3	1	A
3	1	B
5	0	A
8	1	A
12	1	A
13	0	B
15	0	A
18	0	A
18	0	B
22	1	B
24	1	A
26	1	B
28	0	A
29	1	A
31	0	B
33	0	A
33	0	B
35	1	B
36	1	A

One way *to compare two Kaplan-Meier survival curves* is to use log-rank test, the most commonly reported survival statistic test in medical literature, based on the null hypothesis stating there is no difference between the to populations in respect for the probability of an event occurring at any specific time. The test results in a χ^2 value, that may be compared to the one in tables for various p values (2,8,9).

The test is based upon calculating the sum of expected number of events in each group, at the specific time of each event occurring in any of the groups. The expected value in a specific group at every single time is calculated by multiplying the probability of event occurring in total number of patients at risk with the number of patients at risk in that specific group (1,2).

Table 5. Expected number of events calculating model

Time (weeks)	Event in both groups	Event in group A	censored total	censored group A	Patients at risk both groups	Patients at risk group A	Expected events in group A (E_A)
2	1	1	0	0	20	12	0.6
3	2	1	0	0	19	11	1.157895
8	1	1	1	1	16	9	0.5625
12	1	1	0	0	15	8	0.533333
22	1	0	4	2	10	5	0.5
24	1	1	0	0	9	5	0.555556
26	1	0	0	0	8	4	0.5
29	1	1	1	1	6	3	0.5
35	1	0	3	1	2	1	0.5
36	1	1	0	0	1	1	1
	11	7					6.409284
	O_A+O_B	O_A					E_A

In our example (data depicted in Table 5), at time 2 weeks, one event occurs in group A; the number of patients at risk in both groups is 20 (12 in group A, 8 in group B). Therefore the probability of event is 1 in 20 (=0.05), and as number of patients at risk in group A is 12, the expected number of events (if the two survival curves were the same) is 12 multiplied by 0.05, i.e. 0.6. Note that the number of patients at risk equals the number of patients in anterior interval minus the number of patients died (event occurred) minus the number of censored patients. For example, number of patients at risk at week 8 is 16 (19 patients at time 3 weeks, minus the 2 patients at week 3, minus the censored patient at week 5).

Overall calculations lead to a total number of expected events in group A of 6.409284; of note, the number of events in group B may be calculated from the following formula:

$$E_B = (O_A+O_B)- E_A \quad [4]$$

In our example, $E_{B=}$ 4.590716. Number of events observed in group A (O_A) is 7, and the number of events observed in group B (O_B) is 4. The log-rank statistics may be calculated as follows (1.2,9):

Log-rank test statistic=$(O_A-E_A)^2/E_A + (O_B-E_B)^2/E_B$ [5],

which in our case is 0.131. Transforming the value to a z-score with *normal distribution* (2,10), we get a $z=\sqrt{0.3612}$, corresponding to a p-value of 0.7188, therefore we cannot reject the null hypothesis (there is no significant difference between he curves, as p-value 0.7188>0.05). Other formulas to calculate log-rand test statistic use variance at each time an event occurs; to mention, the log-rank calculation formula above is a conservative method, offering a slightly higher p-value (11); log-rank test may also be computed *in silico* by various statistical software applications (9,12).

Another way to assess the difference between two survival curves is to compute the *hazard ratio*, defined as (2):

$$HR=(O_A/E_A)/ (O_B/E_B) \quad [6]$$

In our example, HR is 1.092/0.871=1.253, showing a slight hazard of event occurring (death of the patients) in group of patients subjected to treatment A.

CONCLUSIONS

Kaplan-Meier survival curves offer a good approach to analyse the effect of various treatments on sample of patients, as well as to foresee the probability of an event occurrence at a given point of time in a sample of patients. Calculating the cumulative probability leads to designing the survival curves; even if two survival curves may look quite dissimilar, there might be no statistical difference between them; an easy to understand arithmetic apparatus may be used to assess this difference of the survival curves in statistical terms. Comprehanding the exact methods for using the survival curves may be of a paramount importance to both the medical researcher and the clinician, in order to understand the data presented in clinical studies.

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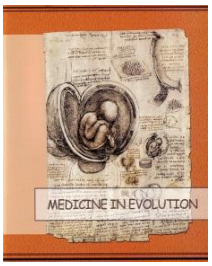
RESECTION OF THE LIVER: THE TREATMENT OF CHOICE FOR HEPATIC COLORECTAL METASTASES



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ABSTRACT

This study reports the combined experience on 243 patients diagnosed with colorectal cancer at the Second Surgical Clinic of the Emergency County Hospital Constanta between January 2007 and December 2011. Patients were identified from prospective databases and records were retrospectively reviewed. From these cases, 71 were complicated with hepatic metastases. Clinical analyses of the data have been made considering the gender, age, origins, metastases location, secondary associated determinations, and the type of surgical intervention. Colorectal cancers with liver metastases showed to appear mostly in males (73.2%) being more frequently between the age of 61 and 90 (67.60%), and from urban areas (69.02). Considering the hepatic metastases location, the most frequent encountered cases affected both of the lobes (50%). Furthermore, from 71 cases of patients with colorectal cancer with secondary liver determinations, we have noted that 16 (22.53%) of them showed associated metastasis, as follows: 50% patients having peritoneal carcinomatosis, 31.25% pulmonary metastasis and diaphragmatic, pancreatic and osseous localizations equally distributed in 6.25%. Therapeutic methods that have been used consisted in electrorezection (34.37%) followed by electrocoagulation (18.75%), atypical metastasectomy (12.50%) and metastasis alcoholization (3.12%). Patients with a low tumor load are the best candidates for a liver resection. In adequately selected patients, surgical resection of liver metastasis from colorectal cancer can offer long-term survival and cure in patients with metastatic colorectal cancer isolated to the liver.

Key words: *colorectal cancers, liver metastasis, electrozection, electrocoagulation, metastasectomy*

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INTRODUCTION

The liver is a favorable place for the metastasis, as observed from the great occurrence of the hepatic metastasis. This fact may be explained by two hypothesis: the favorable tissue development land side of many histological tumors, as well as the hemodynamic characteristics of the liver (1). The double hepatic circulation renders the hepatic blood flow very high. It is exceeded in the visceral hemodynamics only by the pulmonary circulation. Therefore, hepatic metastases depends on age, sex, the location of the primary tumor, its histological type and evolutionary time (2).

Untreated patients with hepatic colorectal metastases usually have a poor prognosis, with a median survival of 6 to 12 months (1, 3). Chemotherapy modestly extends median survival to 12 to 18 months, but cure remains unlikely (4, 5). Interestingly, surgical resection of liver metastasis from colorectal cancer can offer long-term survival and cure in patients with metastatic colorectal cancer isolated to the liver. Five- and ten-year survival rates of 25% to 39% and 22% to 23% after hepatectomy have been reported (6-13). Therefore, liver resection currently represents the best and a potentially curative treatment for hepatic colorectal metastases.

The incidence of the colorectal origin of hepatic metastasis is estimated to be of two-thirds or three quarters of all liver metastases and only about 10-30% are synchronous with the primary surgery (14).

However, only 60% to 70% of patients undergoing liver resection for colorectal liver metastases will develop recurrence of the disease (6, 7). Of these, one third will have recurrent metastases isolated to the liver. Since liver resection has become safer through improvements in surgical techniques and perioperative management, repeat hepatic resection is being more frequently performed in patients with isolated hepatic recurrence (15).

The purpose of the present study was to determine the best treatment option of hepatic colorectal metastases, which implies the resection of the liver.

MATERIAL AND METHODS

The study was conducted on 243 patients submitted to the Second Surgical Clinic of the Emergency County Hospital Constanta between January 2007 and December 2011 and diagnosed with colorectal cancer. In this group a number of 71 patients diagnosed with hepatic colorectal metastases were identified.

Patients were identified from prospective databases, and office and hospital charts were retrospectively reviewed. Data analyzed included the gender, age, origins, the metastases location, secondary associated determinations, and the type of the surgical intervention.

The extent of liver resection was classified according to the nomenclature by Goldsmith and Woodburne (16). Wedge, segmental, and bisegmental resections were summarized as minor procedures. Liver involvement was classified as unilobar if liver metastases at the hepatic resection were restricted to one lobe. The presence of tumor in both the right and left lobe at resection was defined as bilobar involvement. An informed consent was obtained from the patients in accordance with the Helsinki Declaration and guidelines of the local Committee of Second Surgical Clinic of the Emergency County Hospital Constanta, Romania.

Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Hepatic metastases are the most frequent hepatic tumors. The treatment of primary and metastatic liver tumors depends both on the intra- and extra-hepatic extension of the disease and the functional reserve of the liver. The treatment options include surgical or non-surgical procedures (2, 14). Figure 1 shows the distribution of the patients by gender.

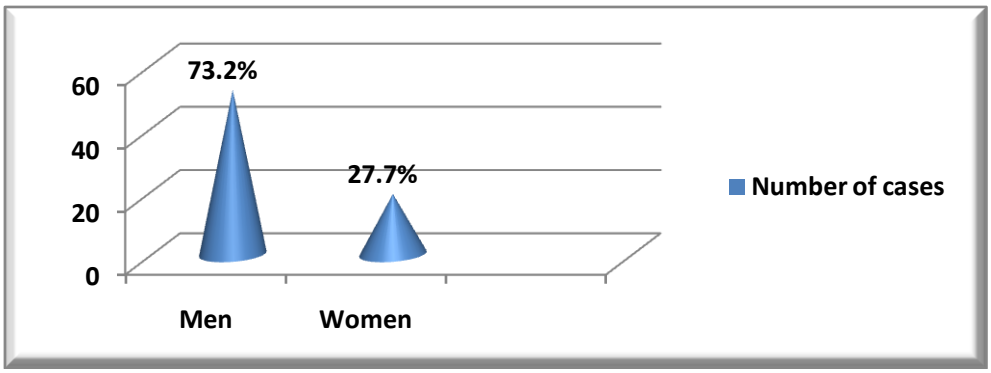

Figure 1. The distribution of the patients by gender

The difference of the genders' affection showed a higher significance, with males being more affected than the females. Our result shows a 73.2% percentage in men in respect to women (27.7%).

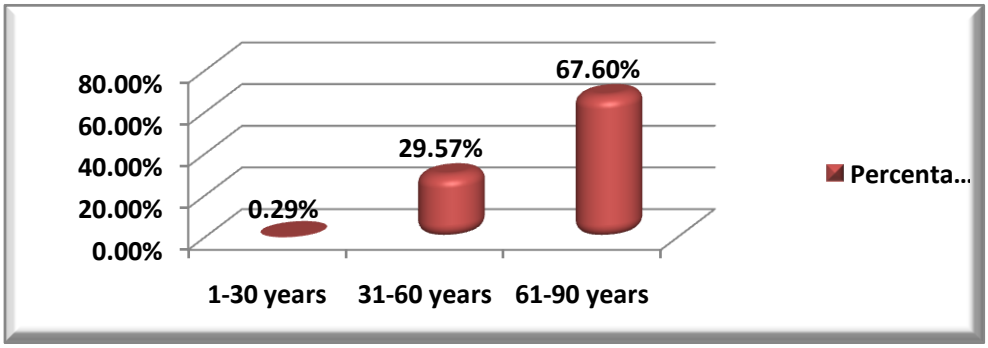

Figure 2. Percentages of the hepatic metastasis patients by age

Figure 2 shows that the highest frequency of colorectal cancer with secondary liver determination which was encountered between the age of 61 and 90. The minimum age was 20 and the maximum 88. Our results showed an unequal distribution of the colorectal cancers with liver secondary determinations by age, the highest percentage (67.6 %) being represented by the group of patients over 60 years-old.

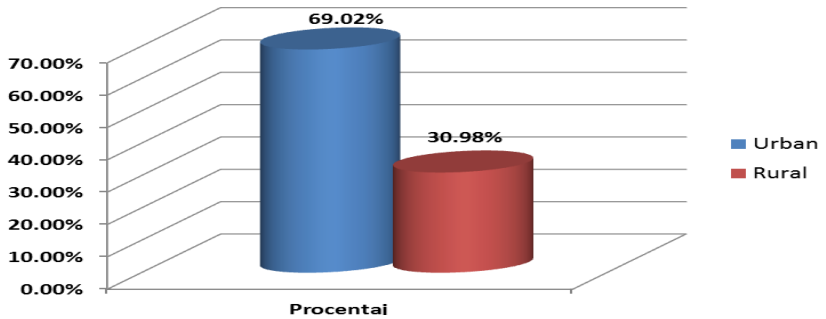

Figure 3. The distribution of patients in respect to the demographic origin

The environment is usually related to the occurrence of the colorectal cancers with liver secondary determinations. The most frequent cases come from the urban areas (69.02%). The rural percentage (30.98%, Figure 3) was probably due to the patient adherence at physician recommendations.

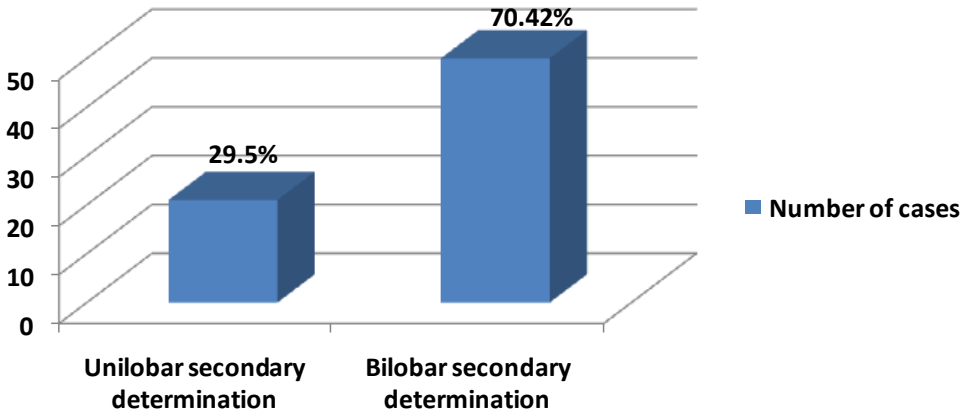

Figure 4. The distribution of patients by the metastasis location

For the metastasis location, we found 21 (29.5%) patients having unilobar secondary determinations of which 11 had solitary determinations, the rest of them having between 2 to 4 metastases (50 patients, 70.42%). Therefore, it can be noticed that most of the metastases can be found in the right hepatic lobe, the other 10 determinations being multiple bilobar (Figure 4).

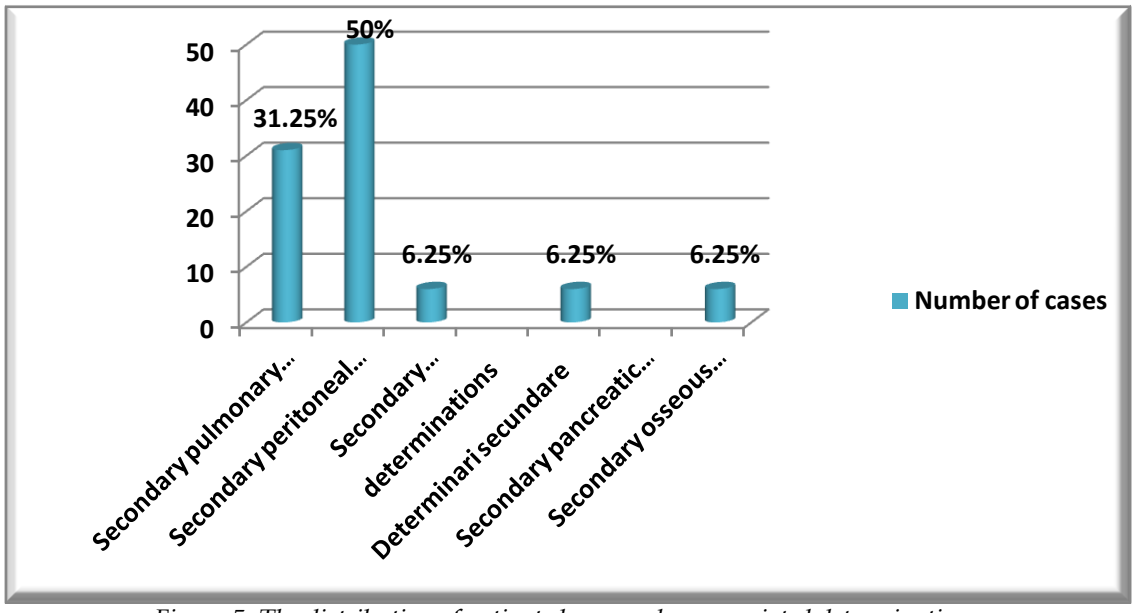

Figure 5. The distribution of patients by secondary associated determinations

Out of 71 cases of patients having colorectal cancer with secondary liver determinations we showed that only 16 (22.53%) of them presented associated metastases as follows: 8 patients having peritoneal carcinomatosis, 5 (31.25%) pulmonary metastases, and 1 (6.25%) for each diaphragmatic, pancreatic and osseous metastases (Figure 5).

Table 1. The type of surgical intervention at hepatic colorectal metastasis.

Type of surgery	Number of cases	Percentage
Electrorezection	11	34.37%
Atypical metastasectomy	4	12.50%
Electrocoagulation	6	18.75%
Alcoholization	1	3.12%

Specifically, we showed that out of 32 subjects that have been operated for surgical ablation of metastases, 8 have presented unresectable metastases, and in the other 22 remaining patients,

surgical techniques according to the metastases' sizes were conducted (Table 1). A remarkable difference have been shown for the electrorezection which was applied to 11 patients, the atypical metastasectomy has been applied to 4 of them, 6 had the elecrocoagulation, and 1 had the metastases alcoholization. The associated techniques as electrocautery thermal ablation and ethanol injection were used only in 2 patients.

DISCUSSIONS

Liver resection represents probably the only potentially curative treatment for hepatic colorectal metastasis (15). However, about 5% to 10% of patients who undergo liver resection will develop hepatic recurrence that is amenable to a further liver resection, experience and data on results after repeat resections are sparse. Therefore, most reports on liver resections are based on small populations or on combined populations from many different institutions. The present study highlights an experience on 71 liver resections for colorectal cancer that develop liver metastasis (16).

Our data indicate that liver resections are safe and effective in the treatment of recurrent metastatic disease. Interestingly, having in the view that liver resections are technically more demanding and difficult, there was concern that resections may be associated with higher rates of death and further complications. Many studies show an in-hospital death rate of less than 5% for first hepatic resections. Results of studies on repeat liver resection show a similar range of death rates compared with those reported for primary hepatic resections (6-10).

Five-year survival rates can be achieved through repeat hepatic resection in well-selected patients with recurrent hepatic disease. Therefore, liver resection has become the treatment of choice for resectable liver metastases from colorectal cancer because neither chemotherapy nor other nonsurgical therapies can achieve such favorable results. Several studies had attempted to find predictors of outcome that could identify patients with a favorable prognosis after liver resection (12).

Nevertheless, the presence of resectable extrahepatic disease did not influence survival in this multivariate analysis. In our study, we identified number (one vs. more than one) and largest tumor size of hepatic lesions as independent risk factors related to the resection. Thus, in selecting patients for repeat resection, medical fitness, small solitary tumors, ability to clear all disease and possibly disease-free interval are the most important criteria for consideration (17, 18).

Recent technologic advances have also made ablative treatments for different tumors, such as cryoablation or radiofrequency, which could represent safe option. Interestingly, many patients with small central recurrences after a prior major liver resection are often treated by ablative therapy. These ablations can often be performed avoiding the complications associated with open surgery. Whether such ablations will be equivalent to resection for tumors that are easily resectable warrants direct clinical comparison with short-term complications (19).

CONCLUSIONS

Our data showed that hepatic resection for hepatic colorectal metastases is safe. Patients with a low tumor load (small number and size) are the best candidates for a resection. In adequately-selected patients, further

resection of the liver can provide prolonged survival and is currently the treatment of choice in hepatic colorectal metastases.

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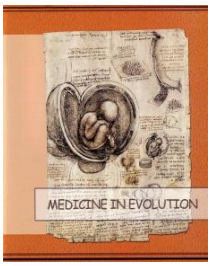
LAPAROSCOPIC TRANS-GASTRIC REMOVAL OF THE INTRA-LUMINAL MIGRATED LAPAROSCOPIC ADJUSTABLE GASTRIC BAND – TECHNICAL NOTE



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ABSTRACT

One of the most used method in bariatric surgery is lap-adjustable gastric banding(LAGB). We present three cases with intra-gastric migrated LAGB, in which the eroded band was removed by a laparoscopic trans-gastric approach. The start-up symptoms were epigastric pain in 3 out of 3 patients, port site infection in 2 out of 3 cases, and weight regain in 2 out of 3, dysphagia in one. The excess weight loss(EWL) was more than 50 % until the start of the symptoms. We suspended to the anterior abdominal wall the stomach on both sides of the planned gastrotomy, using sutures. This maneuver provides us with a better vision inside the gastric cavity and lowered the risk of the spillage of the gastric content. No post-operative leakage was recorded. The laparoscopic trans-gastric LAGB removal is safe performed by experienced surgeons. Patients with eroded LAGB should be referred to tertiary centers with experience in bariatric surgery.

Key words: *Gastric erosion; Laparoscopic adjustable gastric band; Lap band removal*

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INTRODUCTION

One of the most used techniques in the world for losing the excess weight is the lap-adjustable gastric-banding (LAGB). This method had a relative high rate of late complications – one of the fearsome is the migration of the ring inside the stomach cavity by eroding the gastric wall occurring in 0.5–11% of cases [1, 2]. Sometimes the removal of migrated LAGB cannot be achieved by trans-oral endoscopy. We propose a technique for migrated LAGB using a modified laparoscopic trans-gastric approach described by Basa [3].

METHODS

LAGB for obese patients had been performed for the first time in our clinic, at the Surgical Clinic 2 of County Emergency Hospital Timisoara in 2002, since then until December 2012, 234 patients underwent this procedure. The technique for placing the LAGB was the same as described by Fielding [4,5]. Out of these 234 patients we had 3 cases of intra-gastric migrated LAGB, in which the removal of the band was performed laparoscopically trans-gastric.

The time between initial surgery and the start of the symptoms of migrated band was 38, 47, and 41 months. The presentations symptoms were epigastric pain in 3 out of 3 patients, port site infection in 2 out of 3 cases, and weight regain in 2 out of 3, dysphagia in one patient. The EWL was more than 50% until the start of the symptoms; only the patient with dysphagia maintained the loss. [Tabel I].

The period from the start of the symptoms until diagnosis of the eroded band was 72, 78 and 38 days, the surgical removal of the band was performed during the first week after upper gastrointestinal endoscopy (UGIE) revealed the intra-gastric migration of LAGB.

UGIE showed the migration of more than 50 % of the band length, including the buckle. The patients were taken to the operating room (OR) and several attempts for endoscopic removal were made in our first patient. The reason for trying to remove the eroded band in the OR was that there are few possible complications of endoscopic maneuvers: bleeding, perforation of gastric wall after removal of the band, and an unsuccessful procedure; all of this might require surgical solutions.

Pre-operative work-up: the health status of the patient was assessed; special attention was addressed to concomitant comorbidities. Deep vein thrombosis prophylaxis was made by low molecular weight heparins 1 mg/kgc/day one night before procedure.

The patient was placed in modified lithotomy position with the hips and the knees slightly flexed and tied up to the operating table to prevent the patient from slipping down, position recommended for all the bariatric procedures. Using an anti-Trendelenburg position we obtained the displacement of the intra-abdominal viscera and the remaining free fatty omentum downward, so the upper part of the abdomen including the stomach was proper exposed. The patient abdomen was cleansed with povidone-iodine solution and draped sterile.

The operating surgeon was placed between the patient legs with straight access to esophageal-gastric junction area. The camera-assistant surgeon was placed on the right side of the patient, sitting on a chair in a manner that he didn't interfere with

the operating surgeon and still was comfortable to provide good image during the entire procedure.

The pneumoperitoneum is obtained through a Veress needle introduced through a supra-umbilical incision; usually there are no adhesions from initial surgery as the site for camera-trocar is inserted between the xiphoid and the umbilicus in the obese patients. The pressure insufflated in obese patients might be higher than regular pressure of 12 mmHg because they have sometimes a higher baseline pressure due to abdominal wall weight; we used 14 mm Hg in our series.

The standard sites for trocar insertions are showed in picture 1. The landmark used for insertion of the trocars is the xiphoid bone, because the umbilical scar is often moved caudally in the obese patients. We used same insertions sites as in the initial surgery. Camera trocar site was placed at 2/3 from the xiphoid lateral left from the xiphoid-umbilical line. Then the abdominal cavity was inspected and the region of esophageal-gastric junction assessed. If laparoscopic procedure was possible the next two trocars were inserted under direct view. 2nd trocar (5mm) was placed 5 cm laterally from the median line on the right side. 3rd trocar (15 mm) was placed 5 cm under the left costal margin on the mid clavicle line.

The LAGB was all hidden by inflammatory dense adhesions between the omentum, the lesser curvature of the stomach and the left liver lobe, as we were able to see only the calibration tube. This whole inflammatory pseudo-tumor was between 10 and 15 cm diameter. As we were unable to see any portion of the band and endoscopy showed that anterior gastric wall was eroded we decided that dissection of the esophageal-gastric junction pose a great risk of perforating the esophagus or the stomach. Also bleeding from the underneath surface of the left liver lobe could occurred. A much more appropriate approach was trans-gastric laparoscopic removal of the eroded LAGB [3].

First we cut the calibration tube near the inflammatory process and remove it together with the port by an incision to the subcutaneous site of implantation of the original surgery.

Then we elevated the anterior gastric wall towards the abdominal wall using two sutures (2-0 PROLENE™ Polypropylene Suture, Ethicon, USA). The sutures are passed through gastric sero-muscularis layers, and then passed through the abdominal wall with the fascia closure device (BERCI Fascial Closure Instrument, Karl Storz, Germany), clamped and anchored with a Kocher grasper.

The gastrotomy was performed along the avascular line of the anterior gastric wall, way below the area of inflammation and had 3 cm in length. First the gastric wall was perforated with the hook, and then LigaSure (LigaSure™Covidien, USA) was used for enlargement of the breach. Traction on the sutures along the breach revealed the gastric cavity; aspiration was performed if needed [Picture 2]. After establishing a good view we found the eroded LAGB which had a greenish color and was migrated through the anterior gastric wall more than 50% of his length. We searched the stomach for other lesions, and then we cut using the laparoscopic scissor the band and removed it from the stomach [Picture 3]. The LAGB was extracted through the 15 mm left trocar, usually it fits inside the trocar lumen and there is no need for trocar removal and then repositioning.

A new evaluation of the stomach cavity was performed searching any bleeding after the extraction of the band. We didn't have any bleeding in our 3 cases series.

The gastrotomy was closed using continuous double layer sutures (2-0 PROLENE™ Polypropylene Suture,

Ethicon, USA), first layer was total, second one sero-serosal. [Picture 4]

A 50 cc methylene-blue test was performed through nasogastric tube under camera vision, while the gastro-duodenal passage was closed using pressure at the level of anterior wall with the left flank laparoscopic instrument. No leak was observed either to the tube site of insertion in the inflammatory area, either to the suture line of the gastrotomy.

Peritoneal lavage was done with 500 cc of saline, the hemostasis was secured. A 24 Fr silicone drainage tube was placed through the right trocar beneath the liver just near to the inflammatory process. Nasogastric tube was placed for 24h.

The site for extraction was closed using fascial closure instrument, and then was heavily washed out with saline solution.

Oral intake was resumed first postoperative day and gastrografin swallow test was performed after 24h and 1 month postoperatively. Discharge was in the POD 2 or 3.

30 days postoperative evolution was without any complications.

DISCUSSIONS

LAGB has a relatively high reoperation rate compared to other bariatric procedures, mainly related to slippage, pouch dilatation, gastric erosion or ante-gastric positioning of the band[6]. More than 55% of LAGB erosion occurs in the first two years [7] and are related to the surgeons' experience, later erosions are not linked to the surgical technique.

Basa described an adapted trans-gastric laparoscopic technique for removing the LAGB migrated inside the stomach cavity. With increasing laparoscopic skills of our contemporary surgeons this method seems feasible. We added one new feature to this technique – we suspended the gastric anterior wall and so we created more working space for removing the LAGB, without adding significant time to the operating time or any other adverse event.

Why laparoscopy? - these obese patients have a high risk of surgical site infections (SSI) and opening the stomach can increase this risk in a thick fatty abdominal tissue.

Laparoscopic trans-gastric technique was used first for removing the benign gastric tumors [8], than for ERCP at patients with previous Roux-en-Y gastric bypass [9], also to remove the migrated Angelchick prosthesis [10]. The advantages of this technique are that we were not supposed to dissect the tight adhesion between the stomach, the left liver lobe and the structures surrounding/nearby the esophageal-gastric junction preventing an extended operating time or larger amount of blood loss. Gastric wall incision and suture are made in healthy tissue, with no inflammation, leading to faster and safer healing. We did not have any major complications after our 3 cases series, any leak, deep space infection or post-operative bleeding. Our patients resume liquid diet in the POD 1, and were discharge in the POD 2 or 3, with no readmission, some authors advocate placement of nasogastric tube for gastric drainage up to 7 POD [11]. This favorable outcome might be related to the fact that our patients are young, active and in a better state of health, after losing a large amount of the excess weight due to LAGB placement.

LAGB erosion of the gastric wall is not an emergency if it is not complicated with signs of abdominal sepsis either gastric bleeding; our opinion is that these patients should be referred to tertiary centers with experience in bariatric and laparoscopic surgery. In a large series of 6382 cases Kirshtein et al report 14 emergencies procedures, from a total of

539 re-operations in the whole series [12].

With the increasing numbers of procedures performed we expect a raised in the number of long term complications of LAGB, in a systematic review of complications after laparoscopic adjustable gastric banding, the erosion represents an overall 1.46% in 15775 patients [13]. Regaining, epigastric pain, dysphagia in a patient with LAGB should be followed by a UGIE.

After LAGB removal there is always a regain in weight, so we have to imagine another bariatric procedure. Some authors propose re-banding during same operative procedure with the removal [14], we don't think this is feasible; we planned to perform gastric plication either sleeve gastrectomy in the near future for our 3 patients [15].

CONCLUSIONS

Eroded LAGB can be removed with a trans-gastric laparoscopic procedure; patients should be referred to tertiary centers with experience. The procedure is safe in hands of experienced laparoscopic surgeons with selected patients. Our technique with the suspension of the gastric wall to the anterior abdominal wall prevents spillage and offers a better intra-gastric view.

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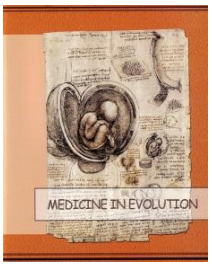
PREDICTION OF TREATMENT PANCYTOPENIA - PROGNOSTIC FACTOR IN HODGKIN LYMPHOMA



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ABSTRACT

Bone marrow impairment with the onset of pancytopenia may occur as a result of cytotoxic effects of medication (polychemotherapy). All the studies on HD evolution, regardless of histological aspect, show pancytopenia correlates with an unfavourable evolution; administration of more aggressive chemotherapy, although it may favourably influence tumour mass reduction, adds in turn a severity degree to the global evolution of disease; common side effects include bone marrow toxicity leading to worsening of bone marrow failure and pancytopenia. Pancytopenia correlates with the presence of increased tumour mass and extranodal localisations of disease.

Aim: This study aims to evaluate the survival of pancytopenia patients and to establish pancytopenia (anemia, neutropenia and thrombocytopenia) as a prognostic factor in the onset of second neoplasia.

Methodology: We have conducted a retrospective, analytical study on 151 patients diagnosed with Hodgkin Lymphoma in the Hematology Department Timisoara between May 2008 and April 2013. The main diagnostic method was biopsy, followed by histopathological and immunohistochemical examinations of harvested tissue. Tumour staging was performed by computed tomography (CT). The type of polychemotherapy and the number of cycles were decided according to the disease histological stage and grade. Patients' data regarding medical history, as well as laboratory tests performed, were extracted from their medical records.

Results:

The mean age of patients included in the study is 49.69±17.46, with a minimum age of 18 years and a maximum of 89 years, out of which 37.7% were women and 62.3% men. The follow up period from diagnosis was 13.92±6.24 months up to complete remission (33.7% of patients); partial remission was seen in 45.7% of patients, 17.2% had progressive disease, 0.6% relapsed and 2.5% died (fig. 1). Hemoglobin, platelet and leukocyte levels were monitored in the study patients and the survival curve was observed depending on the three parameters (Fig 1-7). To establish whether anemia, neutropenia and thrombocytopenia are predictive factors for the onset of second neoplasia we have applied the ANOVA analysis, which showed statistical significance ($p<0.01$) of the three independent variables (anemia, neutropenia and thrombocytopenia) on the dependent variable, namely the onset of second neoplasia (Table I).

Conclusions:

In conclusion, this study results suggest pancytopenia is associated with low survival rate, which indicates the possibility that host immunity and inflammatory response play an important role in clinical manifestations occurring in Hodgkin lymphoma. Low hemoglobin, leukocyte and platelet levels taken together could be an important prognostic factor in these patients' evolution.

Key words: *Hodgkin lymphoma; Neutrophil; Lymphocyte; Prognosis*

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INTRODUCTION

Bone marrow impairment in HD is responsible for the onset of pancytopenia or decrease in the levels of blood elements in one of the hematopoietic cell lines. It is considered to be among the factors with the greatest prognostic value as it is specific to stage IV of disease, associated with extranodal localisations and accompanied by low rate of complete remission and short-time survival. Bone marrow impairment with the onset of pancytopenia may also occur as a result of cytotoxic effects of medication (polychemotherapy). All the studies on HD evolution, regardless of histological aspect, show pancytopenia correlates with an unfavourable evolution; administration of more aggressive chemotherapy, although it may favourably influence tumour mass reduction, adds in turn a severity degree to the global evolution of disease; common side effects include bone marrow toxicity leading to worsening of bone marrow failure and pancytopenia. Pancytopenia correlates with the presence of increased tumour mass and extranodal localisations of disease.

British National Lymphoma Investigation (BNLI) has published in 1985 a prognostic index in localised Hodgkin lymphoma based on the analysis of over 2,000 patients. [1] EORTC (European Organisation for the Research and Treatment of Cancer) has identified several elements that would indicate an unfavourable prognosis in stages 1 and 2 of the disease and has used them in the stratification of treatment.

The international prognostic score in advanced disease had been developed based on the analysis of 5,141 patients originally treated with anthracycline chemotherapy regimen. Seven factors were identified, each of them increasing the disease progression rate by 8%. [2]

Lymphocytopenia is one of these factors, with the same unfavourable significance as pancytopenia and showing severe immunological disturbances, decrease of general immunity and favouring the onset of second neoplasia in the evolution of HD cases with prolonged survival [3,4].

Aim:

This study aims to evaluate the survival of pancytopenia patients and to establish pancytopenia (anemia, neutropenia and thrombocytopenia) as a prognostic factor in the onset of second neoplasia.

METHODOLOGY

We have conducted a retrospective, analytical study on 151 patients diagnosed with Hodgkin Lymphoma in the Hematology Department Timisoara between May 2008 and April 2013. The main diagnostic method was biopsy, followed by histopathological and immunohistochemical examinations of harvested tissue. Tumour staging was performed by computed tomography (CT). The type of polychemotherapy and the number of cycles were decided according to the disease histological stage and grade. Patients' data regarding medical history, as well as laboratory tests performed, were extracted from their medical records.

The acquired data were collected in a database and processed by the means of SPSS 17 programme. Survival rates and predictive factors were calculated using Kaplan-Meyer curves and ANOVA analysis, respectively.

RESULTS

The mean age of patients included in the study is 49.69±17.46, with minimum age of 18 years and a maximum of 89 years, out of which 37.7% were women and 62.3% men. The follow up period from diagnosis was 13.92±6.24 months up to complete remission (33.7% of patients); partial remission was seen in 45.7% of patients, 17.2% had progressive disease, 0.6% relapsed and 2.5% died.

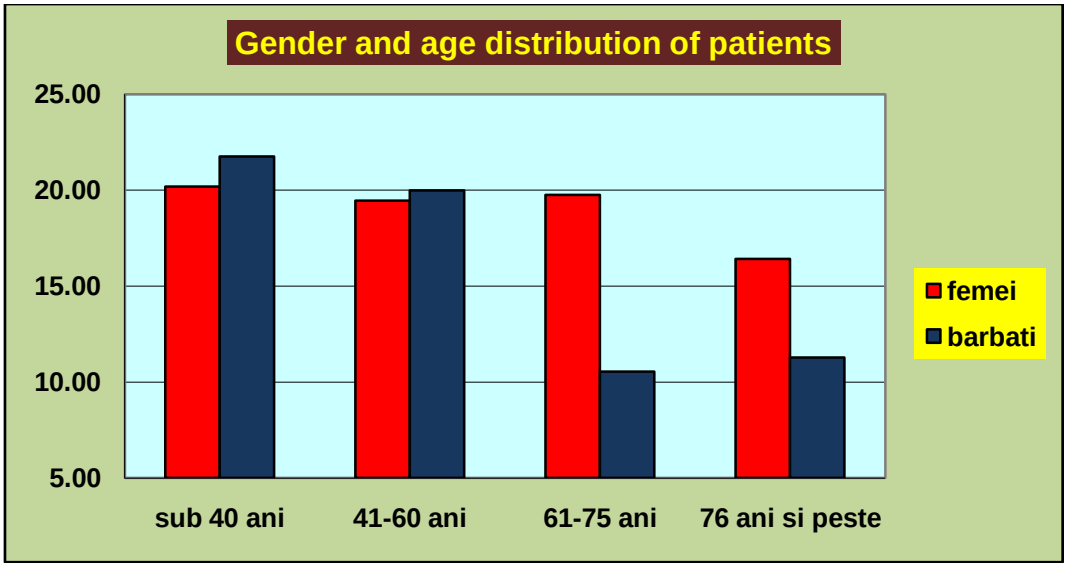

Figure 1. Distribution of patients by age groups and gender

T Hemoglobin, platelet and leukocyte levels were monitored in the study patients and the survival curve was observed depending on the three parameters.

Anemia was estimated as hemoglobin levels of 6.5-7.9mg/dl. Survival mean in months is 14.275±1.844 (CI 95%) for levels between 8 and 10mg/dl, 14.101±1.299 (CI 95%) for levels of 10-13mg/dl and 16.554±0.945 (CI 95%), being greater for patients with Hb levels of 13-17mg/dl (17.546±1.664; CI 95%). No statistically significant differences were recorded between the four groups of patients.

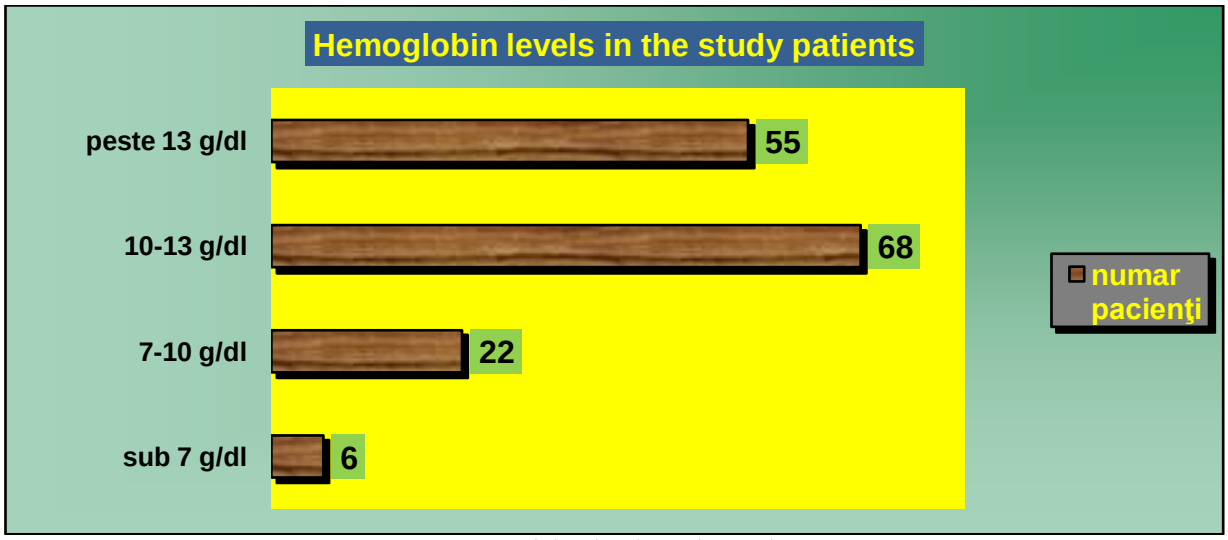

Figure 2. Hemoglobin levels in the study patients

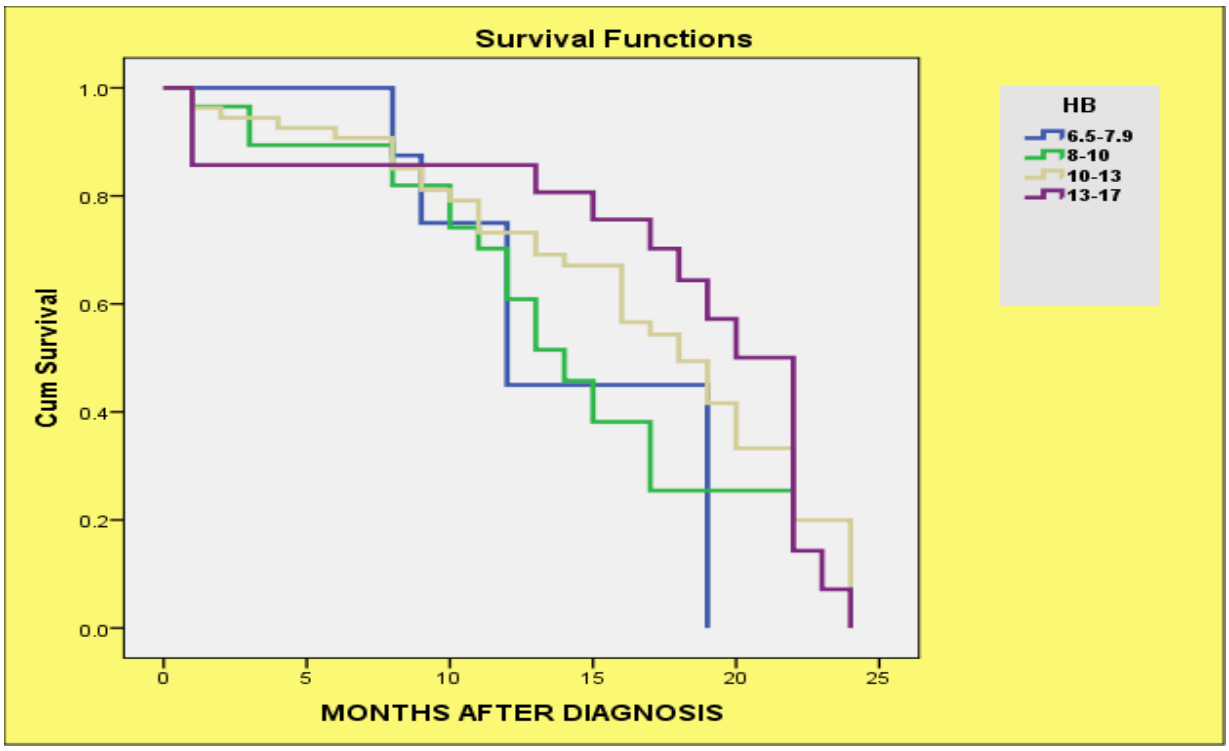

Figure 3. Survival curve according to hemoglobin levels

Patients were divided into four groups according to platelet levels, as seen in Figure 4. Although patients with platelet levels over 410,000 have a rather stable survival curve on the long run, those with platelet levels under 400,000 have lower survival curve (15,742±1,302, CI 95%) that decreases markedly within one year after diagnosis (Figure 5).

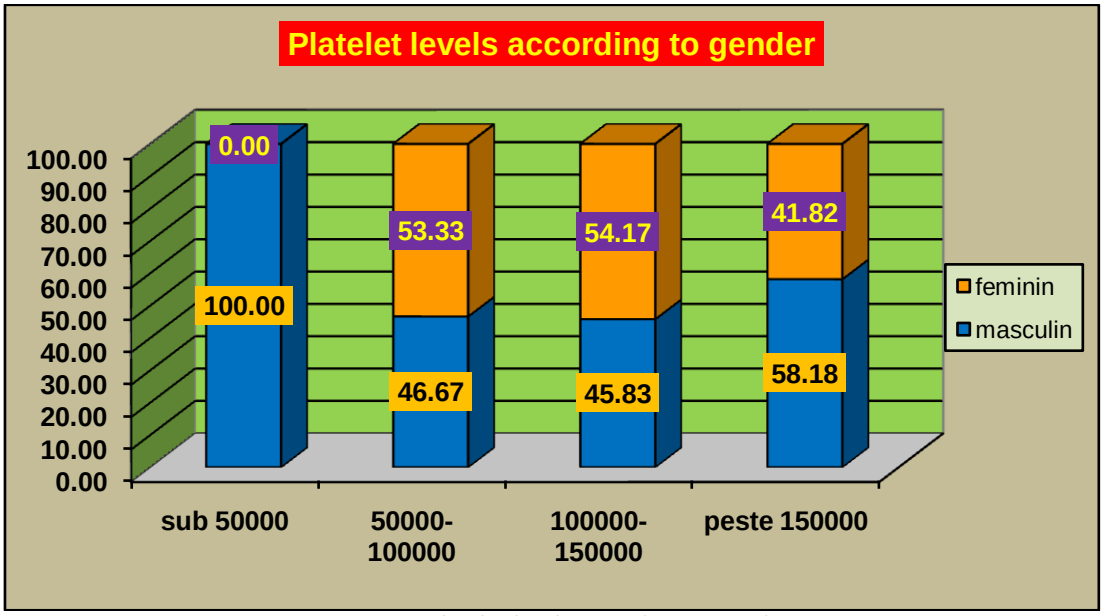

Figure 4. Platelet levels according to gender

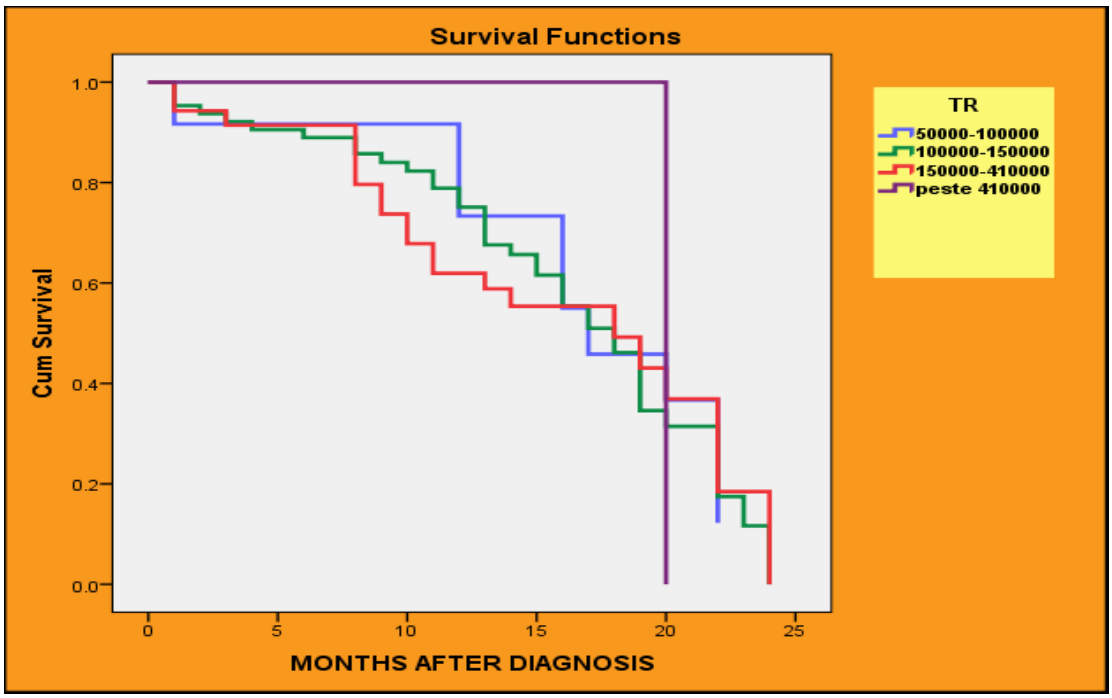

Figure 5. Survival curve according to platelet level

Leukopenia, mainly due to neutropenia, is a significant prognostic factor for the survival of Hodgkin lymphoma patients. It can be seen in our study a survival rate dropping sharply in patients with leukopenia in only about 12 months from diagnosis (mean value 12,500±0,500, CI 95%). Survival rate decreases gradually and more slowly in patients with normal leukocyte levels or in those with leukocytosis (Figure 7).

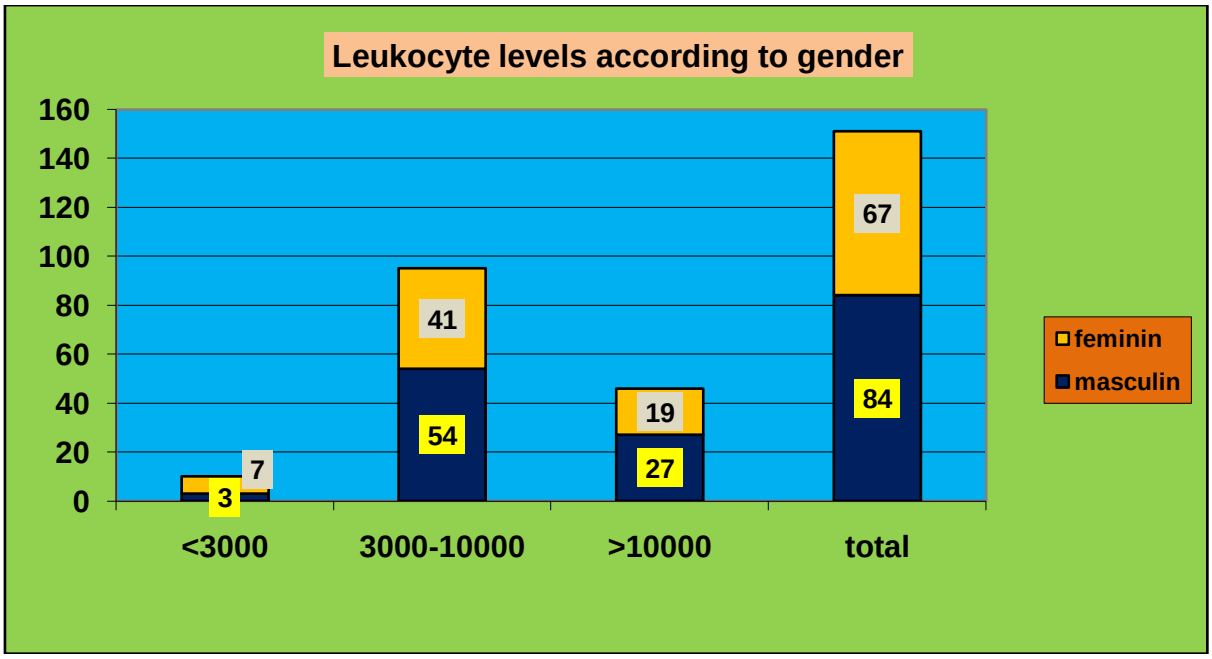

Figure 6. Leukocyte levels according to gender

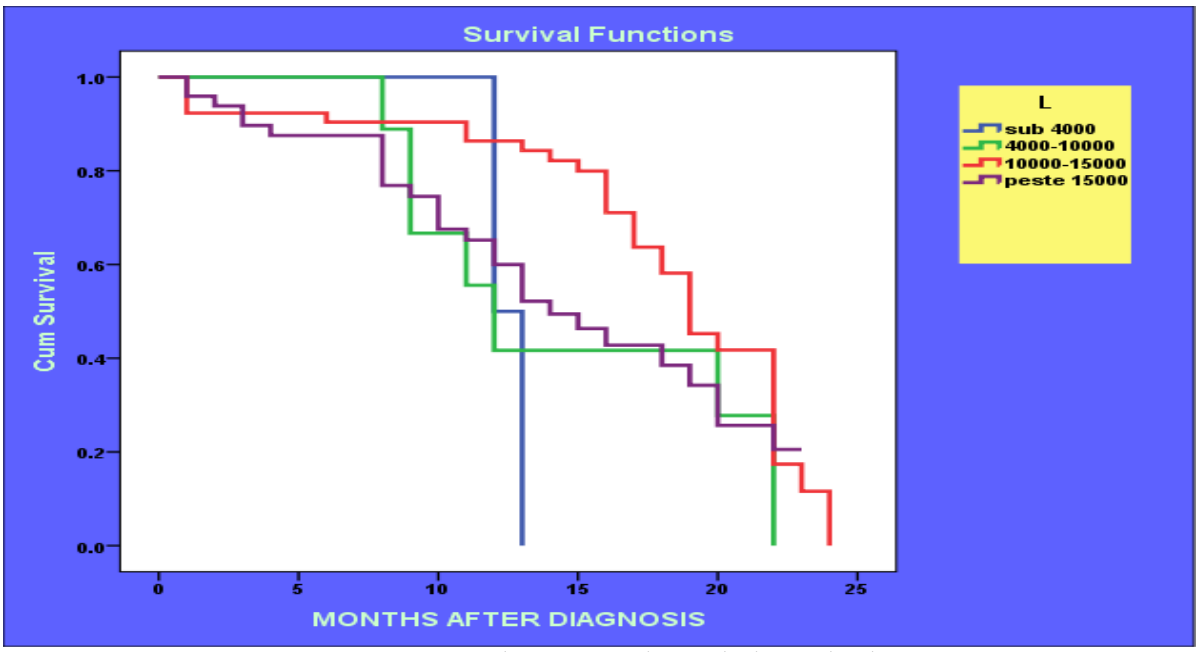

Figure 7. Survival curve according to leukocyte levels

In order to establish whether anemia, neutropenia and thrombocytopenia are predictive factors for the onset of second neoplasia we have applied ANOVA analysis, which showed statistical significance ($p<0.01$) of the three independent variables (anemia, neutropenia and thrombocytopenia) on the dependent variable, namely the onset of second neoplasia.

Table 1. Predictive factors for the onset of second neoplasia

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	3,792	3	1,264	5,485	,001[a]
	Residual	33,877	147	,230		
	Total	37,669	150			

a. Predictors: (Constant), ANEMIA, NEUTROPENIA, THROMBOCYTOPENIA

b. Dependent Variable: Second neoplasia

DISCUSSIONS

A marked trend towards finding new prognostic factors for Hodgkin disease has been seen in the recent years [5-7]. Previous research established lymphocytopenia is a negative prognostic factor for Hodgkin disease. It is frequently found in these patients, being seen in 8-11% of the patients in other studies and in 13.94% of the patients in this study.

A set of clinical, biological and morphological parameters are considered to be prognostic factors for Hodgkin lymphoma. By applying multiple regression analysis, the number of factors considered important for the individual assessment of patients significantly decreased [8-11]. In this study, by using ANOVA analysis, we have seen that anemia, neutropenia and thrombocytopenia are prognostic factors for the onset of second neoplasia, being statistically significant ($F=5.485$ $p<0.01$).

CONCLUSIONS

In conclusion, this study results suggest pancytopenia is associated with low survival rate, which indicates the possibility that host immunity and inflammatory response play an important role in clinical manifestations occurring in Hodgkin lymphoma. Low hemoglobin, leukocyte and platelet levels taken together could be an important prognostic factor in these patients' evolution.

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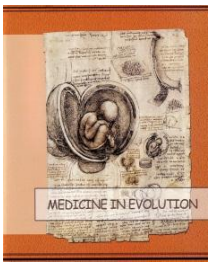
PATHOPHYSIOLOGICAL MECHANISMS IN MACULAR EDEMA



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ABSTRACT

Macular edema is the final pathway of several vascular and inflammatory diseases of the posterior pole who's final result is vision loss. Among these diseases are diabetic retinopathy, retinal vein occlusion, posterior uveitis and other pathologies that lead to a fluid accumulation in the outer plexiform layer and inner nuclear layer of the macular region. A combination of factors that disturb the blood retinal barrier , inflammatory agents and several existing diseases can lead to the formation of macular edema.

This article is intending to identify the different causes and conditions that lead to macular edema in several retinal diseases. These elements like the dysfunction of retinal blood barrier, inflammatory proteins and mediators under the existence of different retinal disorders of the retina contribute to the development of macular edema.

Key words: *macular edema, diabetic retinopathy, inflammation factors*

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INTRODUCTION

Macular edema represents a common pathway of several chronic systemic and intraocular diseases involving the retinal blood vessels. Macular edema (ME) is a slow progressive, painless diseases who's only sign is unilateral or bilateral vision loss. .Macular edema is a nonspecific sign of several other retinal diseases. ME is characterized as an accumulation of fluid in the outer plexiform layer and inner nuclear layer that leads to an expansion of the extracellular space of the macular region. The fluid accumulation leads to a cytotoxic edema altering the intercellular ionic exchange. Edema of the extracellular layer is more common and directly associated with the disruption of the blood retinal barrier(BRB). In cytotoxic edema there is a neuron cell swelling accompanied by intracellular Na ions accumulation with an intact BRB. Cytotoxic edema can be induced by several excitatory neurotransmitters such as glutamate and excessive accumulation of lactic acid as a result of ischemia, trauma or cellular damage [1,2].

PHYSIOLOGICAL STATUS OF THE MACULAR AREA

Macular edema is produced by an abnormal permeability of the perifoveolary retinal capillaries leading to retinal thickness. Macular edema persisting over 6 months is rated as being chronic. ME is predisposed to develop because of central retinal area specific anatomical features:

- High cellular count
- increased metabolic activity
- sufficient space for the accumulation of extravascular fluid due to the macular thickness and weakness of the retinal fibers of the outer plexifomr layer
- avascular macular zone creating an obstacle between choroid and retinal circulation ,decreasing the absorption of the extravascular fluid

The physiological status of the macular area is maintained by a few factors that prevent the accumulation of intraretinal extracellular fluid and proteins. This factors are represented by osmotic, hydrostatic forces and capillary permeability. This status is also maintained by blood retinal barrier that separates blood from other retinal areas ,protein and molecule passage of any type. The sum of all pathological conditions that lead to the disturbance of the blood retinal barrier causing protein retention , followed by consecutive water retention leads to the development of macular edema.

Macular edema is often associated with and ischemic state that leads to a rupture of the retinal capillary network that can be illustrated by fluorescein angiography. The macular retinal area can become irregular by expanding it's space because of the non- perfusion of the peripheral capillaries. Closure of the retinal arterioles can lead to the enlargement of the non- perfusion area which leads to the development of ischemia. The expansion of the sub retinal avascular area with more than 1000 microns will lead to a decreased visual acuity[3].

INFLAMMATORY MEDIATORS IN MACULAR EDEMA

Inflammation plays an important role in the development of macular edema and also maintains this status by the disturbance of the blood retinal

barrier. Several inflammatory mediators (angiotensin II, vascular endothelial growth factor[VEGF],cytokines, prostaglandins, interleukins, vascular adhesion molecules) and inflammatory cells(macrophages, neutrophils) act and are present at a cellular level interacting by a complex system not fully understood. Angiotensin is an oligopeptide that causes vasoconstriction, increased blood pressure and there are studies that confirm it's active role in maintaining a permanent state of inflammation at a local cellular retinal level. Angiotensin II is part of the renin-angiotensin system and is produced in the wall of an inflamed retinal vessel playing an important role in diverse vascular diseases which includes the development of macular edema. Angiotensin II acts as a key player of inflammation by 3 mechanisms: leukocyte infiltration ,increased vascular permeability, extracellular matrix remodellation but the most important remains the disturbance of the vascular endothelium.

The most important mediator of inflammation is the vascular endothelial growth factor (VEGF). Physiologically its role is to participate together with other factors in embryogenesis, wound healing and inflammation. Under pathological conditions it plays a role in tumour growth, arthritis, cardiac disorders and several other ocular disorders like diabetic retinopathy, age – related macular degeneration and retinal occlusive vascular diseases. The VEGF family is made up of 5 different components VEGF A-E. From all 5 factors only VEGF A is implicated in ocular pathological processes and is also co responsible of the development of macular edema. VEGF is induced, regulated and released by a state of retinal ischemia/hypoxia, angiotensin II, oxidative stress and inflammation. VEGF has multiple effects on other tissues from the body :angiogenesis, vasculogenesis, chemotaxis, inflammation, increased vascular permeability. Besides these effects, the most important ones who lead to macular edema are inflammation and vascular permeability. The inflammation produced by the VEGF is localised within the blood retinal barrier(BRB) and is operated by leukocytes producing leukostasis. Another property of VEGF, is inducing vascular leakage 50,000 times more faster than histamine. Disturbance of the BRB by diverse inflammatory mediators leads to lesions of vascular endothelium mediated by leukocytes and the destruction of tight junctions cells. Local intraretinal state of ischemia/hypoxia sets the premises for the development of macular edema bye high intracellular K rates who eventually will have the effect of water accumulation in the retinal cells[7].

SPECIFIC MECHANISMS THAT LEAD TO MACULAR EDEMA

1.Diabetic macular edema

Diabetic macular edema (DME) is the main cause of vision loss in patients with diabetes .The mechanism that leads to the development of DME is complex ,multilateral and not fully understood. Two subtypes of macular edema have been identified, a focal and a diffuse form. Focal macular edema is referring to a localised area of retinal thickening caused by vascular abnormalities and micro aneurysms. This type of edema evolves to fluid leakage and hard exudates. Diffuse macular edema is caused by fluid leakage from the dilated capillaries and micro aneurysms from across the entire posterior pole. Cellular damage in diabetes mellitus and in consequence diabetic retinopathy are caused by hyperglycaemia. Endothelial retinal cells are sensitive to hyperglycaemia because they lack a proper auto regulation and intracellular clearance

of glucose. Constant high levels of glucose can alter the cell structure and function starting a metabolic disturbance which finally leads to its own destruction. Diabetic retinopathy is characterized by a vascular circulatory disturbance, high vascular permeability and capillary occlusion or non-perfusion. The initial phase of diabetic retinopathy is marked by a microcirculatory disturbance (arterioles, capillaries, venules) which will affect the anatomical integrity and structure of the retinal microcirculation. The mechanism responsible for the above changes are: loss of pericytres, damages to vascular endothelial cells, thickening of the capillary basement membrane. All these changes will lead to a disturbance of auto regulatory cell function, changes of erythrocytes structure and activation of the aggregation process of thrombocytes. The inflammatory mediators mentioned above present in the development of ME , among these are leucocytes(damage to endothelial cells), VEGF and angiotensin II. The main pathological feature of diabetic retinopathy is high glucose blood level and especially the metabolic end products. Therefore high levels of sorbitol are detected, which is a degradation end product of the polyol cycle present in states of hyperglycaemia. High levels of sorbitol produce the following changes: increased intracellular levels of sorbitol and fructose, disruption of cellular osmotic balance, breakdown of retinal blood barrier, loss of pericytes, activation of protein kinase C. Reactive oxygen species as a result of oxidative stress are also present as a consequence of hyperglycaemia. Vascular endothelial damage is caused by all these factors and they are all present in the start phase of diabetic retinopathy [8,9,10].

2.Retinal vein occlusions

Central retinal vein and branch occlusions can cause cystoid macular edema. The pathophysiological changes that are present in macular edema as a cause of retinal occlusive diseases are related to the destruction of the perifoveal capillary wall caused by blood flow turbulences and high pressure that result in fluid leakage. This ischemic injury of the retinal capillaries attracts the activation of VEGF at a local level initiating an inflammatory response disturbing the blood retinal barrier[11].

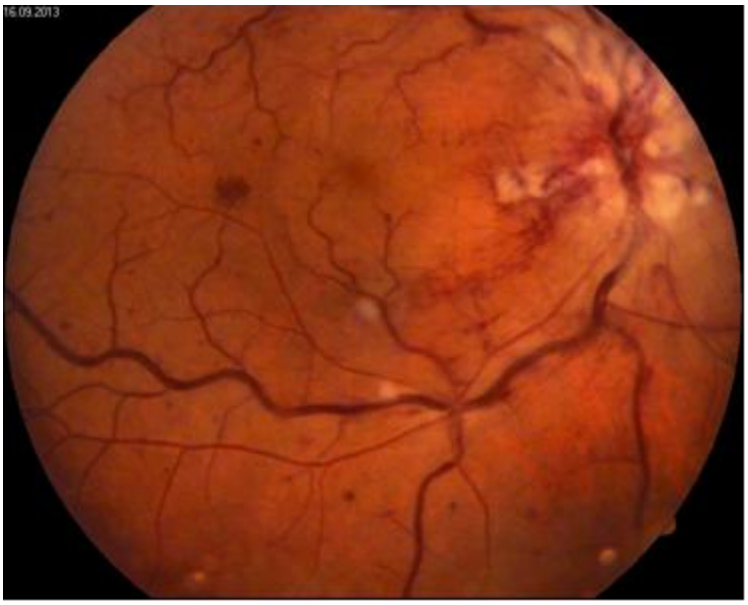

Figure 1. Macular edema post Central retinal vein occlusion(CRVO)

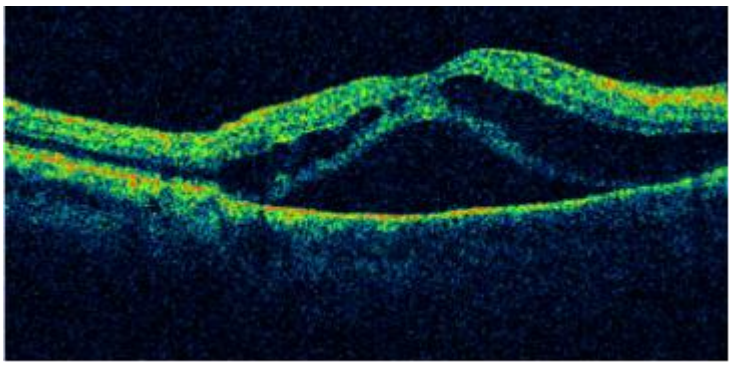

Figure 2. OCT Macular edema after CRVO

3.Pseudophakic and Aphakic macular edema(Irvine- Gass Syndrome)

This type of ME usually occurs in a time period of 4- 20 weeks after cataract surgery and it is a cystoid macular edema. This type of edema appears after the disruption of the blood vitro- retinal barrier after prostaglandins release. During the course of cataract surgical manoeuvres small traumas to the iris release prostaglandins and other inflammatory mediators. This type of edema resolves slowly and there are no visual acuity issues. Intra surgical incidents like posterior capsular rupture predisposes the central area of the retina to cystoid macular edema.

4.Inflammatory diseases

The best known inflammatory disease causing macular edema is uveitis. This type of edema can persist even after the resolution of the underlying disease. The most frequent types uveitis that can cause macular edema are: iridocyclitis, pars planitis, posterior uveitis, birdshot retinopathy. The mechanism responsible for the development of macular edema is the production and the massive release of inflammatory factors and mediators like prostaglandins. These inflammatory mediators will lead to a high vascular permeability of the perifoveol capillaries with massive exudation. Clinical studies have confirmed that a central role in the development of uveitis macular edema belongs to the CD4 subtype of lymphocytes.

A series of other diseases can have as a consequence macular edema with common mechanism that affect the blood retinal barrier. This has as a consequence the disruption of the vascular endothelial cells ,the retinal microcirculation, leading to the accumulation of sub retinal fluid in the macular area. Among these disorders that cause macular edema are : age related macular degeneration, Coats disease, radiation retinopathy, macular dystrophies and others [12].

CONCLUSIONS

Macular edema is a major complication of several retinal diseases that lead to the destruction photoreceptors and retinal neuron cells.

These retinal damages begin with the disturbance of the of the blood retinal barrier affecting the ions cellular channels which eventually lead to fluid accumulation.

Despite of multiple clinical studies, the complete mechanism of macular edema has not yet been completed.

Although in the last years there have been several intravitreal therapies developed with promising results, in the future there is a need for further research to fully understand this vision threatening disorder.

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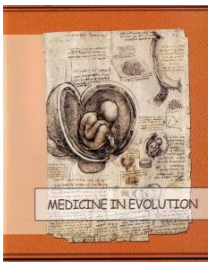
VENOUS THROMBOEMBOLISM IN PATIENTS WITH CANCER



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ABSTRACT

In cancer patients, venous thromboembolism represents one of the most important causes of morbidity and mortality. Patients with cancer often develop venous thromboembolism, which is the second cause of mortality in oncology patients. Deep vein thrombosis and pulmonary embolism may also delay or interfere with the treatment of malignant process, extend the period of hospitalization and increase healthcare costs. The incidence of venous and arterial thrombotic events in patients with cancer is increasing, partly because of the aging population and partly due to use of more effective cancer treatments, but often more thrombogenic. Few studies have assessed the efficacy and safety of anticoagulants in paraneoplastic thrombosis. Most international guidelines support the use of low molecular weight heparin in the initial and long term treatment of paraneoplastic thrombosis. It is possible that newer oral anticoagulant agents to be more efficient, but clinical studies to evaluate their effectiveness in oncology patients are still missing.

Key words: *venous thromboembolism, cancer*

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INTRODUCTION

Professor Armand Trousseau first identified thrombosis as a complication of cancer in 1865, and the combination of the two conditions is still often called Trousseau's syndrome. Prof. Trousseau (Lectures in Clinical Medicine, New Sydenham Society, 1865): "I have always been struck with the frequency with which cancerous patients are affected with painful oedema of the superior or inferior extremities…"; "In other cases, in which the absence of appreciable tumor made me hesitate as to the nature of the disease of the stomach, my doubts were removed, and I knew the disease to be cancerous when phlegmasia alba dolens appeared in one of the limbs" [1]. Ironically, Trousseau died of gastric carcinoma 6 months after writing to his student, Peter, on January 1st, 1867: "I am lost … the phlebitis that has just appeared tonight leaves me no doubt as to the nature of my illness" [1].

In cancer patients, venous thromboembolism represents one of the most important causes of morbidity and mortality. Patients with cancer often develop venous thromboembolism (VTE), which is the second cause of mortality in oncology patients. Deep vein thrombosis and pulmonary embolism may also delay or interfere with the treatment of malignant process, extend the period of hospitalization and increase healthcare costs. The incidence of venous and arterial thrombotic events in patients with cancer is increasing, partly because of the aging population and partly due to use of more effective cancer treatments, but often more thrombogenic.

Epidemiological data reveals that:

- Patients with cancer have a 4- to 6-fold increased risk for VTE vs non-cancer patients [2,3];
- Patients with cancer have a 3-fold increased risk for recurrence of VTE vs non-cancer patients [2,3,4];
- Death rate from cancer is 4-fold higher if patient has concurrent VTE [2,3,4];
- Cancer patients undergoing surgery have a 2-fold increased risk for postoperative VTE [2,3];
- Up to 50% of cancer patients may have evidence of asymptomatic deep vein thrombosis/pulmonary embolism (DVT/PE) [2,3].

VTE has a significant negative impact on quality of life and can be the first manifestation of an occult malignancy. 10% of patients with idiopathic VTE are diagnosed with cancer within 2 years, 20% have recurrent idiopathic VTE and 25% have bilateral VTE [5].

The key questions that have been raised concerning venous thrombosis in patients with cancer are:

1. Does activation of blood coagulation affect the biology of cancer positively or negatively?
2. Can we treat tumors more effectively using coagulation protein targets?
3. Can anticoagulation alter the biology of cancer?

And the possible answers are:

1. Epidemiological data suggests that VTE is a bad prognostic sign in cancer.
2. Experimental data supports the use of antithrombotic strategies for both prevention of thrombosis and inhibition of tumor growth.
3. Results of recent randomized clinical trials of low molecular weight heparin (LMWH) in cancer patients show superiority in preventing recurrent VTE and suggest increased survival.

Risk factors for VTE in medical oncology patients depend on tumor type (ovary, brain, pancreas, lung, colon), stage, grade and extent of cancer (metastatic disease), type of antineoplastic treatment and miscellaneous VTE risk factors

(previous VTE, hospitalization, immobility, infection, thrombophilia) [6]. In men, cancers of the pancreas, prostate, stomach, kidney, lung and primary brain tumors are associated with the highest rates of VTE [6]. In women the highest rates of VTE appear in cancers of the breast, ovaries, lungs [6]. Surgical and systemic treatment, along with insertion of central venous catheters, is associated with increased risk for VTE. According to studies, about 4% of central venous catheters generate clinically relevant VTE [6].

Until recently, sparse data specifically related to cancer patients was available. Cancer patients are a small subset (<20%) in most of the largest trials of antithrombotic therapy. Therefore, until the last 2-3 years, the information was extrapolated from non-cancer patients, having in mind that cancer patients are in the highest risk group.

Few studies have assessed the efficacy and safety of anticoagulants in paraneoplastic thrombosis. Most international guidelines support the use of low molecular weight heparin in the initial and longterm treatment of paraneoplastic thrombosis. It is possible that newer oral anticoagulant agents to be more efficient, but clinical studies to evaluate their effectiveness in oncology patients are still missing.

The major objectives of venous thromboembolism treatment are to relieve symptoms, to decrease the incidence of long-term complications as recurrent thrombosis, fatal pulmonary embolism, pulmonary hypertension and posttrombotic syndrome. In patients with reduced life expectancy there is a debate whether anticoagulants provide net benefits, taking into account the cost of low molecular weight heparin, the need for monitoring of coagulation parameters during treatment with warfarin and the possible risk of bleeding.

The standard treatment of an acute episode of venous thromboembolism in the general population is initial heparin therapy followed by long term treatment with warfarin or other vitamin K antagonist. This regimen is not valid for cancer patients, because warfarin is usually poorly tolerated and the risk of recurrent thrombosis remains high, despite anticoagulation. We know now that the natural history of venous thromboembolism in cancer patients is more aggressive and often unpredictable, compared with patients without cancer and treatment with heparin followed by warfarin has a high rate of failure. Other complications, such as bleeding, are also more common in cancer patients. Prospective studies have reported that up to 21% of cancer patients develop recurrent venous thromboembolism and up to 13% develop major bleeding during warfarin therapy [6].

Antithrombotic therapy is pharmacological and non-pharmacological. Non-pharmacological treatments available to us are intermittent pneumatic compression, elastic compression stockings and inferior vena cava filters. Pharmacological therapy includes unfractionated heparin, low molecular weight heparins and oral anticoagulants (Table 1).

CLOT trial, a landmark cancer/VTE trial, had the goal to compare efficacy of a LMWH with an oral anticoagulant agent in preventing recurrent thrombosis in patients with cancer. The trial included 677 patients with cancer and acute venous thrombosis or pulmonary embolism, from 48 clinical centers across 8 countries [8]. The patients were randomly assigned to receive the LMWH dalteparin at a therapeutic dose of 200 IU per kilogram of body weight given subcutaneously once daily either for five to seven days, followed by six months of therapy with standard-dose warfarin (target INR 2.5), or for one month, followed by a reduced dose of dalteparin (approximately 150 IU daily. Primary

endpoints were recurrent VTE and bleeding, and secondary endpoint was the duration of survival. The incidence of recurrent thromboembolism in the dalteparin group was half that in the warfarin group. The probability of recurrent thromboembolism at six months was 9% in the dalteparin group and 17% in the warfarin group. The incidence of major bleeding in the 2 groups was not significantly different: 6% in the dalteparin group and 4% in the warfarin group. 90% of deaths in each group were due to progressive cancer [8] (Table 2).

The new standard of care in VTE at patient with cancer is LMWH at therapeutic doses for a minimum of 3-6 months (Grade 1A recommendation, American College of Chest Physicians, ACCP); oral anticoagulant therapy to follow for as long as cancer is active (Grade 1C recommendation, ACCP) [7]. Dalteparin is the only LMWH approved for both treatment and secondary prevention of VTE in cancer.

The main "therapeutic tools" are:

- LMWH, unfractioned heparin, fondaparinux, warfarin, argatroban, vitamin K antagonists.
- Inferior vena cava filters.
- Graduated compression stockings and intermittent pneumatic compression.

Fondaparinux is a selective inhibitor of activated factor X, without antithrombin activity. Argatroban is a direct thrombin inhibitor reserved for patients with heparin-induced thrombocytopenia. The majority of new oral anticoagulants are direct thrombin inhibitors (eg dabigatran) or activated factor X (rivaroxaban, apixaban). New oral anticoagulants are attractive to physicians and patients because are administered in fixed doses and do not require laboratory monitoring. Their main limitation is imposed by the lack of available tests to measure the anticoagulant effect when needed, ie in case of bleeding. This also means that compliance cannot be easily evaluated in case of treatment failure. Finally, lack of specific antidote for these agents continues to represent a problem. To date, similar data were reported on the efficiency and bleeding for rivaroxaban and heparin (followed by warfarin), but studies have included few patients with cancer. The only new anticoagulant agent studied in cancer patients was apixaban; given for 12 weeks in 125 patients with locally advanced or metastatic cancer apixaban was well tolerated, without bleeding [9]. However, there are insufficient data on efficacy and safety of new oral anticoagulant treatment in paraneoplastic thrombosis. Because patients with cancer have more aggressive thrombosis, are more prone to drug interactions and organ dysfunction, clinical trials are needed to evaluate these new anticoagulants in oncology patients.

Of parenteral anticoagulants, low molecular weight heparins are widely used in the initial treatment, due to benefits as reduced risk of heparin-induced thrombocytopenia, simple dosing, no need to monitor coagulation parameters, lower costs. The literature suggests that treatment with low molecular weight heparins provide better efficiency, safety and survival than unfractionated heparin. Unfractionated heparin remains the treatment of choice in hemodynamically unstable patients with severe renal impairment or high risk of bleeding, which require rapid reversal of anticoagulation.

Fondaparinux has an efficacy and safety comparable with heparin, the incidence of thrombocytopenia being low; it is contraindicated in patients with significant renal impairment. Unlike heparin, fondaparinux's effect cannot be reversed by protamine sulfate, having a long half-life, approximately 18 hours. None of anticoagulants has been formally studied in oncology for the initial treatment of venous thromboembolism. Because cancer

patients represents only 10-15% of patients studied in clinical trials, the efficacy and safety of anticoagulants in patients with cancer are not very well known. Based on limited data published so far, it appears that low molecular weight heparins administered subcutaneously and intravenous infusions of unfractionated heparin have similar efficacy in the initial treatment of venous thromboembolism in cancer patients. However, fondaparinux appears to be less effective than low weight heparins in patients with cancer and deep vein thrombosis, but is more effective than unfractionated heparin in patients with cancer and pulmonary embolism [10].

Immediately upon diagnosis, treatment with LMWH or unfractionated heparin anticoagulant is initiated. The doses of LMWH used are dalteparin 200 IU/kg sc daily, enoxaparin 1 mg/kg sc every 12 hours, Tinzaparin 175 U/kg sc daily, Fondaparinux 5 mg (<50 kg), 7.5 mg (50-100 kg), 10 mg (> 100 kg) sc daily [7]. Unfractionated heparin is administered as initial bolus of 80 U/kg, then 18 U/kg/h, targeting an APTT of 2-2.5 times higher than control.

On short term, in transition to chronic treatment, LMWH is preferred as monotherapy in patients with DVT or pulmonary embolism and for recurrent VTE prophylaxis in patients with metastatic cancer [7]. If the patient is on unfractioned heparin or factor Xa antagonist, the transition to LMWH or warfarin can be made. The initial warfarin dose is 2.4-5 mg, subsequent doses being based on the value of INR (target INR 2-3) (Table 3, Table 4, Table 5, Table 6).

The main recommendations of American Society of Clinical Oncology (ASCO) are [11]:

- "Consider all hospitalized cancer patients for VTE prophylaxis with anticoagulants, in absence of bleeding…"
- "Give routine prophylaxis to outpatients receiving thalidomide or lenalidomide".
- "LMWH represents the preferred agent".
- "Impact of anticoagulants on cancer patient survival requires additional study".

The evolution of cancer patients involves recurrent venous thromboembolism despite maintaining INR in the therapeutic range. Studies have reported an annual risk of recurrent thromboembolism 21 to 27% in patients with cancer who are treated with warfarin, ie 2-3 times higher than patients without cancer [12]. Also, cancer patients who received warfarin have an annual risk of major bleeding of 12-13% compared to 3-4% in patients without cancer [13,14]. This risk of bleeding does not correlate with the INR. Not to be neglected is the psychosocial impact of treatment with warfarin: the need for INR control by venous puncture is problematic, because these patients generally have poor venous access after multiple cycles of chemotherapy, going to the hospital or laboratory may be difficult due to fatigue, chronic pain, reduced mobility, etc. Frequent changes in dose can be frustrating and even dangerous for them, especially in the elderly, if they are being treated with narcotics for pain control.

Studies suggest that the presence of metastases, young age and a short interval between diagnosis of cancer and venous thromboembolism (less than 3 months) are predictors of recurrent thrombosis despite anticoagulation. Lacking randomized controlled trials to guide optimal management of recurrent paraneoplastic thrombosis, observational data and clinical experience support the use of low molecular weight heparin. Although randomized controlled trials to guide optimal management of recurrent paraneoplastic thrombosis still lack,

observational data and clinical experience support the use of LMWH.

The patients anticoagulated with vitamin K antagonists, who make VTE when INR has a subtherapeutic value, can be retreated with unfractioned heparin or LMWH until INR reaches a value between 2-3 [12]. If recurrence occurs when the INR is 2-3 we have two options: either move to another anticoagulant as unfractionated heparin (maintaining APTT between 1,5-2.5 times higher than control) or LMWH, or increase INR to a value of 3.5 [12].

It should be mentioned also the contraindications of anticoagulation: active bleeding, pericarditis, active peptic ulcer disease, uncontrolled hypertension, thrombocytopenia <50 000/ml, severe platelet dysfunction, recent surgery with high risk of bleeding.

Another aspect that has not been sufficiently studied is related to the duration of anticoagulant therapy after a first episode of venous thromboembolism in cancer patients. However, most of these patients receive anticoagulant therapy more than 6 months. After this period, usually the treatment is recommended indefinitely in patients with metastases, due to known risk of recurrence of thrombosis. Of course, these patients should be reviewed frequently to determine the risk/benefit ratio of anticoagulation therapy. The decision to extend treatment should consider the quality of life of these patients and their life expectancy.

In relation to prognosis of anticoagulated patients, a recent meta-analysis found a significant reduction in overall mortality in cancer patients without VTE, treated with anticoagulants. This effect was more pronounced in the case of LMWH (relative risk reduction by 13.3%) than warfarin (relative risk decreased by 5.8%) [15]. However, due to certain limitations of these studies, there are no sufficient data to support improved prognosis of cancer patients without VTE after anticoagulant therapy.

RESULTS

Table 1. 8th ACCP (American College of Chest Physicians) Consensus Guidelines [7]

Grade	Recommendations for Cancer Patients
1A	Patients undergoing surgery should receive LDUH 5000 U tid or LMWH daily in hospital (enoxaparin 4000 U daily, dalteparin 5000 U)
1B	No routine prophylaxis to prevent thrombosis secondary to central venous catheters, including LMWH (1B) and fixed-dose warfarin (1B)
1C	No routine thrombophylaxis (except myeloma) for chemo or hormonal therapy
1B	Routine primary thrombophylaxis should NOT be used to improve survival of the cancer patient

Table 2. Bleeding events in CLOT trial [8]

Bleeding events	Dalteparin N=338	Oral anticoagulants N=335	P-value*
Major bleeding	19 (6%)	12 (4%)	0.27
Any bleeding	46 (14%)	62 (19%)	0.09

Table 3. ASCO Guidelines – hospitalized patients with cancer [11]

Role of VTE Prophylaxis	Evidence
Patients with cancer should be considered candidates for VTE prophylaxis with anticoagulants (UFH, LMWH, or fondaparinux) in the absence of bleeding or other contraindications to anticoagulation.	Multiple RCTs of hospitalized medical patients with subgroups of patients with cancer. The 8th ACCP guidelines strongly recommend (1A) prophylaxis with either low-dose heparin or LMWH for bedridden patients with active cancer.

Table 4. Ambulatory patients with cancer, without VTE, receiving systemic chemotherapy [11]

Role of VTE Prophylaxis	Evidence
Routine prophylaxis with an antithrombotic agents is not recommended except as noted below	Routine prophylaxis in ambulatory patients receiving chemotherapy is not recommended due to conflicting trials, potential bleeding, the need for laboratory monitoring and dose adjustment, and the relatively low incidence of VTE.
LMWH or adjusted dose warfarin (INR ~ 1.5) is recommended in myeloma patients on thalidomide or lenalidomide plus chemotherapy or dexamethasone	This recommendation is based on nonrandomized trial data and extrapolation from studies of postoperative prophylaxis in orthopedic surgery and a trial of adjusted-dose warfarin in breast cancer

Table 5. Patients with cancer who undergo surgery [11]

Role of VTE Prophylaxis	Evidence
LMWH for up to 4 weeks may be considered after major abdominal/pelvic surgery with residual malignant disease, obesity, and a previous history of VTE	Recent RCTs suggest that prolonging prophylaxis up to 4 weeks is more effective than short-course prophylaxis in reducing postoperative VTE.

Table 6. Prophylaxis of recurrent VTE in patients with cancer [11]

Role of VTE Prophylaxis	Evidence
LMWH is the preferred approach for the initial 5-10 days in cancer patient with established VTE.	LMWH for 3-6 months is more effective than vitamin K antagonists given for a similar duration for preventing recurrent VTE.
LMWH for at least 6 months is preferred for long-term anticoagulant therapy. Vitamin K antagonists with a targeted INR of 2-3 are acceptable when LMWH is not available.	

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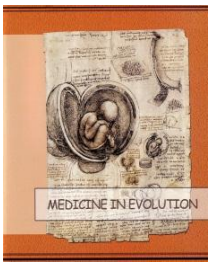
CURRENT CONCEPTS IN CERVICAL PATHOLOGY



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ABSTRACT

The etiology of cervical cancer has undergone several stages.The evidence gathered concerning the natural history of the preinvasive cervical lesions shows that, if those lesions are not treated, they can progress into invasive cancer in a substantial proportion

The medical practice in treating patients with squamous intraepithelial lesions has changed over the years, along with the progress made in understanding the disease evolution and aetiology, and the progress in technology, ranging between two extremes, represented by the electrocautery and the total hysterectomy.In this context, the conization has both diagnostic and therapeutic value when dealing with the invasive lesions of the cervix.

The diagnosis and treatment files, the cytology and colposcopy examinations were studied for 126 cases with preinvasive lesions of the cervix that required surgical treatment which consisted of:

- *wide excision of the transformation area with the diathermy loop : 25 cases*
- *classic conization - 90 patients*
- *cervical amputation - 11 patients*

Studying the cytology of these patients we found that 73.56% had CII at the cytological examination, in other cases 28.73% being CII.

We also monitored the correlation between the BABEŞ – PAPANICOLAU cytological examination, the colposcopy and the result of the histopathological examination. We noticed a perfect concordance in 120 cases (95.24%), indicating cervical cancer only in 6 cases, representing 4.76%.

The histological appearance of the fragments extracted by cervical conization showed:

- *61 patients - 48.41% - CIN I*
- *48 patients - 38.09% - CIN II*
- *17 patients 13.49% - CIN III.*

Key words: *colposcopy,cone biopsy,cytology,cervical lesion,H-SIL*

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INTRODUCTION

The etiology of cervical cancer has undergone several stages. Many population studies tried to establish a causal relationship between certain habits and ways of life and the cervical lesions occurrence (1). The precancerous lesions are very important for the carcinogenesis. The evidence gathered concerning the natural history of the preinvasive cervical lesions shows that, if those lesions are not treated, they can progress into invasive cancer in a substantial proportion (2, 3,4).

Today the viral theory, incriminating the HPV in more than 95% of cervical cancers cases, prevails in the etiology of cervical cancer (5, 10, 18).

The intraepithelial neoplasia concept (CIN) introduced by Richard in 1968 showed that all the dysplasia cases have a development potential (17).

The mitotic activity degree, the mature cells and nuclear abnormalities proliferation determine the neoplasia degree. The existing lesions at the squamous-cylinder junction have an important role in the cancer lesions genesis.

The medical practice in treating patients with squamous intraepithelial lesions has changed over the years, along with the progress made in understanding the disease evolution and aetiology, and the progress in technology, ranging between two extremes, represented by the electrocautery and the total hysterectomy (6).

In this context, the conization has both diagnostic and therapeutic value when dealing with the invasive lesions of the cervix.

The conization is performed (7,9):

• For all the patients with abnormal cytology and unsatisfactory colposcopy (squamous-cylinder junction, invisible lesion margins)

• For normal colposcopy, but persistent abnormal cytology or positive endocervical curettage

• For the colposcopic suspicion of occult or invasive carcinoma

• When there are significant cytocolpohystological discrepancies.

The conization is therapeutically suitable for:

• the treatment of histologically confirmed cervical intraepithelial neoplasia (CIN) in patients with unsatisfactory colposcopy

• the in situ AIS treatment of the endocervical adenocarcinoma.

From a technical point of view, the conization may be:

1. Classical conization, with the scalpel, the hemostasis being performed by applying Stumdfort threads.
2. Conization according to Mc Donald method
3. Conization according to Palmrich – Bielecki method
4. Conization according to Masterson method
5. Conization with the ultrasonic scalpel, which is a tool that cuts and coagulates by converting electrical energy into mechanical ultrasonic vibrations
6. The CO2 laser conization is a modern alternative to this procedure
7. The conization with the diathermy loop, which is an alternative to conventional or laser conization, being performed with a large loop, with a 2,5 / 2,5 cm diameter or with a medium-sized loop with which the transforming area is excised(13,14)
8. Cervical conization, using the "two cones" method (12).

The diagnosis of the cervical lesions is based on the tripod diagnosis of cervical lesions (cytology, colposcopy, pathology). The colposcopy which is complementary to

the cervical cytology helps us locate the changes indicated by the smear, to appreciate their seriousness and to take the most appropriate therapeutic decision for each case.(8)

Regardless of how the excisional surgery treatment is performed, the patient must be integrated in a medical short and long term surveillance system, the cytology , colposcopy and the prophylactic vaccination being very important in this system (1, 3, 10,17).

Among the modern diagnostic possibilities for the cervix dysplasia, besides the cytology and colposcopy, with the possibility of performing a targeted biopsy (colposcopically directed) the conization is a diagnosis and treatment method used predominantly for the dysplasia that is large and extended towards the cervical canal (5, 7,15).

Often the lesions located at the squamous - cylindrical junction in the endocervix are not suitable for biopsy, but can be diagnosed with the fragment extracted by conization (20, 21, 22).

At the same time, the cervical conization or even the cervical amputation represents for the benign dysplastic lesions and the premalignant lesions a therapeutic method which can be carried out in a single session (11, 19, 21). The histopathological detection of some invasive carcinoma lesions requires immediate radical treatment (1, 16, 18).

The diagnosis management and the therapy based on the histopathological examination of the cone removed by conization (12) implies the following procedures:

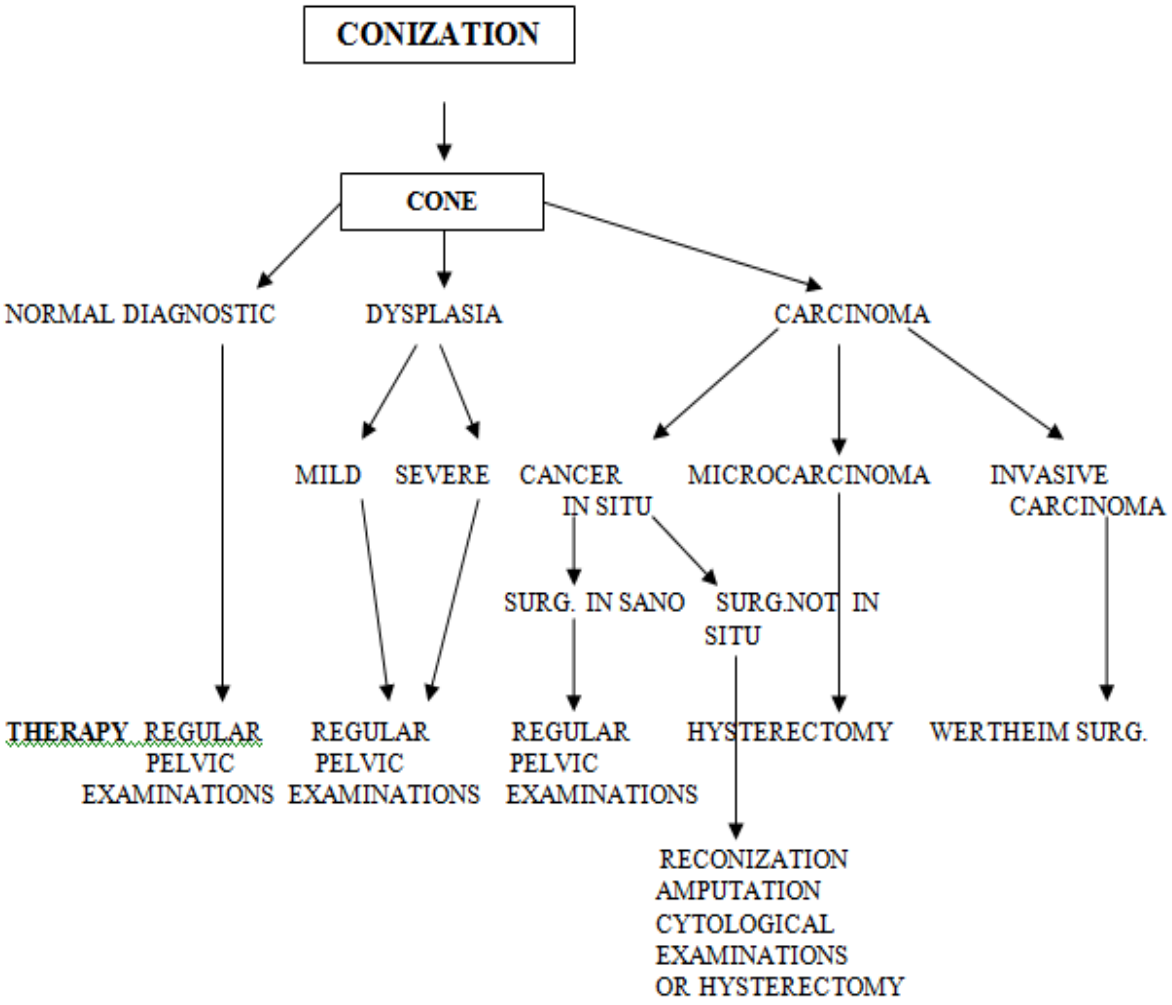

Figure 1. ***Algorithm of treatment in cervical lesions***

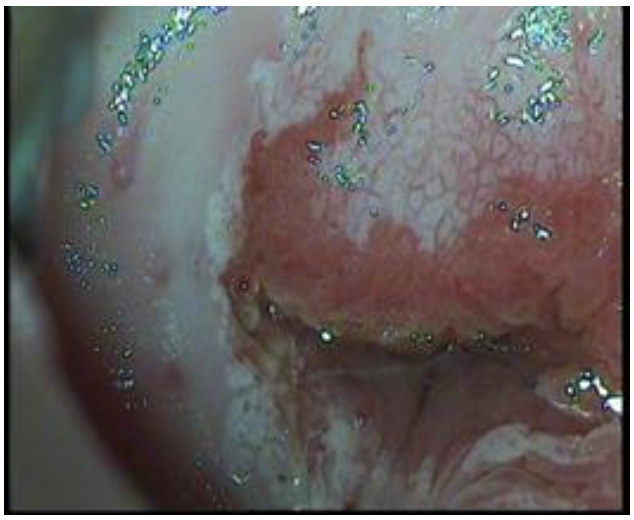

Figure 2. The cervix after aplication of 3% acetic acid demonstrating an easily observed acetowhite cin 3 lession on the anterior cervix noted only following acetic acid application

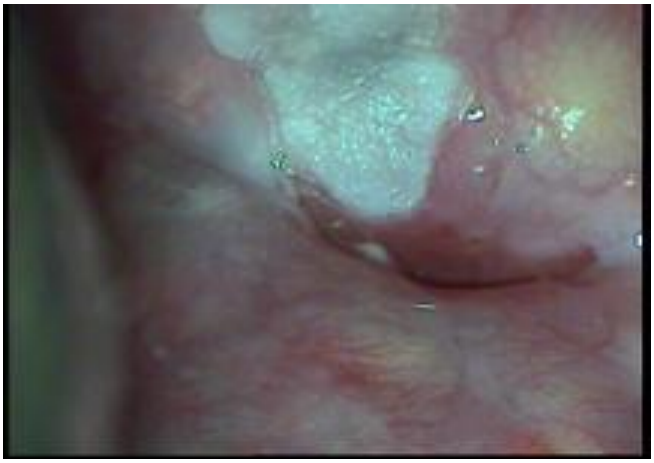

Figure 3. An acetowhite high-grade lession gradually appears on the anterior lip of the cervix. An nabothian cysts with overlying dilated,but normal branching blood vessels,also on anterior and posterior lip

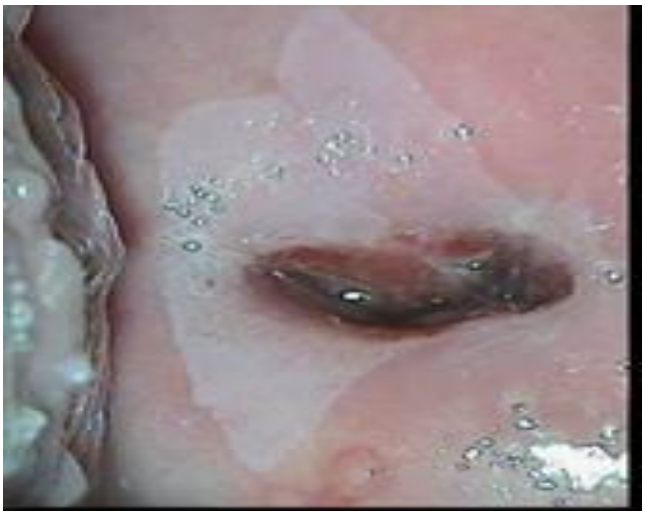

Figure 4. Leukoplakia of the cervix,demonstrating white,thinked,raised epithelium prior to the aplication of 3% acetic acid

MATERIAL

The diagnosis and treatment files, the cytology and colposcopy examinations were studied for 126 cases with preinvasive lesions of the

cervix that required surgical treatment which consisted of:

- wide excision of the transformation area with the diathermy loop (LLETZ technique): 25 cases, 19%
- classic conization - 90 patients - 71.42%
- cervical amputation - 11 patients 8.7%

According to the provenance, 96 (76.19) patients were from urban areas and the remaining 30 (23.8%) from rural areas.

The group distribution analysis, according to age, shows that the peak incidence is between 28-40 years - 90 patients representing 71%, the remaining 36 (29%) having ages between 41-50 years.

Studying the cytology of these patients we found that 73.56% had CII at the cytological examination, in other cases 28.73% being CII.

Performing the conization, we applied 4 standard non-absorbable threads instead of 2, which are applied in the original process. 6 weeks after the surgery we extracted the threads.

We also monitored the correlation between the BABEŞ – PAPANICOLAU cytological examination, the colposcopy and the result of the histopathological examination. We noticed a perfect concordance in 120 cases (95.24%), indicating cervical cancer only in 6 cases, representing 4.76%.

From these cases, in 5 cases – representing 83.33% the invasive cancer was confirmed upon the histopathological examination of the uterus, after performing hysterectomy, in a single case, representing 16.67% obtaining a false negative result, reconfirming the histopathological result from the cone obtained by conization.

All the suspected cases, for which the total hysterectomy was performed were classified in the CIN III with H-SIL or carcinoma in situ category.

The histological appearance of the fragments extracted by cervical conization shows:

- 61 patients - 48.41% - CIN I
- 48 patients - 38.09% - CIN II
- 17 patients 13.49% - CIN III.

We specify that we have included all patients in the therapeutic management scheme for the preinvasive lesions of the cervix.

CONCLUSIONS

1. The conduct adopted by us for the non-invasive lesions of the cervix was an active one, implying a diagnosis as correct as possible of these lesions and their proper treatment.
2. We consider the electrocautery as an obsolete procedure, performing it only for a satisfactory colposcopy, on a cervix with extended ectopy that secreted mucus in a in a disturbing manner for the patient with normal cytology .
3. Regardless of the technique used for performing the conization, the healing was safe, but we prefer the classical conization in order to obtain a piece of cervix (cone) that allows us to perform a histopathological diagnosis as accurate as possible.
4. Performing the conization allowed an early diagnosis of invasive cancer in 5 cases that otherwise would have been omitted until a later stage .
5. In the H -SIL cases, at the histopathological examination of the cone obtained by conization, we prefer performing a total hysterectomy in cases where there is no interest for the obstetrical prognosis or the reconization, for young women without children, taking the final decision after the second histopathological result.

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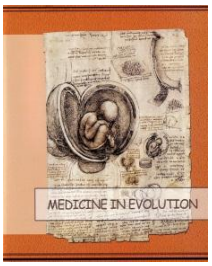
TRANSFUSION THERAPY, LIMITS AND ADVERSE REACTIONS- A SINGLE-CENTER RETROSPECTIVE STUDY



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ABSTRACT

Introduction: *The increased usage of blood products in recent years is claiming a more accurate hemovigilance and a periodic monitoring of clinical transfusion practices.*

Aim and objectives: *We aimed at evaluating the dimension of transfusion therapy, the type of blood products used and an estimation of adverse reactions.*

Material and method: *The study was undertaken over a period of one year (January 2012- December 2012). Data were obtained from patient's record files and from the hospital transfusion registry.*

Results: *During the year 2012, substitution with 4208 units of blood products was performed in Children's Emergency "Louis Țurcanu" hospital, representing 21,86 % of the total units collected in Blood Transfusion Center Timişoara (CTST). The greatest proportion was used in oncology, hematology, stem cells transplantation department and intensive care unit. From all of units used in those fields, a percent of 0,47 % resulted in adverse reactions.*

Conclusions: *A relatively low rate of transfusion reactions was observed during this study. This can be related to underreporting of minor symptoms that pediatric patients had experienced. Type of blood products, age and comorbidities can influence the appearance of undesirable blood transfusion related outcomes. Promoting a high hemovigilance will result in a progressively improved security of the transfusion act.*

Key words: *blood transfusion, adverse reactions, pediatrics*

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INTRODUCTION

The decision for using blood products should be carefully evaluated and considered applicable especially as a life-saving measure.

The benefit of blood therapy is incontestable, although still persists the concern about the viral and bacterial contamination, the storage lesion related changes in red cells and platelets and the immunological reactions of the transfusion act. However, the confidence to use blood products increased in the last years. New screening techniques development minimized and in most of the cases eliminated the undesirable viral complications, increasing especially the safety concerning human immunodeficiency virus, hepatitis B and C virus. Bacterial contamination of blood products continues to remain a major issue on platelet products. Noninfectious complications of transfusions can result in low or no morbidity, especially when it is about minor allergic reaction or acute, non-hemolytic fever.

Generally, an accurate estimation of undesirable reactions cannot be done because many of them are concomitantly associated with the underlying disease. It is also to be mentioned that in many cases an efficient reporting system is lacking in most of the medical centers (1).

Aim and objectives

Confronted with these aspects, aware that an alternative choice is lacking, we analyzed the profile of one year transfusion therapy, focusing on the dimension and type of blood products used and their undesirable reactions.

MATERIAL AND METHODS

A retrospective study was performed from January to December 2012, using data from the patient medical files and the transfusion registry of "Louis Țurcanu" Children's Emergency Hospital Timisoara, considering:

-the type and number of the blood units used: whole blood (WB), packed red blood cells (PRBC), pool random-platelet concentrates (PR-PC), single donor (apheresis) platelet concentrates (SD-PC), fresh frozen plasma (FFP) and cryoprecipitate (cryop.),

-the correlation between the type of blood used, patient's diagnosis and adverse reactions,

-the number of units involved in the undesirable blood therapy complications,

-the impact of leukocytes depleted blood products used in order to decrease the immunological reactions and some of the viral transmitted infections: cytomegalovirus (CMV), Parvovirus B19, West Nile virus [2]

-the role of irradiation of blood units in order to prevent transfusion associated graft-versus-host-disease (TA- GVHD) [2].

RESULTS

During one year a total of 4208 blood units where administrated, representing 21,86 % of the total units collected in CTST. The greatest number was used as follow: 1206 (28,65 %) for oncology, 853 (20,27 %) for hematology, 1436 (34,12 %) for those on intensive care unit and stem cells transplant department.

Type of blood distribution units was as follows: 5- WB, 1283- PRBC, 2213- PC (741- SD-PC and 1472-PRD-PC), 622-FFP, 85- cryop. (table 1).

Table 1. Repartition of blood products units used in dependence on the diagnosis of patients

Type of blood units	WB	PRBC	SD-PC	PRD-PC	FFP	Cryop	Total
Oncology							
Leukemia/Lymphoma		304	300	238	29		871
Solid tumors		96	140	74	25		335
Hematology							
Severe anemia		43					43
Beta thalassemia		113					113
Aplastic anemia		130	292	90			512
Thrombocytopenia		66	119				185
Stem cells transplant and intensive care unit	1	303	673	148	201	70	1396
Intensive care unit							
Septic shock				3	37		40
Other pediatric departments	1	55					56
Severe anemia		15					15
Secondary anemia (HIV infection)		6	1	4	33		1 43
Premature infants department					297	15	312
Septic shock	3	218					221
Severe anemia					65		65
Secondary thrombocytopenia							
Type of units total	**5**	**1283**	**1472**	**741**	**622**	**85**	**4208**

The high number of onco-hematological patients and their diagnosis severity are correlated with number of blood products used, described in figure 1. We note that most of the RBC indicated where especially on leukemia, lymphoma, intensive care and stem cells transplant unit.

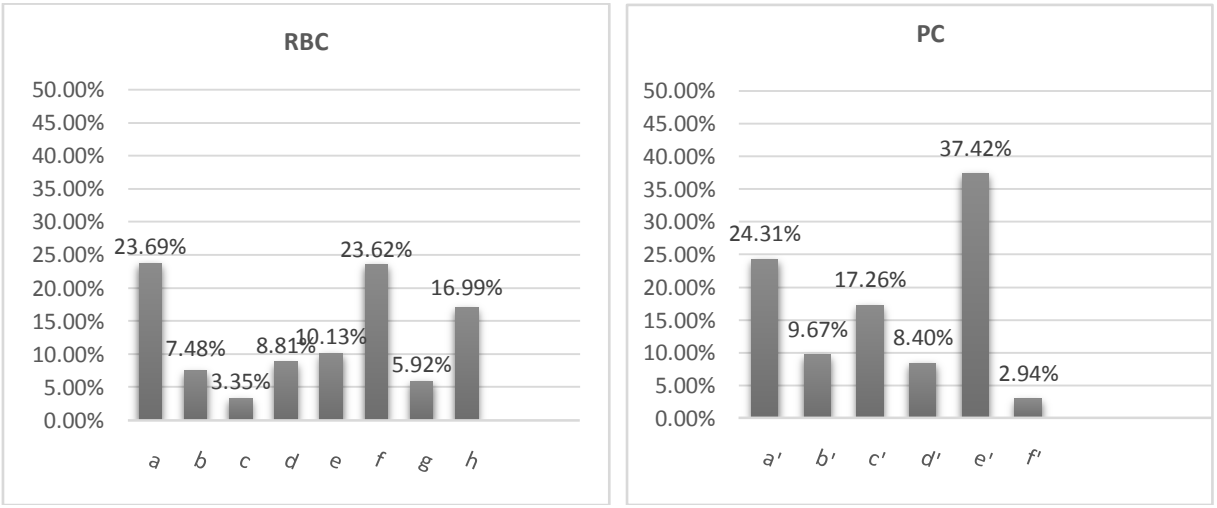

Figure 1. Distribution of one year RBC and PC units used

a, a′- leukemia, lymphoma; ***b, b′***- solid tumors; ***c***- severe anemia of diverse causes; ***d***- βthalassemia; ***d′***- primary and secondary trombocitopenia; ***e, c′***- aplastic anemia; ***f, e′***- stem cells transplant and intensive

care unit; ***f'-*** premature infants septic shock; ***g***- other pediatric departments; ***h***- anemia of premature infants

Regarding the platelet transfusions, most units were used in patients candidate or undergoing to stem cells transplant and those admited on intensive care unit (especially on onco-hematology intensive care) (Figure 1). FFP was most indicated on premature infant septic shock (47,75 %).

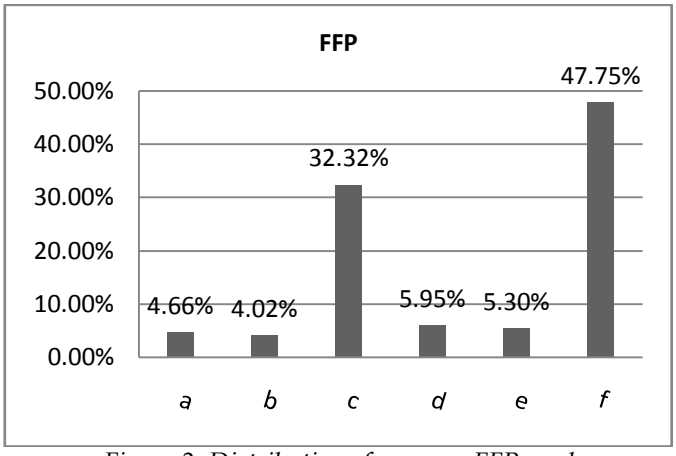

Figure 2. Distribution of one year FFP used

Table 2. Preparation of most often transfused blood products- RBC and PC

	Number of units	%
Transfusions	4208	
Leukocyte filtrated	1524	36,21 %
Irradiated and filtered	2157	51,25 %

From the blood products used in 2012, 58 RBC units and all platelet products obtained by apheresis where leukocyte depleted on CTST. All patients candidate to hematopoetic stem cell transplantation and also those with aplastic anemia received filtered and irradiated blood products. From all of blood units, 1524 (36,21 %) products were leukocyte filtered and 2157 (51,25 %) were irradiated and filtered (Table 2).

Our institutional transfusion registry and patients record files revealed a total of 20 adverse events: 8 febrile non-hemolytic transfusion reactions (FNTH), 5 allergic transfusion reactions (ATR), 6 acute hemolytic transfusion reactions (AHTR) and one transfusion-associated circulatory overload (TACO) (Table 3).

Table 3. Blood transfusion's reactions (%) (out of 4208 blood units)

Type of reactios	**FNHT**	**ATR**	**AHTR**	**TACO**	**Total**
Number of acute transfusion-related reactions	8 (0,2 %)	5 (0,11 %)	6 (0, 14 %)	1 (0,02 %)	20 (0,47 %)

Regarding the blood products involved in adverse reactions, RBC was the most frequently associated, representing 85 % of reactions, followed by platelet concentrates, 15 %.

Most of the unfavorable events occurred in patients who had not previously transfusions reactions, but we note that all of them have been multitransfused. We observed that all of events occurred mainly to those admitted on oncology department (Table 4).

Table 4. Correlation of the patient's diagnosis, type of blood used and adverse reactions

Age group	Patients number	Diagnosis/number of reactions	Blood product	Reaction type	Grade of severity/ number of reactions
> 18 years	2	Multiple myeloma (1) β thalasemia (5)	RBC	hemolysis	moderate (1) mild (5)
< 18 years	3	AM L M4 (1) AM L M5 (1) ALL (2)	PR-PC RBC RBC	rash exanthema exanthema TACO	mild (14)
	1	Hodgkin lymphoma (2)	RBC	chills chills, fever	
	2	βthalassemia (2)	RBC	chills chills, fever	
	3	Aplastic anemia (2) (1)	RBC SD-PC	chills chills, fever chills	
	1	Desmoplastic tumor (1)	RBC	rash	
	1	Ewing sarcoma (1)	SD-PC	rash	
	1	Neuroblastoma (1)	RBC	chills	

AML- Acute myeloid leukemia, ALL- Acute lymphoblastic leukemia

DISCUSSIONS AND CONCLUSIONS

Blood therapy is an important, frequent life-saving supportive treatment in oncology, hematology and intensive care. The appropriate use of blood components according to pre-defined policies helped to minimize complications, reducing their frequency and severity. The European Union (EU) (2012) set standards for collection, testing, processing, storage and distribution of human blood and blood components. Most of reactions consist of mild FNTR and ATRs. This is due to the fact that children have a great susceptibility to develop such events. The mild adverse reaction appear in 0,1 - 0,3 % of RBC transfused. Fortunately, the risk of infectious complications is almost absent, the majority of reactions, like in our experience, being minor (Table 5) [1, 3, 4].

Table 5. International Society Blood Transfusion (ISBT) grading of acute allergic reactions

Severity	1= mild	2= moderate	3= severe
Febrile type reaction	A temperature ≥ 38° C and a rise between 1-2° C from pretransfusion values, but no other symptoms/signs	A rise in temperature of ≥ 2° C, or fever ≥ 39°C and/or rigors, chills, other inflammatory symptoms/signs such as myalgia or nausea which precipitate stopping the transfusion	A rise in temperature of ≥ 2° C, rigors, chills or fever ≥ 39°C, or other inflammatory symptoms/signs such as myalgia or nausea which precipitate stopping the transfusion, prompt medical review AND/OR directly results in, or prolongs hospital stay
Allergic Type reaction	Transient flushing, urticaria or rash	Wheeze or angioedema with or without flushing/urticaria/rash but without respiratory compromise or hypotension	Bronchospasm, stridor, angioedema or circulatory problems which require urgent medical intervention AND/OR, directly result in or prolong hospital stay, or Anaphylaxis (severe, life-threatening, generalized or systemic hypersensitivity reaction with rapidly developing airway and/or breathing and/or circulation problems, usually associated with skin

			and mucosal changes
Reaction with both allergic and febrile features	Features of mild febrile **and** mild allergic reactions	Features of both allergic and febrile reactions, at least one of which is in the moderate category.	Features of both allergic and febrile reactions, at least one of which is in the severe category.
Hypotensive reaction		Isolated fall in systolic blood pressure of 30 mm or more occurring during or within one hour of completing transfusion **and** a systolic blood pressure 80 mm. or less in the absence of allergic or anaphylactic symptoms. No/minor intervention required.	Hypotension, as previously defined, leading to shock (e.g., acidaemia, impairment of vital organ function) without allergic or inflammatory symptoms. Urgent medical intervention required.

A study developed over 3 years, in France, including patients under 18 years of age, reported from 2165 transfusions, a proportion of 6,5% of adverse reactions assessed on pediatric patients. Mostly of them were allergic (48,2 %) and the clinical signs were cutaneous (70,6 %) and pulmonary (4,4 %). Regarding the severity of those events, one was severe (grade 2) and two were life-threatening (grade 3) [5].

From the non-infectious complications, TACO is a serious, under-recognized complex adverse reaction. It is important to raise awareness of it for early recognition and intervention [6].

From the immunological complications, transfusion associated graft versus host disease (TA-GVHD) can be expected transfusing HLA homozygous blood to HLA heterozygous patients. In Japan, 66 of the 290 patients included in study, developed TA-GVHD, supported with microsatellite DNA analysis. None was observed after the universal irradiation of blood components [7].

A 8 years Norwegian study assessed in 0,12 % of transfusion adverse reactions. Most of them were mild ATR and FNHR. From the transfusion-related infections, one bacterial and four viral transmitted diseases- hepatitis C, but no HIV or hepatitis B viruses have been reported. The Norwegian Hemovigilance System became consequently a part of their national and local guidelines [8].

It is largely accepted that under-reporting of minor symptoms determined by blood products is responsible for the low proportion transfusion-related adverse events.

The purpose of haemovigilance system is to identify complications related to transfusions, to analyze them and learn in order to avoid adverse reactions in the future. It is not a voluntary activity, being an authority task, according to the EU blood directive and reporting serious adverse events is mandatory. Improving and performing haemovigilance plays an important role in reporting blood products adverse events. Physicians awareness in hospital transfusion practice and analysis of those reactions, will help future reducing transfusion-related morbidity and mortality.

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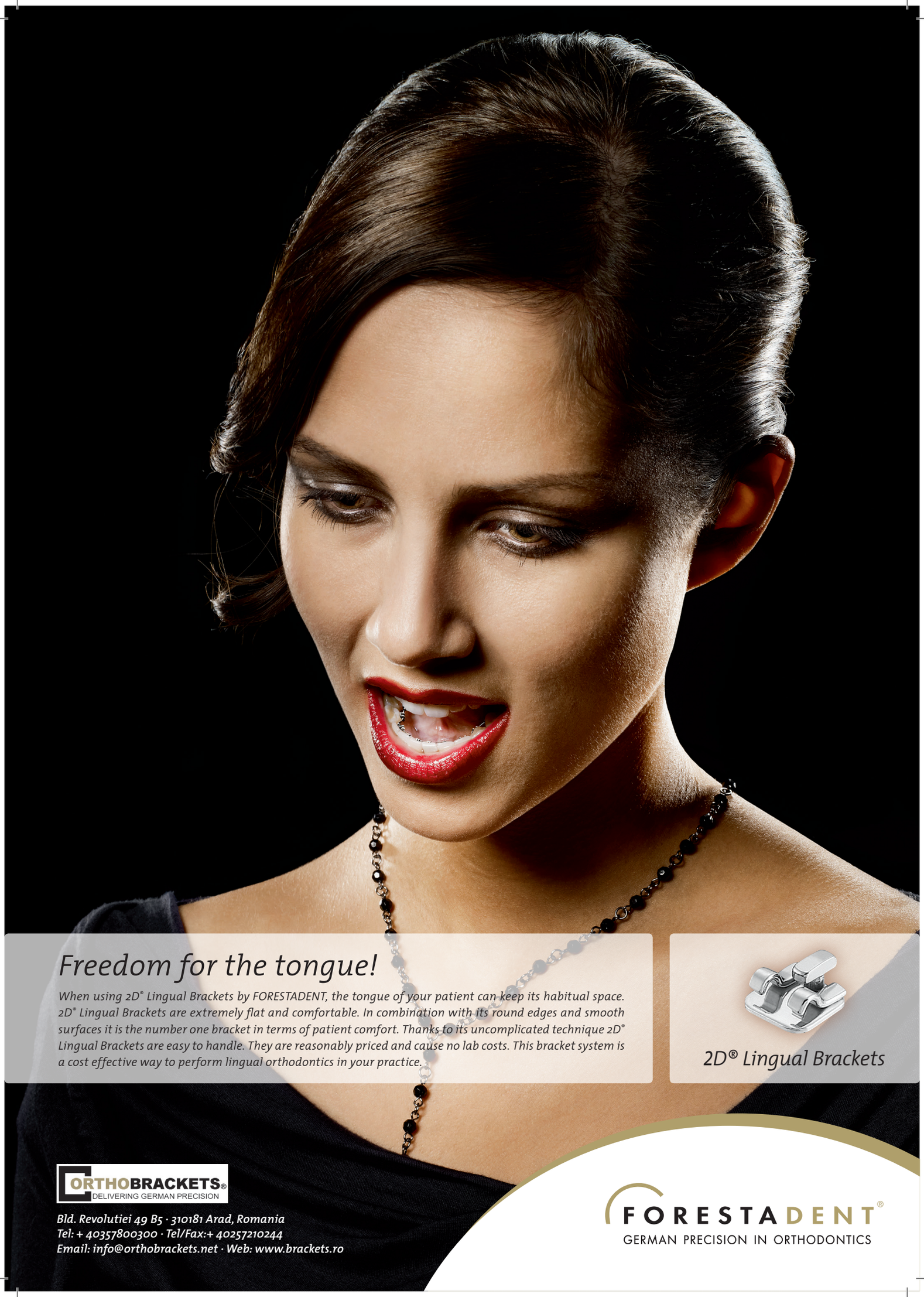
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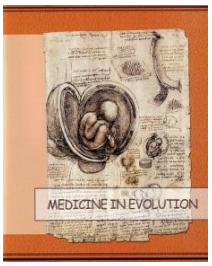
INCIDENCE AND PATTERNS OF BASAL CELL CARCINOMA IN ORAL AND PERIORAL REGION – RETROSPECTIVE STUDY



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ABSTRACT

Aim and objectives: *To determine the frequency and pattern of basal cell carcinoma(BCC) in oral and perioral soft tissue tumoral lesions with an emphasis on site and histological variant of BCC.*

Materials and methods: *We performed a descriptive, retrospective study on 1355 patients with oral and perioral soft tissue tumoral lesions admitted into the Oral and Maxillofacial Surgery Clinic of Timisoara between 2008 and 2010. This data was correlated with the histopathological findings for all benign and malignant tumors.*

Results: *Out of 1355 patients, 42.1% presented tumors of a malignant nature, 229 in the perioral skin. Basal cell carcinoma of the oral and perioral region was found in 190 patients (31.9%). The age range of the patients with BCC was between 24 and 92 years with a mean age of 70.41±11.68. The distribution of the subjects was: 59.4% female patients (mean age of 72.34±9.92)and 40.6% male patients(67.58±13.13), 46.8% patients from urban areas (71.51±10.52) and 53.2% patients from rural areas (69.45±12.58). The most common site of BCC was the perioral skin (92.11%), with the skin of the nose with the highest incidence (33.11%), cheek (22.3%), eye lids (13.7%) and the lowest incidence was in the skin of the zigomatic region (1.7%). The histological subtypes of BCC found were: nodulocystic(52.6%), diffuse (infiltrative) (25.8%), superficial (15.8%) and pigmented (5.8%).*

Conclusions*: In our study, basal cell carcinoma was the second most common tumoral lesion in the oral and perioral region, with the highest incidence in skin out of all malignancies. The most common sites were the nasal skin, the cheek and the eye lids. The incidence of BCC was higher in patients from the rural area and significantly higher in females than in males, females being affected at an older age. The most common subtype of BCC in the perioral region is the nodulocystic variant while the superficial variant of BCC affects younger patients.*

Key words: *oral and perioral region, descriptive study, basal cell carcinoma*

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INTRODUCTION

Basal cell carcinoma (BCC) is the most common form of malignancy [1] and the most common skin cancer in white population,[2][1][3][4][5]with 70% of primary BCC cases occurring on head and neck skin.[9]

Similar to other nonmelanoma skin cancers, its incidence is rising worldwide,[2][5]increasing by 3—6% each year in Europe, the U.S.A., Canada and Australia.[4]

Although the mortality due to BCC is low, due to its high prevalence, it is associated with substantial morbidity and represents a significant and costly health problem.[1][4]

The surgical treatment of BCC in the perioral skin is a surgical challenge due to its location, the likelihood of recurrence and its disseminating pattern, thereforerequiringa compromise between safe excision margins and obtaining a satisfactory cosmetic result.[2][7]

The aim of our study on benign and malignant tumoral soft tissue lesions in the oral and perioral regions was to determine the frequency and patterns of basal cell carcinoma in oral and perioral soft tissue tumoral lesions with an emphasis on the siteand histological variants.

MATERIALS AND METHODS

We performed a descriptive, retrospective cross-sectional study on patients with oral and perioral soft tissue tumoral lesions admitted into the Oral and Maxillofacial Surgery Clinic of Timisoara between 2008 and 2010. The study included a total of 1355 patients aged between 1 and 95 years, males and females, from rural and urban areas. In our study we analyzed data from the patients' medical records and histopathological findings. From the hospital database we extracted data on all patients registered between January 2008 and December 2010 with tumoral lesions of the soft tissue in the oral and perioral regions. This data was correlated with the histopathological findings for all benign and malignant tumors. A report was made that included the following parameters for each patient: gender, age, social background, tumor location, histopathological diagnosis.

The patients had incisional or excisional biopsy performed in the Oral and Maxillofacial Surgery Clinic of Timişoara. The diagnoses were confirmed by the histological exam of the specimens in the Laboratory of Pathology - Municipal Hospital of Timisoara.

RESULTS

In the 3 year period, 1355 patients with oral or perioral soft tissue lesions were admitted in our clinic with an age range between 1 and 95 years. The distribution of patients on the clinical and histopathological exam of the tumoral lesions was: 597 of a malignant nature (44.05%) and 758 of a benign nature (55.95%).

In our study, the histological types of the malignant tumoral lesions of soft tissue in oral and perioral regions were: 334 patients with squamous cell carcinoma (SSC) (56%), 190 patients with basal cell carcinoma (BCC) (31.9%), 12 with malignant melanoma(2%), 10 with lymphomas (1.7%), 9 with mucoepidermoid carcinoma (1.5%), 7 with adenocarcinoma (1.2%), 5 with adenoid cystic carcinoma (0.8%), 4 with anaplastic carcinoma (0.7%), 5 with

malignant pleomorphic adenoma (0.8%), 2 with sebaceous carcinoma (0.3%), and 2 with small-blue-round-cell carcinoma (0.3%), 2 with mioepitelioma (0.3%), 2 with malignant fibroushistiocytoma (0.3%) and one with Merkel cell carcinoma, one accinar cell carcinoma, one metatypic carcinoma, one pleomorphic sarcoma, one chondrosarcoma, one papillary thyroid carcinoma, one multiple myeloma and one hemangiopericytoma.**(Table 1)**

The number of patients with BCC on each year of our study was: 93 patients in 2008, 52 patients in 2009 and 45 patients in 2010 with an overall age range between 24 and 92 years. In the 3 year period,113 patients were female (59.5%) with a mean age of 72.34±9.92years and 77 patients were males (40.5%) with a mean age of 67.58±13.13 years while the overall mean age was 70.41±11.68 years. The distribution of patients with BCC on social background was: 89 patients (46.8%) from urban areas(71.51±10.52) and 101 patients (53.2%) from rural areas (69.45±12.58).(**Table2**)

Table 1. Histological types of malignant tumoral lesions of oral and perioral region

SSC	334	56%
BCC	190	31.9%
malignant melanoma	12	2.0%
lymphomas	10	1.7%
mucoepidermoid car.	9	1.5%
adenocarcinoma	7	1.2%
other	35	5.7%
Total	597	100%

Table 2. Patients with BCC distribution on gender and social background

	Female	Male	Total
Urban	49	40	89
Rural	64	37	101
Total	113	77	190

As for the location of the BCC in the oral and perioral region, the distribution of cases was: 175 in the perioral skin (92.11%) (mean age 70.58±11.87) with the highest incidence, 13 in the connective tissue (6.8%) (mean age 68.92±9.66), one in the gingiva(0.5%) (61 years old) and one in the palate (0.5%) (70 years old). **(Table 3)**

When we appliedthe unpaired t-test for the data in table 3 we found that the age for female patients is significantly higher for overall BCC (with 0.01 level of significance) and for BCC of the skin (with 0.01 level of significance) and for the BCC of the connective tissue(with 0.05 level of significance).

The distribution of cases of BCC of the skin was: 58 in the skin of the nose (33.1%)(mean age 71.34±9.92), 39 in the skin of the cheek (22.3%)(mean age 70.25±11.72), 24 in the eye lids (13.7%)(mean age 64.54±16.41), 20 in the lip (11.4%)(mean age 77.15±10.81), 11 in the skin of the frontal region (6.3%)(73.91 ±8.03), 8 in the skin of the temporal region (4.6%)(mean age 72.75±7.67), 8 in the skin of the ears (4.6%)(mean age 65.13±15.35), 4 in the skin of the chin (2.3%)(mean age 65±8.76) and 3 in the skin of the zigomatic region (1.7%)(mean age 68±3.61). (**Table 4**)

Table 3. Location of BCC and mean age for each gender

	Male		Female		Total		p^{sign}
Skin	72	67.93±13.66	103	72.43±10.11	175	70.58±11.87	0.013^{s}
Connective tisssue	5	62.60±9.07	8	72.88±8.15	13	68.92±9.66	0.057^{s}
Palate	0		1	70	1	70	
Gingiva	0		1	61	1	61	
Total	77	67.58±13.13	113	72.34±9.92	190	70.41±11.68	0.006^{s}

Table 4. Distribution of the BCC of the skin

Region	**Male**		**Female**		**Total**		$\mathbf{p^{sign}}$
Frontal	5	71.40±10.26	6	76±5.76	11	73.91 ±8.03	0.372^{ns}
Cheek	11	67.82±15.39	28	71.25±10.10	39	70.25±11.72	0.418^{ns}
Temporal	4	76.75±8.26	4	68.75±5.12	8	72.75±7.67	0.151^{ns}
Eye lids	10	57.80±18.94	14	69.36±12.98	24	64.54±16.41	0.089^{ns}
Ears	4	66.25±14.95	4	64±17.96	8	65.13±15.35	0.854^{ns}
Zigomatic	2	67	1	68.50±4.95	3	68±3.61	0.846^{ns}
Nose	24	67.79±10.32	34	73.85±8.96	58	71.34±9.92	0.021^{s}
Lip	10	75.90±13.39	10	75.90±13.39	20	77.15±10.81	0.618^{ns}
Chin	2	57.50±2.12	2	72.50±0.71	4	65±8.76	0.011^{ss}

Legend: ^{ns} *– insignificant difference*

^{s} *– significant difference*

In our study we found the following histological subtypes of BCC: nodulocystic basal cell carcinoma in 100 patients (52.6%)(mean age 70.03±10.16), diffuse (infiltrative) basal cell carcinoma in 49 patients (25.8%) (mean age 73.39±12.13), superficial basal cell carcinoma in 30 patients (15.8%) (mean age 67.77±15.8) and 11 cases of pigmented basal cell carcinoma (5.8%) (mean age 67.82±11.23).(**Table 5**)

Table 5. Histopathological subtypes of BCC

Histological variant	**Incidence**	**Percent**	**Mean age**
nodulocystic basal cell carcinoma	100	52.6%	70.03±10.16
diffuse (infiltrative) basal cell carcinoma	49	25.8%	73.39±12.13
superficial basal cell carcinoma	30	15.8%	67.77±15.8
pigmented basal cell carcinoma	11	5.8%	67.82±11.23
Total	**190**	**100%**	**70.41±11.68**

DISCUSSIONS

Soft tissue tumors account for less than 1% of all tumors, the annual incidence of soft tissue tumors being approximately 300 per 100,000 people in the general population.[10]

Basal cell carcinoma (BCC) is the most common skin cancer in white population.[1][2][3][4][5], accounting for about half of all cancers and approximately 80 percent of all non-melanoma skin cancers.[6] The incidence of BCC is rising worldwide with850 000 new cases occurring each year only in USA.[1][3][6]

Despite its very high prevalence, BCC is generally a low-grade neoplasm,[2] slow-growing asymptomatic tumor,[1] locally invasive malignant epidermal skin tumour predominantly affecting caucasians. The tumour infiltrates tissues in a three-dimensional fashion through the irregular growth of subclinical finger-like outgrowths which remain contiguous with the

main tumour mass. Metastasis is extremely rare while morbidity results from local tissue invasion and destruction particularly on the face, head and neck.[5]

This substantially rising in incidence during the past two decades, which may reflect an increase in recreational sun exposure. A further absolute increase is expected because of the aging of the population and greater exposure to solar ultraviolet radiation due to depletion of the ozone layer.[1]

In our 3 year retrospective study we found that a number of 190 patients with BCC of the oral and perioral region. The histology of malignant tumors in our study revealed that BCC was the second most common type of cancer in the oral and perioral region affecting 31.9% of patients out of all 597 malignant tumoral lesions of the oral and perioral soft tissue tumors while squamous cell carcinoma was the most common with 56% of all malignancies. The patients with BCC in oral and perioral soft tissue included in our study had a mean age of 70.41±11.68 higher than the mean age for SCC (64.08±12.80).

The small percentage of BCC compared to SCC may be explained by the fact that our study focused on the tumors of the oral mucosa and also the tegument and the soft tissue of the perioral region.

In our study 175 patients had BCC of the skin that represents 76.42% out of 229 patients with malignant tumors of the perioral region skin. Our data suggests that BCC is the most common malignancies of the skin in the perioral region.

The female were more affected by BCC than men, both in rural and in urban area, with a male to female ratio of 0.68:1 compared to 1.54:1 the ratio for all malignant tumors. Many studies report higher incidence of BCC among men, although patients with this diseaseare increasingly likely to be young women.[6][9]

The mean age for BCC in men was overall significantly lower than in females 67.58 to 72.34 (with 0.01 level of significance). In the group of patients with BCCof the skin the age for female patients is significantly higher than in men (72.43 to 67.93) (with 0.01 level of significance).This is the case in almost all specific locations except for the BCC of the ears and that of the temporal region skin where the mean age for male patients is insignificantly higher than that of female patients ($p>0.05$).

The most significant risk factors for BCC are genetic predisposition and exposure to ultraviolet radiation.[5]Ultraviolet (UV) radiation from sunlight exposure has been accepted as the primary etiological factor for developing BCC [1][4].Lots of studies concluded that light hair and eye color, north European ancestry and a skin that burns easily and tans poorly associated with intermittent recreational sun exposure during childhood and adolescence, characterized by infrequent, intense increments, sunburns increases BCC risk more than a similar dose delivered more continuously [6][1].

Other recognized risk factors include exposure to ionizing radiation, increasing age, male sex, fair skin types I and II, immunosuppression, exposure to chemical carcinogens like arsenic, a high dietary fat intake and possibly infection with human papillomaviruses, [4][5][9] while cigarette smoking doesn't increase the risk of BCC. [1]

In our study the incidence of BCC in patients from rural areas (53.2%) is higher than in those of urban origin with a lower mean age, 69.45±12.58 compared to .71.51±10.52. The higher incidence in the rural area and an earlier appearance of the BCC might be explained by prolonged exposure to the sun during agricultural activities.

Regarding the site of BCC of the skin, we found that the nose was the most common (33.19%), followed by

the chic (22.3%) and the eye lid (13.7%), and the lowest incidence of BCC was in the skin of the zigomatic region (1.7%). Our finding is similar to other studies with nose, cheek, eyelid and temple as location with higher risk of developing BCC.[9]

Although BCC can be locally invasive and destructive, it rarely metastasizes and is readily amenable to excisional management.[2] BCC occurs predominantly on the head and neck[4] and is particularly concerning because of the often cosmetically delicate location.[2][4][9]

Location of BCC at the midface or ear is associated with a more aggressive clinical course. The significantly higher recurrence rate is due to the proximity of the nasal and orbital skin to the bone and cartilage.[9] Clinical appearances and morphology of different subtypes of BCC are diverse. They include nodular, cystic, superficial, morphoeic (sclerosing), keratotic and pigmented variants,[5] with certain types like morpheaform, infiltrative and sclerosing that tend to be aggressive, likely to recur, or to have positive margins at excision.[3]

Regarding the histological subtypes of BCC, in our study, nodulocystic variant had the highest incidence (52.6%), followed by diffuse(infiltrative) variant (25.8%) and superficial (15.8%), while pigmented variant had the lowest incidence, just 5.8%.The mean age for patients with superficial BCC is the lowest compared to all other variants (67.77±15.8).These findings are comparable with other studies which state that the nodular, superficial spreading, and infiltrating variants are the 3 most commonly encountered types of BCC in descending order of prevalence. [2] The nodular BCC predominantly occurs on the head and neck, while patients with superficial BCC are significantly younger than patients with other BCC subtypes.[4] Nodular and superficial variant of BCC tends to be less aggressive.[9]

Surgical excision with either intraoperative or postoperative histological assessment of the surgical margins is a highly effective treatment for primary BCC with a recurrence rate of less than 2% following histologically complete excision or with 30% to 41% recurrence rate following histologically incomplete excision.[5]Due to the fact that BCC of the head and neck has one of the highest recurrence rates of anyBCC, appropriate diagnosis and therapy are essential.[2] The surgical treatment of BCC in the perioral skinis a surgical challenge due to its location, the likelihood of recurrence, and its disseminating pattern therefore requiringa compromise between safe excision margins and obtaining a satisfactory cosmetic result.[2][7]This is also a cosmetically sensitive site, which may result in an inadequate early treatment.[9]The surgeon should preserve the maximum amount of normal surrounding skin, but completely remove the tumour with standard wide margins of 4 mm, or have Mohsmicrographic surgery for histologic margin control, in order to avoid repetitive operations and the risk of recurrence in anatomically sensitive areas. [8][7]

When the surgical excision and the wound repair is performed by an experienced surgeon, the overall cosmetic results are generally good.[5].

CONCLUSIONS

In our study, basal cell carcinoma was the second most common tumoral lesion in the oral and perioral region, with the highest incidence of all malignancies of the skin. The nasal skin, cheek and of the eye lids are the most common affected sites. The incidence of BCC was higher in patients from the rural area and significantly higher in females than in

males, females being affected at an older age. The most common subtype of BCC in the perioral region is the nodulocystic variant while the superficial variant of BCC affects younger patients.

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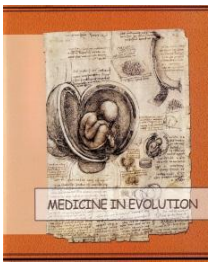
EARLIER ERUPTION OF SECOND PERMANENT MOLAR



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ABSTRACT

Aim. *To analyze the frequency of earlier eruption of second permanent molar (SPM) in children aged 9 and 10 years.*

Material and method. *A cross-sectional study on a sample of 450 children (227 boys) aged 9 and 10 years attending Pediatric Dentistry Department was performed. The frequency of earlier eruption of SPM and the eruption sequence of canines and premolars were assessed.*

Results. *15.77% of all children had already at least one SPM: 11.59% (9 years), 19.34% (10 years). The earliest age for SPM eruption was 9 year and 1 month for both sexes. 12.22% of lower SPM and 3.88% of upper ones had earlier eruption.*

Conclusions. *1) Earlier eruption of SPM was more frequently associated with the presence of second premolar 2) Earlier eruption of SPM necessitates both individualization of caries prevention measures and greater attention concerning the space for eruption of permanent canines and premolars.*

Key words: *Second permanent molar, earlier eruption*

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INTRODUCTION

The eruption of permanent teeth occurs in two stages: in the first stage (6-9 years) permanent first molars and incisors erupt, and in the second stage (between 9 and 12-13 years) - canines, premolars and second permanent molars. Classically, it is described that the second stage of the eruption ends with the second permanent molar (SPM) eruption [1-3]. Studies show that there is great variability in the order of the canines and premolars eruption, but not in terms of SPM, which erupt around the age of 12 years.

In a longitudinal study conducted upon a group of Caucasian children, Kochhar and Richardson (1998) reported that the mean age for SPM eruption was: 12.09±1.10 years in boys and 12.14±1.11 years in girls for the upper jaw and 11.80±1.06 years in boys and 11.89±1.15 years in girls for the lower jaw [4].

The eruption is considered physiological if the eruption interval is within the range of + / - twice the standard deviation of the average age of eruption (calculated on large populations). Standard deviation in the permanent dentition is +/- 6 months for teeth that erupt earlier (incisors and first molars) and up to +/- 1.5 years for teeth that erupt later (canines, premolars, second and third molars). The eruption is considered accelerated/delayed if is outside this range limit (Kreiborg et al, 1991, quoted by [1]).

In patients referred to Pediatric Dentistry Department we can observe a high frequency of children aged 9 and 10 with SPM already erupted. Also there are a large number of children aged 12 with caries lesions in these teeth.

Aim and objectives

The aim of this study was to analyze the frequency of earlier eruption of SPM in a group of children aged between 9 and 10 years, and the order of eruption of the canines and premolars in these children.

MATERIAL AND METHODS

A cross-sectional study on a sample of 450 children (227 boys, 223 girls) aged between 9 years and 10 years, 11 months (mean age = 10.05±0.59 years) referred to Pediatric Dentistry Department, Carol Davila University Bucharest during January 2009 – December 2010 was performed. 207 children (101 boys) aged 9 years and 243 children (126 boys) aged 10 years were examined (fig. 1).

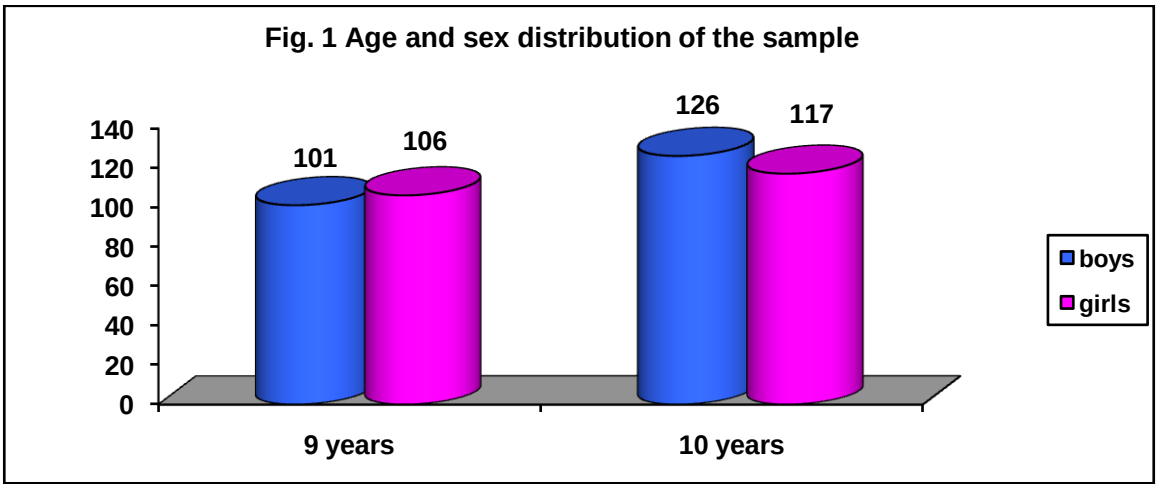

Figure 1. Age and sex distribution of the sample

Only children without growth or congenital anomalies or severe medical conditions were included in the study. Also, for the homogeneity of the sample, only Caucasian children were taken into account.

Children were examined in dental office by one pediatric dentist (A.M.). No X-ray examination was taken. In each patient were noted: all erupted teeth, type of dentition (mixed or permanent) and the presence of treated and untreated caries.

The frequency of earlier eruption of SPM both for the entire sample and separately for children aged 9 years and for children aged 10 years was determined. Also, the distribution of children with early eruption of SPM according to sex was analyzed and the eruption sequence of canines and premolars was assessed.

Data were statistically analyzed using Mann-Whitney test ($p<0.05$).

RESULTS

Among children aged 9 to 10 years examined, 88.22% had mixed dentition (91.30% at 9 years, 85.59% at 10 years) and 11.78% had already only permanent dentition (8.70% at 9 years and 14.40% at 10 years).

Of the 450 children from the study, in 71 children (representing 15.77%) at least one SPM was erupted. For children aged 9 years, 24 of them (11.59%) had at least one SPM erupted and for children aged 10 years the number was double – 47 (19.34%) (SS, $p<0.05$) (fig. 2).

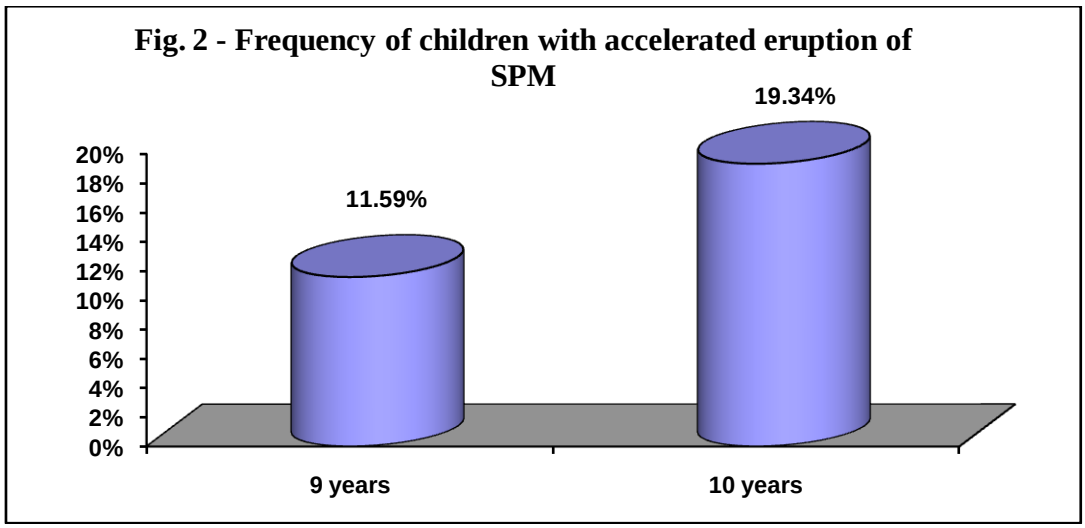

Figure 2. Frequency of children with accelerated eruption of SPM

T Regarding sex distribution, at the age of 9 years 15% of girls and about 8% of boys had at least one SPM, but differences were not statistically significant. At the age of 10 years, the percentages were almost equal (19%) (table I).

The earliest age at which SPM were noticed was 9 years and 1 months both in boys and girls. Mean age of children with erupted SPM was 10.27±0.56 years (table II).

At the age of 9 years, 2.77% of all SPM were erupted and at the age of 10 years -5.27% of SPM.

More frequently SPM were erupted in the lower jaw – 12.22% comparing to the upper jaw – 3.88% (SS, $p<0.001$).

59.15% of children with early eruption of SPM had mixed dentition and 40.85% had already permanent dentition (Table III).

Table I. Earlier eruption of SPM according to age and sex

	Erupted SPM				p
	Boys		Girls		
	n	%	n	%	
9 years	8	7.92%	16	15.09%	NS
10 years	24	19.04%	23	19.65%	NS
Entire sample	32	14.09%	39	17.48%	NS

Table II. Distribution of patients with early eruption of SPM according to the number of SPM erupted

No. of SPM	No. of patients			Mean age (years)
	Total	Boys	Girls	
1	27	16	11	10.31±0.45
2	25	6	19	10.11±0.61
3	8	2	6	10.22±0.80
4	11	8	3	10.55±0.45
Total	71	32	39	10.27±0.56

Table III. Distribution of patients with early eruption of SPM according to age and type of dentition

Age (years)	Total (n)	Mixed dentition		Permanent dentition	
		n	%	n	%
9	24	12	50	12	50
10	47	30	63.83	17	36.17
Entire sample	71	42	59.15	29	40.85

Children with early erupted SPM in mixed dentition still had between 1 and 12 primary teeth, with an average number of 2.10±2.74 teeth. Most common, both second primary molars and primary canines or only second primary molars were still present.

Regarding the order of eruption of permanent teeth in canine-premolars area, on the hemiarch with SPM, in most cases (72.41%) canine and the two premolars were erupted, followed by canine and first premolar – in 11.03% of cases. Referring strictly to the presence of second premolars in hemiarch with SPM, in 80.69% of cases second premolars was present, in 15,86% of cases second primary molars was still present and in a percentage of 3.45% primary tooth was exfoliated but the permanent tooth did not yet erupted. The appearance of SPM was 2.1 more frequently associated with the presence of second premolar (p=0.006).

In 2 children with earlier eruption of lower SPM, first permanent molars were extracted. It is important to mention that 93.12% of all examined children had carious lesions on first permanent molars and/or primary teeth.

DISCUSSION

The most commonly used parameter for assessing dental maturity has always been the assessment of dental eruption because it is both rapid and convenient. Historically, the first use of eruption as a maturity indicator is recorded in England 1837, and it was stipulated that a child without a second permanent molar would not be allowed to work in factories. Since that time dental criteria were used as an indicator of maturity for school purposes (Demirjian, 1976 cited by [3]).

Knowledge related to the chronology and sequence of dental

eruption is essential for establishing a standard criterion for dental and preventive healthcare, as well as for diagnosis and treatment of children [2]. Also, age estimation is an important activity that is frequently required to be carried out in medico legal work [5, 6].

In this study group it was observed a high percentage of children with early eruption of SPM - 11% in children aged 9 years and almost 20% in children aged 10 years. This aspect highlights the importance of individualizing caries preventive strategies for children. Thus, given that over 90% of children with early eruption of SPM had treated or untreated caries on first permanent molars and/or deciduous teeth, it is essential to seal early erupted SPM soon after eruption to avoid the appearance of carious lesions at this level, given the low degree of maturation of their crowns. A study conducted by King et al (1980) on a sample of 1104 children aged 11-12 years examined annually for a period of three years, with a mean age of eruption of SPM of 12.2 years showed that one year after the eruption 45% of SPM had already carious lesions. At age of 15 years, 68% of SPM had treated or untreated caries or were extracted because of caries [7].

There is an agreement from studies on teeth emergence that permanent teeth erupt earlier in girls than in boys [5, 8]. Earlier eruption of permanent teeth in females is attributed to earlier onset of maturation [9]. Only one study reported earlier emergence of second molars in boys than in girls and explained this phenomenon as a catch-up development by the age of eruption of second molars even if the onset of puberty in the males is later [4]. In present study, earlier eruption of SPM was observed more frequently in girls than in boys at the age of 9, but differences were not statistically significant.

The earliest age at which SPM were observed was 9 years and 1 months both for boys and girls. These results differ somehow from those reported by Ekstrand et al. (2003), who found in a group of 112 Danish children that the eruption time for girls varied from 8 years and 11 months to 14 years and 4 months (mean 11.3 years) and for boys from 9 years and 11 months to 13 years and 11 months (average - 12.0 years) [8].

When the maxillary and mandibular arches are compared, previous studies have shown that for both genders mandibular SPM erupted before the maxillary ones, the differences being statistically significant [2, 4, 5]. The same results have been obtained in our study also.

Regarding the percentage of SPM with earlier eruption, in the present study at the age of 9 years 2.77% of SPM were erupted and at the age of 10 years – 5.27%. In a research conducted by Skeie et al. (2006) on a sample of 186 children aged 10 years from Norway, it was found that 3.6% of SPM were already erupted [10].

Among local factors that could influence the eruption of SPM is quoted primary molars and first permanent molars early loss [3, 11]. In present study, only in 2 cases early eruption of SPM associated with the extraction of the lower first permanent molars was noted. In change, in almost 80% of cases, on the hemiarch with SPM second primary molar was already replaced by the second premolar.

Furthermore, in this study more than half of children with earlier eruption of SPM had mixed dentition and in 20% of cases on the hemiarch with SPM second primary molar was still present or was exfoliated without the appearance of second premolars. The appearence of SPM before second premolars eruption cause a significant reduction in space for canine-premolars eruption because SPM

migrate mesial during the eruption process [12].

Earlier eruption of SPM, occurred more frequently in girls and favored by the early loss of second primary molars, is a phenomenon that requires attention because of the risk of the occurrence of caries and scarcity of space in the canine – premolars area.

CONCLUSIONS

1) For both sexes, the earliest age at which SPM were observed was 9 years and 1 months and the mean age of children with erupted SPM was 10.27±0.56 years; 2) the earlier eruption of SPM was more frequently in lower jaw and was more frequently associated with the presence of second premolar; 3) earlier eruption of SPM necessitate both individualization of caries prevention measures at this level and a greater attention concerning the space for eruption of permanent canines and premolars.

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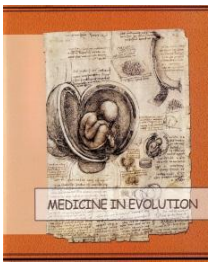
IMAGISTIC EVALUATION OF THE CERAMIC FIXED PARTIAL PROSTHESIS



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ABSTRACT

The common investigations methods of fixed partial dentures imply sectioning and metallographic microscopic analysis. These methods could lead to damage of the small dimension material defects.

Purpose: *This paper aims to provide information related to the possible help of some imagistic investigation methods such as Rx, microscopy and transillumination for the fractures and materials defects detection inside the ceramic layers of different dental constructs.*

Material and Methods:*Rx, noninvasive microscopy and transillumination methods were employed in order to evaluate the fracture lines and the material defects from the ceramic layers of metal ceramic and integral ceramic dental prosthesis.*

Conclusion:*The transillumination method along with the Rx evaluation can be very helpful methods in evaluation the quality of different ceramic fixed prosthetic constructs.*

Key words: *metal ceramic, integral ceramic, transillumination, noninvasive microscopy, Rx*

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INTRODUCTION

All ceramic and metal ceramic fixed partial prosthesis are the dedicated for the esthetic dental treatments. However there are only few methods dedicated for in vivo and ex vivo non evaluation.

The common investigations methods of fixed partial dentures imply sectioning and metallographic microscopic analysis. These methods could lead to damage of the small dimension material defects. Also these methods are limited to the dimensions of the cutting devices [1, 2].

Noninvasive research methods are very useful in characterizing the infrastructure of the fixed partial brides, due to the possibility of using the support after the evaluation in order to make a good and much more resistant dental bridge.

One of these characterizing methods is the penetrating liquids method. This method allows discovering the materials defects of the infrastructure, but only the ones that are connected to the surface. The method is based on the flowing property of the liquids. In order to discover the defects in the dental bridge infrastructure, a penetrating liquid, containing three sprays chit is used. The first spray is used for cleaning the surface of the fixed partial denture. The second spray contains the penetration liquid. This one is going to fill all the materialimperfections of the bridge. The last spray contains the revelator liquid and this one reveals the areas where the defects are. In the first phase, the bridge is cleaned by using the first spray. The reason for this action is that the little particles of dust can obdurate the access of the liquid in the defect areas. After this first phase, the bridge needs to be dried in order to use the second spray. Using the second spray is the next step in this procedure. Between the second and the third spray, a break of ten minutes must be made to permit the penetrating liquid to fill all the defects of the structure. After this break, the excess of the penetrating liquid is cleaned out. Afterwards, the revelator liquid is used to point out the areas with material discontinuities. The penetrating liquids method is a nondestructive method used for evaluating the continuity of the materials from which the dental works are made. By using this method, every defect zone that has any connection to the surface of the bridge can be revealed. The cost of this method is very low and the results are obtained rapidly and accurate. However, for the defects that are included in the core of the fixed partial dentures, this method has no applications. [2].

Aim and objective

This paper aims to provide information related to the possible help of some imagistic investigation methods such as Rx, microscopy and transillumination for the fractures and materials defects detection inside the ceramic layers of different dental constructs.

MATERIAL AND METHODS

Ten metal ceramic single crowns, twenty metal ceramic fixed partial prosthesis and twenty five integral ceramic fixed partial prosthesis were used for this study. The Love System (Degudent) was used for the metal ceramic samples. This system is characterized by: two phases: Leucite phase and glass phase; innovative production process; ultra-fine microstructure; homogenous distribution of the leucite and glass phases; elevated firing temperature, in the range of the classic metal veneering

ceramics (first dentine firing at 900°C); high strength (95 MPa); optimized surface homogeneity and stability of the CTE. IPS e.max Press ceramic system (Ivoclar) was used for the all ceramic fixed partial prosthesis. These ingots have been developed on the basis of a lithium silicate glass ceramic. The ingots are produced by bulk casting. A continuous manufacturing process based on glass technology (casting/pressing procedure) is utilized in the manufacture of the ingots. This new technology uses optimized processing parameters, which prevent the formation of defects (pores, pigments, etc) in the bulk of the ingot.

The microstructure of IPS e.max Press consists of lithium disilicate crystals (approx. 70%), $Li_2Si_2O_5$, which are embedded in a glassy matrix. Lithium disilicate, the main crystal phase, consists of needle-like crystals. The crystals measure 3 to 6 µm in length.

The microscopic evaluation was performed by AM-4000 Series Dental Microscope (Alltion, China). The lenses inside the microscope are made by Schott ® Optical Glass imported from Germany. All lenses are multi-coated and anti-reflective, combining with infinity corrected optical system and brilliant apochromatic optics, which offers a good optical performance, including: high resolution, real 3-dimensional precise image reproduction, large depth of field, wide field of view and good contrast. Apochromatic optics design could correct the chromatic aberration of three types of colored light effectively. It ensures the reduction and saturation of image color and improves the resolution, contrast and view depth of image (Fig.1, a).

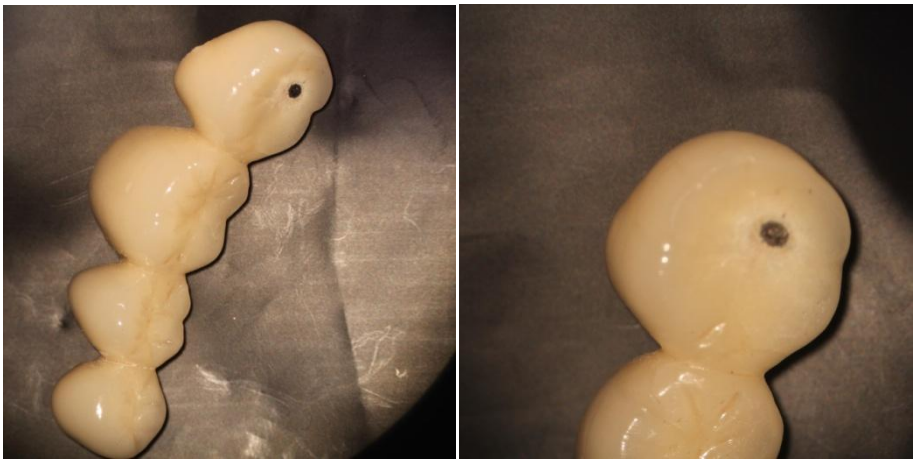
The Rx investigation was performed by using the Fona X 70. Main feature of the system is the great energyoffering obtained by combining the voltage potentialof 70 kVp and the anodic current of 7 mAwith a widerange of exposure times, from 60 ms to 3.2 s.The penetration power of the radiation beam at 70 kVpgrants sharp images with good radiographic contrast foroptimal detail perception. The microprocessor in the timer assures consistent filmblackening in a wide range of operating conditions.The AutoSet timer has a flat keyboard and is microprocessor controlled. Itfeatures automatic setting of exposure time from 60 ms to 3.2 s throughobject programmed selection according to tooth type and patient size. For the study the 3.2 s setting exposure was selected (Fig.1, b).

a b

Figure 1. The microscopic evaluation was performed by a professional dental microscope (AM-4000, Alltion, China - a) and the rx investigations with Fona X 70 (b)

The possible defects were investigated with the DIAGNOcam using the transillumination method. In contrast to conventional technology with an interdental light source, DIAGNOcam practically uses the entire tooth as a light propagation medium. At places where there is a possible defect which blocks light propagation, a shadow is aspect to be produced. This is captured by an integrated video camera that relays the images in real-time to the computer screen. The device is equipped with a lighting laser diode, with a wavlenght of 780 nm and an optic power of 15 mW.

RESULTS



a *b*

Figure 2. Defect identified inside of the ceramic layer on the occlusal surface of the second mandibular molar of the metal ceramic fixed partial prosthesis: a. an overall aspect of the defect after the opening the defect using a conventional drilling device; b. detail of the defect that affect all the ceramic occlusal layer and touch the metal component of the retainer

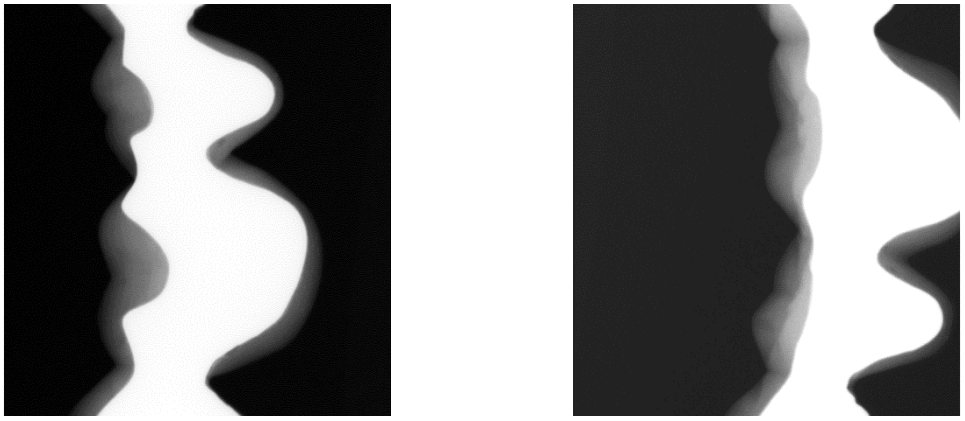


Figure 3. Rx of the sample from the fig.1: the defect observed there is impossible to detect on the Rx investigation because of the scattering light from the metal infrastructure. The area of interest is pointed out by the arrows

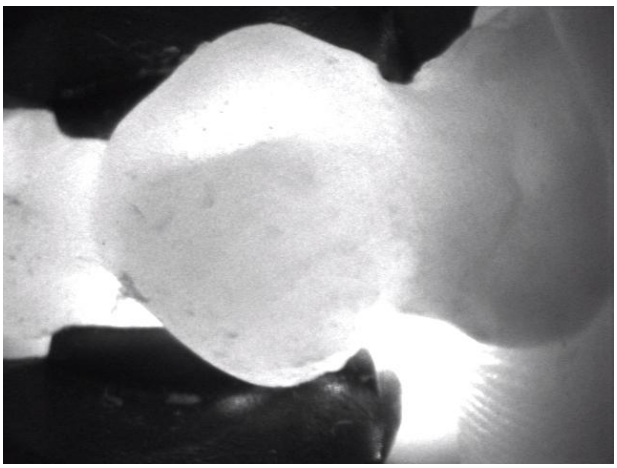
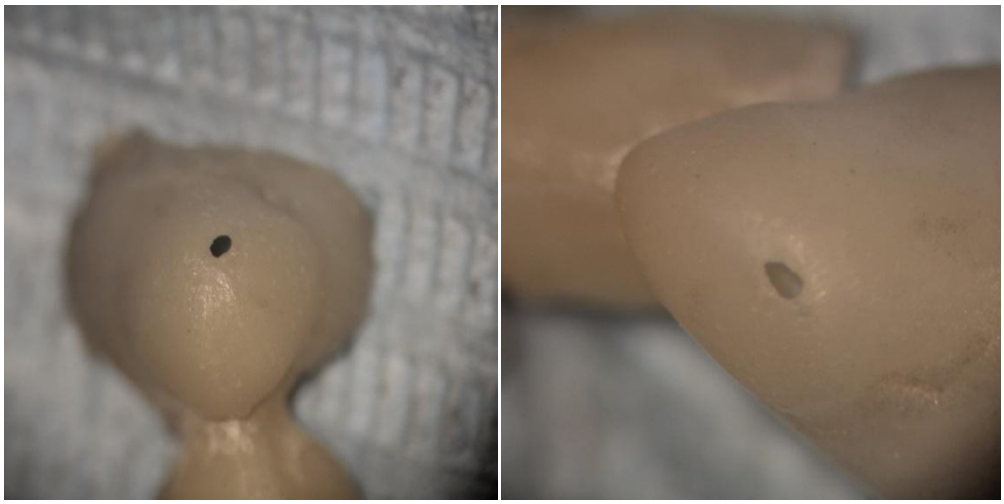


Figure 4. No defect was revealed by the transillumination method



a *b*

Figure 5. Defect observed on the frontal integral ceramic fixed partial prosthesis; this defect affects the entire ceramic layer along with the retainer: a. occlusal view of the defect; b. proximal aspect of the defect; also it is possible to observe fracture line in the ceramic layer

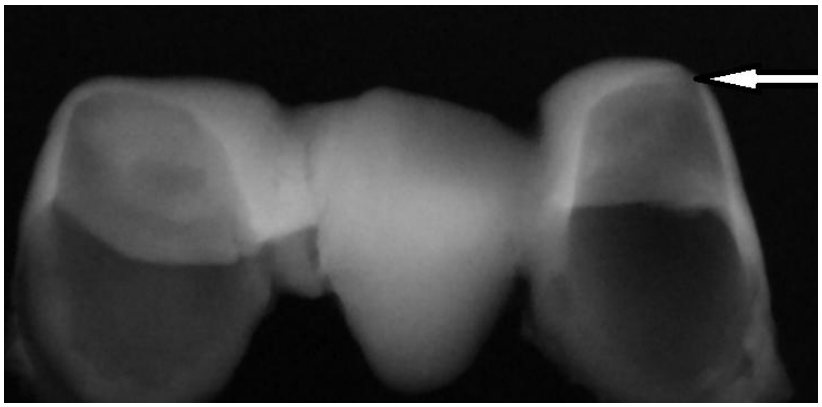


Figure 6. Rx of the sample from the fig. 5: the defect presented is identified on the Rx investigation (white arrow)

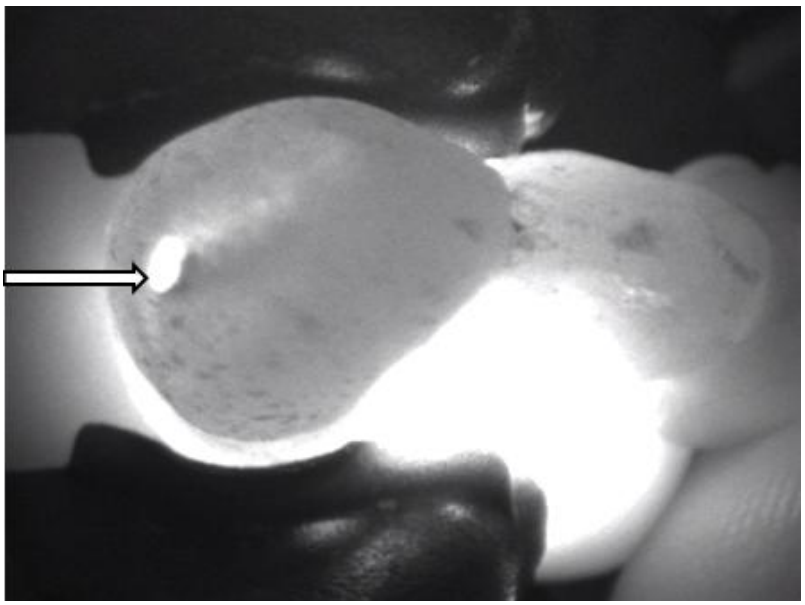


Figure 7. The defect revealed by the transillumination method

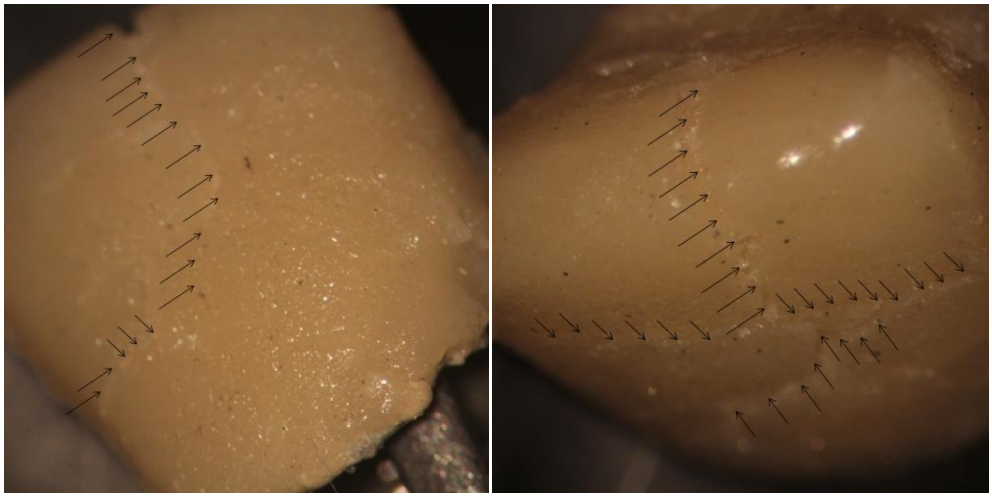


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Figure 8. Fracture lines depicted on the vestibular and incisal area of the metal ceramic incisor before the final sintering: a. vestibular aspect of the ceramic incisor with the fracture lines (arrows)

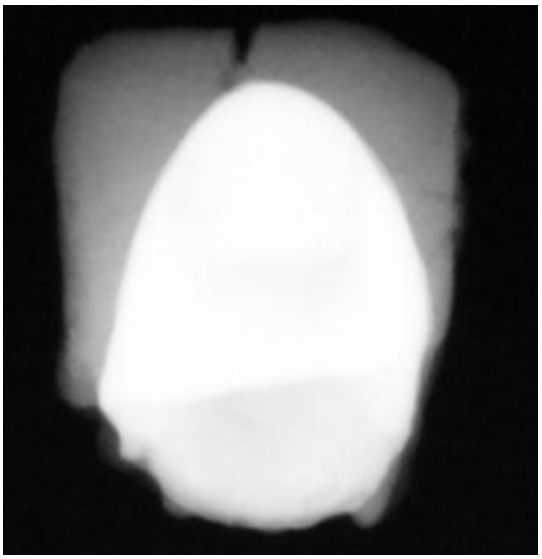


Figure 9. Rx of the sample depicted in fig. 5: the fracture lines are possible to be observed only in the incidence that avoid the metal infrastructure. Those fractures presented in the vestibular area of the metal ceramic crown are not possible to be identified

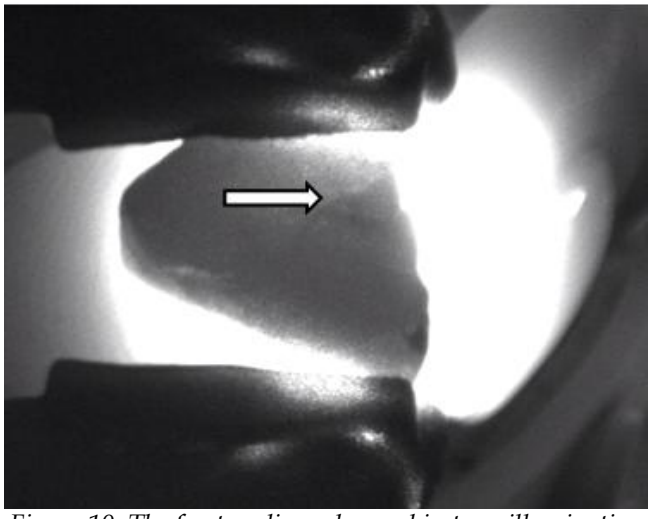


Figure 10. The fracture lines observed in transillumination

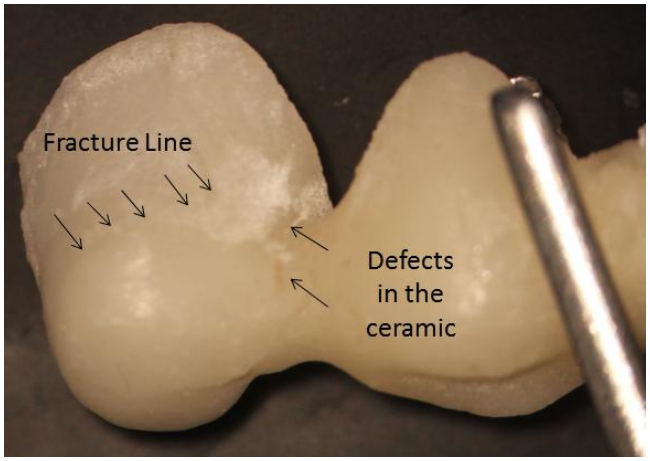


Figure 11. Integral ceramic fixed partial prosthesis with fracture lines and defects imbedded in the ceramic layer

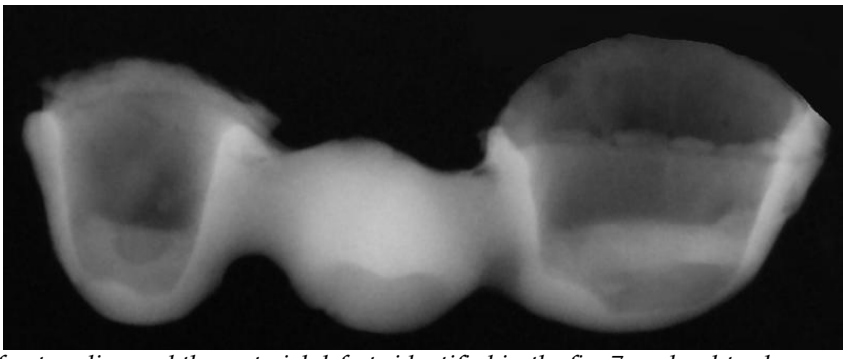


Figure 12. The fracture line and the material defects identified in the fig. 7 are hard to observe on the Rx of the same integral ceramic sample because of the over imposed ceramic layers

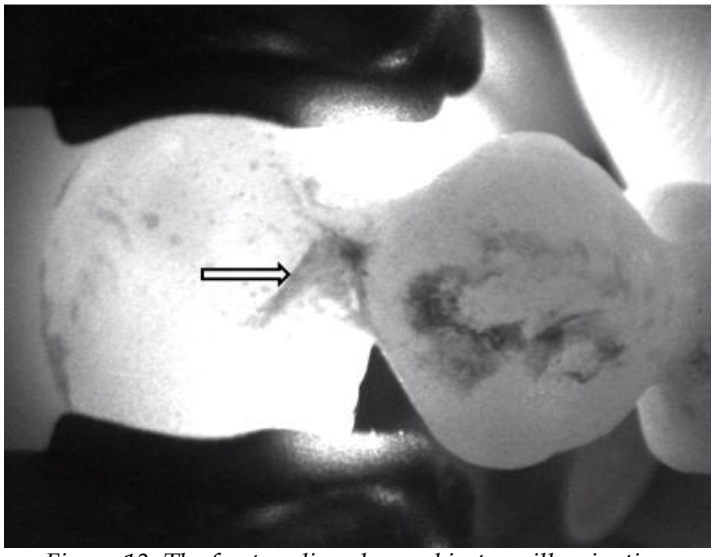
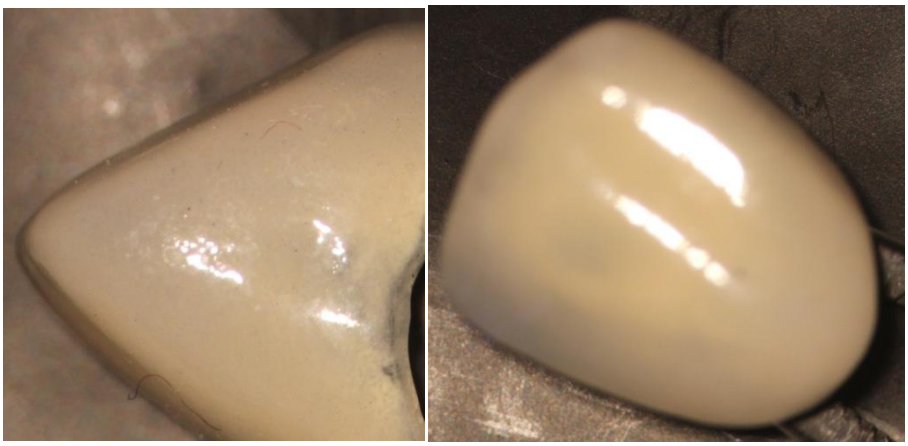


Figure 13. The fracture line observed in transillumination



a *b*

Figure 14. Possible defects inside the ceramic layer observed in light inspection: a. proximal view and b. vestibular incidence.

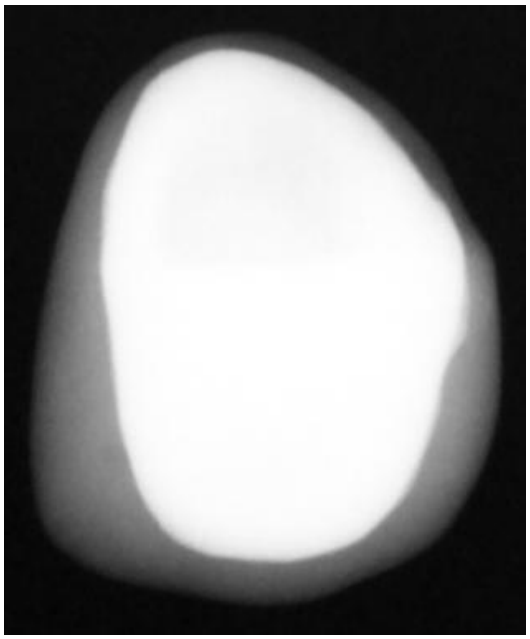


Figure 15. The possible defects identified on the metal ceramic sample in the fig. 9 are not observed on the Rx of the same sample because the over imposed ceramic layers

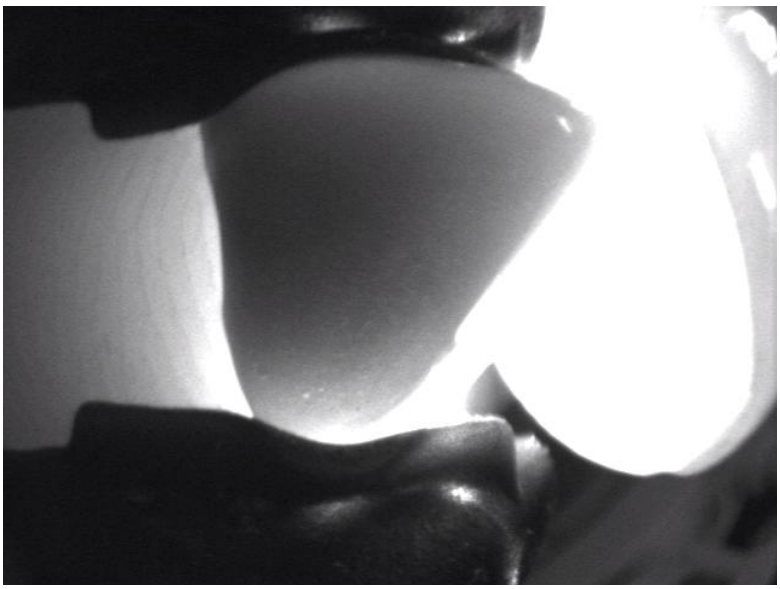


Figure 16. No defect was revealed by the transillumination method

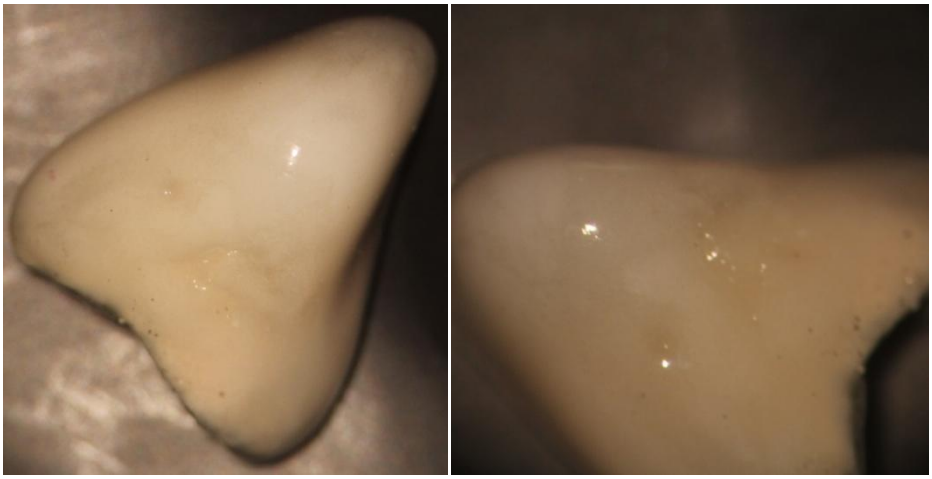


Figure 17. Possible defects inside the ceramic layer observed in light inspection: a. proximal view and b. vestibular incidence

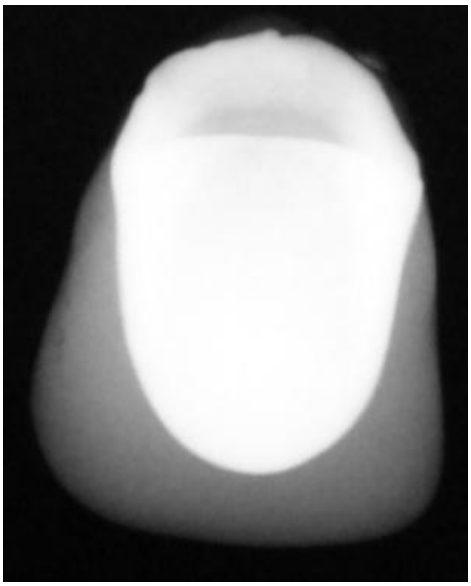


Figure 18. The possible defects identified on the metal ceramic sample in the fig. 11 are not observed on the Rx of the same sample because the over imposed ceramic layers

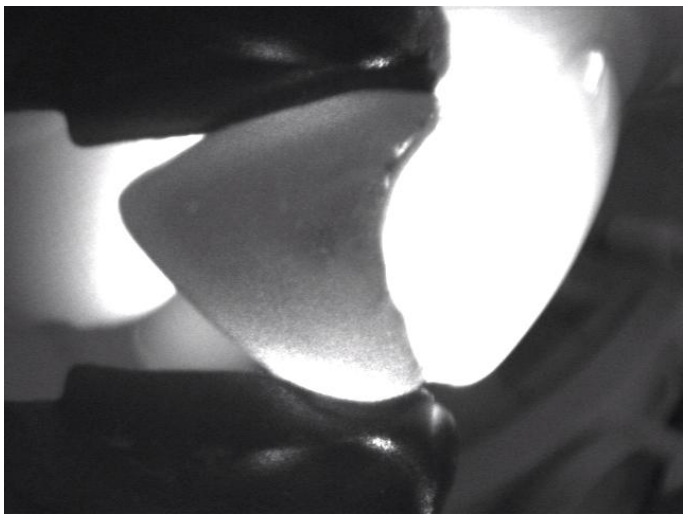


Figure 19. No defect was revealed by the transillumination method

DISCUSSIONS

Nondestructive defectoscopy plays an important role in testing of dental prosthesis. After the imagistic noninvasive evaluation of different dental prosthetic construct (crowns and fixed partial prosthesis, metal ceramic and integral ceramic structures), different aspects were observed. The microscopy method allows detecting de fractures from the ceramic layers, but only the ones situated in the outer part of the ceramic layer. All these fractures were identified on the Rx evaluation. The transillumination allows exploring the 3D positioning of the fracture lines when different positions were considered. In this way the prognosis of the prosthetic construct can be evaluate.

The materials defects were hard to observed in microscopy and Rx. Some of the defects could be visualize in transillumination but only in integral ceramic prosthetic construct. For the metal ceramic prosthesis the angle of the transillumination is very important in order to obtain a good evaluation. Otherwise the metal infrastructure will block the light and no result was obtained.

CONCLUSIONS

The transillumination method along with the Rx evaluation can be very helpful methods in evaluation the quality of different ceramic fixed prosthetic constructs. The noninvasive microscopy evaluation of the ceramic layers provides very little information related to the material defects trapped inside the ceramic. Further studies are necessary to develop a defectoscopy methodology for the dental ceramic prosthesis.

Acknowledgments

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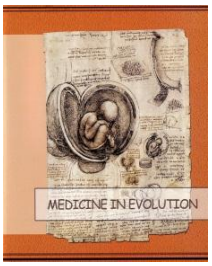
SINUS COMPLICATIONS IN IMPLANT DENTISTRY



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ABSTRACT

Introduction: Implant dentistry is a biological option in treating the edentulous ridge. In the upper maxilla when there is bone atrophy, the practitioners must use methods for sinus lifting. This can lead to a serious of accidents and complications. Matherial and methods: Based on 15 year clinical experience in the field of implantology and taken into account the literature, the authors highlight the main complications associated with sinus lifting and their management. Conclusions: Every dentist who performssinus lifting procedures should be able to manage the complications associated with these procedures.

Key words: *dental implant, sinus lifting, maxillary sinusitis*

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INTRODUCTION

Sinus lifting as a surgical method in implant dentistry has been performed for over 50 years. Although it is a well known surgical technic, there are various failures, accidents and complications. Currently the most used technics are the lateral wall and the osteotomes technic. The lateral wall allows the gain of a larger amount of bone but is thought to be more traumatic for the patient.Theinternal lift is considered a less invasive surgery technic. It can be perfomed using osteotomes or with specially desgined burs for the slow handpiece.A more recent approach is the crestal method using the piezo device and the hydrodinamic elevation of the sinus mucosa. This technic has the advantages of the classic methods: a good gain of bone and is very atraumatic for the patient.

MATERIAL AND METHODS

1450 dental implants were placed in a group of 950 patients. At 10% of these patients various sinus lifting procedures were performed. After a careful analysis and looking at the literature, the complications were divided into *immediate*(intraoperative) and *secondary*(after the primary healing).

The immediate complications are: schneiderian membrane perforation (14,7%) and hemorrhage (3,1%). The secondary complications are: maxillary sinusitis (2,1%), oro-antral fistula (1%), graft failure (1%).

RESULTS

Membrane perforation was encountered in 14 patients. It was the results of misproper use of rotary instruments when accesing the lateral wall (4 patients, 4,2%), improper use of the membrane elevators (6 patients, 6,3%), sinus septa (4 patents, 4,2%). The perforations were divided according to their size in: A. Small, less than 5mm (8 patients, 56%); B. Medium, between 5-10 mm (4 patients,28%); C. Large, over 10 mm (2 patients, 14%). For the small ones there was no need for a special treatment, elevating the membrane allowed for a fold to cover the defect. For the medium perforations, regenerative barrier membranes with slow resorbtion were placed and the sinus grafting was accomplished. In the case of large perforations in one patient an autlogous bone block was fixed in the sinus and the defect covered with slow resorbtion barrier membrane. In the other case the procedure was abandoned and a reentry was tried 3 weeks after. Slow resorbtion barrier membranes were also used.

Sinus bleeding was encountered in 3 patients. Bleeding appeared when performing the lateral wall technic with detaching the bony window thus injuring the intrabony arteries. The hemorrhage was stopped by using electric cauterization and grafting was accomplished safely.

Only one patient presented with oro-antral fistula following sinus lifting. Improper mangement of the flap lead to a dehiscence of the surgical wound. The graft failed leading to an oro-antral fistula. The fistula was closed in 2 layers with a vestibular colar covered by a palatal pedicle flap. After soft tisuue healing the floor of the sinus was reconstructed with an autologous bone block taken form the ramus.

Maxillary sinusitis was found in 2 patients. In first case it was trigerrred by a peri-implantitis that became

symptomatic 4 years after the fixture was inserted. The implant had to be removed allowing a better drainage of the infection (Pic1). In the second case the partial migration of the grafting material into the sinus lead to the onset of a sinusitis (probably due an undiagnosed perforation). After specific antibiotic treatment, an endoscopic procedure was performed to remove the misplaced graft, leaving the rest of the material on the sinus floor. After the healing time the dental treatment was carried on with no somplications (Pic2).

Bone graft failure was seen in one case. A patient that needed dental implants presented with a large sinus cavity. A 2 stage procedure was planned. After 6 months from the first stage (lifting the sinus membrane and grafting with xenograft) at reentry, the graft failure was observed. The graft was removed and the sinus was grafted using this time autologous chips mixed with xenograft.

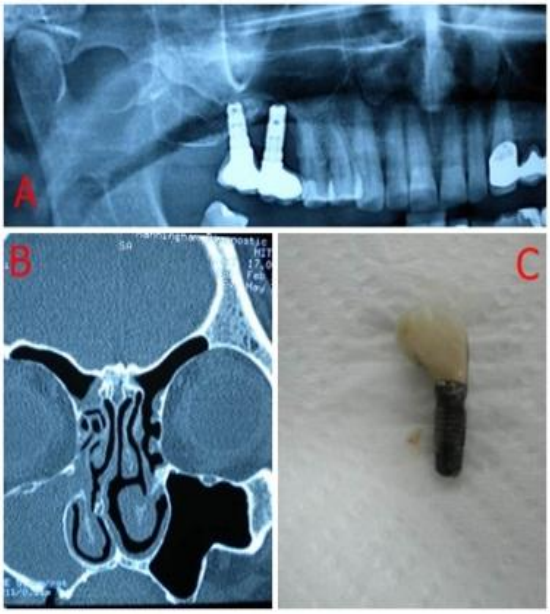

Figure 1. Implant fixtures placed 4 years before; the patient is diagnosed with a right maxillary acute sinusitis: A. Panoramic exam that reveals total bone loss around implant 16 with opaque diffuse process in the maxillary sinus; B. CT scan shows total inflammation of the maxillary right sinus; C. Eximplantation for drainage

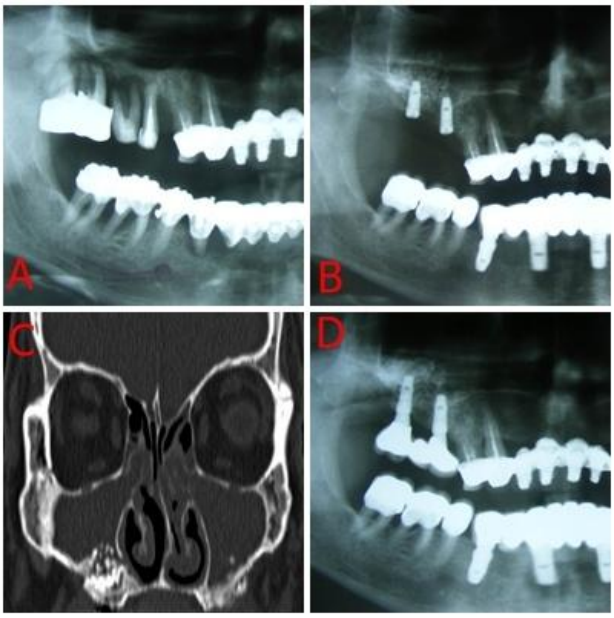

Figure 2. A. Severe periodontal disease around teeth 15,16,17 that present class III mobility, B. Dental extraction, lateral sinus lifting, post extraction dental implants 15,16,17; C. CT scan shows partial extrusion of the graft into the sinus and inflammation around the graft; D. Panoramic scan 1 year after endoscopic treatment

DISCUSSIONS

Membrane perforation is the most encountered complication related to sinus lifting procedures. The literature reports an incidence of 7% (1) up to 25% (2) and even above 50% (3). There are numerous articles that clasify these perforations. The authors use the classification of Alfaro et al (4) (depending on size and treatment). Improper conduct in medium and large perforations can lead to graft material slipping into the sinus cavity, resulting in the blockage of the ostium and leading to maxillary sinusitis or the extrusion of graft material (particulate) through the nasal fossa. When a small perforation is spotted intraoperative, the elevation can be continued. Because of the progresive elevation of the membrane, it tends to fold on itself, thus covering the defect (5). For this to happen there has to be a 5 to 10 mm elevation around the perforation.

When dealing with medium perforation, the use of slow

bioresorbable collagen mebranes seems to be a simple and effective method of closing the defects (6). In the case of large perforations the barrier membranes must be fixed to the sinus walls to prevent slipping of the graft into the sinus (7). The membrane must be placed in such manner not to cover large amounts of the sinus walls, because it will lead to improper vascularization of the graft. The sinus membrane once elevated from the sinus floor has a small role in the blood supply of the graft (8).

Some authorsreport that perforations do not play a major role in long term prognosis of implants placed in grafted sinuses, but there studies that have shown implant failure up to 50% in perforated sinuses compared to non perforated ones (9). Proper management can tip the scale regarding the prognosis when it comes to sinus lifting procedures.

With the introduction of piezo cutting devices, the incidence rate of schneiderian perforations decreased to 7% (11). The developpment of specific sinus tips allowed for some methods to be used without classic membrane manual elevators. A new technic in sinus grafting is to use plasma derived factors that can be applyed over the perforations (12).

The second most encountered complication is sinus hemorrhage. The incidence can ne as hihh as 20% (13). The bleeding is the result of direct trauma of the sinus anastomosis of the infraorbitary artery and the posterior-superior alveolar artery. This anastomosis is found 100% in the anterior wall (14) and it can be visualised in CT scans in 50% of the cases (15). The management implies using compressive force over the point of bleeding if it's located in the bone or electric cauterization.

Maxillary sinusitis is the most severe complications in sinus lifting procedures. It's incidence can vary from 5% up to 20% (16,17). The onset of sinusitis is directly depended of: a decrease in ostium size (18), pre-existing sinus inflammatory processes (19), misdiagnosed perforation, implant failure with oro-antral fistula. An oversized graft can lead to ostium blockage, thus reducing the ciliary clearance, resulting in a maxillary sinusitis. In acute processes the treatment consists of wide range antibiotics (βlactamins, macrolide), nasal sprays and removing the causative factor (dental implant, graft material). In chronic processes the hyperplasic membrane can be removed with the use of endoscopy by an ENT specialist. The oro-antral fistula must be closed in 2 layers using a vestibular flap or a palatal pedicle flap. After soft tissue healing a reentry can be performed, often with the use of bone blocks to reconstruct the sinus floor.

CONCLUSIONS

Although the succes rate is usually over 90% in sinus lifting implantology, there a number of complications that can occur. Some of them can lead to severe infections of the maxillary sinuses. Some times their managent is simple and predictible for the dentist but there are cases when the patient must be refferaled to a maxillofacial surgeon or an ENT surgeon.

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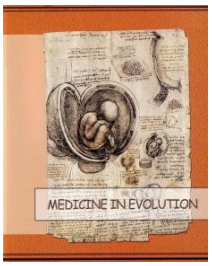
CAD/CAM NANO-CERAMIC PROSTHETIC RESTORATIONS OF EXTENSIVE CARIES WITH MINIMAL INVASIVE PROCEDURES



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ABSTRACT

Restorative treatment of the severely destroyed dentition is typically indicated to replace deficient tooth structure, limit the advancement of tooth destruction, improve oral function, and enhance the appearance of the teeth. Minimizing removal of additional tooth structure while also fulfilling the patients desire to have highly functional and esthetic restorations, can represent a prosthetic challenge when the existing tooth structure is already diminished. This article presents a comprehensive minimally invasive prosthetic approach usinga new restorative material (Nano-ceramic particle reinforced composite – Lava Ultimate CAD/CAM Restorative) on natural teeth for a male patient diagnosed with multiple decay lesions.

The results showed that this material is highly suitable for prosthetic restoration on naturalteeth.

Key words: *nano-ceramic material, usage behavior, mini-invasive treatment, CAD/CAM, adhesive restorations*

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INTRODUCTION

In situations where the coronaldestructionsare massive,a prosthetic approach for an esthetic and functional rehabilitationis recommendedinstead of composite fillings. The aim of this therapy is to stop the caries advancement and to restore the dental arches and tooth relationships essential for occlusal harmony (1,to reduce tooth sensitivity;and to enhance the overall esthetic appearance of the patient.

Clinical procedures to improve the mechanical retention for the restorations ofextensive destructions consisted of devitalizing the teeth and performing endodontic therapy, placement of a post and core restoration and sometimes crown lengthening. Historically, restoring the teeth by prosthetic meanswas a commonly used treatment modality because it was formerly thought that the mechanical retention is the only retention for mixed metal-ceramic restorations.With this type of restoration it was needed to create a certain amount of space for the restorative material, thus being more invasive.

Regardless, in the presence of a sever destruction, there is still the need to maintain as much of the remaining tooth structure as possible and use only adhesive restoration (2. This would be beneficial to avoid the aggressive reduction of the remaining tooth structure and preserve the maximum amount of enamel.

Though traditional metal-ceramic restorations have predictable strength and reasonable esthetics metal free crowns have been reported to have better optical properties and a superior gingival response (3.

For improved esthetics and reestablish the function has advanced the developments of all-ceramic systems and core materials, such as lithium disilicate, aluminum oxide, and zirconium oxide. On the other hand new biocompatible materials with properties similar to dental enamel were researched.

Nano-ceramic particle reinforced composites were created by incorporating Al_2O_3 ceramic particles into the surface of AA6061-T6 alloy plate with multiple pass friction stir processing (4.According to the manufacturer's information, the nano-ceramic particles are inorganic-organic hybrid particles. Both, nano-ceramic particles and nano-fillers have methacrylate groups available for polymerization.

Recent studies reveal that the reinforcement by nano-sized ceramic powder exhibit superior wear resistance, thus having significantly low wear rates and desired abrasive wear (5. Strength is an important aspect of the material for mechanical and particular applications under loading and static pressure. For applications where surface contact is involved, the useful life of components is mainly determined by their surface properties such as wear resistance.

The advantage of nano-ceramic technologyis the elastic modulus that's comparable to dentin, which is much lower than what brittle ceramic materials or metalo-ceramic prostheses can provide. This enables Lava Ultimate CAD/CAM restorative material to better absorb chewing forces and reduce stress (occlusal chipping); having 200 MPa toughness. With this material the enamel wear is normal and chipping is less probable.Therefore, the use of the monolithic material in occlusion with a full-contour design, even with reduced thickness (0.8 to 1.0 mm), may provide sufficient strength, even in the posterior areas.

The patient was an 18-year-old male unhappy with the appearance of his teeth, experiencing difficulty in chewing and sensitivity to cold. He was diagnosed with multiple decays, which affected the majority of his teeth. In the clinical interview regarding his expectations to improve his smile, he emphasized the desire to have highly esthetic restorations without the use of metal. Thorough clinical oral examination and radiographic evaluations were performed. The intraoral examination revealed generalized severe decays on the cervical area of the teeth as well as on the posterior occlusal surfaces; abundant plaqueaccumulation; and low salivary flow (Fig 1). The first step was the removal of all decays, followed by dentine hybridization, base filling and coronal build-up with composite materials (Fig. 2). Gingivectomy was required in order to obtain ferrule effect, thus assuring the correct restorability of the affected teeth. The gingivectomy was made by biological width consideration (Fig. 3). These modifications were evaluated through a diagnostic wax-up. The initial study casts were mounted on a semi-adjustable articulator (Artex CT, Amann Girrbach, Germany) using an arbitrary face-bow transfer (Artex Facebow, Amann Girrbach, Germany), and the diagnostic wax-up was completed in accordance with the clinical findings. In order to evaluate function and esthetics CAD/CAM technology was used to scan the wax-upandcreate the indirect mock-up prior to teeth preparation.

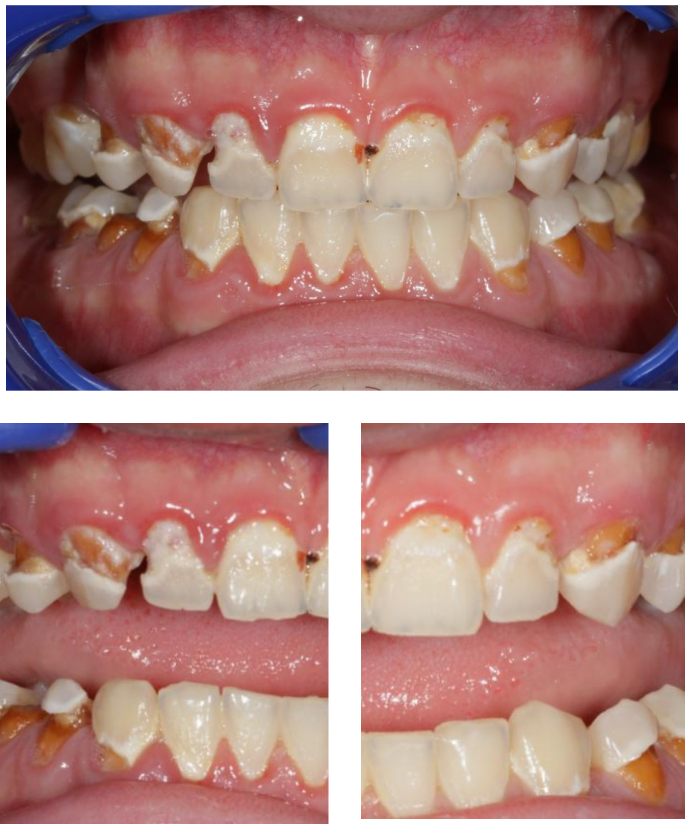


Figure 1. Preoperative clinical photographs of a 18-year-old man. Erosion and caries lesions with different degrees of tissue loss were evident throughout the dentition.

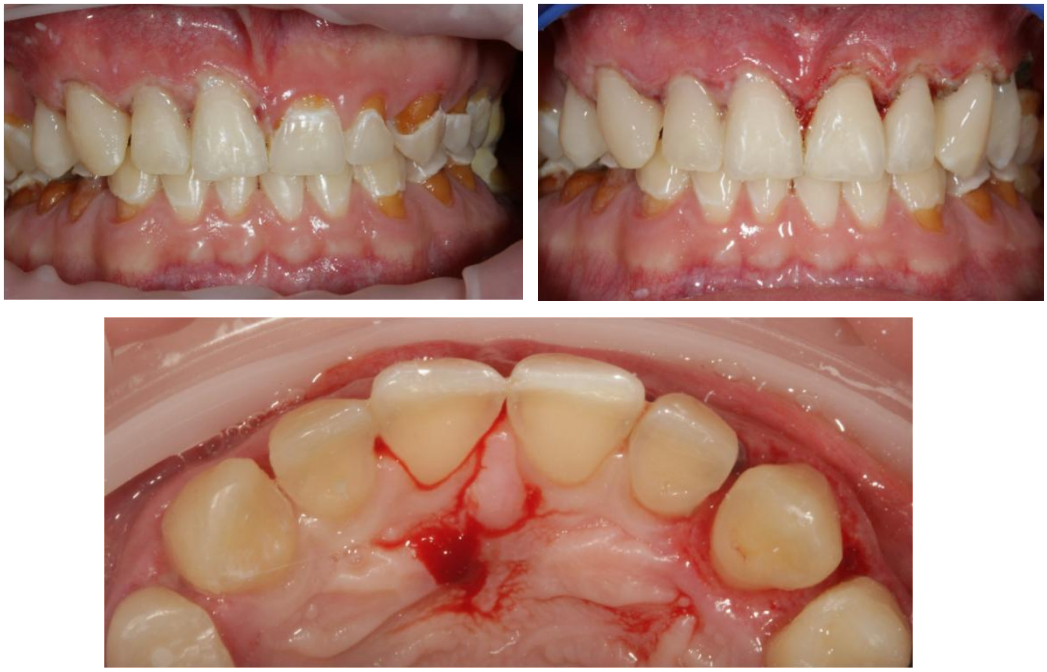


Figure 2. The gingivectomy of the upper arch using laser therapy to obtain ferrule effect for correct prosthetic restoration

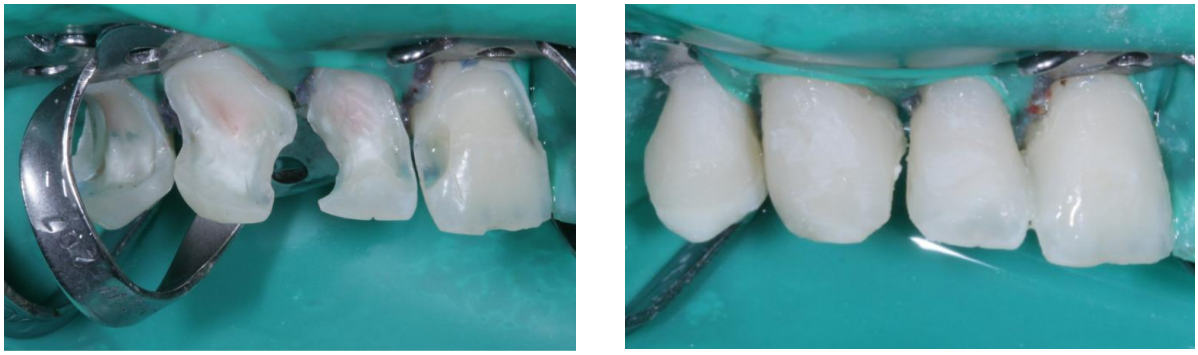


Figure 3. Preprosthetic treatment using rubber dam: a - preoperative view; b - build up with core composite

The guidedteeth preparation was performed through the mock-up with the appropriate burs to achieve overall reductions of 0.8 mm on the occlusal faceand 0.4 to 0.6 mm axially (Fig 4). Tooth structure removal on the occlusal surface was limited to only 0.8 mm in the posterior teeth because this is the minimal space required for the use of the monolithic material. In this way it was also possible to maintain most of the remaining enamel on the abutment previously built with the composite resin reconstruction (Fig 5). The finish line on the cervical area was positioned in the sulcus (intra-sulcular preparation) to optimize the esthetic result and to include any possible existing tooth structure deficiency in the restoration designthus enhancingthe resistance. CAD/CAM provisional restorations were fabricated at the new status, cemented temporarily with zinc oxide noneugenol cement (Temp-Bond Clear, Kerr Dental, US)(Fig. 6). The patient's comfort, speech, and the integration of a new appearance were evaluated periodically (at 1 week) and aftera healing period of 3 month for the soft tissue the final impression was obtained. The sulcus wasconditionedthrough the double cord technique(Ultrapack, Ultradent, US)(Fig 7), the final impression was taken with a polyether material (Impregum Penta L DuoSoft, 3M ESPE, US) using a custom tray. The impression was carried out using the single impression double mixing

technique including also fluid material (Impregum Garant L DuoSoft,3M ESPE, US)carefully placed on the preparations. Afterwards, an intraoral face-bow and centric relation records were taken with the new clinicalsituationin order for the stone cast replicas of the provisional restoration to ensure the cross-mounting with the master cast of the tooth preparation.

The CAD/CAM machine used for obtaining the prosthetic restorations belongs to 3M ESPE LAVA.Specially designed blocks Lava Ultimate Restorative, size S (small) and A2 shade with LT-Low Translucency and HTwere used.The milling of the restorations was carried out with the CAM milling machine, also belonging to 3M ESPE LAVA, resulting in the final restorativeprostheses (Fig. 8).

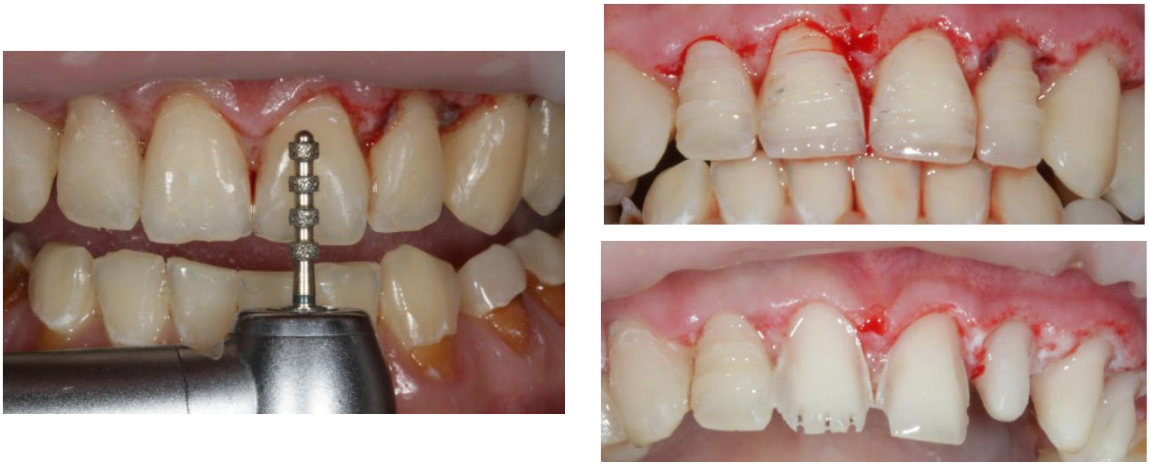


Figure 4. Preparation of teeth for the definitive crown could be performed with calibrated burs to achieve an optimal reduction of: (a and b) 0.4 to 0.6 mm axially and (c) 1.5 to 2.0 mm in the incisal aspect of the anterior teeth

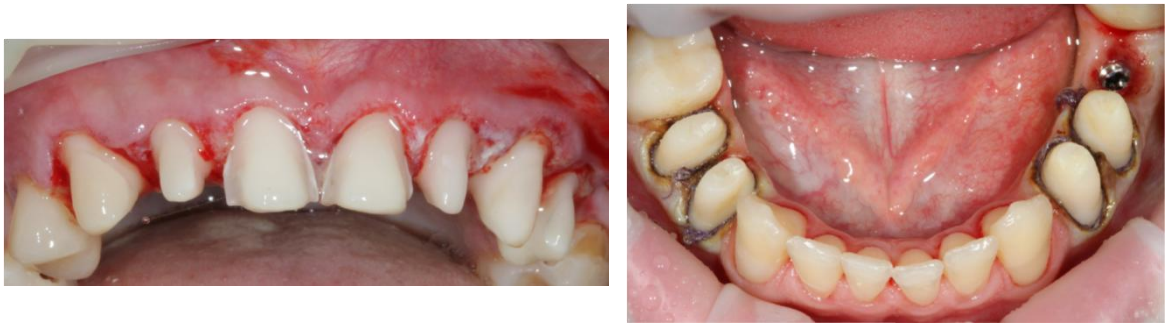


Figure 5. A light chamfer preparation was performed, slightly deepening the margin in the intrasulcular position. Note the minimum preparation thickness and remarkable maintenance of enamel

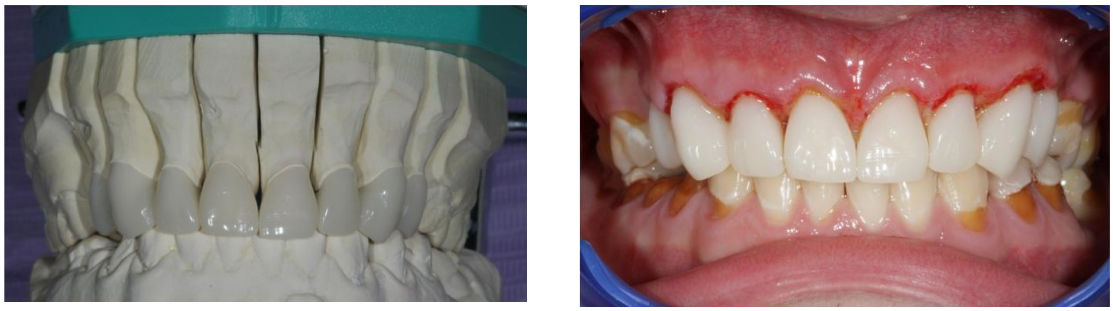
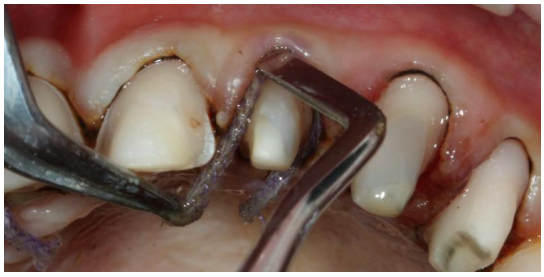


Figure 6. Provisional restorations in place immediately after the gingivectomy



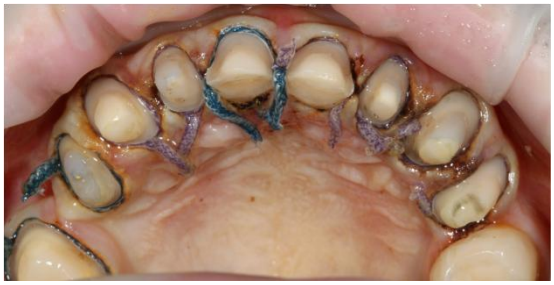


Figure 7. Conditioning the sulcus using double cord technique

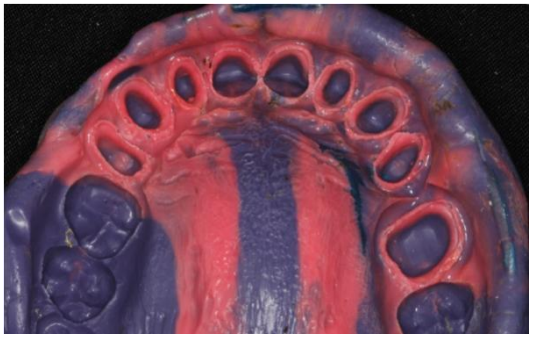
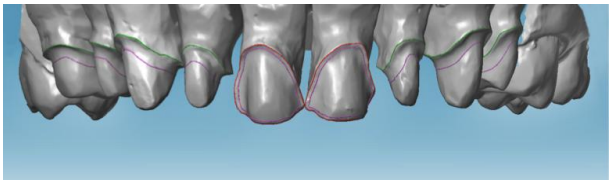


Figure 8. Final impression taken with a polyether material



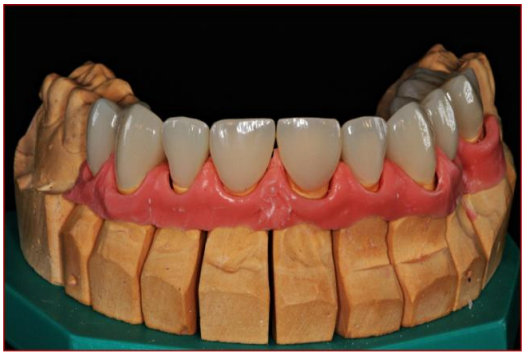


Figure 8. Final restoration: a - CAD/CAM design of restoration; b - all restoration on cast

Adhesive cementation

The cementation phase had to follow a precise protocol. Retraction cords and rubber dam were placed in the sulcus of every abutment to minimize the humidity from the crevicular fluid and to act as a barrier for the penetration of the resin cement to the base of the sulcus. The inner surfaces of the restorations were sandblasted and etched with 37% phosphoric acid (Total Etch, Ivoclar Vivadent) for 20 seconds, thoroughly rinsed with water. After thorough air-drying, the intaglio surface was silanized (Monobond- S, Ivoclar Vivadent) and dried for60 seconds. Tooth preparations were cleaned with pumice and rubber burs (Opticlean, KerrHawe), etched for 30 seconds on enamel and 15 seconds on dentin with 37.5% phosphoric acid (Total Etch, Ivoclar Vivadent), rinsed, and dried. Both fitting surfaces, restorations and teeth were coated with the adhesive system (Syntac, Ivoclar Vivadent), and because of the reduced thickness of the nano-ceramic restoration, a light-polymerized composite resin cement (Variolink II, Ivoclar Vivadent) was selected to lute the restorations (Figs. 9 and 10).

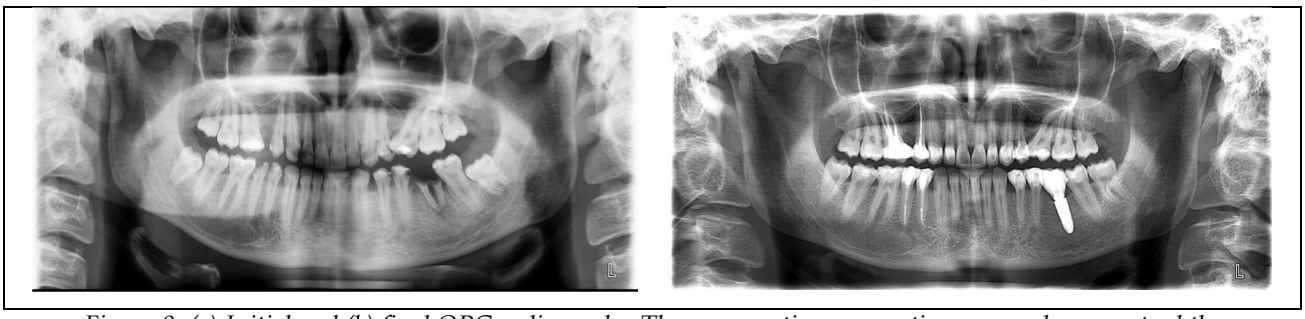


Figure 9. (a) Initial and (b) final OPG radiographs. The conservative preparation approach guaranteed the maintenance of vitality for the majority of teeth

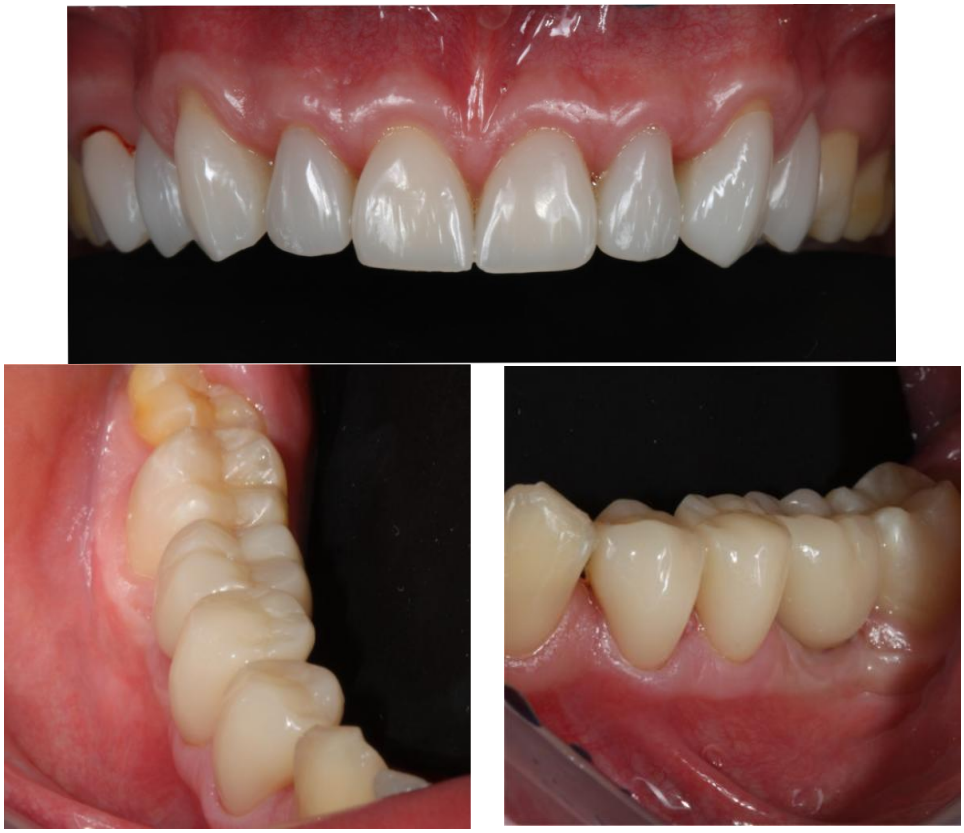


Figure 10. The final result shows a satisfactory biologic, functional, and esthetic integration of the full-mouth rehabilitation

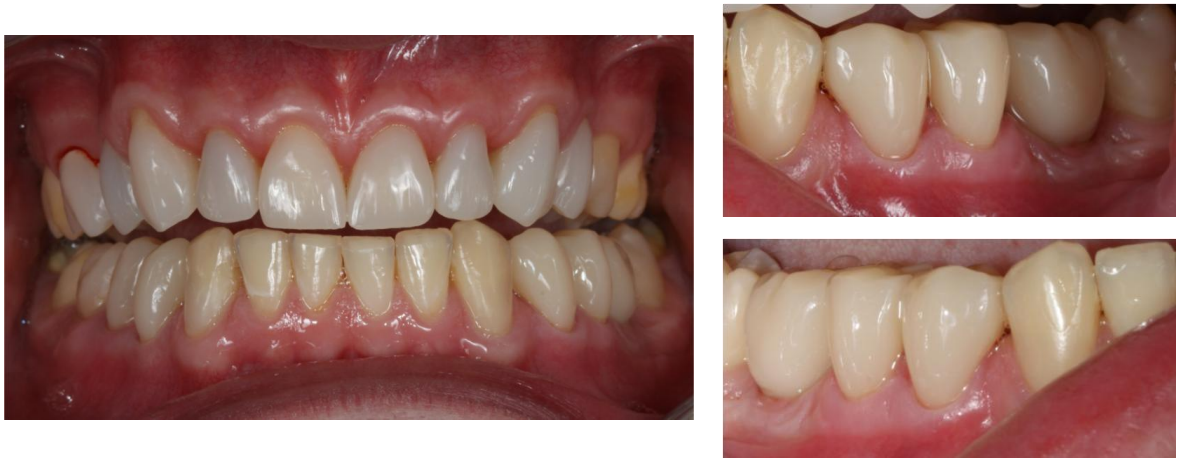


Figure 11. Appropriate function helped maintain the integration achieved after 2 years of service

DISCUSSIONS

The minimally invasive prosthetic procedure is a comprehensive treatment modality recommended especially in cases of severely injured dentition involving the following procedures:

- Minimally invasive tooth preparation. The goal is to reduce tooth structure removal, especially in the occlusal area, to create a restoration with a thickness not exceeding 0.8 to 1.0 mm and to preserve more enamel surfaces along the axial walls and the light chamfer finish line for a superior bond over dentin (6.
- Bonding the restorations. Adhesively bonding the restorations, mainly in enamel with an etchable ceramic material, is likely the key element for the success of this restoration.

It is sensible and beneficial to maintain pulpal vitality and prevent endodontic treatment and the need for a post core restoration because these more invasive approaches violate the biological balance and compromise the performance of restored teeth over time (7. The choice of a metal free monolithic restoration was done in order to achieve high esthetics with a reduced thickness. This type of restoration offers exceptional estheticsin time (2 years recall) (Fig. 13).

The use of this monolithic material eliminates concerns regarding chipping of the overlay porcelain, which has been shown to occur with bilayer ceramic systems. Bilayer ceramic restorations consist of a strong ceramic core (eg, zirconia) veneered with a weaker overlay porcelain and have been reported to show chipping, fracture, or delamination of the veneering porcelain between 3% and 25% in the first 5 years (8.

This revolutionary new material, called as Resin Nano Ceramic (RNC), is unique in durability and function. The material is not a resin ora composite. It is also not a pure ceramic. The material is a mixture of both types of material and primarily consists of ceramic. Similar to a composite, the material is not brittle and is fracture resistant. Similar toa glass ceramic, the material has excellent polish retention for lasting esthetics. This new material is highly heat cured through a controlled, proprietary manufacturing process, which eliminates the need for a firing step after milling.

Lava Ultimate CAD/CAM Restorative is the direct result of this true nanotechnology, which distinguishes itself by precise manipulation of the ceramic architecture at the nano-scale (about 1-100 nm), yielding unique and controllable properties (9. The nanotechnology in Lava Ultimate restorative is coupled with resin technology to achieve a combination of strength and esthetics beyond what current feldspathic ceramics or composite blocks offer. Nanomer particles are monodisperse, nonaggregated, and nonagglomerated nanoparticles. Lava Ultimate restorative material contains two types: silica nanomers of 20 nm diameter, and zirconia nanomers of 4 to 11 nm diameter. The engineered nanoparticles are treated with a silane-coupling agent using a proprietary method. This functionalized silane bonds chemically to the nano-ceramic surface and also bonds chemically to the resin matrix during manufacturing of the blocks.

CONCLUSIONS

The minimally invasive technique for patients with extensive decays presented in this case reportis a viable solution for replacing tooth structure with the least amount of trauma to the already structurally compromised dentition.

The mechanical properties of this new material suggest that it can be successfully used in fixed prosthetics. Long-term studies will be necessary to assess its intraoral behavior.

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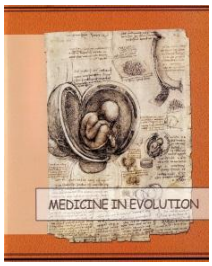

THE USAGE OF DIGITAL IMAGING FIBER-OPTIC TRANSILLUMINATION IN ASSOCIATION WITH LASER-FLUORESCENCE AS A COMPLEMENTARY METHOD IN PROXIMAL CARIOUS LESIONS DIAGNOSIS

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ABSTRACT

Backgroud: *Currently, the diagnostic of carious lesions include visual, tactile and radiographic examination. Often, this traditional methods are not sensitive enough to detect early carious lesions. Digital imaging fiber-optic transillumination (DIFOTI) in association with laser-fluorescence, allows an early diagnosis in order to approach a remineralization treatment for the carious process to become reversibile.*

Purpose: *The present study aims to evaluate the correlation between digital imaging fiber-optic transillumination (DIFOTI), laser-fluorescence, clinical examination and digital bitewing radiographic images in early proximal carious lesions diagnostic, in posterior teeth.*

Methods: *There were evaluated 20 proximal caries susceptible teeth on a number of 11 patients, aged between 20 and 31 years (7 women, 3 men). On all patients was perfomed professional cleaning, clinical, radiographic and optical examination. Digital imaging fiber-optic transillumination was performed using DIAGNOcam device (KaVo) and the degree of demineralization was assessed by laser-fluorescence method using DIAGNOdent Pen (KaVo).*

Results: *The evaluation of the results obtained with DIAGNOcam and DIAGNOdent Pen (Kavo) systems allowed the identification of 12 inicipient carious lesions which through visual inspection could not have been detected and the X-rays were inconclusive.*

Conclusion: *Complementary examination of the patients with DIAGNOcam and DIAGNOdent Pen showed that both systems represent a useful tool in diagnosis and evaluation of the incipient carious lesions which can benefit of noninvasive treatment in order to achieve remineralization.*

Key words: *DIAGNOcam, DIAGNOdent Pen, digital imaging fiber-optic transillumination, laser-fluorescence, incipient carious lesions, remineralization*

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INTRODUCTION

Currently, the diagnostic of carious lesions include visual, tactile and radiographic examination. Often, this traditional methods are not sensitive enough to detect early carious lesions. Digital imaging fiber-optic transillumination (DIFOTI) in association with laser-fluorescence, allows an early diagnosis in order to approach a remineralization treatment for the carious process to become reversibile.

The modern management of dental caries has three major components: prevention, control and treatment. It is based on appropriate diagnosis of the disease and detection of pathological changes (lesion formation in its earliest stages). Visual inspection, detection with anexplorer, radiographicexamination, and electrical conductance measurementhave beenused for diagnosing caries in clinicalsituations .

Becauseit is difficult to diagnoseearly caries objectively using these methods, the reproducibilityof these evaluations for the same examiner orbetween examiners has been low. In addition,probing pressure during detection with an explorer maycause iatrogenic damage of the enamel and the lesions capable to remineralize.

Today's commonly used diagnostic methods for approximal caries and fissure caries detection exhibit high specificity but low sensitivity.In most studies, the specificity, that is the correctrecognition of sound teeth, appears to be greater than80% for all traditional methods only a few sound teeth (i.e. without dentinal fissurecaries) are diagnosed wrongly as having dentinal cariesand are therefore erroneously treated by operativeintervention. The correct clinical diagnosis of teeth with dentinal caries under macroscopically intact surfaces (often called hidden caries) has been shown lower – sensitivities 12%. In view of today's relatively low cariesincidence, this particular characteristic of a test methodis important: teeth which can be kept unrestored formany years with adequate prevention should not betreated with restorations.

The modern therapy of dental caries consists of: early diagnosis, preventive measures, long term monitoring of initial carious lesion and assessing the outcome of preventive interventions.

In the late 90', a laser fluorescence device: the DIAGNOdent(KaVo, Biberach, Germany) hasbeen developed for more objective caries diagnosis.

Diagnosis using this device is based on the fact that the fluorescence emitted from carious surfaces is greater thanthat emitted from sound surfaces when they are irradiatedwith a laser beam with a wavelength of 655 nm.The DIAGNOdent consists of a probe, a fiber-optic lead and a main unit that generates the laser beam. It displays the real time values and maximum values of the fluorescence in the test site. Changes in the tooth substancesassociated with progression of the cariousprocess are reflected in an increased amount offluorescent light. The cause of thisincreased level offluorescence was the presence ofchromofores associated with bacteria present in theinfected tooth structure. A numerical value (0-99) is assignedto the degree of fluorescence as an indicator of theextent of caries.

Thanks to the DIAGNOcam device (Kavo, Biberach, Germany), approximal hidden caries can be diagnosed more easily. It operates completely without X-ray radiation and uses the new DIFOTI technology (DigitakFibre-Optic Transillumination).

KaVoDIAGNOcam delivers images, which are reminiscent of X-rays but which are completely

radiation free – by means of a light that is especially adapted to this examination method. The tooth structures allow the passage of light with the wavelength of 780nm from the entry site to the camera. Areas that block light transmission (e.g. carious lesions) show up clearly as well delimited, dark areas. A digital videocamera captures the actual situation and makes it visible in real-time on the screen. (www.kavo.com). With this method, thw caries can be detected at an early stage and treated gently and painlessly, retaining the dental substance.

PURPOSE:

The aim of the present study was to test the two devicesunder field conditions in the dental office and to evaluate the correlation between digital imaging fiber-optic transillumination (DIFOTI), laser-fluorescence, clinical examination and digital bitewing radiographic images in early proximal carious lesions diagnostic, in posterior teeth; in order toprovide recommendationsin relation to the clinical utility.

METHODS

- There were evaluated a number of 20 proximal caries susceptible teeth on a number of 11 patients, aged between 20 and 31 years (7 women, 3 men).
- On all patients was perfomed professional cleaning, clinical, radiographic and optical examination.
- Digital imaging fiber-optic transillumination was performed using DIAGNOcam device (KaVo) and the degree of demineralization was assessed by laser-fluorescence method using DIAGNOdent Pen (KaVo).

In the following pictures we present three of the cases, in order: visual inspection; digital imaging fiber-optic transilumination, radiography and demineralization degree.

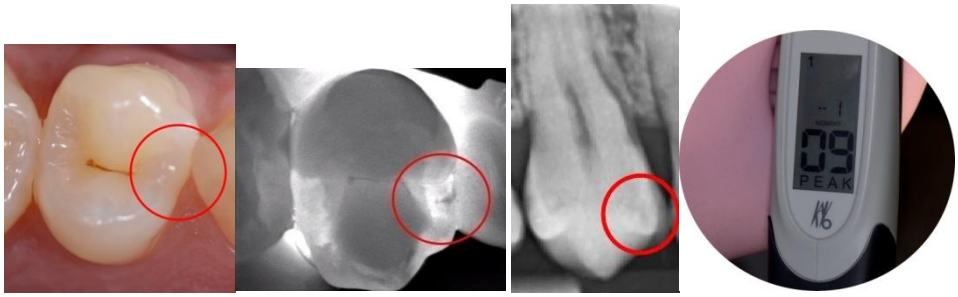

Figure 1. Case 1

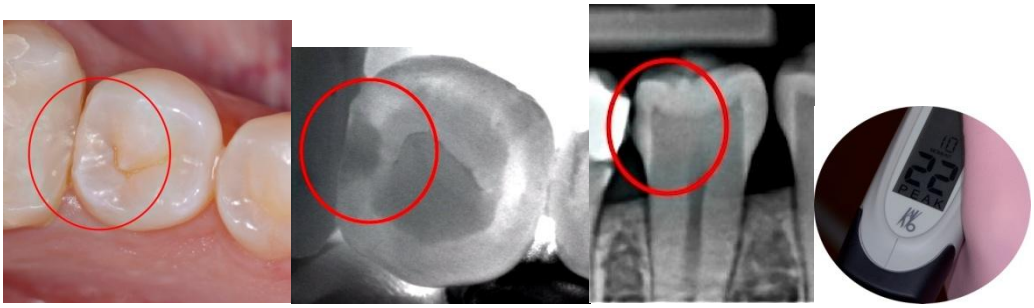

Figure 2. Case 2

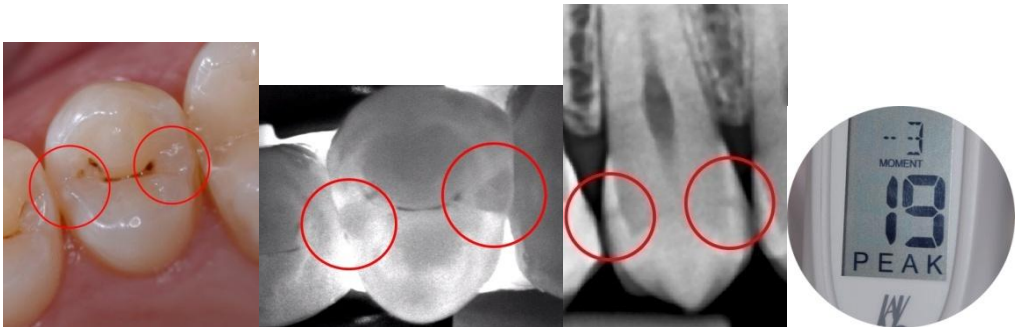

Figure 3. Case 3

RESULTS

The evaluation of the results obtained with DIAGNOcam and DIAGNOdent Pen (Kavo) systems allowed the identification of 12 inicipient carious lesions which through visual inspection could not have been detected and the X-rays were inconclusive.

Compared to traditional methods the DIAGNOcam and DIAGNOdent Pen device clearly improves diagnostic accuracy of carious lesions, thus facilitating the introduction of appropriate preventive measures sufficiently early. Such measures may prevent or at least delay restorative treatment. The two devices could be used for monitoring the effects of an intensive prophylactic program and the comparison of at least 2 consecutive measurement of the same site within a few months could indicate the level of caries activity.

CONCLUSIONS

Complementary examination of the patients with DIAGNOcam and DIAGNOdent Pen showed that both systems represent a useful tool in diagnosis and evaluation of the incipient carious lesions which can benefit of noninvasive treatment in order to achieve remineralization. This diagnosis method is realy accurate, conservative, safe reliable and very easy in dental office.

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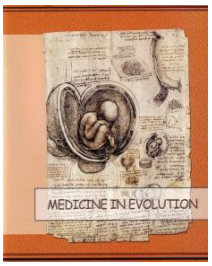
THE VALUE OF CBCT IN PRE AND POSTOPERATIVE DIAGNOSIS ASSESSMENT OF INFLAMMATORY RADICULAR CYSTS



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ABSTRACT

The aim of this paper is to point out the value of CBCT scan in pre and postoperative diagnosis assessment of inflammatory radicular cysts together with regional oral cavity extent and bone repair evaluation.

There were evaluated through a statistically retrospective method the pre and postoperative results of CBCT and x-ray examinations of 37 patients with inflammatory radicular cysts clinically, biologically and histopathologically assessed and surgical removed at Oral and Maxilo-Facial Surgery Clinic Timisoara.

The CBCT preoperative scans clearly showed the anatomic reports, the extent and the morphological characteristics in all 37 cases of inflammatory radicular cysts together withregional endodontic status. About 12 months after surgical removal, the postoperative CBCT scans revealed nearly complete bone repair with no residual cysts.

Due to specific abilities in bone tissue 3D evaluation,the CBCT scan is the imaging method of choice in pre and postoperative diagnosis assessment of inflammatory radicular cysts.

Key words: *inflammatory radicular cysts, pre and postoperative diagnosis assessment, CBCT scan*

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INTRODUCTION

The inflammatory radicular cystsare by far the most common pathological conditions within the teeth and jaw bones that will affect the integrity of the oral cavity with serious implications of all his functions. The so common, inflammatory radicular cysts could be the cause of regional and general complications which concern the whole organism with a great impact on health population (1, 2).

Examination and diagnosis of inflammatory radicular cysts by radiological and imaging modalities is the immediate of choice algorithm after clinical evaluation. Not only with the teeth and their surrounding bone the oral radiology concern, but also with the entire oral and maxillofacial complex (3, 4).

Among the imaging techniques of dental radiology the most common are panoramic and periapical radiographies together with the classical projections used in the diagnosis of maxilla and mandible pathology (4, 5).

Due to the ability of assessment of both the bone structures and the regional endodontic status with additional possibility of high-quality multiplanar reconstructions CBCT exam has proved to be an excellent procedure for characterizing the anatomy and related abnormalities of all oral regions (2, 3).

AIM AND OBJECTIVES

The aim of this paper is to point out the value of CBCT scan in pre and postoperative diagnosis assessment of inflammatory radicular cysts together with regional oral cavity extent and bone repair evaluation.

MATERIAL AND METHODS

We retrospectively reviewed the pre and postoperative results of CBCT and x-ray examinations of 37 patients with inflammatory radicular cysts clinically, biologically and histopathologically assessed and surgical removed at Oral and Maxilo-Facial Surgery Clinic Timisoara.

All patients were pre and postoperative X-ray examined by dental radiographies obtained after the classical projection techniques protocol and by panoramic radiographies achieved with the usual orthopantomographic procedure.

Preoperative and 12 months after surgical removal CBCT scans were done with the same unit with multiplanarand 3D reconstructionin order to precise regional oral cavity extent and bone repair evaluation.

RESULTS AND DISCUSSIONS

From the 37 patients with inflammatory radicular cysts, 20 cases (54%) were detected in the mandibular antero-lateral regions and 17 cases (46%) were found in maxillary regions with maxillary sinus involvement: 16 cases in maxillary antero-lateral regions and in 1 case the site was in maxillary posterior region.

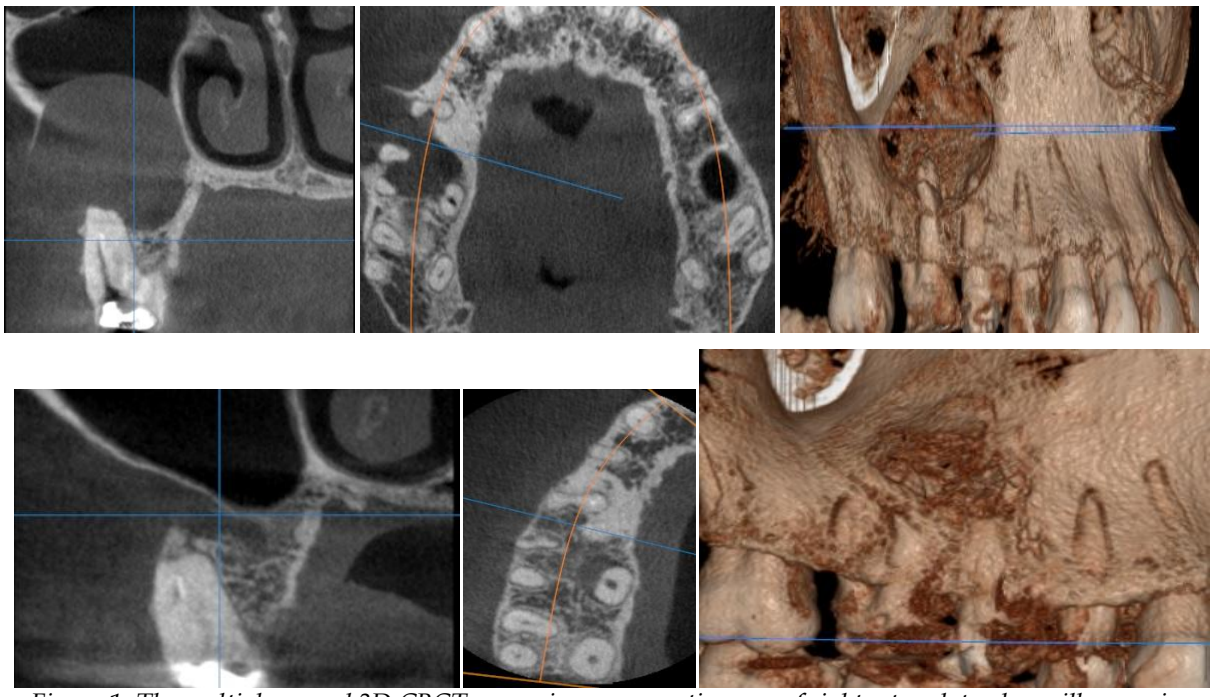

Figure 1. The multiplanarand 3D CBCT- scans in a preoperative case of rightantero-lateral maxillary region inflammatory radicular cysts with maxillary sinus involvement and the same examination done 12 months after surgical removal with bone repair revealed

In all patients periapical and panoramic radiographiesrevealedcomplete bone lysis done by inflammatory radicular cysts but the CBCT scans were a great deal more accurate in describing the orientation, vicinity and extent in all 3 plans of the lesions.

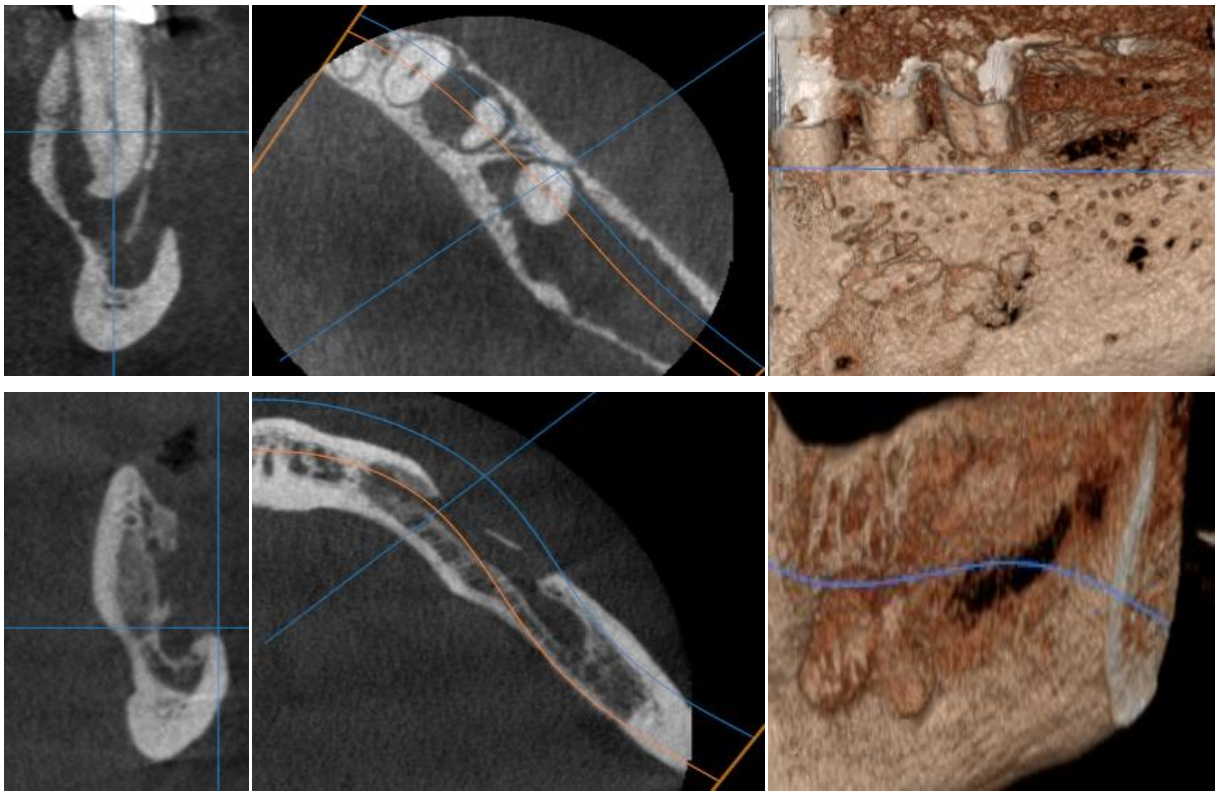

Figure 2. The multiplanarand 3D CBCT- scans in a preoperative case of leftantero-lateral mandibular region inflammatory radicular cysts and the same examination done 12 months after surgical removal with bone repair revealed

Postoperative X-ray examined, 12 months after surgical inflammatory radicular cystsremoval, demonstrated natural nearly complete bone repair with added extra information by postoperative CBCT scans tissue3 D analyses.

CONCLUSIONS

TheCBCT - exam offer a detailed evaluation of the hard and soft tissues of the entire maxillo-facial skeleton being the elected method in accurate assessment of the patient's dento-maxillary region together with the accompanying vital structures: the floor of the sinus, the floor of the nose, the roof of the mandibular canal and the position of the mental neurovascular bundle.

Due to specific abilities in the evaluation of bone tissue and in multiplanar and 3D reconstruction CBCT - exam is the imaging modality of choice in the diagnosis algorithms of inflammatory radicular cysts.

In patients with inflammatory radicular cysts CBCT - scan are of great importance value in order to offer to the clinicians subtle and no doubt datas for precise diagnostic and clearly cuantificated treatment with accurate capacities in postoperative evaluation.

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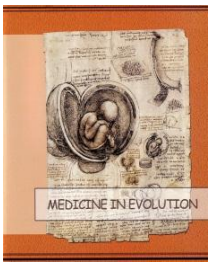
FACIAL PROFILE CHARACTERISTICS EVALUATION IN A POPULATION OF CENTRAL ROMANIA REGION



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ABSTRACT

Objectives. The aim of the study was to evaluate the variables that define the facial profile of a sample of the population in the centre of Romania, and to compare male's and female's soft tissue profile. These values could be useful in elaborating the aesthetic objectives for treating the population in this area.

Material and methods. 50 subjects were included in the study – patients and students of UMF Tg-Mures (29 females and 21 males) between 18 to 28 years of age, having dental class I and a balanced profile. The photographs were taken in the natural head position (NHP). The anthropometric points were recorded and four of the angles that characterize a harmonious profile were traced and measured: the nasofrontal angle (G-N-Nd), the nasolabial angle (Cm-Sn-Ls), the mentolabial angle (Li-Sm-Pg), the facial angle (G-Sn-Pg).

Results. The values obtained for the two sexes were compared. To compare the sexes the t-student test was used. All angles had values that were bigger for females (nasofrontal: girls 137,1 degrees; boys 135,79 degrees, p=0,0019; nasolabial: girls 105,3 degrees; boys 102,19 degrees, p=0,00002; mentolabial angle: girls 126,07 degrees; boys 118,27 degrees, p=0,000009; facial angle: girls 170,32 degrees; boys 168,85 degrees, p=0,0033).

Conclusions. Differences between the two sexes were obtained, all angles were statistically significant larger in females. These results show that for the population in the centre of Romania the treatment objectives are different for girls than for boys. The angular values range between those that characterize the Caucasian population.

Key words: *facial profile, photographic examination, facial angles*

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INTRODUCTION

A person's preoccupation with beauty is a life constant, irrespective of the time in history they live in. The dental-facial aesthetics has a series of social implications, because human beings associate beauty with success or happiness, the aesthetic reason being the main factor for which a patient will seek treatment.[1]

Normality in orthodontics can be defined within a range of variations around the average or the most frequent form. The notion of "normal" is also linked to the aesthetic ideal specific to each epoch.[1]

Determining the attractiveness of a face is dominated by subjectivity and in close correlations with age, sex, ethnicity and the level of culture and professional development. In order to evaluate the aesthetics of the face, different methods were used: anthropometric, photographic, cephalometric, computer imaging.

Profile photographs have received an increasing attention because they are non-invasivness and inexpensive compared with lateral cephalograph .New models of analysis lateral photograph continued to be developed.[2]

The profile examination of the face is one of the components in evaluating the facial aesthetics and highlights the ratio that exists between the protrusion of the forehead, the nose, the chin and the proportion of the lips. A profile is considered beautiful if there is a balance between all the aforementioned references. Ever since 1958, respectively 1959, Burston, respectively Subtenly, defined various parameters and anthropometric points in analysing the soft facial parts.[3,4]

An analysis of these parameters based on the profile photograph was developed, successively, by several authors: Stoner 1955 [5], the Peck brothers 1970 [6], Arnett and Bergman 1993 [7,8]. They used the nasolabial angle measured on photographs taken in NHP.

Legan and Burston (1980) described the profile angle or the facial angle formed by the cutaneous Glabela, Subnasal and Pogonion points [9]. Its normal value is 170 degrees [10]. Powell analyses four angles: nasofrontal (G-N-Nd) with a normal value of 130 degrees, nasofacial, nasomental and mentocervical to describe an ideal profile [11].

Other measured angles on the profile photograph is the mentolabial (Li-Sm-Pg). This angle expresses the turn-over degree of the inferior lip towards the mentonier protrusion and consequently, towards the super-mentonier groove. This angle varies with age according to Peck, 1970, quoted by Firu. Bewteen 20-39 years it is 104 degrees, between 40-59 it is 120 degrees and over 60 years it reaches 134 degrees [12].

The aim of this study was to measure the angular variables that define the cutaneous profile of a sample of the population in the centre of Romania, and to compare male's and female's soft tissue profiles. These values could serve to elaborate the specific aesthetic objectives of treatment for the population in this area.

MATERIAL AND METHODS

We made a prospective longitudinal study.

Inclusion criteria: 50 subjects were included in the study – patients and students of UMF Tg-Mures (29 females and 21 males) with ages ranging from 18 to 28 years with ended cranio- facial growth , having dental class I occlusion with normal overjet and overbite,all permanent teeth

present and fully erupted up to third molar and a balanced profile.The balanced profile was judged by all of the authors. The patients didn't have orthodontic or surgical treatment in the past.

Exclusion criteria: orthodontic or surgical treatment in antecedents.

We use the profile photos with the whole of the right side of the face clearly visible.The

photos were taken with a digital camera. To capture the patient's profile, he/she is placed against a neutral background, at a large enough distance so that no shadows are formed. The photographs were taken in a natural position of the head (NHP), which was obtained by placing a mirror in front of the subject at a distance of 120 cm, the patients being asked to look into their own eyes in the mirror, with relaxed lips and their forehead and ears visible. The camera was placed horizontally on an adjustable tripod according to each patient's height.The photographic records were analysed. The following cutaneous points were marked on the photographs: Glabela (G), Nasion (N), Nasal-dorsum (Nd) ,Pronasale (Prn), Columella (Cm), Subnasale (Sn), Labiale superior (Ls), Labiale inferior (Li), Supramentale (Sm), Pogonion (Pg)(Figure 1). The angles that were going to be measured were traced: the nasofrontal angle (G-N-Nd), nasolabial angle (Cm-Sn-Ls), mentolabial angle (Li-Sm-Pg), the facial angle (G-Sn-Pg)(Figure 1). All these measurements were made by the same operator.

Statistical analysis

To compare the angles measured for girls and boys, the t-student test was used. The statistical data are presented in table I. The descriptive statistical analysis was used with Statistic Analysis in Excel.

RESULTS

The values obtained for the two sexes were compared. As we can observe in table I the angles has following values:

For the nasofrontal angle (G-N-Nd) average values are 137,1±1,53 degrees for girls and 135,79±1,2 degrees for boys. The differences are statistically significant p=0,0019.

For the nasolabial angle (Cm-Sn-Ls) average values were for girls 105,3±2,71 degrees and for boys 102,19±1,55 degrees, indicating a great difference, which is statistically significant p=0,00002

For the mentolabial angle (Li-Sm-Pg) average values are 126,07±3 degrees for girls and 118,27±7,73 degrees for boys.We found the greatest variability for this angle for males. In this case, too,we have a statistically significant difference between boys and girs p=0,0000097.

For the facial angle (G-Ns-Pg) average values are 168,85±0,7 degrees for boys and 170,32±2,09 degrees for girls. The difference between the sexes was again statistically significant p=0,003. All angles had values that were bigger for females.

DISCUSSIONS

The purpose of this study was to measure and evaluate the values of four of the angles that define the soft parts of the facial profile for a sample of the population of the centre of Romania, and to compare male's and female's soft tissue profiles. Similar studies have also been made by other authors, all of them using profile photographs taken in NHP (Yuen and Hiranaka, 1989 [13]; Arnett and Bergman, 1993[7,8]; Fernandez – Riviero et al., 2002, 2003[14]).

The nasofrontal angle (G-N-Nd) of the investigated population has the following values: 137,1±1,53 degrees for girls and 135,79±1,2 degrees for boys, unlike Epker (1992)[15] who didn't find differences between the values of the nasofrontal angle for girls and for boys (130 degrees). The differences arise from racial and age differences, and they are statistically significant p=0,0019.

The nasolabial angle (Cm-Sn-Ls) depends on the anterior-posterior position of the superior frontal group. Its value is important because it indicates the position of the superior lip and it influences the decision to treat some cases by extraction or non-extraction. The value of this angle for Caucasians is 90-100 degrees for men and 95-105 degrees for women according to Nanda [16]. According to Bergman (1999)[17] its value has to be 102±8 degrees. In this study, the values we obtained values we obtained were the average for girls 105,3±2,71 degrees and for boys 102,19±1,55 degrees, indicating a great difference, which is statistically significant p=0,00002. Legan and Burston (1980)[10] have found values of 102±8 degrees for both sexes.

The mentolabial angle (Li-Sm-Pg) has a great variability. It reflects the position of the inferior incisors. The average value obtained by Burston (1967)[18] is 122±11,7 degrees. In our study we obtained values of 126,07±3 degrees for girls and 118,27±7,73 degrees for boys. In this case, too, we have a statistically significant difference between boys and girs p=0,0000097. Fernandez-Riviero et al.(2003)[14] and McNamara et al.(1993)[19] found bigger values both for girls and for boys (129±9 degrees for boys and 134,5 ±9 degrees for girls). Lines et al. (1978)[20] reported values between 120 and 130 degrees, concordantly with the values measured by us. In conclusion, male have a smaller labiomentonier angle, which corresponds with a labiomentonier angle deeper for male than for female with a more pronounced menton.

The facial angle (G-Ns-Pg) has a normal value of 170 degrees. We obtained values of 168,85±0,7 degrees for boys concordantly with the values obtained by Fernendez-Riviero et al (2003)[14] of 168±5 degrees and Arnett and Bergman (1993a,b)[7,8] of 169,4±3,2 degrees. The values for girls were 170,32±2,09 degrees and they were in relative agreement with the values found by Arnett and Bergman (1993a,b)[7,8]; 169,3±3,4 degrees, the difference between the sexes was again statistically significant p=0,003. Similar gender differences were obtain in other studies[21].

These measurements can serve as a comparison guide in determining the diagnosis and in elaborating the individualized treatment plan. The orthodontist has to take into account the beauty norms specific to each patient and the differences between the sexes. The bigger values of the angles measured in this study can be explained by the fact that the girls have a gentler contour of the soft parts than the boys, especially in the area of the nose, lips and chin.

The numerous analyses made to the soft facial parts have shown different values of the angles, the differences resulting from the criteria of including the patients in the study, by the racial differences, by age, by the existence of malocclusions, by the measurement methodology, by the orientation of the head when taking the photographs. Firu[12] said that the facial profile angles calculated on the anthropologic photography of the patient have rough values and their values differ from the values of the cranial angles measured on the profile x-ray. Nevertheless, in the orthodontic treatments the thickness of the soft parts is taken into account, as these can compensate for the unaesthetic profiles of the bone relief.

The photographic examination is a valuable complementary examination

which, together with the cephalogram, brings physiognomic and dimensional values that are useful in determining an orthodontic treatment. It is a document that highlights the physiognomic and aesthetic values in the orthodontic treatment.

Table 1.

Nasofrontal angle	Mean	Standard Deviation	Mean +/- Standard	Sample Variance	Standard Error	Sample Size	Confidence Level (95,0%)	Median	Range
Female	**137,1034**	1,522799	**137,1 +/- 1,523**	**2,318916**	0,282777	29	0,554232	137,1	5,8
Male	**135,7857**	1,21379	**135,79 +/- 1,214**	**1,473286**	0,264871	21	0,519137	136	4,6
p =	**0,00194025**								
All pacients	136,55	1,535598	136,55 +/- 1,536	2,35806	0,217166	50	0,436412115	136,3	6,9

Nasolabial angle	Mean	Standard Deviation	Mean +/- Standard	Sample Variance	Standard Error	Sample Size	Confidence Level (95,0%)	Median	Range
Female	**105,3**	2,710034	**105,3 +/- 2,71**	**7,344286**	0,503241	29	0,986334	106,3	9,1
Male	**102,1905**	1,557853	**102,19 +/- 1,558**	**2,426905**	0,339951	21	0,666292	102,4	6,0
p =	**0,00002106**								
All pacients	103,994	2,755137	103,99 +/- 2,755	7,59078	0,389635	50	0,783001	103,6	10,0

Mentolabial angle	Mean	Standard Deviation	Mean +/- Standard	Sample Variance	Standard Error	Sample Size	Confidence Level (95,0%)	Median	Range
Female	**126,0655**	3,033418	**126,07 +/- 3,033**	**9,201626**	0,563292	29	1,104031	126,2	13,1
Male	**118,2714**	7,730016	**118,27 +/- 7,73**	**59,753143**	1,686828	21	3,306122	119	24,7
p =	**0,00000974**								
All pacients	122,792	6,689341	122,79 +/- 6,689	44,747282	0,946016	50	1,90109	124,85	29,4

Facial angle (G-Su-Pg)	Mean	Standard Deviation	Mean +/- Standard	Sample Variance	Standard Error	Sample Size	Confidence Level (95,0%)	Median	Range
Female	**170,3172**	2,096608	**170,32 +/- 2,097**	**4,395764**	0,38933	29	0,763073	170	12,3
Male	**168,8476**	0,700442	**168,85 +/- 0,7**	**0,490619**	0,152849	21	0,299579	168,9	2,7
p =	**0,00339713**								
All pacients	169,7	1,802493	169,7 +/- 1,802	3,24898	0,254911	50	0,512263	169,5	12,3

Tabel 1

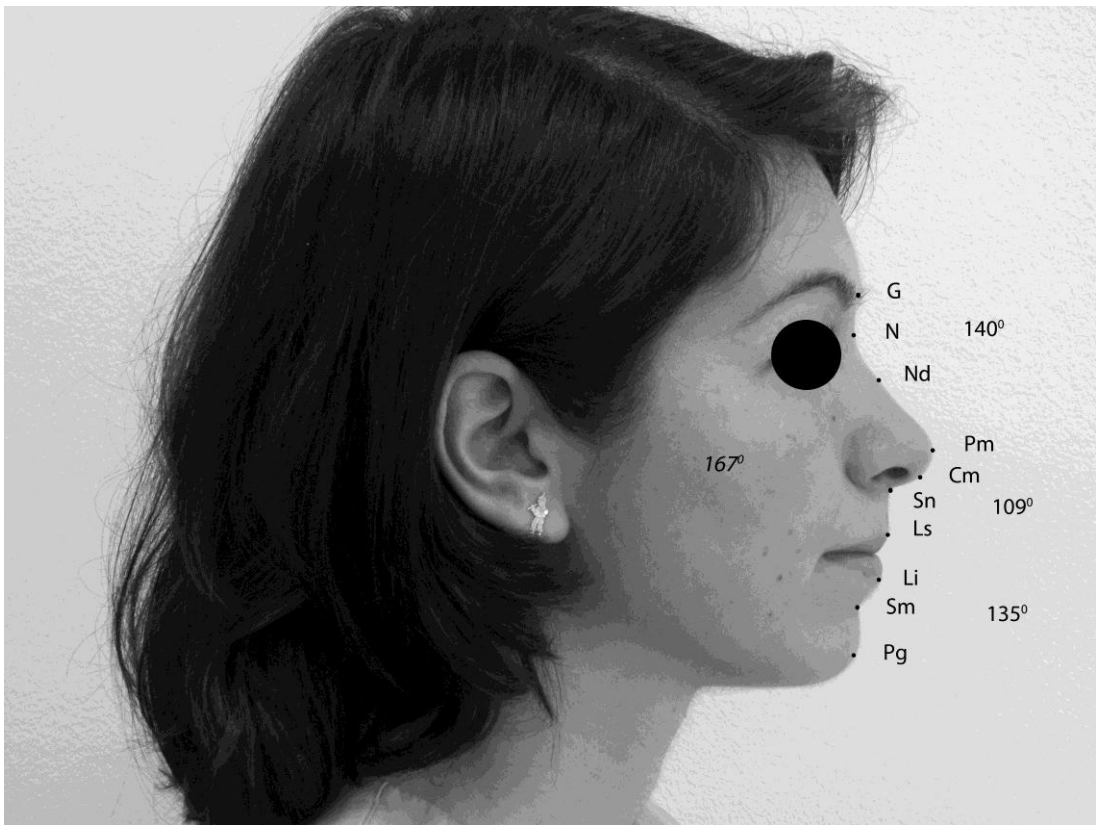

Figure 1. The Landmarks :Glabela (G), Nasion (N), Nasal Dorsum (Nd), Pronasale (Prm), Columella (Cm), Subnasale (Sn), Labiale Superior (Ls), Labiale Inferior (Li), Supramentale (Sm), Pogonion (Pg). Angular measureaments :nasofrontal angle, nasolabial angle, mentolabial angle, facial angle.

CONCLUSIONS

The values of the angles obtained in this study can be used as standard values in comparing the subjects with the same racial and ethnic characteristics that have dental class 1. They can constitute reference values in determining the objectives of the orthodontic treatment. we have to also take into consideration the differences between the sexes, girls having a less defined profile than boys, especially in the area of the nose, lips and chin. These values could serve to elaborate the specific aesthetic objectives of treatment for the population in this area.

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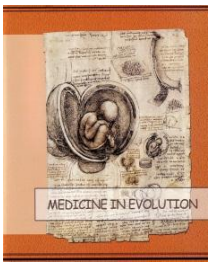
SINUS ELEVATION WITH AUTOGENOUS BONE GRAFT: A THREE-DIMENSIONAL FINITE ELEMENT STUDY



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ABSTRACT

The purpose of this study was to determine the influence of autogenous bone graft in sinus lift on stress distribution using three-dimensional finite element models. Within the limitations of the study, the autogenous bone grafting in augmentation of the maxillary sinus floor should be considered.

Key words: *finite element analysis, autogenous bone graft, implant*

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INTRODUCTION

Augmentation of the maxillary sinus floor is a surgical procedure aiming to create an increased bone volume in the maxillary sinus floor in order to enable installation of fixtures in the region. The surgical procedure has undergone development, and variations exist. Autogenous bone, regarded as the preferred option but with an important drawback of an unpredictable rate of resorption, has later been replaced by many surgeons by the use of bone substitutes.

The aim of this study is to compare the efficiency of autogenous bone augmentation by means of the finite element method, in terms of relative strength and stiffness of the assembly and impact on the surrounding bone tissue.

MATERIAL AND METHODS

A three-dimensional block-shaped anatomical model was developed using the CT scan images in a patient with pre-treatment of dental implant. The model was consisted of maxillary bone including cortical and cancellous bone, maxillary sinus and dental implant, created by CAD software of Solidworks (Figure 1).

A single implant with a length of 13 mm was modeled. The implant was placed in the center of the three-dimensional reconstruction and inclined 25 degree away from the horizontal plane. In order to facilitate the implant's performance, the bone–implant interface was assumed to be perfect.

Further the model was imported into ANSYS, a finite element analysis software. The finite element type used for discretization of the model (SOLID186) has 20 nodes and three degrees of freedom for each node.

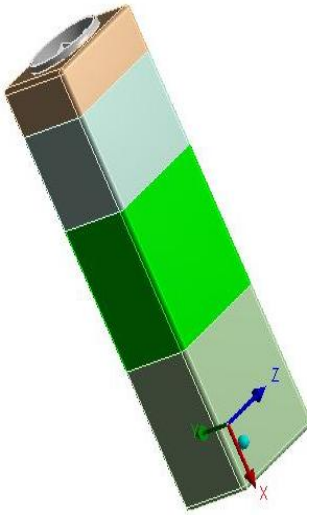

Figure 1. 3D model consisting of the maxilla, the augmented area, the bone graft, and the implant

The healing condition of autogenous bone graft was simulated with two types of material properties, such as concellous and cortical bone, to investigate mechanical effects of the different bone grafts for understanding the stability of dental implant.

The materials used for the implants and human bone have the mechanical properties of titanium alloy, cortical bone and cancellous bone. These data are exposed in the Table 1.

Table 1. The mechanical properties of the materials used in the analysis

Material	Young's modulus (MPa)	Poisson's ratio
Titanium alloy	105000	0.33
Compact bone	10500	0.4
Cancellous bone	800	0.3

Occlusal forces of 300 N and boundary fixation were applied reasonably for clinical consideration in the three-dimensional maxillary model (Figure 2). This value corresponds to magnitude of the maximal masticatory forces.

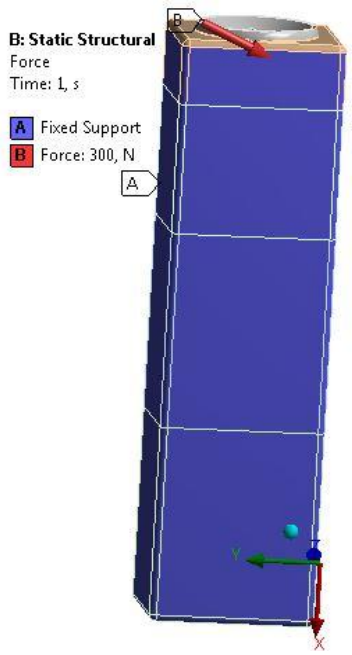

Figure 2. The orientation of the forces acting on the graft-implant model

RESULTS

In order to asses susceptibility for implant failure, we monitored the von Mises equivalent stresses.

In Table 2 maximal von Mises stresses from different simulation setups are shown.

Table 2. maximal von Mises stresses from different simulation setups are shown

Model	X-load (MPa)	Y-load (MPa)	Z –load (MPa)
Implant with cancellous bone graft	0,0035948	0,0026651	0,00081541
Implant with cortical and cancellous bone graft	0,0031381	0,00016744	0,00081541

From finite element simulation of von Mises stresses in all axis directions the maximum stresses are achieved near the area of cortical alveolar bone of the maxilla. In the autogenous cortical bone graft the stresses are lower than in the alveolar cortical bone area.

DISCUSSIONS

The stress distributions confirm additional stabilization with the autogenous bone graft. Simultaneous implant placement with augmentation and bone graft is possible. Double anchorage of the implants in alveolar

bone and in the autogenous bone graft block provides stabilization and fixation of the implants during the healing phase. This should minimize loss rates in the healing period and should lead to a better oseointegration of the implants.

Our study has several limitations. Thus, the bone is not isotropic, nor does it possess a homogenous structure. The materials used in the finite element analysis for bone tissue were homogenous and isotropic, due to technical difficulties.

CONCLUSIONS

The results of this finite element confirms that autogenous bone graft addition may be a useful approach to decrease stresses around implants placed into the grafted sinus.

These results are to be confirmed by the forthcoming laboratory tests and future clinical studies.

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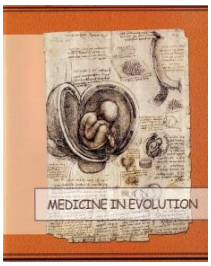
THE „ALL-ON-FOUR" TREATMENT CONCEPT WITH IMMEDIATE FIXED REHABILITATION OF THE EDENTULOUS PATIENT



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ABSTRACT

The „All-on-four" concept, also known as „TotalFix" concept, provides edentulous patients immediately loaded fixed prosthesis after implants insertion. This article provides the benefits and success rate of immediate load implants and the protocol used in this procedure.

Key words: *immediate dental implants, immediate loading, dental implant*

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INTRODUCTION

Elderly patients are frequent in imminence of tooth loss, edentulous, and often this kind of cases are considered to be the most difficult; the first factor seems to be the low acceptance age corresponding, and second, the assent of conventional dentures with a negative impact on patient social life.

A literature review showed that immediate loading of implant-supported fixed prostheses increases the quality of life and offers high standards regarding esthetics, phonetics and functionality and all these benefits can be achieved by using the „All-on-four" concept.

MATERIAL AND METHODS

During the last three years, we managed to apply the Total Fix concept at 112 eligible patients. We inserted 896 Euroteknica implants using eight implants for each case.

Study inclusion criteria were:

- good general condition
- good oral hygiene
- jaw bone profile suitable for the placement of minimum 4 implants (10 mm in length and 5 mm in width is needed)
- implants achieved stability at insertion (minimum insertion torque of 35 Ncm and/or minimum test value ISQ=65)

Paraclinic examination uses dental radiographs to reveal the appropriate existing bone level, panoramic x-ray or cone-beamed tomography (CBCT) before the procedures.

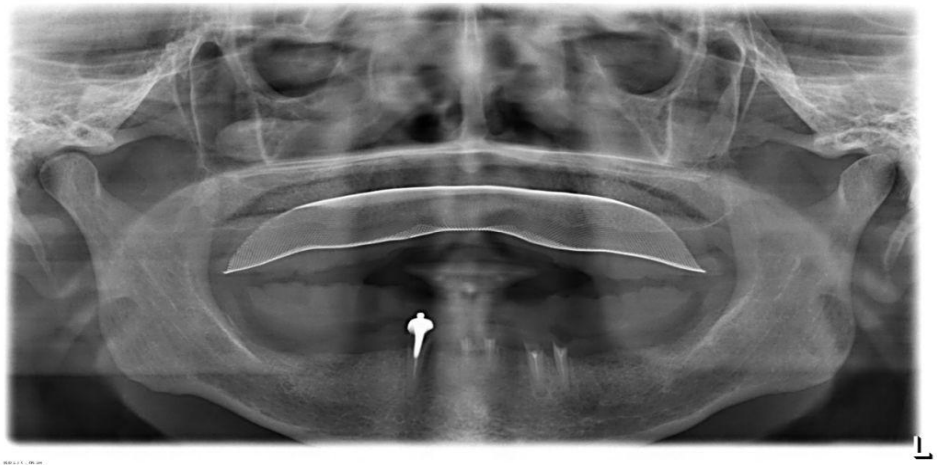

Figure 1. Preoperative panoramic radiograph

At the maxillary four implants were inserted in the anterior region between the maxillary sinuses and in some cases of poor density bone structure six implants insertion were recommended.

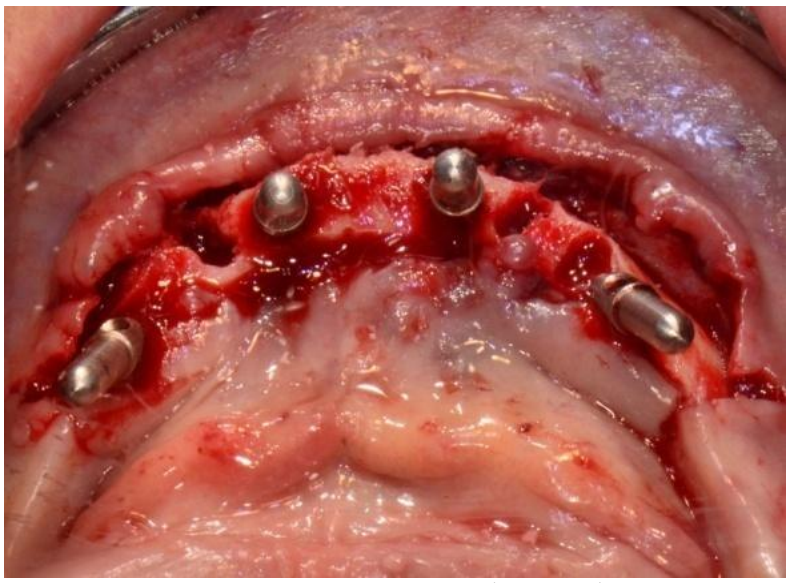

Figure 2. Post-extraction Euroteknica implants

The distal implants angulations varied between 30 and 45 degrees meanwhile the anterior implants were axial. Regarding the mandible, the four implants were inserted between the mental foramen and the distal ones were angulated as those inserted at the maxillary.

Immediate application of an easy and passive prosthesis without distal extensions was required to connect the implants, to avoid overloads and accidental fractures.

Follow-up examination was performed 6 months after implant placement.

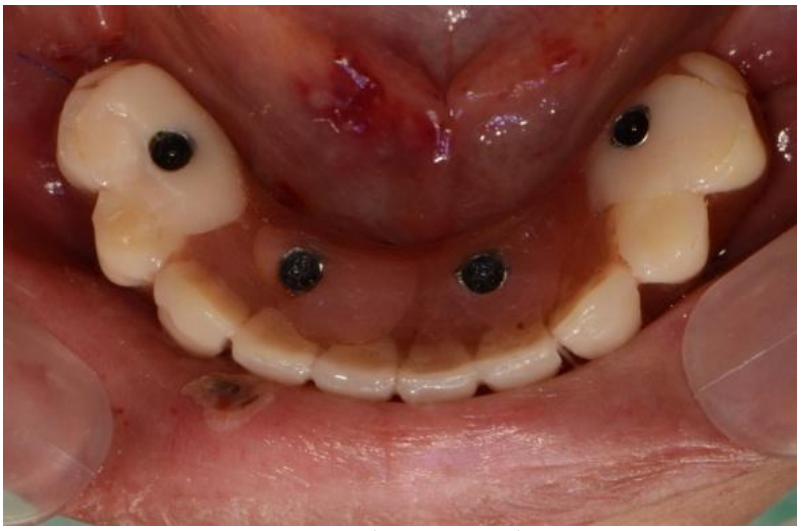

Figure 3. Seven days post-implantation

RESULTS AND DISCUSSIONS

The result compares favorably with other reported immediate/early loading protocols for the same indication.

All-on-four respects the basic items for the patient's satisfaction; it is total, fix, quick (provisional restoration applied in maximum 24-48 hours), it is no need for horizontal or vertical ridge augmentation or sinus surgical interventions and eliminates the associated comorbidities and offers the ideal costs predictability.

Numerous studies have demonstrated the predictability and safety of post-

extraction implant placement; it achieves success rates similar to those obtained with a

deferred surgical approach, and the substantially reduced treatment time undoubtedly

improves patient satisfaction

Important biological and mechanical studies have revealed that four implants fixed prosthesis loaded are capable to maintain the biological reserve. Angulation provides the implant primary stability by increasing the contact surface bone-implant with the possibility of using the opposite cortical bone for anchorage and offers the possibility to choose an increased length.

The results at 6 months were satisfactory with regard to the implant insertion,

stability, and surgical protocol management for implant placement. Healing was uneventful and there were no postoperative complications.

Studies are warranted with larger samples to compare Euroteknica implants with other implant systems.

CONCLUSIONS

The results obtained in the present study confirm that the success rates obtained with immediate implantation are similar to those achieved with deferred techniques.

All-on-four concept offers the patients the possibility for an excellent social life and eliminates the disadvantages of classical prosthesis and the low patient acceptance improving the quality of life.

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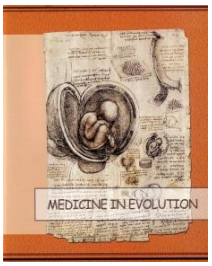
INTERDISCIPLINARY TREATMENT IN A CASE OF HEMIFACIAL MICROSOMIA



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ABSTRACT

Introduction: *Hemifacial microsomia (HFM) is the second most frequently encountered form of facial anomaly. It is a syndrome of the first and second branchial arches, involving the underdevelopment of the aural, oral, and mandibular areas, predominantly on one side of the face. The aim of this paper was to present the clinical case report of a patient diagnosed with HFM and the management steps to improve the patient's facial and occlusal characteristics, using a combined orthodontic and plastic surgical treatment approach.*

Case report: *A 13-year old male patient with right HFM presented for orthodontic treatment. He was diagnosed with Class II division 1 malocclusion, with anterior open bite and unilateral crossbite on the affected side. The CT and orthopantomographic exams showed a hypoplastic, malformed right mandibular body, hypoplastic mandibular ramus and condyle, with the absence of the glenoid fossa. The right zygomatic arch was incomplete, while the maxilla and the squamous temporal bone on the same side were underdeveloped, with bony atresia of the external auditory canal. The right pinna showed only a part of a malformed lobule, with the rest of the pinna absent.*

Treatment results: *Orthodontic treatment of the malocclusion and partially improved aesthetics using a silicone implant on the affected side improved the overall facial appearance and facilitated the patient's integration into society. In our case, the poor financial situation of the patient did not allow for other complex reconstructions.*

Conclusions: *The treatment of patients with hemifacial microsomia always requires an interdisciplinary approach including at least orthodontics, plastic surgery and maxillofacial surgery. The cooperation with the patients and their families, but also within the multidisciplinary team is essential in order to achieve optimal results.*

Key words: *hemifacial microsomia, orthodontic treatment, plastic surgery, interdisciplinary treatment*

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INTRODUCTION

Hemifacial microsomia (HFM) is included in a spectrum of malformations primarily involving structures derived from the first and second branchial arches, affecting the development of aural, oral, and mandibular areas, predominantly on one side of the face.

HFM is one of the most frequently encountered forms of congenital facial anomalies, second only to cleft lip and palate [1-3]. HFM has an estimated prevalence of 1 in 5600 to 1 in 26,550 births, possibly an underestimate, considering the numerous criteria used to define the disorder and the misdiagnosis of milder cases [4]. Males are affected more often than females (the male/female ratio is at least 3:2) [4,5] and the right side of the face is affected more often than the left side [6].

The disorder varies from mild to severe and can be bilateral in 31% of the cases, with more severe expression on one side [7-9]. In 48% of the cases, the condition is a part of a larger syndrome such as Goldenhar Syndrome, characterized additionally by vertebral anomalies and epibulbar dermoids [10].

The first documented cases may have been those recorded by Canton [11], in 1861 and by von Arlt, in 1881 [12], but the term "hemifacial microsomia" was first used by Gorlin when referring to patients with macrostomia, unilateral microtia and aplasia of the mandibular ramus and condyle [13].

A number of other terms have been used to describe this disorder: first and second branchial arch syndrome, Goldenhar syndrome, Goldenhar-Gorlin syndrome, otomandibular dysostosis, oculo-auriculo-vertebral dysplasia, lateral facial dysplasia, craniofacial microsomia, unilateral intrauterine facial necrosis, auriculo-branchiogenic dysplasia and facio-auriculo-vertebral malformation complex.

The cause of HFM is uncertain. Several teratogenic (retinoic acid, primidone and thalidomide) and genetic components have been incriminated in the etiology of this disorder [14-20]. HFM usually occurs sporadically, as a simplex case. However, several cases have had a positive family history suggesting an autosomal dominant, an autosomal recessive or a multifactorial pattern of inheritance. In families with one child affected by HFM, the chance of having another child with HFM is about 2-3%, but this may be an inaccurate estimate because of the difficulty in obtaining an accurate family history [4].

Murine studies have reported that HFM is a developmental abnormality caused by hemorrhage and rupture of the stapedial artery [21,22], but the results of these experiments in mice cannot be extrapolated to humans. There are no published reports indicating that intrauterine trauma or excessive motion of the mother might cause similar abnormalities in humans.

The management of HFM largely depends on the severity of the anomaly, as well as the patient's age. The complex treatment of HFM patients usually involves the use of orthodontic functional appliances and/or surgical intervention [23].

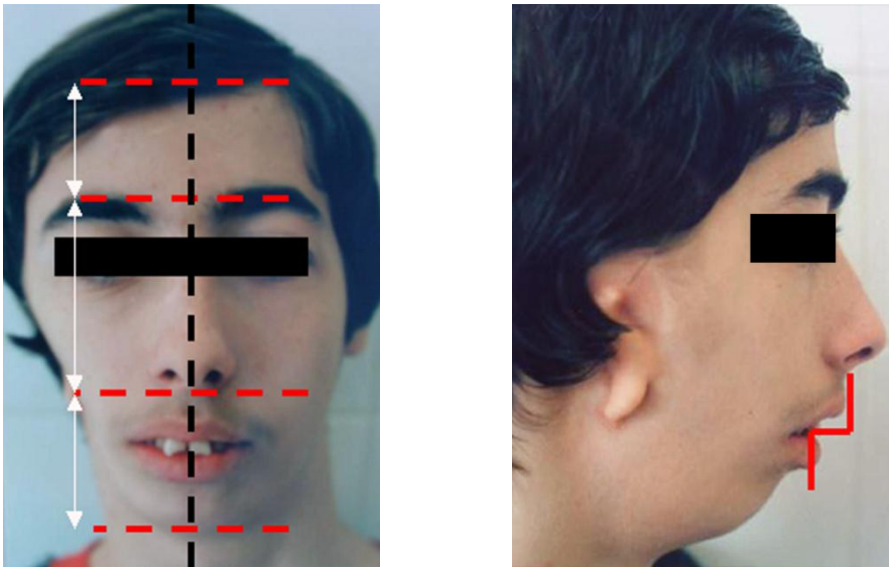
The aim of this paper was to present a clinical case report of a patient diagnosed with right HFM and the management steps to improve the patient's facial and occlusal characteristics, using the combined orthodontic and plastic surgical treatment approach.

CASE REPORT

A 13-year old male patient presented for orthodontic treatment in the Department of Pedodontics and Orthodontics, at the Faculty of Dental Medicine, "Victor Babeş" University of Medicine and Pharmacy Timişoara. The extra-oral examination showed a severe facial asymmetry affecting the right side, a convex profile, a retrognatic mandible and incompetent lips (Figure 1). The right pinna showed only a part of a malformed lobule, with the rest of the pinna absent. Hypoplasia of the facial muscles, such as the masseter, temporalis, pterygoideus and the muscles of facial expression on the involved side has also been observed.

From an orthodontic perspective, the patient had a Class II division 1 malocclusion with anterior open bite, decreased palatal width and unilateral crossbite on the affected side (Figure 2).

The 3D CT reconstruction images and the orthopantomography showed a hypoplastic, malformed right mandibular body, hypoplastic mandibular ramus and condyle, with the absence of the glenoid fossa (Figure 3 and 4). The right zygomatic arch was incomplete, while the maxilla and the squamous temporal bone on the same side were underdeveloped, with bony atresia of the external auditory canal (Figure 5).



a) *b)*

Figure 1. Extra-oral examination: a) frontal view; b) lateral view

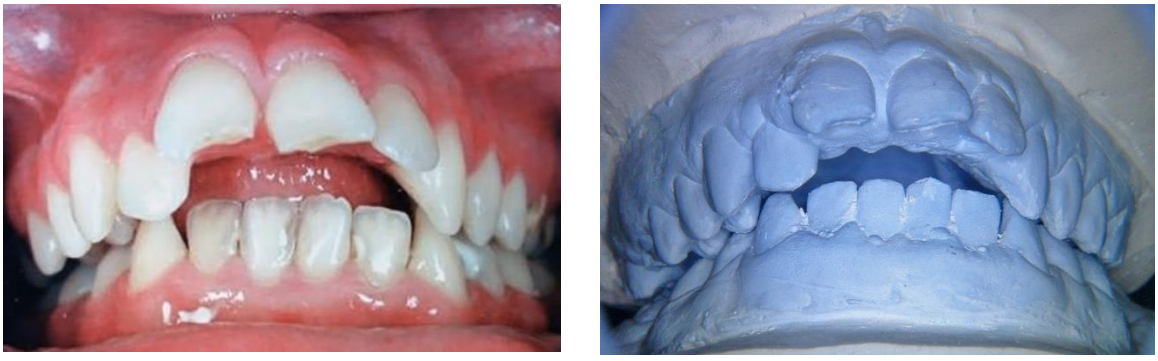


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Figure 2. a) Intra-oral examination - frontal view; b) cast model - frontal view

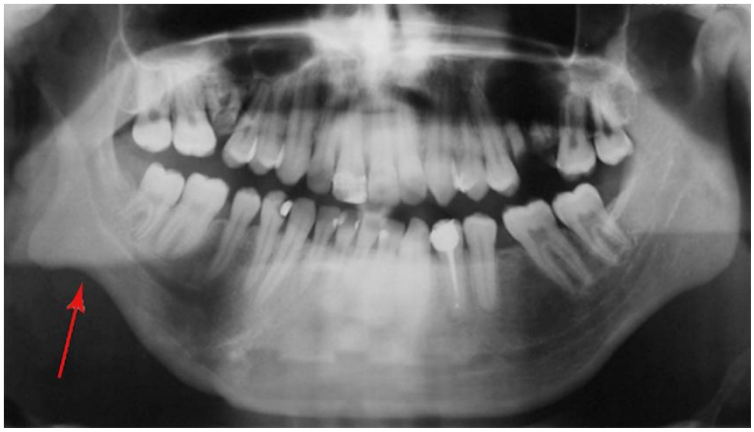
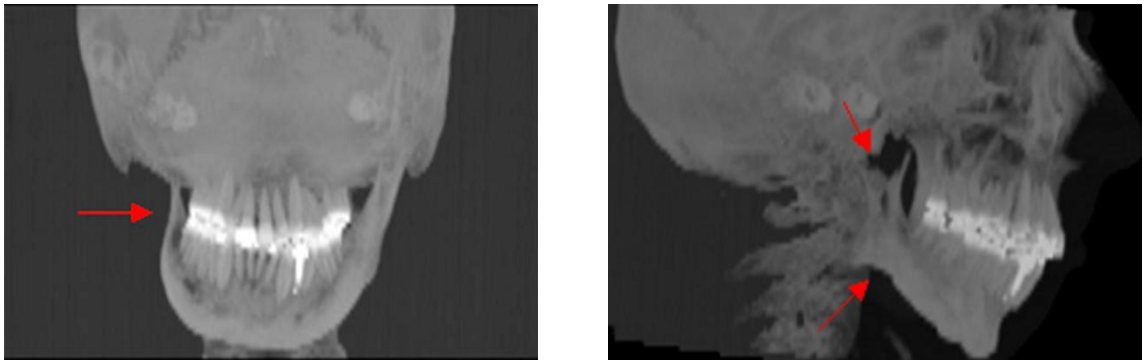


Figure 3. Orthopantomographic exam



a) *b)*

Figure 4. 3D CT reconstruction images: a) frontal view; b) right side view

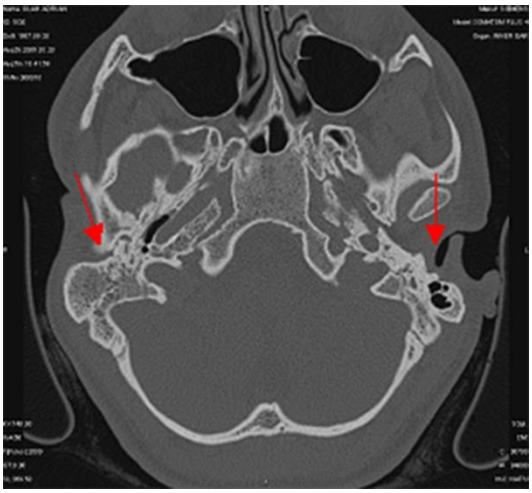
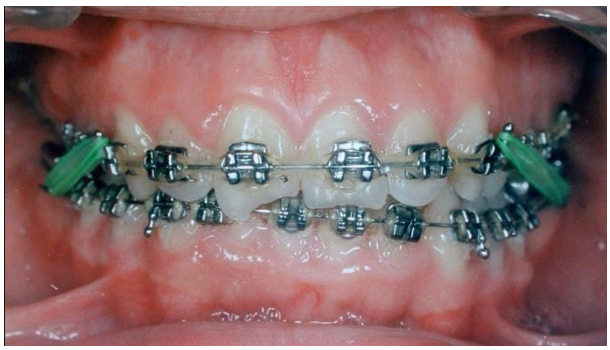


Figure 5. 3D CT reconstruction images showing the bony atresia of the external auditory canal

The dental and skeletal Class II anomaly was confirmed by the cephalometric analysis.

The main objectives of the orthodontic treatment plan were to correct the Class II division 1 malocclusion and the unilateral lingualized occlusion, without altering the transverse occlusal relationships on the opposite side.

Fixed orthodontic appliances (Roth OMNI 0.18", GAC brackets) were applied using the straight wire technique (Figure 6). Overjet reduction started slowly at the beginning of the treatment, using Class II mechanics. A non-extraction treatment approach was adopted.



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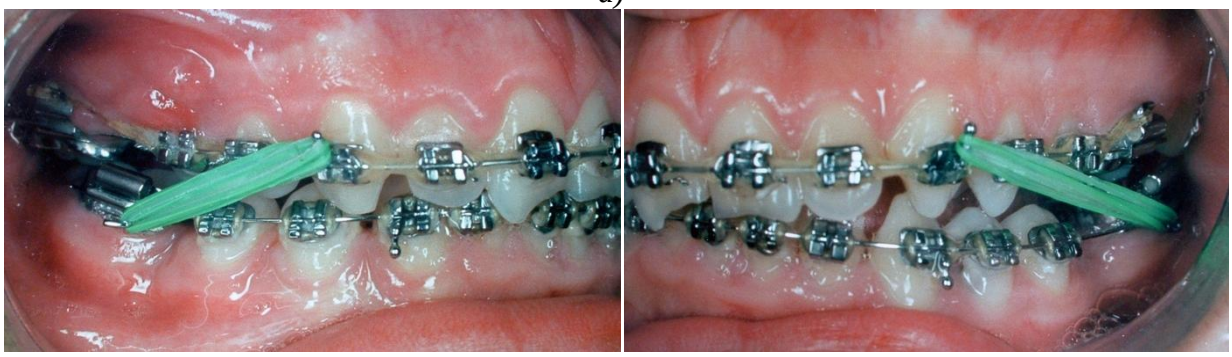
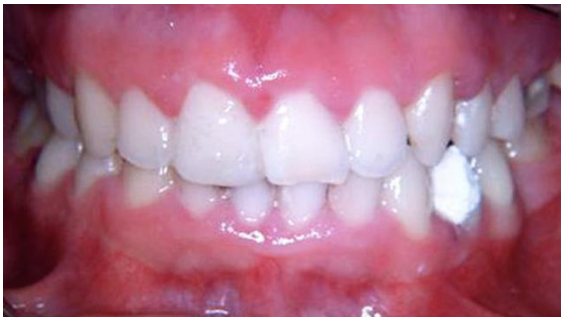


b) *c)*

Figure 6. Intermediate treatment phase after the brackets and Class II intermaxillary elastics were applied: a) frontal view; b) right lateral view; c) left lateral vie

TREATMENT RESULTS

Orthodontic treatment of the malocclusion and partially improved aesthetics using a silicone implant on the affected side improved the overall facial appearance and facilitated the patient's integration into society (Figure 7 and 8).



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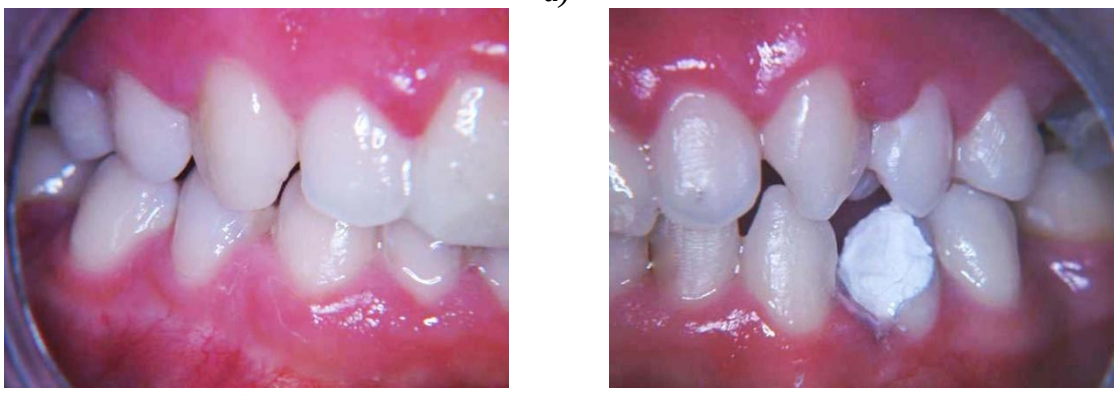
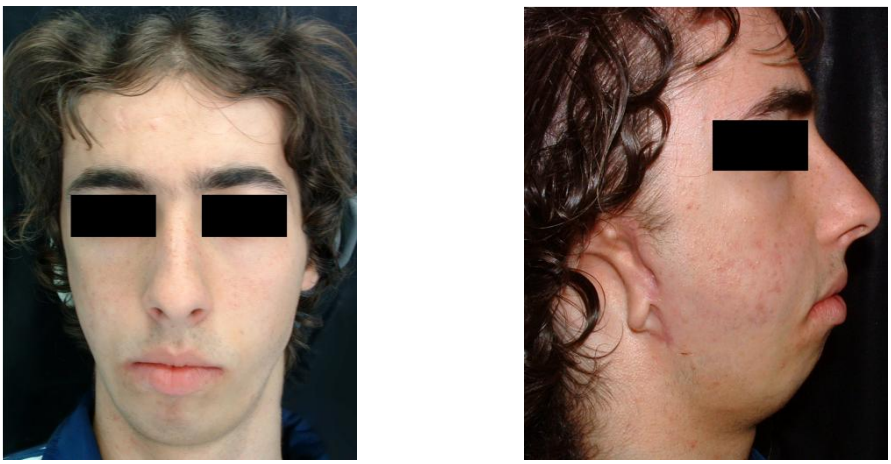


b) *c)*

Figure 7. Treatment results (intra-oral examination): a) frontal view; b) right lateral view; c) left lateral view



a) *b)*

Figure 8. Treatment results (extra-oral examination): a) frontal view; b) lateral view

DISCUSSIONS

The orthodontic and plastic surgical treatment facilitated good results for the patient.

Current modern treatment modalities in patients with HFM also include bite-jumping appliances (functional appliances), low-intensity pulsed ultrasound (LIPUS), photobiomodulation and gene therapy [24], but in our case, the patient's poor financial situation and the limited access to these treatment alternatives did not allow for other complex therapies.

In the literature, the optimal timing for HFM treatment has often been discussed. The opinions are usually divergent: some authors argue in favour of early surgical intervention, because they believe that the asymmetry will accentuate during growth, while others prefer to delay the surgical treatment after the growth period is completed, because the immediate results are supposed to remain stable. Distraction osteogenesis is a good alternative to classical surgical interventions (bone grafts, osteotomies) and an increasingly popular surgical treatment option in treating patients with HFM. However, this method is contraindicated in situations in which TMJ reconstruction is needed. The distraction can lengthen the body of the mandible and the ramus, but is unable to promote the development of a normally functioning TMJ [23].

Ideally, the patients diagnosed with HFM should be placed in the care of an experienced multidisciplinary craniofacial team, in order to achieve an optimal treatment outcome. These patients require properly coordinated assessments and time-sensitive interventions at appropriate stages of craniofacial growth and development to assure adequate respiratory support and feeding in infants with severe facial malformations, to improve hearing, to optimize occlusal relationships and to improve facial symmetry [4].

CONCLUSIONS

The treatment of patients with hemifacial microsomia (HFM) always requires an interdisciplinary approach including at least orthodontics, plastic surgery and maxillofacial surgery. The cooperation with the patients and their

family, but also within the multidisciplinary team is essential in order to achieve optimal results.

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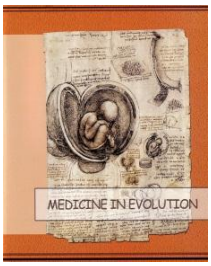
DETECTION AND MINIMALLY INVASIVE TREATMENT OF INCIPIENT CARIES – CLINICAL CASE



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ABSTRACT

The detection of incipient caries is important for the implementation of the preventive techniques and minimally invasive treatment. This clinical case presents a 42 years old patient, with incipient caries on premolars 15, 45. In order to depict the therapeutic method, to choose the preventive methods or the minimally invasive restorations, the diagnosis of the caries was made through the association of various detection methods, as for example clinical examination, bitewing x-ray and fluorescent laser (DIAGNOdent) and as restorative material, giomer has been chosen for it's physical, aesthetic and preventive qualities.

Key words: *incipient caries, bitewing x-ray, fluorescent laser, dental diagnosis*

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INTRODUCTION

The modern approach of dental caries involves detection and the delay of the operational intervention, as long as this is possible, and monitoring its evolution. In a broader sense, the idea is to preserve as much tooth enamel and demineralised but also non-cavity dentine as possible. The restoration is postpone until the illness is controlled (balanced) and the operational intervention becomes necessary due to the cavity,

Nowadays along with the clinical and radiologic analogue examination, the diagnosis of incipient dental caries can be carried out with the help of several methods among which fibre optic transillumination (FOTI), the quantitative light-induced fluorescence (QLF), the fluorescence laser (DiagnoDent), the digital photography. Each of these methods presents advantages and disadvantages, so that for a certain diagnosis several methods should be associated [1].

CASE STUDY

The patient, aged 42, came to the dental office due to the colour change on the level of the occlusal surface 45,15 and on the level of the distal surface 45, where the clinical aspect is typical for the stationary caries determined by the absence of the contact point between 45 and 46 by creating the conditions of cleaning and self-cleaning and the creation of the sclerotic dentine which is resistant to the carcinogen attack (fig.1).

In order to make a diagnosis, the patient was recommended to make a bitewing radiography to identify the proximal caries lesion from 45, with a localisation in 1/3 in the internal lacquer, the occlusal lesions are not visible during the radiology. In exchange there were shown incipient lesion of the distal face of 12,13 (fig.2).

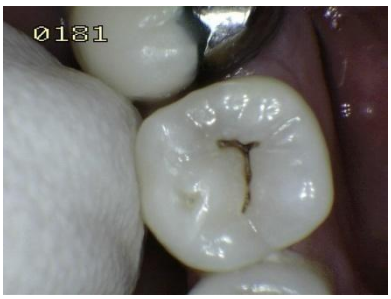

Figure 1. Initial aspect 45

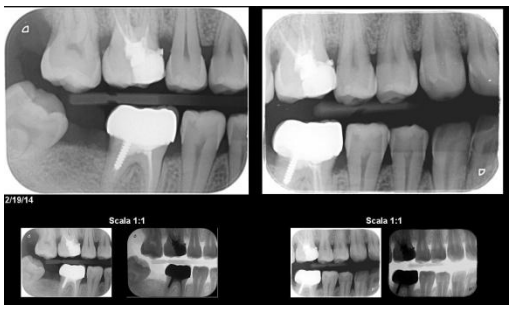

Figure 2. Bitewing Radiography

For the assessment of the depth of the occlusal caries the fluorescent laser method was used with the DiagnoDent device (KaVo, Biberach, Germany). The probe 1 was used (for occlusal surfaces) and probe 2 (for proximal surfaces) the device being initially calibrated for the reverence porcelain piece and then on a healthy surface for each analyzed tooth.

The values of laser induced fluorescence for each of the examined areas were automatically set, registering the highest value. Therefore, for the occlusal surface 15 and the distal surface 45 the values are in the category of evolving caries lesion (interval 36-50), and on the level of the occlusal surface of 45 the incipient lesion with the potential of remineralisation (interval 21-35) (fig. 3).

The therapeutic protocol

Before starting the treatment, the dental prophylaxis with prophy jet was

carried out (3M ESPE Clinpro Prophy Powder).

The treatment of the occlusal caries was made with the help of preventive resin restorations. After applying rubber dam (Coltene Hygenic Non-Latex Rubber Dam) the access was made with the help of a diamond pear shaped bur, the edges of the enamel have to be just, without micro-fissures, the affected dentine is preserved in order to be re-mineralized. For the proximal caries, the tunnel preparation method was used. The access is made with the small round diamond bur, leaving a minimum 2 mm width on the marginal groove of the tooth. The access channel is widened and then bucco-lingual similarly to the standard preparation of the 2nd class cavity, by placing the dental bur vertically without touching the marginal groove (fig. 4).

The restoration was made has been done using an adhesive system Gluma 2Bond (Heraeus Kulzer) and giomers Beautifill low flow and Beautifill II (Shofu Inc.), after the insulation with rubber dam and the desiccation of the cavities.

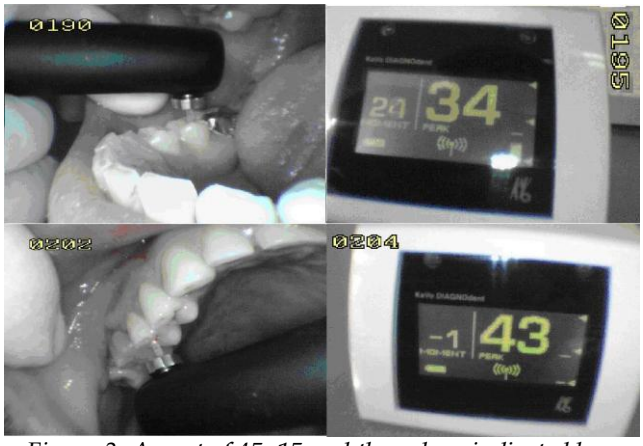

Figure 3. Aspect of 45, 15 and the values indicated by DiagnoDent

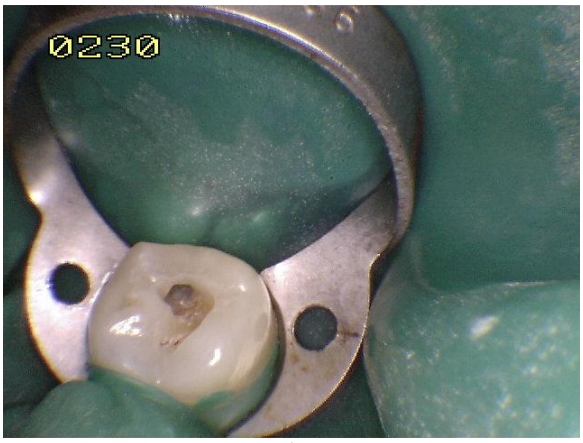

Figure 4. Tunnel preparation 45

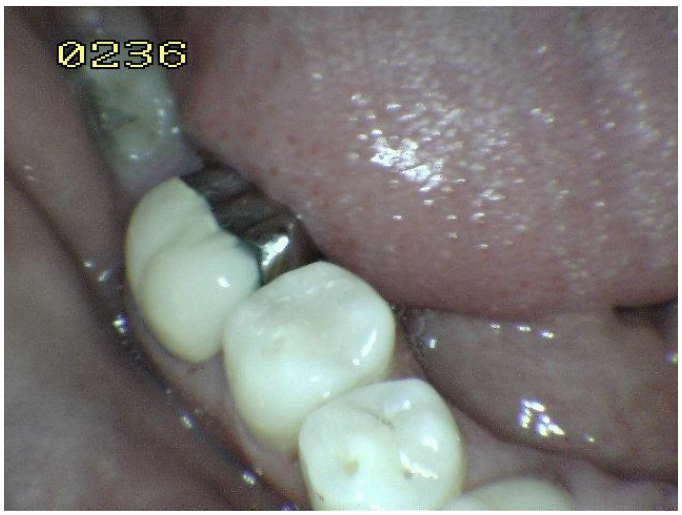

Figure 5. 45- Final aspect of giomer's restoration

The remineralisation of the incipient lesions 12,13 was carried out through fluoridation, the topical application of a varnish (Clinpro™ XT -3M ESPE contains 5% sodium fluoride) associated with a brushing with fluorite (Clinpro™ 3M ESPE contains 0,21% sodium fluoride and calcium triphosphate) mouth rinsing 2 a day with Na fluoride 0,05% for 1 minute, in the evening before going to bed, the patient being monitored.

DISCUSSIONS

Although there are varied methods for the diagnosis of the incipient caries with good clinical results, choosing them is not always easy.

The visual examination for the detection of the incipient occlusal caries has a high specificity due to the changes in colour (brown, white) caused by the demineralisation process on the level of the pits and fissures but also a low sensibility due to the incapacity of determining the level of destruction of non-cavity lesions. Moreover, using the probe for the diagnosis is not indicated because it might damage the structure of the enmel with the reduction of the re-mineralisation potential. [2,3].

Detection of the proximal caries is a challenge for dentists because the contact points hinder the direct visual inspection of the dental surface. Therefore conventional methods have to be used, the visual inspection being the most widely used method, easy and fast and which creates the less discomfort. [4].

The bitewing radiography, although it is not a screening method, it represents an important complementary way to depict caries. It is the most common technique to detect the proximal caries for the posterior teeth although it exposes the patient to a relatively high degree of ionic radiations. Although the radiologic method might increase the sensitivity of visual inspection, it cannot estimate the real depth of the caries. [5].

The laser induced fluorescence (DiagnoDent) is a quantitative and non-invasive method for the diagnosis of the dental caries [6].

Studies showed that this technique has sensibility values between 73-96% and specificity in the interval 63-95% and proved to be more precise in the early depiction of the dental caries as compared to other conventional methods [7]

The minimally invasive restoration method consists in carrying out minimal surgical interventions in for the cavity lesions, stopping the development of new caries lesions and the evolution of the existing lesions.

The following properties as for example aesthetics, manageability, polishing and easy finishing, long term clinical stability, resistance to wear for the posterior teeth, high level of radio-opacity, anti-plaque effect, bio-compatibility and a high level of releasing and adding flours make the giomer an ideal material for the restoration of the dental caries.

CONCLUSIONS

The association of precocious detection methods for the caries lesions, monitoring the therapeutic intervention and choosing the suitable materials represent the solution for an optimum management of the dental caries lesions.

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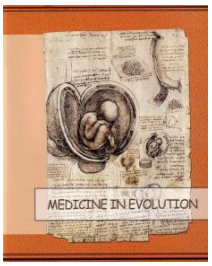
COMMUNICATION STRATEGIES IN ORAL HEALTH PROMOTION AT CHILDREN'S BETWEEN 3 AND 11 YEARS



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ABSTRACT

Conventional oral health education is neither effective nor efficient. Many oral health programmes are developed and implemented in isolation from other health programmes (2). This often leads, at best to a duplication of effort, or worse, conflicting messages being delivered to the public. In addition, oral health programmes tend to concentrate on individual behavior change and largely ignore the influence of socio-political factors as the key determinants of health. Oral health is determined by diet, hygiene, smoking, alcohol use, stress and trauma. As these causes are common to a number of other chronic diseases, adopting a collaborative approach is more rational than one that is disease specific. The common risk factor approach can be implemented in a variety of ways. Childhood oral disease has significant medical and financial consequences that may not be appreciated because of the separation of medicine and dentistry. The infectious nature of dental caries, its early onset, and the potential of early interventions require an emphasis on preventive oral care in primary pediatric care to complement existing dental services. ***Methodology*** *In this study we took 576 children from 5 kindergartens and 3 schools from Timisoara. The study lasted for three years between 2011 and 2013, when I did oral health education lessons using various communication methods for the children's and their parents and annual oral evaluation.* ***Results:*** *the oral status was improved significant p= 0.03, by the oral health lessons, where I applied different types of communicational methods.* ***Conclusions:*** *Oral health is integral to overall health and is necessary to correct information at community level, which is part of the existing trends and global interest in their own health. Effective communication is the backbone of health promotion and disease prevention. People need to understand health information to apply it to their own behavior.*

Key words: *oral health; health promotion; communication in educational health, children oral health*

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INTRODUCTION

Oral health is an integral element of general health and well-being. Good oral health enables individuals to communicate effectively, to eat and enjoy a variety of foods, and is important in overall quality of life, self-esteem and social confidence (1). Oral diseases affect a significant proportion of the world's population and exact a heavy toll in terms of morbidity and mortality (2). A range of diseases and conditions can be classified as oral diseases including dental caries, periodontal diseases, oral cancers, noma, dental erosion and dental fluorosis (3). Oral diseases are highly prevalent and their impact on both society and the individual is significant. Pain, discomfort, sleepless nights, limitation in eating function leading to poor nutrition, and time off school or work as a result of dental problems are all common effects of oral diseases.

Oral diseases are however largely preventable. The challenge is to create the opportunity and conditions to enable individuals and communities to enjoy good oral health. Although advances in clinical operative techniques have made dental treatment more effective and acceptable, treatment approaches alone will never eradicate oral diseases. Indeed in many low-income countries in the developing world, the total costs of providing traditional operative dental care would exceed the entire health care budget (4). Effective public health approaches are therefore required to prevent oral diseases and promote oral health across the population.

Public health strategies should tackle the underlying social determinants of oral health through the adoption of a common risk approach. Isolated interventions which merely focus on changing oral health behaviors will not achieve sustainable improvements in oral health. Radical public health action on the conditions which determine unhealthy behaviors across the population is needed rather than relying solely on the high-risk approach. Many studies that compare the reading difficulties of health materials with the skills of the reading public indicate that there is a broad gap between the readers and the materials (1-9). At the same time, many health professionals also give information orally that cannot be understood by their listeners. The most poorly educated adults, those with the lowest literacy levels, suffer the highest rates of morbidity and mortality from chronic diseases and conditions. The fact that they cannot either read or understand the information necessary to improve their health would seem to be an important contributing factor.

Children's health is an indicator of the health of the community. Fundamentals of oral health are established in childhood. Therefore, the existence of optimal oral health in children paves its perpetuation in adolescent and then to adulthood. At the same time, improving on with age, knowledge and sanogene attitudes ensure the existence of a state of optimal health and then to older adults, with positive effects on quality of life in terms of oral health.

The aim of the study in the thesis has considered the assessment of oral health status in preschool and school children in the municipality of Timisoara, changing behaviors to both the child and the parents on oral health care and establishing the best communication strategies to promote oral health in school communities in the City.

METHODOLOGY

The study began in 2011 and included five kindergartens with pre-school children and three schools of the Timisoara. Kindergartens were chosen to include families with different socio-economic statuses. I also chose both kindergartens with prolonged (where children carry about 2/3 of the daily activities in the presence of teachers, their activities cultural, sleep, eat food cooked by professional staff in kindergarten) and kindergartens with normal (short program - children are active only for a period of 4-5 hours. they do not sleep and do not eat in kindergarten eventually serve a sandwich prepared at home). In this study I proposed to study the children's by age categories, so I split them in 2 groups:

- Group 1- with 236 preschooler children's, with age between 3 and 5 years;
- Group 2- with 342 primary school children's, with age between 6 and 11 years old

Study assessments were performed annually, so each group will have annually evaluation in 2011, 2012 and 2013 respectively. Given that during this 3 years of the study there were outflows of the lot, the objective cause for assess the overall progress of oro-dental status have taken into account all children: For all children was completed questionnaires, for the first group the questionnaire was completed by parents, and for the second group was completed by the students with help or not from their parents. After the oro-dental evaluation, we recorded the the CAO Index (cavities simple, complicated root residues, missing teeth, filling materials used in dental caries) and the Dental Neglect Scalen (SND).

In the proper education for oral health we initially approached through discussion in large groups, in which we involved children with information about the role of teeth in the oral cavity, the importance of nutrition in maintaining dental health. As a next step in implementing the program, we have opted for discussions in small groups (one group of children) in which we emphasize elements decay, tooth brushing role in oral health, the importance of visiting the dentist. I implemented also a lot of plays with the oral health theme.

Children were educated and convinced to carry home brushing 2 times a day, morning and evening mandatory bedtime brushing as part of daily activities. For this we organized meetings with parents where we discussed the importance and role of teeth in child development, the importance of tooth brushing to remove plaque, caries prevention, parental support in forming and changing behaviors and attitudes of children regarding oral health. It was also explained to parents the importance of regular visits to the dentist in accordance with World Health Organization, which recommends two annual inspections, at intervals of six months, even before the age of 3 years old child.

RESULTS

Analysis of group I study cases indicate that the age of 4-4.5 years 71.26% of the children teeth indemnities. Also note that as the child grows the percentage of teeth caries free (caod = 0) decreases and increases the prevalence of dental caries. If in 2011 – 28.74% of children caries lesions, cavitary lesion rate in 2013 is 49.62%. (See table 1).

Table 1. Distribution of caries free and the cases of caries assessment year round

Group 1	2011		2012		2013	
	nr of cases	%	nr. of cases	%	nr. of cases	%
Caod = 0	168	71.26%	155	64.56%	121	51.38%
Caod = 1	68	28.74%	81	35.44%	115	49.62%

We removed cases urged teeth caries (Caod = 0) to assess only teeth with caries (Caod ≥ 1). By analyzing statistical indicators found an average index ≥ 1 Caod equal value 3.59 in 2011, 3.75 in 2012, and 4.12 in 2013. Analyzing Caod index ≥ 1, for each year of assessment, it appears that each component of the index increases. Caod index values are much higher relative to the other indices, so that in 2011 the mean caries index was 3.59, in 2012 - 3.85, and in 2013 reached an average value of 4.30.

Table 2. Statistics indicators of Caod Index (Caod ≥ 1) for the group 1 assessment year round

Group 1 Caod ≥ 1	Mean Caod	Mean		Std. dev
		- 95%	- 95%	
2011	3.59	2.87	4.32	2.88
2012	3.85	3.41	4.31	3.01
2013	4.30	3.88	4.66	3.60

Analysis Caod index, overall, the group II study indicates that the average value of the index increases with caod assessment year, so in 2008 the index was 3.72, in 2011 – 4.22, and in 2013 had an average value of 4.12. Following the analysis of nonparametric tests for comparing mean values of the Caod index depending on the years of assessment, in group II study, statistically significant difference between these values (p = 0.0000, 95% CI).

Table 3. S Statistics indicators of Caod Index (caod ≥ 1) for the group 2 assessment year round

Group 1 Caod ≥ 1	Mean Caod	Mean		Std. dev
		- 95%	- 95%	
2011	3.72	3.23	4.21	2.75
2012	4.32	4.12	4.87	3.60
2013	4.22	3.64	4.96	3.59

Analyzing the Caod index ≥ 1 for each year of study, we find that the highest value presents caries index (cd). In 2011 the value of the cavity (cd) of 3.72 was increased considerably in 2012, up from 4.32 in 2013 to note that only a slight increase in the index to the value of 4.22.

NDS mean scores for all children was 13.2 (SD = 3.8, mean = 13, 6-23). Average for boys was 13.6 (SD = 4.2, mean = 14, 6-23). For girls, the mean was 12.8 (SD = 3.3, mean = 13, between 7-23). Overall, only 3.5% of mothers were sure that their child's oral health was very good, 20% said that the teeth were good, 46.5% satisfactory noted the oral status, 23% reported that their child had affected teeth, and 6% of mothers could not answer.

Regarding the need for dental care, 69% of mothers responded that their child needs one or more dental treatment, 24% reported not need dental care and 7% of the mothers did not answer the question. In assessing their own oral health 26% of mothers said that their teeth are in good condition and did not need dental care and 74% said that their teeth were in poor condition and need for treatment dental.

Regarding the question about the causes of gingival bleeding, the following risk factors were selected: brushing incorrectly performed (75%), plaque (60%), general diseases (50%), unhealthy diet (35%), heredity (15 %), eating hot and cold (12%) and 3.3% of teachers do not know the causes of bleeding gums.

DISCUSSIONS

The level of oral health knowledge of mothers is higher the average value of the CAO Index in children is lower. There is a very high proportion of mothers who lack information and knowledge about the sanogene comportment in general and about the correct Oro-dental hygiene.

Following oral health education program conducted in pre-schools, increased frequency of tooth brushing twice a day both children and parents. Even if there is an increase in the interest of parents in the educational factor, visits to the dentist is not a priority in this moment.

Although the mean caries index increased from an assessment to another, there was an improvement in the accumulation of knowledge and change attitudes and behaviors among preschoolers.

Making SND highlights groups that may benefit from intensive efforts to promote oral health, but can evaluate the effects of oral health promotion programs.

The family is responsible for the proper behavior of the child as it is the first source of information regarding oral health. One way to increase interest in children's oral health by providing continuously updated information, education and motivation of parents permanently. At the same time the school has great potential for forming sanogene habits, due the long time that children spend in this location. The results of this study show that adult sanogene habits and level of knowledge are important factors in the oral health education of children.

CONCLUSIONS

he results of this study show that adult sanogene habits and level of knowledge are the key factors in oral health education of children.

Health education campaign for preschool children, mothers and teachers led to awareness of dental care, food factor, to control regular dentist; led finally to the conclusion that the primary role in oral health education bears primary prevention in dentistry.

In health education, family and teachers play an important role, but the impact of health professionals and the media are decisive. Health education success is confidence in the medical profession, the benefits of good dental.

Clinical prevention and health education alone will not achieve sustainable improvements in oral health. In addition these approaches are very costly and are dependent upon the availability of appropriately trained oral health personnel. In both developed and developing countries public health strategies based upon the common risk approach are more likely to be effective in achieving significant oral health gains.

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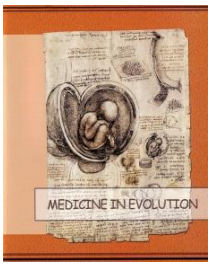
PREVALENCE OF ORAL PRE-MALIGNANT LESIONS AND ITS RISK FACTORS



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ABSTRACT

Oral cancer constitutes 5.5% of all malignancies globally and is the sixth most common cancer world-wide. non-significant. Red and white lesions were highly significant (i.e. 1.2 % and 10.9% respectively) in the subjects with pan chewing and smoking habits (p=0.001). A significant proportion (8.9%) of the subjects with pan chewing habit showed evidence of oral precancerous lesions (p=0.001). Conclusions: Even though smoking and pan chewing were two significant risk factors detected in this population, their prevalence and occurrence of premalignant lesions are low as compared to the studies. Oral squamous cell carcinomas (OSCCs) are generally associated with tobacco habits (mainly chewing with/without smoking or alcohol consumption) and usually preceded by premalignant lesions. Materials and Methods: This cross sectional study assessed the prevalence of risk factors and occurrence of oral precancerous lesions in a low income group expatriate community from the Indian subcontinent residing in Qatar. Results: Among the 3,946 participants screened for oral premalignant lesions 24.3% (958) were smokers and 4.3 % (169) were pan chewers while 6.3% (248) were users of both smoked and smokeless forms of tobacco. Significantly higher proportion of industrial laborers (49.9%) followed by drivers (24.1%) were found to be smokers (p=0.001). The prevalence of white lesions was higher in smokers versus non-smokers 3.5% versus 2.3% (p=0.111), however this difference was statistically.

Key words: *Oral premalignant lesions - risk factors*

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INTRODUCTION

Oral cancer constitutes 5.5% of all malignancies globally and is the sixth most common cancer world-wide.[1] Oral squamous cell carcinomas (OSCCs) are generally associated with tobacco habits (mainly chewing with/without smoking or alcohol consumption) and usually preceded by premalignant lesions, most often a persistent leukoplakia.[2] The overall incidence of malignant transformation of oral leukoplakia varies from 8.8% in females versus 5.1% in males with a 30 years follow-up period[3] and similar findings were noted by Silverman in their study for a follow-up period of 7.2 years.[4] Several etiological factors, particularly tobacco/alcohol consumption and human papilloma virus (HPV) infection, have been shown to be linked with the OSCC.[5] Some studies on HPV, known to be linked with cervical and various other anogenital (i.e. vulvar, penile, perianal and anal) cancers,[6 7] have shown that the prevalence of HPV in OSCC was higher than in normal mucosa; thus, HPV is being regarded as a risk factor and important determinant in oral carcinogenesis. Some studies have suggested that HPV exerts its oncogenic property by inhibiting the function of the tumor suppressor proteins p53,[8] but confirming literature is still lacking. Reduced access to treatment, low prioritization of the disease and the specific cultural and social habits are the main reasons for increased incidence of oral cancer in this underserved population [9]. It has been consistently shown that total incidence of and mortality from cancer is higher in underprivileged socioeconomic groups [9 10 11]. The oral cancer is the eighth most common cancer globally and its incidence levels among men range from one to 10 cases per 100,000 which is twice as high in developing countries as they are in developed countries [12].

It is known that the social and cultural habits in this population remain prevalent even after migration to better resourced countries [12]. Countries that once rarely experienced high levels of oral cancer are likely to see a considerable increase of this disease

Studies have shown that between less than 1 and up to 18% of oral pre-malignant lesions will develop into oral cancer [13]. Early detection of premalignant lesions can improve the prognosis and is well proved as an effective aid in disease prevention. This cross sectional study assess the prevalence of oral precancerous lesion and its risk factors in the low income group. The prevalence of possible etiological factors in different nationalities mainly focusing on smoking and pan chewing are also detected.

MATERIAL AND METHODS

A population-based cross-sectional study was conducted. Workers in different fields were randomly selected from medical camps organized on a yearly basis during 2012 to 2013. Participants below 18 years and those with history of oral malignancy were excluded from the study. Workers were transported from the hostels and private accommodations to a venue equipped with screening facilities.

On the day of screening, all the participants were explained about the purpose of the study and then a written informed consent was taken from each of them before the screening. The participants were given the options not to participate in the study

if they wanted while waiting for medical assessment.

The first stage comprised of an interview to get demographic and preliminary data for the study and was done by trained members of the organizing voluntary associations. The close-ended questionnaire contained questions relating to risk factors of oral cancer and socio-demographic situation. The questionnaire was tailored for the study by modifying the WHO oral health assessment form.

The main outcome measures from the preliminary data collection were socio-demographic variables associated with oral cancer. The following data were collected. Habits of 1) Smoking; 2) Alcohol use; 3) Reverse smoking; 4) Different methods of chewing tobacco.

In the second stage, the entire recruited participants underwent an oral examination by at least one locally practicing licensed dentist. Suspected lesions were further seen by specialist dental surgeons who were the principal investigators. All non scrapable lesions not pertaining to any disease, not a normal variant, detected by a general practitioner are considered as suspected lesions. Further exclusion was done by specialist dentist to group them into mainly two types i.e. white lesions and red and white lesions. Sub-mucous fibrosis is grouped into any one of these groups according to the clinical presentation. Any ulcerative or mixed lesions are grouped into red and white category. All the red and white lesions and confirmed pre malignant lesions which required histopathological study were referred for further definitive treatment .

Analysis of data was performed by using SPSS-20.0. Results of categorical responses were presented in terms of frequencies and percentages. Chi-square test was applied to compare the demographic and soft-tissue lesion characteristics between tobacco and non-tobacco users, also with regards to type of lesions. p value ≤0.05 was considered significant.

RESULTS

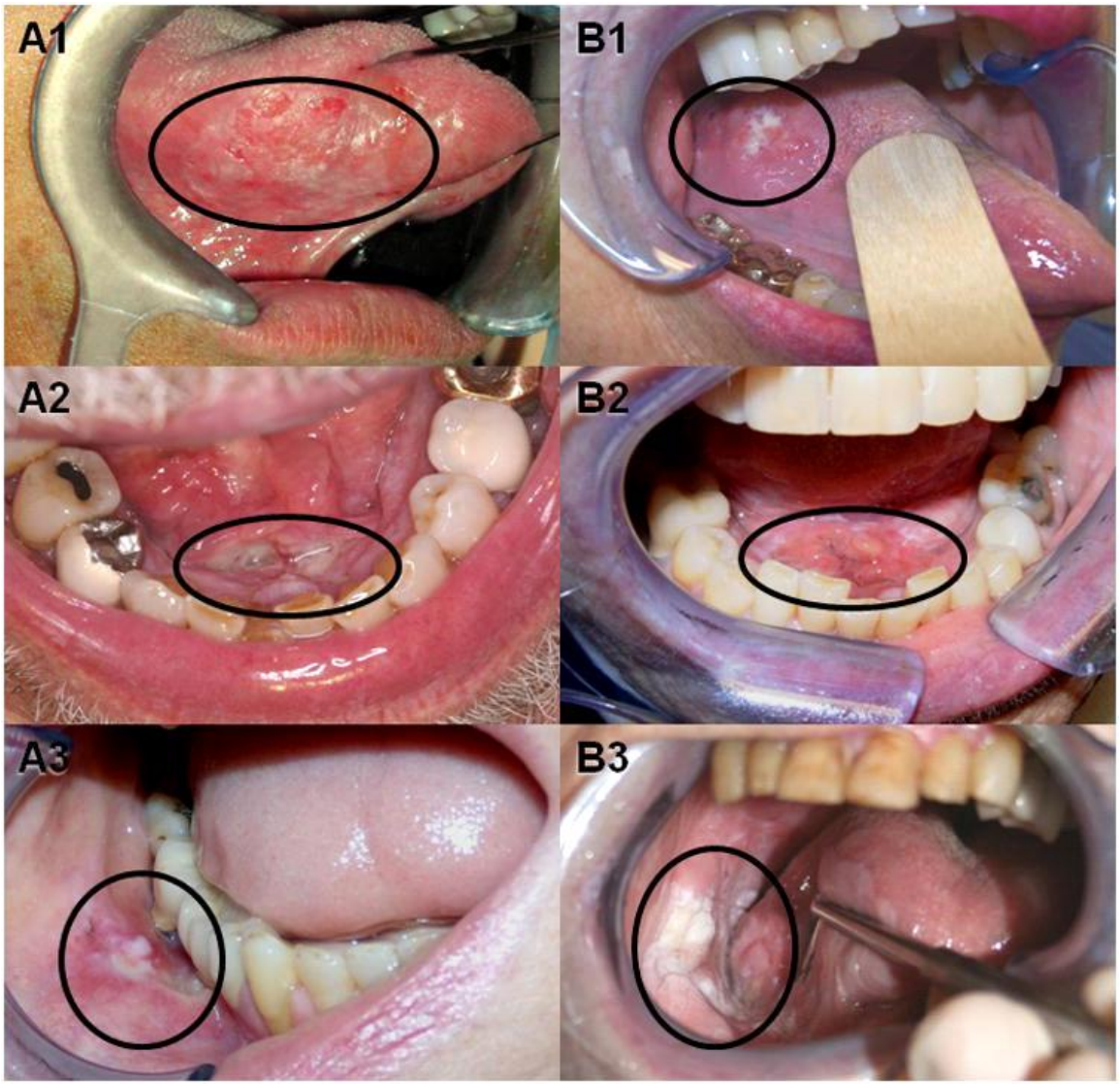
Prevalence of risk factors

The prevalence of use of tobacco smoking and pan chewing were found 24.2% and 10.6% respectively. While considering major professions, significant proportion of unclassified or multiple job holders were the major tobacco users (34.8%) followed by industrial laborers (26.9%) and drivers (25.2%) (p=0.001). Construction workers were found to be a significant proportion of tobacco users (36%) followed by taxi drivers (26.2%) and others (24.9%) (p=0.001). Out of 9 patients with red & white lesions, only 2 of them (22.2%) were tobacco users while 7 (77.8%) were non tobacco users. Among 103 white lesions, 33% were tobacco users. Data reveals statistically insignificant prevalence of soft tissue lesion (p=0.111) in tobacco user population.

Among the 3946 participants 958 (24.3%) were smokers and 169(4.3%) were pan chewers while 248(6.3%) were users of both smoked and smokeless forms of tobacco. Of the 958 smokers majority were using filtered cigarettes alone where a very small group (9) were using other types of tobacco along with cigarettes. Most of the pan chewers (237out of 248) were using pan betel leaf/Nut with tobacco and 11 were using pan masala with tobacco. The prevalence of smoking is higher among the age group of 31 to 40 (24%), and the majority were using 5 to 10 cigarettes per day for at least 3 years. Significantly higher proportion of Industrial laborers' (49.9%) followed by drivers (24.1%) were found to be smokers (p=0.001). The prevalence of white lesion was higher in smokers versus non-smokers 3.5% versus 2.3%

(p=0.111), however this difference was statistically non-significant. The red & white lesions were equally prevalent in tobacco and non-tobacco users.

Data on consumption of alcohol as a causative factor was not taken into account due to insufficient and unreliable data.



Precancerous lesions such as carcinoma *in situ* affecting the lateral tongue (**A1**), floor of mouth (**A2**), and buccal mucosa (**A3**) are not distinguishable from their respective squamous cell carcinoma counterparts (**B1, B2,** and **B3**) on physical examination alone. Black circles indicate approximate extent of oral lesion.

Ratio of occurrence of pre malignant lesions in the oral cavity

All the lesions detected were in male patients. No females (82) reported to have any smoking or chewing habits. Soft tissue lesions detected in the oral cavity were less compared to other similar studies conducted in their home countries. Only 2.83% of the participants were found to have any one of the soft tissue lesions. White lesions was the most common lesion detected (2.52%). Leukoplakia and nicotine stomatitis and chewer's keratosis were the most common white lesions detected. Red lesions (erythroplakia) were detected in 0.12 % of the population out of which one of the lesions was diagnosed as squamous cell carcinoma on histopathologic study following referral to the hospital. 55% of the oral lesions were detected in the age group of 31 to 50 years. No

lesions were detected in the age below 30 years. However, the proportion of lesions was significantly high in age group 61-70 years (p=0.002).

DISCUSSIONS

The selected population is a cross section of the low income socioeconomic group However the life style changes after migration and the lack of availability of some specific type of tobacco products may have altered these habits and its effects.

Smoking and chewing tobacco are the main two risk factors detected in the subject population. Due to the restricted availability of alcohol and its legal consequences of illegal consumption in the country, the data collected in relation to alcohol consumption was not reliable. This data had been discarded suspecting impurity. This is the main pit fall of the study.

The majority of the diagnosed cancer involving head and neck region were observed in the male population from Indian subcontinent. All the lesions detected in this study were in male participants. Since a vast majority of the low income work force are male, the female population reported to our study was only 2.1%. The male predominance in oral cancer prevalence cannot be supported in this study. The overall prevalence of oral lesions in the population (2.83%) is less when compared to other similar studies [15]. The prevalence of white lesions (2.61%), and red and white lesions (0.22%) were also less when compared to those found in other previous studies [161]7.

Effect of nature of job and stress related to work site in developing and continuing causative habits are well documented. The overall prevalence of smoking was 24.2% in this study. Out of all different professions studied, industrial labourers were one of the major groups found to have high (26.8%) percentage of smokers when compared to home labourers (17.7%). Among industrial labourers 33% of masons were smokers. None of the maids, home nurses and housekeepers reported with smoking or chewing habits explaining the correlation of nature of work to the habits.

Tobacco chewing (10.6%) was found to be at lower rate in this study when compared to the similar studies [18 19 20 21] Ascertaining to previous studies the lesions detected among chewing population was quite high (10.79%) when compared to the non-chewing participants of the study. The occurrence of both habits together (Smoking and chewing) and the relation to the lesions detected was also significant smoking and chewing were found to be the main significant predictors of premalignant lesions in this population. Correlating to the chewing habits a higher incidence rate of oral lesions (4.69%) is seen in this group. Studies have shown that various carcinogens are isolated from different form of smokeless tobacco products. Betel chewing may induce oral cancers via a p53-independent pathway [21] All forms of pan products are proved to be associated with occurrence of precancerous lesions. This necessitates implementation of further awareness programs in this group.

Work related stress, financial burden and trauma of separation from the family are some of the factors that could lead to develop detrimental habits such as tobacco use. Though officially banned, the availability of pan products at the work site among the low income working population may also be a reason for the higher incidence of this habit in some of the study group. However while considering the whole study population the change in the life style, non availability of pan products in the market and fully engaged work

schedule may explain the lower ratio of these habits and incidence of the lesion when compared to similar studies conducted in their home countries.

In conclusion, smoking and pan chewing are two significant risk factors of premalignant lesions of the oral cavity in the low income population. Studies of this nature could potentially help clinicians in identifying risk factors of similar immigrated population and would be beneficial for providing statistical evidence to the local health authorities for better resource planning.

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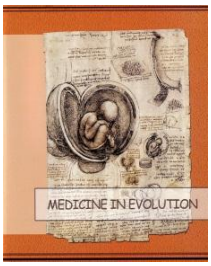

CORRELATION BETWEEN PERIODONTAL DISEASE AND ACUTE MYOCARDIAL INFARCTATION

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ABSTRACT

The aim of the present study was to assess if there is a possible association between occurrence of periodontal inflammatory processes, and the incidence and progression of coronary heart disease. A total of 124 patients after acute myocardial infarction (AMI) with and without ST-segment elevation (STEMI/NSTEMI), aged 51–83 years (mean age 62.3 years), were enrolled in this study, during a period of 1 year (2013–2014). A total of 125 healthy patients matched for age, gender, number of residual teeth and smoking habits served as control subjects. The oral assessment included number of teeth, endodontic treated teeth and caries frequency (DMFT indices). A set of standard periodontal parameters, probing pocket depths (PD), bleeding on probing (BOP), and clinical attachment levels (CAL), were recorded. All subjects were further required to complete a questionnaire and underwent a radiological examination. The dental assessment showed that the oral health of the coronary patients was considerably worse than in the controls subjects. The median number of missing teeth was 7.0, with 2.0 for the first and 15.0 for the third quartile, while it was only 3.0, with 1.0 for the first and 6.0 for the third quartile, in the control subjects, and the difference was statistically significant ($p = 0.001$). The index for caries frequency (DMFT index) lay, therefore, with 20.1 ± 5.4 in the coronary patients clearly above that of the control group (18.6 ± 5.6; $p = 0.001$), and the difference was also statistically significant. Periodontal parameters like PD and CAL were used to determine absence or type of periodontal diseases (localized or generalized). In 48 % of the coronary patients, generalized periodontitis was present, while it was only detected in 39 % of the control subjects ($p = 0.006$). Thus, chronic periodontal diseases were significantly more often found in coronary patients. The presence and frequency of periapical inflammatory processes in the alveolar bone were detected by means of radiographic methods. There was a tendency among the coronary patients toward more individuals with a higher number of inflammatory processes ($p = 0.019$, after Bonferroni correction). The final answer on the causal relation between periodontitis and atherosclerotic cardiovascular disease cannot be provided yet, the range of findings (from no causative to strong causal relationship) is mainly due to inharmonic study designs in regards of population, varying definitions of the diseases, and the chosen end points (measurements).

Key words: periodontal disease, myocardial infarctation, *periapical inflammatory processes*

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INTRODUCTION

Interdisciplinary dentistry has to serve, at least in part, as a communication platform between specialties within medicine. The chronic periodontal inflammation is widely accepted as a cause or a modifier in many diseases such as cardiovascular diseases (CVD), pancreatic cancer, preterm birth, and diabetes [6].

Periodontitis can be defined as a localized chronic inflammatory reaction to bacteria, with the capacity to destroy connective tissue and subsequent bone. Periodontitis is a common finding affecting a huge amount of the general population. Often a consequent treatment is not provided, mainly because of the unawareness of the possible lethal consequences and the asymptomatic course of the disease. Periodontitis is not a disease of developed countries only, high prevalence and incidence rates are reported in developing countries as well. And, in addition, symptoms of chronic periodontal inflammation are not specific and are ignored by the patient.

Chronic Periodontitis has to be understood as a microbial infection. A host-mediated destruction of soft tissue caused by hyper activated or primed leukocytes is the initiator. Production of signaling molecules such as cytokines, eicosanoids (e.g. arachidonic acid) and matrix metalloproteinases is induced. These mediators control many bodily systems, mainly in inflammation or immunity. Cells involved in the activation of immunity, such as neutrophils, play a central role in the host response against invading microorganisms, located in and on the altered periodontal tissues. Germ profile will change in case of an insufficient oral hygiene, especially in case of advanced periodontal diseases. Gram-negative anaerobic bacteria will displace physiologic oral flora. Porphyromonas gingivalis, Treponema denticola and Tannerella forsythia are potent activators of host immune-inflammatory processes and do have the strength to disrupt host mechanisms involved in bacterial clearance.[boala paro-ateroscleroza]

Periodontal disease has been associated with atherosclerosis [13], cardiovascular disease [14], diabetes [15], pre-term low birth weight [16], stroke [17], and premature death [18]. Accordingly, periodontal disease may account for a portion of the risk for cardiovascular disease via a shared pathogenic underlying inflammatory response (figure 1) [8]. [risc cardio-boala paro]

Cardiovascular diseases are a leading cause of morbidity and mortality in developed countries. The disease process that underlies the majority of cardiovascular events is atherosclerosis, an inflammatory disease of the blood vessel wall. The earliest physical evidence of atherosclerosis are fatty streaks, which are typically present in childhood. In the presence of arterial endothelial dysfunction, which is involved in the initiation and progression of atherosclerosis, these early lesions progress through to complex atheromatous lesions in adulthood, finally resulting in occlusion, plaque rupture and ischaemic events [6].

Treating periodontal disease results in a functional improvement in cardiovascular status [19-22]. These studies are consistent with the concept that periodontal disease may be an important source of infectious and inflammatory vascular stress, and that periodontal therapy may be of particular clinical relevance in populations with high prevalence of both periodontal disease and cardiovascular disease. [risc cardio-boala paro]

The aim of the present study was to assess if there is a possible association between occurrence of

periodontal inflammatory processes, and the incidence and progression of coronary heart disease.

METHODS

A total of 124 patients after acute myocardial infarction (AMI) with and without ST-segment elevation (STEMI/NSTEMI), aged 51–83 years (mean age 62.3 years), were enrolled in this study, during a period of 1 year (2013–2014). Inclusion criteria were the presence of an acute myocardial infarction, verified by characteristic electrocardiogram changes and evaluation of serum enzymes, and at least five residual teeth present. All patients had a recent history of AMI, followed by a diagnostic catheterization and reperfusion therapy such as percutaneous coronary intervention (PCI), bypass surgery or thrombolytic therapy. A dental examination was carried out 1–5 months after hospitalization. Only patients clinically stable enough to visit the dental school and undergo a thorough oral assessment were enrolled.

A total of 125 healthy patients matched for age, gender, number of residual teeth and smoking habits served as control subjects. They were in good general health, had no clinical signs of cardiovascular disease, hypercholesterolemia or any other serious diseases. The absence of severe cardiovascular disease, myocardial infarction, arrhythmias or untreated high blood pressure was confirmed by a cardiologist or an internist at least 6–12 months prior to the dental examination.

The oral assessment included number of teeth, endodontically treated teeth and caries frequency (DMFT indices). A set of standard periodontal parameters, probing pocket depths (PD), bleeding on probing (BOP), and clinical attachment levels (CAL), were recorded. All measurements were recorded at six aspects on each of the six Ramfjord teeth (mesio-buccal, midbuccal, disto-buccal, mesio-lingual, mid-lingual and distolingual) using a standard periodontal probe (PCP 15, Hu-Friedy, Chicago, IL, USA).

All subjects were further required to complete a questionnaire and underwent a radiological examination.

Diagnostic methods used for the detection of possible chronic apical lesions either of periodontal (LPO) or endodontic origin (LEO) were panoramic radiography, periapical radiography or in special cases cone beam computer tomography. Teeth were classified as having a chronic apical lesion if they exhibited periapical rarefaction contiguous to the periodontal ligament space with a width of more than 2 mm and absence of an intact lamina dura. In addition, periapical radiolucencies of periodontal and endodontic origin were recorded before and after endodontic treatment.

Statistical analyses were conducted using the SPSS program (version 18.0; SPSS Inc, Chicago IL). For descriptive analyses, means and standard deviations (SD) were calculated for normally distributed continuous variables, and median and quartiles for non-normally distributed continuous and for ordered variables. In addition, absolute and relative frequencies were computed for categorical variables. For confirmatory analyses, univariate pairwise comparisons between the two groups were performed. For continuous normally distributed variables, independent two-tailed t tests were used, and the Mann–Whitney U Test was used for non-normally distributed variables. For categorical variables, Chi-square tests of independence were performed. A global significance level for all statistical test procedures

conducted was chosen to a = 0.05; due to multiple testing, the Bonferroni correction was applied.

RESULTS

124 patients were available for the dental assessment (15.8 % response rate). The patients (94 male, 30 female, mean age: 62.3 years, SD ± 10.1 years), who were all clinically stable, underwent a thorough dental assessment, followed by a radiological examination.

125 "healthy" persons (89 male, 35 female, mean age: 63.5 years, SD ± 10.5) fulfilled the inclusion criteria and thus could be recruited as control subjects for this study (response rate 32%). These patients reported no cardiologic problems during anamnesis and they had no history of any heart disease in the past. No statistically significant differences were seen with respect to age distribution between the coronary patient and control groups.

The dental assessment showed that the oral health of the coronary patients was considerably worse than in the controls subjects. The median number of missing teeth was 7.0, with 2.0 for the first and 15.0 for the third quartile, while it was only 3.0, with 1.0 for the first and 6.0 for the third quartile, in the control subjects, and the difference was statistically significant (p = 0.001). The index for caries frequency (DMFT index) lay, therefore, with 20.1 ± 5.4 in the coronary patients clearly above that of the control group (18.6 ± 5.6; p = 0.001), and the difference was also statistically significant. Periodontal parameters like PD and CAL were used to determine absence or type of periodontal diseases (localized or generalized). (Fig.1)

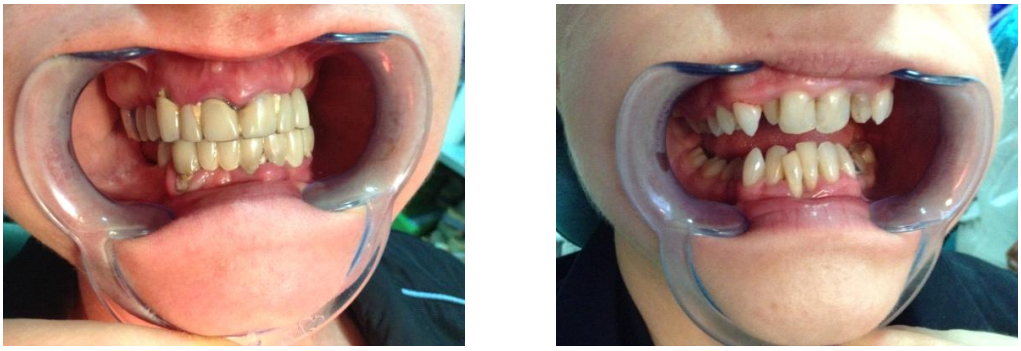

Figure 1. Coronary patients showing high DMFT indexes and localized or generalized periodontal disease

In 48 % of the coronary patients, generalized periodontitis was present, while it was only detected in 39 % of the control subjects (p = 0.006). Thus, chronic periodontal diseases were significantly more often found in coronary patients. The presence and frequency of periapical inflammatory processes in the alveolar bone were detected by means of radiographic methods. There was a tendency among the coronary patients toward more individuals with a higher number of inflammatory processes (p = 0.019, after Bonferroni correction). When judging the apical lesions according to the origin of the inflammation, either endodontic processes (LEO) can play a role, or pathologic probing depths or periodontal diseases (LPO), can be essential. In the coronary group, 47/124 patients showed a total number of 75 LEOs, while in the control group 24/249 patients had a total number of 36 lesions. Also in the coronary group, 30/124 patients showed a total number of 45 LPOs, while in the control group 18/125 patients showed a total number

of 25 lesions. The frequencies of the number of apical lesions (0, 1, 2, C3) per number of patient in the coronary or control groups are listed in detail in Table 1. Here it was also seen that lesions of endodontic origin were found statistically significantly more often in coronary patients (p = 0.001). For those of periodontal origin, no statistically significant difference (p = 0.051) was found between coronary patients and controls.

Table 1. The frequencies of the number of apical lesions

Variable	p value	Odds ratio	Lower limit of the95 % confidence interval	Upper limit of the 95 % confidence interval
Gender	0.010	0.525	0.322	0.858
Age	0.003	0.969	0.949	0.989
Localized periodontal disease	0.116	1.545	0.898	2.659
Generalized periodontal disease	0.622	0.879	0.527	1.466
Number of lesions of endodontic origin	0.012	1.541	1.102	2.156
Number of lesions of periodontal origin	0.349	1.178	0.837	1.658
DMFT values	0.028	0.948	0.904	0.994
Missing teeth	0.001	1.210	1.148	1.276

DISCUSSIONS

The results of the present study showed that in both groups chronic periodontal disease was present as localized or generalized form. Since the age distribution was homogeneous in both groups and they were matched for age, the primary assumption is that their prevalence should be the same in the two groups. However, this assumption could not be confirmed, because the results of the present investigation show among the coronary patients a clear shift in periodontal health toward generalized disease. In 48 % of the coronary patients, generalized periodontitis was present, while it was only detected in 39 % of the control subjects; this increased occurrence of periodontal diseases explains also in part the significantly higher number of missing teeth in the coronary patients in comparison to the control subjects.

Comparable results can be found in a study by Meurman et al. [19] who also observed that the subjects in the control group had about twice as many residual teeth than the CHD patients. In a relatively new study, it was reported that the number of missing teeth in an elderly population was in fact related to coronary heart disease. Holmlund et al. [20] could show in their investigation that the number of missing teeth was inversely correlated with the number of carotid arteries with atherosclerotic plaques. [corelatie infl paro-infart]

Periodontitis and atherosclerosis have many pathogenic mechanisms in common. Both the diseases have complex causation, genetic and gender predisposition and might share many risk factors, such as age, education, smoking, social status, and stress

[25].[prevalenta bacteriana in placi aterosclerotice]

Inflammatory processes within the vascular wall play a central role in the development of cardiovascular disease and have been the objects of complex and extensive research programs in the past, but investigations are still going on. C-reactive protein (CRP) serves as a biomarker in analyzing the risk of future myocardial infarction. CRP may play a role in endothelial cell dysfunction. Erythrocyte sedimentation, chemokines, and cytokines including different interleukins are abnormal in patients with acute coronary symptoms, and are believed to play a role in the pathogenesis process of cardiovascular diseases. Chronic inflammations, such as periodontitis, rheumatoid arthritis, psoriasis, infections of the respiratory and urinary tract, increase the incidence of atherosclerotic cardiovascular diseases. The altered function of blood vessel walls may result in arterial hypertension, known as an additional risk factor for cardiac infarction. The disturbed endothelial function may initiate the development of blood clots, subsequent inducing thrombotic, and embolic events.

The final answer on the causal relation between periodontitis and atherosclerotic cardiovascular disease cannot be provided yet, the range of findings (from no causative to strong causal relationship) is mainly due to inharmonic study designs in regards of population, varying definitions of the diseases, and the chosen end points (measurements). Meta analysis [1, 4] on the causal relation of coronary artery disease and periodontitis concluded an increased risk level ranging from 1.24 to 1.35.

But further studies are needed to find a final conclusion. Periodontitis has been found to be an important risk factor for all forms of cerebrovascular diseases, especially non-hemorrhagic strokes [2, 5, 7]. An association between peripheral arterial disease and periodontitis has been analyzed only in relatively small studies so far, a final answer cannot be provided yet.

Periodontitis has been identified as being a risk factor for CVD. Although the direct causal relation is not yet identified, activation of signaling proteins leads to a cascade of reactions in the inflammatory and immune response. The wall of blood vessels has to be considered as a target for these mediators with the consequence of micro- and macro structural changes. Interdisciplinary dentistry has to take chronic periodontal diseases seriously and consequent diagnoses and treatment in close collaboration with the general medical care and management is required.

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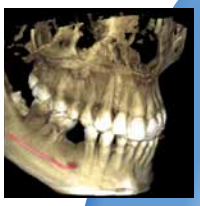

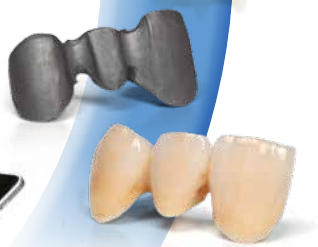

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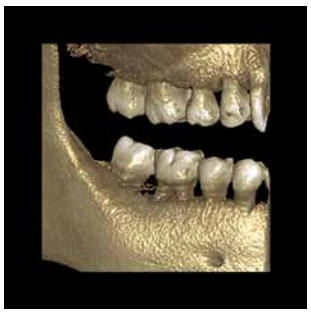

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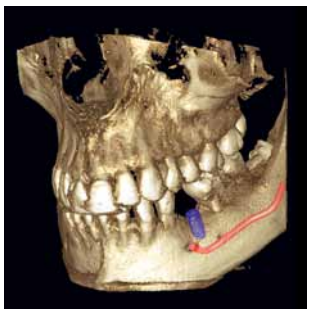

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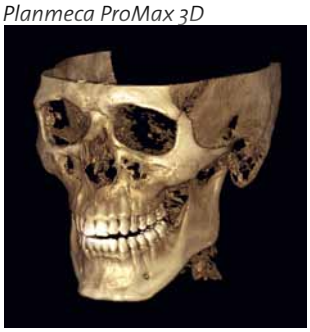

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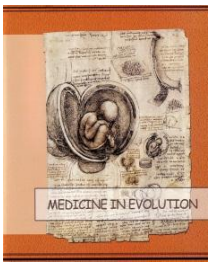
THE RELATIONSHIP BETWEEN THE BRADYKININ, RAAS AND ACE INHIBITORS: AN OVERVIEW



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ABSTRACT

Cardiovascular diseases are the most common cause of mortality worldwide.

Hypertension and atherosclerosis, as well as the consequence of this two pathologies: endothelial dysfunction, are the majors risk factors in the development of the cardiovascular disease.

In this article, I will try to offer an overview on the bradykinin (BK) and its cardioprotective actions, as well as on the renin-angiotensin aldosterone system (RAAS), and the link between the BK and RASS: ACE inhibitors, substances that turned out to be of huge beneficial effects, not only in the diminution of hypertension, but also in the prevention or reversion of endothelial dysfunction and atherosclerosis, and thereby in the reduction of the risk of cardiovascular events.

Key words: *bradykinin, renin-angiotensin aldosterone system, ACE inhibitors, hypertension, endothelial dysfunction*

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INTRODUCTION

Bradykinin (BK), a substance produced by the kallikrein-kinin system (KKS), is an active substance with proinflammatory and cardioprotective actions. It is a polypeptide involved in many pathological conditions and it can cause: inflammation, vasodilatation, pain, increased vascular permeability, cell proliferation and also the contraction of various muscles.

It has been shown that this substance, BK, has also cardioprotective effects and that a decreased activity of the KKS , including BK, can lead to many cardiovascular disease as: hypertension, cardiac failure and also myocardial infarction (renal BK plays an important role in the excretion of the Na, therefore a reduction of renal BK can lead to the accumulation of Na in the body and thus, to hypertension).

Another mechanism involved in the development of hypertension is the rennin-angiotensin-aldosterone system (RAAS). Because of the production of the angiotensin II by this system, a substance with vasoconstrictive action that can cause organ lesions, arteriole remodeling, can increase the release of catecholamines and also the activity of the sympathetic nervous system, this system (RAAS) is a very important target for the treatment of hypertension.

ACE inhibitors are a group of drugs that act on this two main actors: the RAAS and BK. By blocking the kinase II, also called angiotensin-converting enzyme, ACE inhibitors stop the production of angiotensin II and also the degradation of BK, leading to an increase in bradykinin levels.

The Kallikrein – Kinin System

The discovery of the kinin system is not recent, but its study in clinical field has been done only in the last years. [1]

The kallikrein – kinin system (KKS) is an intricate endogenous system thought to be involved in the regulation of blood pressure and inflammation, amongst other processes. [2]

This system includes: enzymes (kalikreins), protein precursors (kininogens) and potent vasoactive peptides (kinines). [2]

The kallikreins (serine proteases) were found in glandular cells, neutrophils and biological fluids. They are divided into two main groups: tissue (glandular) kallikrein and plasma kallikrein. The kallikreins differ in molecular weight, aminoacid composition, types of kinins released and in function. [3]

The kininogens (the substrates) are activated by the kallikreins (specific activators of these substrates) and they realease the kinins (the vasoactive components of the system)

There are three types of kininogens (the substrates): high (HMW), low (LMW) molecular weight kininogen and T-kininogen. These molecules are synthesized by hepatocytes and released into plasma. They play a role in releasing kinin. [4]

The kinins are mediating many physiological actions that are in close connection with the cardiovascular homeostasis, inflammatory and algesic responses, as well as pain – transmitting mechanisms. [3]

The kinins, in humans, refer to the bradykinin (BK), kallidin and carboxy terminal des-Arg metabolites. [4]

Two types of kinins had been found in rats: T-kinins (Ile – Ser – BK) and Met-T-kinin. [4]

The composition of the kinins is:

BK (Arg- Pro – Pro – Gly – Phe – Ser – Pro – Phe – Arg)

Kallidin (Lys – Arg – Pro – Pro – Gly – Phe – Ser – Pro – Phe – Arg)

Kallidin (Lys – BK) [5]

BK and Lys – BK , the two kinins biologically active, are short – lived peptide mediators. [6]

BK is a nonapeptide usually found in all secretions of the body such as urine, saliva and sweat. Also it is found in several tissues such as heart, vasculature, blood, kidney, colon and liver. [7]

Kallidin is a decapeptide found in the heart, urine and circulation. [7]

The levels of kinin peptides in tissues are higher than in blood, confirming the primary tissue localization of the kalli-krein-kinin system. [1]

BK is produced by plasma kallikrein and it can also be produced from kallidin, through cleavage of amino-terminal lysine, by several aminopeptidase. [4]

Kallidin is produced by tissue kallikrein and it is rapidly converted to BK by the enzyme aminopeptidase. [4]

The kinins are peptide hormones that transmit their biological effects via G protein – coupled receptors. [1]. The kinins have been implicated in the regulation of blood pressure, pain sensation and cell – growth. [8]

The biological effects of kinins are mediated by specific receptors called B1 and B2. [1]

The kinin system is involved in many clinical situations, including respiratory allergic reactions, septic shock, hypertension and its treatment, hypotensive transfusion reactions, heart diseases, pancreatitis, hereditary and acquired angio-edema, Alzheimer disease and liver and cirrhosis with ascites. [9]

The stimulation of this system plays and important role in the regulation of blood pressure and in inflammation reactions though the eliberation of bradykinine and its ability to increase vascular permeability and to induce vasodilatation of the arteries and veins of the aorta, gut, uterus and urethra.

Bradykinine

The vasoactive peptide, bradykinine, is formed from either HMW or LMW kininogen, by action of the enzyme called kallikreins. [4]

There are three proteins that are involved in the process: the Hageman factor, prekallikrein and HMW kininogen. Plasma prekallikrein circulates in a complex form with HMW kininogen and this complex, together with Hageman factor (factor XII), which is an enzyme, part of the clotting process, binds to negatively charged surface. Once they are exposed by tissue damage, prekallikrein is rapidly converted to plasma kallikrein by the enzyme prolylcarboxypeptidase. [4] Kallidin is a product of the enzymatic action of kallikrein to kininogens and kallidin is then transformed into bradykinin after enzymatic action of plasma aminopeptidase. [1]

Bradykinin interacts with its G protein coupled receptor at the cell surface. This interaction leads to specific changes in intracellular calcium, involving several different mechanisms, such as: phospholipase C, prostaglandins, protein kinase and phospholipase A2. [10]

The hyperpolarizing phase of the cell response may be due to inositol 1,4,5-triphosphate-dependent release of stored calcium into the cytoplasm, which activates calcium-dependent potassium-channels. [10]

The degradation of bradykinine is made by the enzymes called kinases. The kinases cleave BK at the aminoterminal or carboxyterminal end. [4]

The enzymes that cleave at aminoterminal end are: aminopeptidase M (APM), which can degrade kallidin into BK, and aminopeptidase P (APP), which cleaves the first amino-acid of BK to give BK-(2-9). [4]

The enzymes responsible for carboxyterminal degradation of BK are: angiotensin converting enzyme (ACE), carboxypeptidase N (CPN) and M (CPM) and neutral endopeptidase (NEP). [4]

Receptors of BK

As it was mentioned before, there are two subtypes of BK receptors: B1 and B2 (according to IUPHAR classification). These two receptors have similar structure with seven transmembrane domain coupled to G-protein. [4] Also B3 and B4 receptors have been proposed as additional receptors [11,7]

The B1 receptors are little expressed in healthy tissue and they are inducible following tissues injuries and by endogenous factors (endotoxins, cytokines, and growth factors), while B2 receptors are predominant in constitutively expressed in vascular, non-vascular smooth muscles and the heart. [4]

Both receptors have been cloned and their structures had been elucidated. Singular transduction mechanisms are quite similar for both receptors and they require calcium for signaling. [12]

The bradykinin 1 and 2 receptors are important mediators of cardiovascular homeostasis, inflammation and nociception. [1] The B1 receptors have different roles in function of the localization. In circulation they can cause vasodilatation in the vessels, in cardiovascular system they precondition the heart against ischemic events and protect the heart from arrhythmias. They are involved also in renal functions: natriuresis and glomerular filtration. It has been shown that they are involved also in the pathogenesis of diabetes, leucocytes recruitment in the initiation of the inflammatory responses and that they poses mitogenic properties in fibrotic tissues. [13,14]

The B2 receptors have been shown to have antithrombotic effect in the vasculature, antiarrhythmic effect in the heart, they can cause vasoconstriction or vasodilatation in vasculature, they can reduce infarct size and they precondition the heart against ischemic events. They can improve the myocardial demand of oxygen in heart failure by attenuating the endothelial dysfunction. [4]

They also affect other systems: they interfere with the glucose metabolism, they affect smooth muscle cells of duodenum, ileum and cecum, causing either relaxation or contraction. They have a role in the pathogenesis of asthma: they can cause chloride secretion and bronchoconstriction. Also , the functions of reproductive organs and bladder are affected, by inducing smooth muscle contraction in vas deferens, uterus and bladder. B2 receptors are involved in the physiology and pathophysiology of pain, inflammation and hyperalgesia. [4]

Bradykinin and the cardioprotective effects

This substance has a series of action on the cardiovascular system. These effects are produced through vasodilatation and plasma extravasation properties, which lead to inflammation. [15] The B2 receptors mediate the vasodilatation, however, under inflammatory conditions B1 receptor up regulation mediates BK induced vasodilatation and hypotension. [4]

The vasodilatation action of BK is produced by the stimulation of the endothelial cells, leading to the eliberation of secondary mediators like: nitric oxide (NO) and prostaglandins I2 (PG I2), mediators which affect the vascular smooth muscle. [4]

NO is produced by the action of endothelial nitric oxide synthase (NOS) on L-arginine. After its production, it diffuses from the endothelium to the smooth muscle, where it activates guanylate cyclase. [4]

Prostacyclin (PG I2), the other mediator released by BK, forms in many cell types through cytosolic calcium sensitive isoform of phospholipase A2. It stimulates cyclic AMP production in the smooth muscle cells. [4]

Because of these physiological effects of the bradykinin, this substance is used in the treatment of cardiac pathologies , like hypertension or ischemic disorders, and it protects also the renal function.

Bradykinin can cause coronary dilatation and can increase cardiac output, effects that are helpful in myocardial infarction or post infarction, coronary dilatation which is mediated by the B2 receptors. [4]

The same receptors are involved in the regulatory effect of NO on myocardial oxygen consumption. Recently, experimental evidences have suggested that G-protein mediated "cross-talk" mechanism between B2 receptors, NOS enzyme and AT1 receptors of angiotensin, may play an important role in the cardioprotective effects of BK. Moreover, BK exhibit pleiotropic effects by the inhibition of apoptosis, inflammation, hypertrophy, and fibrosis and by the induction of the angiogenesis in the heart. [4]

Bradykinin and the regulation of the renin – angiotensin aldosterone system (RAAS)

This hormonal cascade begins with the biosynthesis of the renin, by the juxtaglomerular cells (JG) that line the afferent (and occasionally efferent) arteriole of the renal glomerulus. [16,17]

Renin is formed from prorenin, the rennin precursor. The prorenin suffers a proteolytic removal of a 43-amino-acid prosegment peptide from N-terminus and this is how the active renin is formed. The active (mature) renin is stored in the granules of the JG cells and is released by an exocytic process. Also, it appears that the kidney releases unprocessed prorenin via a constitutive pathway. [16]

Renin secretion is stimulated by a fall in perfusion pressure or in NaCl delivery and by an increase in sympathetic activity. Renin is also synthesized in other tissues, including brain, adrenal gland, ovary and visceral adipose tissue, and perhaps heart and vascular tissue. The factors regulating the synthesis and possible actions of renin in these other tissues are poorly understood. [16,18]

Renin cleaves then the N-terminal portion of the angiotensinogen (a large molecular weight globulin) and forms Ang I or Ang-(1-10), a biologically inert decapeptide. The primary source of systemic circulating angiotensinogen is the liver, but angiotensinogen mRNA expression has also been detected in many other tissues, including kidney, brain, heart, vascular, adrenal gland, ovary, placenta and adipose tissue. [19]

Angiotensinogen is secreted constitutively by the liver, so plasma levels are generally stable and do not change acutely; however, both hepatic and extrahepatic synthesis have been shown to rise in response to glucocorticoids, estrogens and other sex steroids, thyroid hormone, inflammatory cytokines (e.g.: interleukin – 1 and tumor necrosis factor) and Ang II. [19]

Long-term elevations in angiotensinogen concentration may be a risk factor for hypertension. [16]

The Ang I (inactive decapeptide) is hydrolyzed by angiotensin-converting enzyme (ACE) to Ang II or Ang-(1-8), by removing the C-terminal dipeptide.

Ang II is a biologically active peptide that induces vasoconstriction and is the primary effector of a variety of RAAS-induced physiological and pathophysiological actions. [16,20,21] At least 4 angiotensin receptor subtypes have been described. [22]

The type 1 (AT1) receptor mediates most of the established physiological and pathophysiological effects of Ang II. These include actions of the cardiovascular system (vasoconstriction, increased blood pressure, increased cardiac contractility, vascular and cardiac hypertrophy), kidney (renal tubular sodium reabsorption, inhibition of renin realease), sympathetic nervous

system and adrenal cortex (stimulation of aldosterone synthesis). [20]

The AT1 receptor also mediates effects of Ang II on cell growth and proliferation, inflammatory responses and oxidative stress. [17]

The type 2 (AT2) receptor is abundant during fetal life in the brain, kidney and other sites, and its levels decrease markedly in the postnatal period. [16] There is some evidence that, despite low levels of expression in the adult, the AT2 receptor might mediate vasodilatation and antiproliferative and apoptotic effects in vascular smooth muscle and inhibit growth and remodeling in the heart. [20, 22] In the kidney, it may influence proximal tubule sodium reabsorption and stimulate the conversion of renal prostaglandin E2 to prostaglandin F2α. [17,20]

Type 4 (AT4) receptors are though to mediate the release of plasminogen activator inhibitor 1 by Ang II and by the N-terminal truncated peptides (Ang III and Ang IV), but the function of the type 3 (AT3) receptors is unknown. [22]

This ACE (also known as kinase II) is a membrane-bound exopeptidase and is localizes on the plasma membranes of various cell types, including vascular endothelial cells, microvillar brush border epithelial cells (e.g.: renal proximal tubule cells) and neuroepithelial cells. It also exists in a soluble form in plasma. [16]

ACE metabolizes a number of other peptides, including the vasodilating peptides: bradykinin and kallidin, to inactive metabolites. [20]

Thus, functionally, the enzymatic actions of ACE potentially result in increased vasoconstriction and decreased vasodilatation.

ACE inhibitors

Studies made in the 1960s showed that some peptides from the venom of *Bothrops jaraca*, a Brazillian arrowhead viper inhibit the kinase II, an enzyme that degrades the bradykinin and that this enzyme kinase II is the same enzyme as ACE (angiotensin – converting enzyme) [17]

Later studies proved that synthetic analogues from this enzyme of shake venom, can lower the blood pressure in patients with hypertension and also it can induce other beneficial hemodynamic effects in patients with heart failure. [16, 17]

With all this evidences, a new class of drugs was developed, that inhibited kinase II, enzyme also known as ACE, called ACE inhibitors (ACEI). The first substance of the class was captopril. There were been developed other substances, that are nowadays much more used because of the lesser side effects than captopril, like: lisinopril, ramipril, perindopril (where the sulfhydryl group of captopril was replaced with a carboxyl group, because of the proteinuria, skin rashes and altered taste that were attributed to the sulfhydryl group) or fosinopril (which has a phosphoryl group) [16,23,24] .The carboxyl group increased the lipophilicity and thus the binding to ACE and also tissue penetration.

ACEIs competitively block the action of ACE and thus the conversion of Ang I to Ang II, thereby reducing circulating and local levels of Ang II. They also decrease aldosterone vasopressin secretion and sympathetic nerve activity, but there is controversy regarding their efficacy in blocking other "tissue" actions of RAAS. [16, 25]

Because ACE is identical to kinase II, ACEIs may also lead to elevation of bradykinin levels in some tissues (but unlikely in the circulation); this effect is potentially associated with increased bradykinin-dependent release of NO and vasoactive prostaglandins, including prostacyclin and prostaglandin E2. [16,25]. These actions may potentially contribute to the vasodilating, antithrombotic, antiatherogenic, and antiproliferative effects of ACEIs [16,25] and their implications in reversing the endothelial dysfunction.

The induce arterial vasodilatation, which reduces peripheral vascular resistance (afterload) and increases cardiac output.[16,25]

They appear to induce also venous vasodilatation, which increases peripheral venous capacitance and reduces right arterial pressure, pulmonary arterial pressure, capillary wedge pressure and left ventricular filling volumes and pressures. [16,26]

ACEIs also decrease renal vascular resistance, increase renal blood flow and promote sodium and water excretion. Mainly through cellular effects in the kidney and though alterations in glomerular hemodynamics, they may prevent the progression of microalbuminuria to proteinuria, reduce proteinuria in patients with established glomerular disease and prevent or delay the progression of renal insufficiency to the end-stage of renal disease. [16, 25, 27, 28, 29]

ACEIs therapy is generally well tolerated by most patients, but is nonetheless associated with some significant side effects as: dry cough, attributed to the accumulation of substance P, which is normally degraded by kinase II; angioedema, which is potentiated by decreased catabolism of kinins and fetal abnormalities and mortalities. Also they can cause hypotension, deterioration of renal function and hyperkalemia. [16,30,31]

ACEIs are currently indicated for the treatment of hypertension, diabetic nephropathy, post-MI left ventricular dysfunction, and chronic heart failure, and their use has been associated with improved survival and considerable cardiovascular and renal benefits in high-risk patients. [16,32,33,34,35,36,37]

CONCLUSIONS

Drugs that block the RAAS have become the most used drugs in the treatment of cardiovascular disease.

Part of the antihypertensive and cardioprotective action of ACE inhibitors is also because of the increased levels of bradykinin, mainly via B2 receptors.

Although the accumulation of bradykinin is also responsible for the most important side effects of the class: coughing and angioedema, ACE inhibitors remain a class of drugs with multiple cardiovascular benefits : reduction of hypertension , prevention or reversion of endothelial dysfunction and atherosclerosis, and thereby in the reduction of the risk of cardiovascular events.

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- for articles: name of the authors and surname initials, title of the article in the original language, title of the journal according to the international abreviation system, year of issue, volume, number, pages;
- for books: name of the authors and surname initials, volume, publisher (editors), city of publishing, year of issue.

Citation of references inside the body of the paper will be put between brackets, Harward style (author, year) or Vancouver style (number in square brackets or superscript). Cited reference titles will be selected, maximum 6 for studies and case presentations and 12 for general reviews. Acceptance, rejection or the need of alterations in sent materials, or in inconography, will be comunicated to the authors in due time. For this, the authors will indicate the person and address for corespondence (phone number, e-mail address). Given the less pleasant experience of the editorial board with some articles being rejected because they did not meet publishing criteria, we decided to support those who intend to publish in this journal by detailing the way such a paper should be elaborated, as well as our requirements.

Except some particular aspects concerning this journal, the following details are general requirements asked or imposed by other journals as well. Conditions to be met in order to propose a paper for publishing. The main author has the

responsability to make sure the article has been approved by all the other authors. The journal will have copyright for papers accepted for publishing. The editorial board reservs the right to change the style and dimensions of an article (major changes will be discussed with the main author) and to decide the date of issue.

2. FIRST PUBLICATION

The editorial board will not consider a paper already reported in a published general review or described in a paper proposed to or accepted by another journal. This does not exclude papers which have been rejected by other journals. Also, papers which have been presented at a scientific meeting will be accepted for discussion if they have not been entirely or partially published in a similar publication. „Multiple" publishing of the same study is seldom justified. One of the possible justifications is publishing in a second language but only if the following conditions are met:

- Editors of both journals involved are fully informed;
- Priority of the initial publication will be respected by a minimum publishing interval of two weeks;
- For the second publication, a shortened version will suffice;
- The second version strictly reflects data and interpretations in the first;
- A footnote may state: „This article is based upon a study initially published in [title of the journal]".

3. PATERNITY

Paternity must reflect the common decision of the coauthors. Each author must have participated enough to take public responsability for the content. A paper with collective paternity must have a key person responsable for the article.

4. COPYRIGHT

In order to reproduce materials from other sources, written agreement from the copyright owner must be obtained:

- photographer – for unpublished photographs;
- hospital where the photographer (physician) is employed – for unpublished photographs performed during the employment period;
- initial publisher – for a table, picture or text which have previously been published elsewhere.

5. ETHICAL ASPECTS

Do not use name of patients, initials or hospital observation charts numbers. If a photograph of a body part which could allow direct or deductive recognition of the patient needs publishing, then the paper must be accompanied by the written consent of the patient and clinician, as well.

6. PRESENTING THE MANUSCRIPT

For the journal *„Medicine in evolution"*, the manuscript must be typed double spaced, on white A_4 paper – 210 x 297mm, on one side (2.5cm upper and lower borders, 3cm left and 2cm right border, respectively), in clear characters, no further corrections or addings. It is advisable that articles are presented on CD or other data transfer methods, in Word format, 12 Times New Roman fonts - using Romanian characters – respecting the same page order, accompanied by a printed version. Graphs – black and white or coloured – may be generated in MS Excel or MS Graph, inserted in the body of the paper or presented in a different file.
Infected materials will not be used.

6.1. FIRST PAGE (TITLE PAGE)

Together with the title and names of the authors, the first page must include the affiliation, professional and university degree (if applicable), marked by asterisc for every author; it is advisable to give at least a phone and/or fax number or e-mail address of the first author who may be contacted by the editors for additional recommendations or explanations.

6.2. ABSTARCT OF THE PAPER

6.2.1 Recommendations for original studies

Original studies must include a structured abstarct of maximum 150 words, containing the following titles and informations:

- Aim and objectives;
- Material and methods;
- Results;
- Conclusions;
- Key words: give 3-5 key words;
- The abstract will be translated into an international circulation language.

6.3 CONTENT OF THE PAPER

6.3.1 For original articles

The text will usually be divided into sections:

- Introduction – presentation of general aspects, in the context of the approached theme
- Aim and objectives – Define the aim of the article. Briefly expose the rationale of the presented study or observation. Make strictly pertinent referals and do not exhaustively review the subject. Do not include data or conclusions from the paper.
- Material and methods – Describe the selection of observations or subjects for the experiment (including controls). Identify methods, equipments (with the name and address of the manufacturer in brackets) and give sufficient details on procedures. Give references for the selected methods, including statistical methods; offer details and brief descriptions for previously published methods which are not well known; describe new or

substantially modified methods, justify their use and assess their limitations. Precisely identify all used drugs and chemicals, including generic names, dosage and administration ways. Describe statistical methods with sufficient details for reported results to be verified. Whenever possible, quantify discovered aspects and present them with appropriate measurement indicators for the uncertainty or error of measurement (such as confidence intervals).

- Results – Present results in a logical succession as text, tables and illustrations. Emphasize or briefly describe only important observations.
- Discussions – Underline new, important aspects of the study. Do not repeat in detail data which have been presented in previous sections. Include implications of revealed aspects and their limitations, including implications for future studies. Connect your observations to other relevant studies. Relate the results to the aim proposed for the study.
- Conclusions – organize conclusions which emerge from the study. In the end state: a) contributions to be acknowledged but which do not justify paternity right; b) thanks for technical support; c) thanks for financial or material support.

6.3.2 Indications for case reports

Themes may be selected from all medical fields. Manuscripts which offer a special gain for daily activity will have priority. The title must be clearly, precisely stated. It may be completed by a subtitle. It is advisable to include in the key words of the title the main message, the special element which may be observed from the case evolution. The content of a case report must be divided into three parts:

- Introduction – It must include a maximum of 15 typed rows (half page). Here, the main medical problem is summarized in order to place the case in a specific domain.
- Case report – It contains essential specific information on the case.
- In order to make a logical, chronological and didactical case report the following 5 chapters are needed:

  I. Anamnesis;
  II. Clinical examination data;
  III. Laboratory data;
  IV. Additional paraclinical investigations;
  V. Treatment and evolution.
- Discussions – The reason for the case report must be stated. The report must be patient-centered. Occasional deviations from typical (characteristic) evolutions, nosologically important facts must be presented in such a manner to expose the clinical picture as completely as possible. The case report must not appear as an appendix of a general review. Dimensions of a case report: maximum 6-8 typed pages, 30 rows of 60 characters/page.

6.4. MEASUREMENT UNITS, SYMBOLS, ABREVIATIONS

All measurements must be expressed in International System (IS) units. Abreviations must be fully explained when first used.

6.5. TABLES

Tables are noted with Roman figures and they will have a brief and concise title, concordant with their content.

6.6. ILLUSTRATIONS

Number all illustrations in Arabic figures in a single succession. Apply a label on the back side of every illustration, containing its number and an arrow indicating the upper side. Coloured illustrations may be accepted but it is the choice of the editors, according to particular technical abilities of each journal issue, or it may involve a fee in special cases.

6.7. EXPLANATIONS FOR DRAWINGS AND GRAPHS

Explanation for drawings and graphs must be clear and in readable dimensions, considering the necessary publishing shrinkage.

6.8. PHOTOGRAPHS

Offer glossy, good quality photographs. Any annotation, inscription, etc. must contrast with the ground. Microphotographs must include a scale marker.

6.9. ILLUSTRATION LEGENDS

Include explanations for each used symbol, etc. Identify the printing method for microphotographs.

6.10. REFERENCES

A numbered list of references must be provided at the end of the paper. The list should be arranged in the order of citation in the text of the publication, assignment or essay, not in alphabetical order(according to the Vancouver rules). List only one reference per reference number. It is very important that you use the correct punctuation and that the order of details in the references is also correct.

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7. COPIES FOR PUBLISHING

In order to accelerate publishing, the main author will send a set of printed sheets presenting the final version of the paper, as it will appear in the journal. It is really helpful that texts to be also sent on electronic support, diacritic characters mandatory.

8. REJECTION OF PAPERS

If a paper does not meet publishing conditions, whatever these may be, the editors will notify the first author on this fact, without the obligation of returning the material. Original photographs or the whole material will be returned only if the author comes to the editor and takes them.

Papers submitted for publishing will be addressed to:

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