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TREATMENT AND PREVENTION OF ORAL MANIFESTATIONS OF COMPLICATIONS OF BISPHOSPHONATE THERAPY IN OUTPATIENT CONDITIONS

Summary of dissertation for the acquisition of the educational and scientific degree "doctor"

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The dissertation consists of 191 pages and is illustrated with: 42 tables, 46 figures and 3 appendices. The bibliography includes 277 literary sources, of which 2 are in Cyrillic and 275 are in Latin. The numbers of the tables and figures do not correspond to their numbering in the dissertation work.

3 publications were made related to the dissertation work.

The studies were carried out in the "DOMFS" Department at the FDM at the Sofia University.

The materials are available in the library of FDM, MU-Sofia, "St. Georgi Sofiyski" 1 and are published on the website of MU-Sofia.

The dissertation work has been discussed and scheduled for the defense of the departmental council of the "DOMFS" Department at the FDM at MU-Sofia, where the doctoral student works as an assistant.

The public defense of the dissertation work will take place on 30.09.2024 from…… in.....auditorium of FDM, MU-Sofia, "St. Georgi Sofiyski" 1, according to Art. 5, para. 2 in connection with Art. 73 of the Regulations on the conditions and procedure for acquiring scientific degrees and occupying academic positions at MU-Sofia and order of the rector of MU-Sofia № РК36-1921/06.08.24, at an open meeting of a scientific jury composed of:

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Contents

Used abbreviations

AAOMS	American Association of Oral and Maxillofacial Surgeons
AB	Antibiotic
BF	Bisphosphonate
BRONJ	Bisphosphonate-related osteonecrosis of the jaw
Ca	Carcinoma
CBCT	Cone beam computed tomography
i.v.	intraveniously
MRONJ	Medication-related osteonecrosis of the jaw
OMFS	Oral and Maxillofacial Surgery
ONJ	Osteonecrosis of the jaw
p.o.	peroral
TFSI	Time from the surgical intervention

Introduction

Bisphosphonates are a group of drugs that are widely used in diseases associated with osteoclast-mediated bone loss. Their widespread use in the treatment of these diseases led to the discovery of a probable link with the subsequent development of osteonecrosis of the jaw.

Bisphosphonates are highly effective antiresorptive drugs that are used to treat bone metastases in malignant diseases – breast cancer, Cancer of the prostate, Multiple myeloma, Paget's disease, fibrous dysplasia, osteogenesis imperfecta. Bisphosphonates are the most widely prescribed drugs for osteoporosis. Although rare, avascular osteonecrosis of the jaw has been recognized as a complication of bisphosphonate use. In 2003, Marx first described "painful bone-exposure" of the upper and lower jaws in patients taking pamidronate (Aredia; Novartis Pharmaceuticals, EastHanover, NJ) and zoledronate (Zometa; Novartis Pharmaceuticals). Since then, the question of bisphosphonate-associated osteonecrosis of the jaw bones (BRONJ) has been raised and a number of authors have published their observed cases.

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is defined as: current or previous treatment with antiresorptive or antiangiogenic agents resulting in exposed bone or bone that can be probed through an intra- or extraoral fistula in the maxillofacial area, which persists for more than 8 weeks, in the absence of evidence of radiation therapy to the jawbones or obvious metastatic disease of the jawbones.

BRONJ is a multifactorial disease, and the risk factors for the development of the disease are divided into risk factors related to bisphosphonate therapy, local risk factors, demographic and systemic factors, genetic factors and preventive factors.

The clinical appearance of BRONJ includes the presence of "exposed non-vital bone". This symptom may be preceded by undefined pain or discomfort in the affected area. Inflammation and superimposed infection are seen in advanced cases and are the leading causes of the symptomatic manifestations of BRONJ.

The treatment of BRONJ is conservative and surgical, with no consensus in the literature regarding the choice of treatment approach. According to current AAOMS recommendations, BRONJ can be controlled with the use of antibiotics, topical antiseptic agents, and surgical debridement, if necessary. A more aggressive approach involving surgery and resection of the jawbones may be necessary in patients with advanced disease.

Prevention of BRONJ is the most effective way to reduce the incidence of BRONJ. It includes establishment of clear protocols for treatment and prophylaxis in patients taking medicines from the bisphosphonate group, that have to be followed by the dentist and the oral surgeon.

Aim and tasks

The aim of the dissertation is to analyze the possibilities of conservative and surgical treatment and prevention of BRONJ, examining the influence of certain risk factors on its development.

To achieve this aim we set the following tasks

1. To examine demographic and clinical characteristics of the patients - age, sex, main disease, presence of previous surgical intervention and the interval from it to diagnosis and to examine characteristics of the BF (type of BF, duration of administration, dosage form (parenteral, oral).
2. To investigate the clinical manifestations of BRONJ in the oral cavity - localization of lesions, clinical symptoms, stage of BRONJ, radiographic changes in the jaw bones of the studied patients.
3. To investigate the effect of the performed conservative treatment (antibiotic and cleaning of necrotic tissues-debridement)
4. To investigate and to follow up cases of development of a healing process or necrosis in patients undergoing therapy with bisphosphonates in connection with malignant diseases or osteoporosis, examining duration of medicine intake, duration of dentoalveolar surgical intervention, age of the patient as influencing factors on the radiographic finding and treatment outcome of BRONJ.
5. To investigate the outcome of tooth extraction in patients on bisphosphonate therapy, in a quadrant of the jaw without necrosis, following a clearly defined surgical protocol.

Material and methodology

Research material and units of observation

The scientific work covers a period of 13 years. The scientific research is clinical and is the activity of the doctoral student with a period of 2009-2022. The present study includes patients treated in the OMFS clinic at the "St. Anna" UMBAL - Sofia from 2009-2014, where the doctoral student performed the observations and took part in the treatment process, as well as patients treated by the doctoral student in outpatient settings and in Department of OMFS Faculty of Dental Medicine, Medical University-Sofia in the period from 2009 to 2022.

The subject of the dissertation work are 74 patients, divided into two groups.

The first group included 44 cases of patients with bisphosphonate-associated osteonecrosis of the jaws. Among them, 21 (47.7%) were treated at the OMFS clinic at the "St. Anna" UMBAL-Sofia and 23 (52.3%) were treated in outpatient settings. Of these, 20 (45.5%) were women and 24 (54.5%) were men. With regard to the main disease, due to which it is necessary to take BF, 40 (90.9%) of the patients have malignancy and 4 patients (9.1%) have osteoporosis. Intravenous administration of BF was registered in 40 (90.9%) of the patients and oral administration in 4 patients (9.1%). 13 (29.5%) patients underwent sequestrectomy, 16 (36.4%) patients underwent surgical debridement, and 15 (34.1%) patients underwent medical treatment alone. In 10 of the patients (22.7%), antibiotic treatment was carried out in combination with chlorhexidine preparations, and in 5 patients only chlorhexidine solutions were used (11.4%). All 44 patients received medical treatment.

In 23 cases (82.6% of surgically treated patients) the dissertation student was the operator, while in 6 cases (17.4% of the surgically treated patients) he was the first assistant and in 15 (34.1% of all patients) - attending physician.

The observed parameters are:

1. Regarding the patients

- Demographic characteristics: the demographic information collected includes data on patients' age at diagnosis and gender.
  - age - we divided the examined patients into six age groups as follows: I group (30-40 years); II group (41-50 years); III group (51-60 years); IV group (61-70 years); group V (71-80 years); VI group (81-90 years)
  - gender - women: men
- Primary disease - malignancy or osteoporosis

- Initiating cause of the necrosis - previous surgical intervention - performed dentoalveolar surgical intervention (extraction of a tooth or placement of a dental implant) or mechanical trauma from a removable prosthesis
- The time to the appearance of necrosis after a surgical procedure - the time interval from the surgical intervention on the jaw bones (if any) to the appearance of clinical symptoms (in months).

2. Regarding the bisphosphonates taken

• Type of bisphosphonate/bisphosphonates

- Zoledronic acid
- Alendronic acid
- Ibandronic acid
- Pamidronic acid

- Zoledronic acid (alone or in combination with another drug from the BF group)
- All other BF

• Duration of BF therapy (in months)

• Mode of administration of BF-oral or intravenous.

3. Clinical features of BRONJ

• Localization - involvement of the maxilla, mandible or both jaws. We divided the maxilla and mandible into two regions: anterior (encompassing the area of canines, lateral and central incisors, and the area of first and second premolars) and posterior (first, second, and third molars).

• Clinical manifestations of BRONJ in the oral cavity - the presence or absence of the following clinical symptoms and signs were recorded: non-specific symptoms and clinical findings, exposed/necrotic bone, pain, erythema of the surrounding tissues, purulent exudate, pathological fracture, extraoral fistula, oroantral/oronasal communication, osteolysis beyond the lower border of the mandible or sinus floor

• Stage of BRONJ at the time of diagnosis - we divided our patients into four stages - stage 0, stage I, stage II, stage III according to AAOMFS recommendations.

• Treatment performed - medical treatment, surgical treatment (sequestrectomy), conservative surgical treatment (debridement)

• Evolution of the disease was recorded on the first and sixth months of the applied treatment, registering:

- stationing of the disease
- clinical improvement

- disease progression
- remission

The study was carried out on the same group of 44 patients with at least two follow-up examinations - on the 1st month and on the 6th month after the applied treatment.

The second group includes patients undergoing bisphosphonate therapy (oral or intravenous), with indications for extraction of one or more teeth. This group includes a total of 30 patients, with the doctoral student being the attending physician for all 30 patients. BF intake was due to malignant diseases in 14 patients (46.7%) and osteoporosis in 16 patients (53.3%). Of these, 13 patients (43.3%) received oral BF and 17 (56.7%) received intravenous BF. In these patients, there are no clinical data on the development of BRONJ, at the time of the primary examination in the quadrant in which the teeth to be extracted are located. In 7 (23.3%) of the patients examined by us with a need for tooth extraction, on BF therapy, necrosis was found in another quadrant. The intended extraction is in a quadrant without necrosis. The remaining 23 (76.7%) were patients requiring tooth extraction in an outpatient setting, without the development of necrosis to date, undergoing BF therapy.

In the patients of the second group, we examined the following signs:

1. Demographic characteristics:

• Demographic information collected includes age at diagnosis and gender.
  - age - we divided the patients examined by us into six age groups, as follows - I group (30-40 years); II group (41-50 years); III group (51-60 years); IV group (61-70 years); Group V (71-80 years); VI group (81-90 years)
  - gender - women: men

• Primary disease - malignancy or osteoporosis

2. Regarding the bisphosphonates taken

• Type of bisphosphonate/bisphosphonates
  - o Zoledronic acid
  - o Alendronic acid
  - o Ibandronic acid
  - o Pamidronic acid

• Duration of BF therapy (in months)

• Mode of administration of BF-oral or intravenous.

We divided the group of 30 patients according to the outcome of the performed tooth extraction into two groups - patients who did not develop BRONJ and patients who developed BRONJ after the extraction. We examined the distribution of the two groups of patients with regard to the following characteristics: Age, sex, main diagnosis, type of BF, method of

introduction of BF, duration of introduction of BF, localization for the tooth intended for extraction (jaw, region), type of the administered antibiotic for antibiotic prophylaxis, duration of antibiotic treatment, presence of BRONJ before extraction in another quadrant and outcome of treatment.

Sources of information

The main source of information at the individual level for each specific case is the history of the disease. The author formed his own database, and the information for each case was collected prospectively. A survey form and a form for collecting information were prepared in accordance with the objectives of the study. All patients were followed up in outpatient and inpatient settings with control examinations at least at the end of the first and sixth months of the treatment.

Methodologies

The material for the study was collected prospectively over the past years. Detailed clinicopathological information was collected for all cases with BRONJ that were diagnosed and treated by the medical team and the doctoral student.

The idea and the selection of the observed parameters are the work of the doctoral student in close cooperation with the scientific supervisor. After formulating the purpose of the study, we developed inclusion and exclusion criteria.

Criteria for inclusion in the study

To the patients of the ***first*** group

- Current or previous treatment with bisphosphonates.
- Age over 18 years
- Presence of advanced jaw bone necrosis meeting the following criteria - exposed bone or bone that can be probed through an intra- or extraoral fistula in the maxillofacial region that persists for more than 8 weeks.
- Lack of data on performed radiation treatment of the jaw bones.

Exclusion criteria from the study:

To the patients of the ***first*** group

- presence of lesions resulting from a neoplastic process in the jaw bones
- presence of lesions resulting from a metastatic process in the jaw bones
- performed radiation treatment of the jaw bones

Criteria for inclusion in the study

The patients of the ***second*** group

- Taking medicines from the group of bisphosphonates for the treatment of an underlying disease (osteoporosis, carcinoma, multiple myeloma)

• Age over 18 years

• Need for surgical treatment (extraction) of one or more teeth not amenable to conservative treatment

• Absence of exposed necrotic bone and absence of clinical and radiographic evidence of BRONJ in the extraction quadrant according to AAOMFS criteria

• they include a subgroup of patients with a need for extraction in a quadrant in which there is no necrosis, but necrosis is observed in another quadrant in connection with the intake of BF.

Exclusion criteria from the study:

The patients of the ***second*** group

• history of previous radiotherapy to the head and neck area

• presence of exposed necrotic bone and clinical and radiographic data or previous history of the presence of BRONJ in the quadrant in which the extraction will be performed.

• metastatic infiltration of the jaw bone

For each patient included in the study, a questionnaire prepared by the doctoral student was filled out, including detailed information on gender, age, underlying disease, type, route of administration and duration of bisphosphonate intake, clinical symptoms, stage of osteonecrosis, localization, performed dentoalveolar surgical intervention, results of microbiological, histological and radiographic examination, treatment carried out and result of treatment.

Research methodology

The conceptual justification of the present development is in accordance with the ethical and deontological requirements of MU - Sofia. The research is clinical, non-experimental.

I. Diagnostic methods

1. Clinical methods

• Anamnesis - during the primary examination, the patient's anamnestic data is taken, including presence/absence of pain, nature of pain, intensity, localization, time of manifestation of the first symptoms. Age, gender of the patient is recorded. For the patients of the first group, it is important to clarify whether a dentoalveolar surgical intervention was performed (tooth extraction, dental implant placement, periodontal, periapical surgery) and if it was performed, when it was performed.

• Inspection, percussion, palpation

In the patients of the second group, the dental status is taken - the presence of a carious defect, mobility, hyperemia, edema in the area of the apex, the presence of a fistula course, pain on percussion (horizontal and vertical), pain on palpation in the area of the root tip.

In the patients of the first group, the macroscopic characteristic of the osteolytic focus is determined - the presence of exposed necrotic bone; localization - involvement of the maxilla, mandible or both jaws; boundaries, size, presence of suppuration, mobility of necrotic fragments relative to the surrounding bone, hyperemia and swelling of soft tissues, near the focus, condition of the vestibular mucosa in the affected area. The lower jaw is examined for the presence of a pathological fracture, the skin of the face is examined for the presence of an extraoral fistula, hyperemia, edema of the overlying skin. The teeth adjacent to the focus are percussed, the vestibular transitional fold is palpated, to clarify the condition of the periosteum, the presence of tissue compaction in this area or fluctuation is examined.

When the upper jaw is affected by BRONJ, the anterior and lateral walls of the maxillary sinus are palpated for the presence of pain and the presence of exudate from the nostrils is examined.

2. Imaging diagnostics - X-ray methods - all patients underwent a radiographic examination (orthopantomography, intraoral retroalveolar segmental radiography, overview radiography of the paranasal cavities, CBCT). The examined signs are osteolysis, osteosclerosis, bone sequestration formation, borders and sizes of the osteolytic focus, involvement of adjacent anatomical structures (maxillary sinus, mandibular canal). To refine the studied parameters, some of the patients underwent computed tomography.

3. Staging - staging was done according to the recommendations of the AAOMS, as follows:

I. ***Risk group*** - absence of necrotic bone in patients treated with oral or intravenous BF.

II. ***Stage 0*** - absence of exposed bone, but presence of non-specific clinical, radiographic or histological signs of BRONJ as described:

1. Symptoms
   - dental pain that cannot be explained by an odontogenic cause.
   - dull pain in the jawbones that may radiate to the temporomandibular joint area.
   - sinus pain, which may be associated with inflammation and thickening of the wall of the maxillary sinus
   - altered neurosensory function

2. Clinical findings
   - increase in tooth mobility that cannot be explained by chronic periodontal disease

- periapical or periodontal fistula not associated with pulpal necrosis caused by caries, trauma or restorations

3. Radiographic findings

- alveolar bone loss or resorption not due to chronic periodontal disease
- changes in the trabecular structure - bone compaction and lack of new bone in the extraction alveoli.
- areas of osteosclerosis involving alveolar bone or surrounding basilar bone
- densification or shadowing of the periodontal ligament (densification of the lamina dura, osteosclerosis and reduced periodontal space)

These nonspecific findings that characterize stage 0 BRONJ may also occur in patients with a history of stage I, II, or III BRONJ disease who are cured and have no clinical evidence of exposed bone.

III. ***Stage I*** - presence of exposed necrotic bone or fistula which reaches bone on probing, without pain or other signs of infection (asymptomatic). In these patients, the radiographic findings described for stage 0, which are located in the area of the alveolar bone, can also be found.

IV. ***Stage II*** - the presence of exposed necrotic bone or a fistula during probing of which reaches bone associated with infection, accompanied by pain and erythema in the area of exposed bone with or without drainage of purulent exudate (symptomatic course). In these patients, the radiographic findings described for stage 0, which are located in the area of the alveolar bone, can also be found.

V. ***Stage III*** - presence of exposed necrotic bone or fistula on probing that reaches bone, with pain or other signs of infection and one or more of the following:

• exposed necrotic bone covering an area outside the boundaries of the alveolar bone (e.g. the maxillary sinus, the lower edge or ramus of the mandible and the zygomatic complex of the maxilla),

• pathological fracture,

• extraoral fistula,

• oro-antral or oro-nasal communication or

• osteolysis extending to the lower border of the mandible or to the sinus floor.

The stage of BRONJ is determined at the first examination and consultation of the patient and recorded in the questionnaire.

4. Histological examination - patients who underwent surgical treatment (surgical debridement or sequestrectomy) underwent routine histological examination - histological preparation including soft tissues in contact with the osteolytic focus and bone fragments from

the exposed necrotic bone. The preparations were fixed in 10% formalin, embedded in a paraffin block and stained according to routine methodology. The tests were carried out by the histopathology laboratory at the "St. Anna" UMBAL - Sofia and FDM-Sofia. Histological examination is necessary to distinguish in the differential-diagnostic aspect of BRONJ from a metastatic process in the jaw bones.

5. Microbiological examination - in 16 of the patients from the second group, material for microbiological examination was taken from the osteonecrotic focus, from exudate from a fistula or in the case of abscess formation - from the incisional wound using a sterile cotton swab. Microorganisms were identified and their sensitivity to antimicrobial agents-antibiotics was determined and an antibiogram was prepared. The microbiological examination was carried out in a microbiological laboratory in the "St. Anna" UMBAL - Sofia and "Kandilarov" laboratories.

6. An analysis of available hospital documentation was performed for all patients. The main source of information for each specific case is the medical history of hospitalizations for the patient's underlying disease or previous hospitalizations for BRONJ. The main diagnosis of the patient related to the need for bisphosphonate treatment, the type of bisphosphonate used, the method of administration into the body (oral, intravenous), and the duration of bisphosphonate treatment were determined. Patients who did not provide medical documentation regarding the underlying disease were not included in the present study.

7. Method for forming a database - a questionnaire was prepared according to the investigated signs, which is a personal development of the dissertation student. For each patient, information collected by the doctoral student from the anamnesis, clinical and paraclinical studies is reflected in an individual card. It includes name, gender, age, ambulatory number/ID number, main diagnosis, type of BF taken, method of introduction into the body, duration of intake, BRONJ stage, localization (upper, lower jaw or both), performed dentoalveolar surgical intervention in this area, time of appearance of the first complaints, relative to the time of the intervention, risk factors, result of the histological, microbiological, radiographic examination, applied treatment and its results.

8. Photo-documentation of intra- and extra-oral manifestations of BRONJ - used to compare patient status over time and to assess disease progression

II. Treatment methods - in the treatment of both groups of patients for applied surgical, conservative and surgical-medication methods.

1. Surgical methods

All patients were operated under local anesthesia.

In the patients of the first group, surgical interventions were performed, which can be summarized in two surgical approaches:

A. Surgical debridement

B. Sequestrectomy

In the patients of the second group, the following surgical protocol was followed: 1. Gargling with chlorhexidine 0.2% 30 mL for 60 s; 2. Local anesthesia with 4% Articain (Ubistesin, Septanest); 3. Luxation and extraction of the tooth, carefully performed with a straight elevator and extraction forceps; 4. If necessary, the sharp bone edges are smoothed with bone forceps. 5. Removal of the pathologically changed tissues from the alveolus, using a curette; 6. Mobilization of adjacent tissues and maximal primary closure of the extraction wound, using single interrupted sutures.

The selected surgical protocol is in accordance with those published in 2006 and 2009 recommendations of the AAOMFS regarding surgical interventions in patients on BF therapy. If extraction or surgical intervention on the bone is necessary, a tissue-sparing surgical technique is applied, and primary tissue closure is recommended. Surgery is followed by gargling with antiseptic chlorhexidine solutions and antibiotic prophylaxis at the discretion of the oral surgeon.

2. Conservative treatment methods

The patients of the first group received medical treatment, which can be divided into the following groups:

- Antibiotic treatment
  - intravenous administration
  - oral intake
- Antimicrobial agents - Flagyl (Flagyl)
- Antiseptic solutions - gargling with 2% chlorhexidine solution

The choice of antibiotic is in accordance with the recommendations of the American Dental Association

15 patients from the first group received medical treatment, 10 of them were given an antibiotic (Penicillin-8, Clindamycin-2), and 5 of the patients were treated with chlorhexidine preparations (Eludril). In 29 patients combined (surgical and medical) treatment was applied.

All patients of the second group underwent surgical and medical treatment.

According to the recommendations of the American Dental Association, surgery is followed by gargling with antiseptic chlorhexidine solutions and antibiotic prophylaxis, at the discretion of the oral surgeon.

The following therapeutic scheme was assigned to the patients of the second group:

- Antibiotic treatment with drugs from the group of Penicillins - the applied antibiotics are Duomox 1000/ Duomox 1000 and Augmentin 1000 mg (Amoxicillin 825 mg + clavulanic acid 175 mg). The daily dose is 2 grams (2000 mg), divided into two doses, orally, every 12 hours for 14-21 days. In patients with an allergy to penicillin, we administered Clindamycin, 300 mg, a daily dose of 900 mg, divided into three doses, every 8 hours, for 14 days.
- Antiseptic solutions - gargling with 2% chlorhexidine solution twice a day - morning and evening, after brushing the teeth, lasting one minute (60 seconds).

Terms for reporting the results

In the patients of the first group, the results are reported at 30 days and at 6 months. Periodic control examinations were carried out with a frequency determined by clinical symptoms and the need for treatment.

In the patients of the second group, the sutures are removed on day 7-10; the results are reported on day 14, day 30 and 6 months after the treatment (extraction under antibiotic prophylaxis).

Methodology for reporting treatment results

In the patients of the first group, the results were reported as follows:

- progression - transition to a more advanced stage of BRONJ;
- stationing - the patient is in the same stage of BRONJ during the different intervals of documentation
- clinical improvement - transition to a lower stage of BRONJ
- remission - complete coverage of the exposed bone with intact oral mucosa, without clinical and paraclinical signs of inflammation.

In the patients of the second group, the results were reported as follows:

- normal healing process of the extraction wound - absence of clinical symptoms; the mucous membrane covering the extraction wound is intact, does not differ in color and consistency from the surrounding healthy one;
- progression of the disease - transition to the first group - clinical and radiographic data on the development of BRONJ

III. Statistical methods

Based on the main purpose and tasks of the study, as well as the volume and type of data, the following statistical methods were applied:

1. Descriptive analysis

It gives a quantitative description of the main properties and characteristics of the studied population. The frequency distribution of the considered signs, broken down by study groups,

the mean values +/- standard deviations and the 95% confidence interval for the mean value are presented in tabular form.

2. Fisher's exact test - when examining the relationship between descriptive (categorical) data with two or more categories.

3. Mann-Whitney test- when comparing two independent groups - used for rank data or when the shape of the frequency distribution is different from the shape of the normal distribution.

The threshold level of significance adopted is $\alpha=0.05$. Statistical significance was assumed when the p value was less than α ($p<0.05$).

4. Statistical method: One-dimensional logistic regression for modeling the dependence of a qualitative two-output variable on quantitative and qualitative predictors (factors) in order to discover prognostic factors through the obtained models.

5. ANOVA analysis- it was applied in order to establish the presence or absence of the influence of two or more factors on the average values of the investigated characteristics (whether there is a dependence between them), without measuring the narrowness or strength of the dependence, as well as its direction.

6. Testing of a statistical hypothesis for the difference of two proportions /of two relative frequencies/ - It is used in researching the effect of the conducted treatment - conservative and conservative surgical.

RESULTS

I. Results on the first task - To examine demographic and clinical characteristics of a group of patients with bisphosphonate-associated osteonecrosis of the jaw - age, gender, underlying disease, location of necrosis.

The results obtained during our analysis of the clinical material are presented in graphic and tabular form and are supplemented with explanatory text.

1. Data results according to the gender of the patients

Regarding the distribution of patients by gender, we found that 20 (45.5%) of the patients examined by us were women and 24 (54.5%) were men, and the difference between the sexes was not statistically significant (p>0.05). The male:female gender distribution is 1.1:0.9

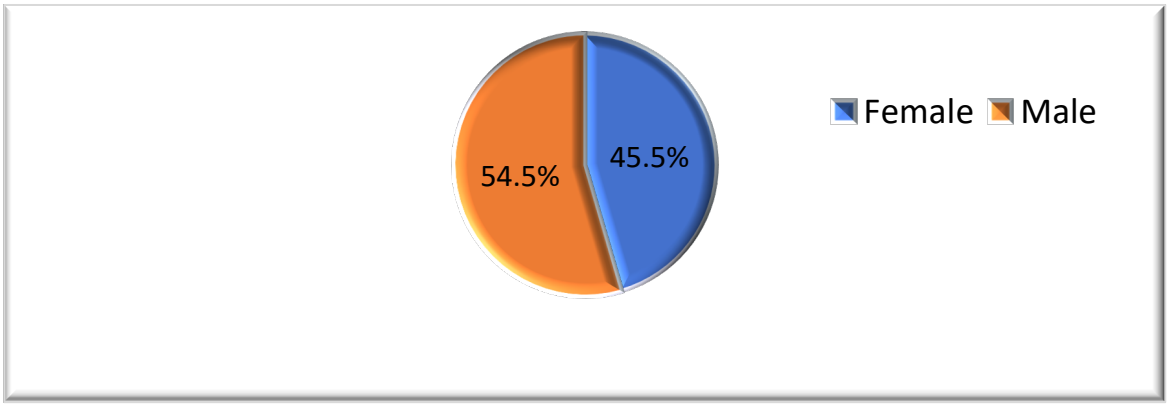

Fig 1. Distribution of patients from the first group by gender

2. Data results according to the age of the patients

Patients were divided into six age groups presented in Table 1.

Age group	Number of patients	Percentage
30-40 years	2	4,545
41-50 years	2	4,545
51-60 years	6	13,636
61-70 years	19	43,182
71-80 years	14	31,818
81-90 years	1	2,273

Table 1. Frequency distribution of patients from the first group in age groups

From table 1 it can be seen that BRONJ occurs most often in the age between 60-70 years. There were 19 (43.2%) patients in this age group. The age between 70-80 years old patients is also highly represented (31.8%). The percentage distribution in the 50-60 age group is lower (13.6%). We observe 2 cases (4.6%) of BRONJ in the 30-40 and 40-50 age groups. Only 1 patient (2.3%) of the examined was aged 80-90 years. In the studied material, we did not find a case under the age of 30 years and over 91 years.

Regarding the age factor of patients with BRONJ, we found a minimum age of 36 years, a maximum of 88 years, an average value of 62 years, with a standard deviation of 10.42.

	Mean age	Minimum age	Maximum age	Standart deviation
Age /years/	65,273	36	88	10,422

Table 2. Frequency distribution of patients from the first group according to the variable Age

We also found that patients with BRONJ under the age of 40 were 2 cases - 4.6% of all cases. 42 (95.4%) cases were found in patients over 40 years of age. The percentage distribution of BRONJ patients under 40 years of age and those over 40 years of age is presented in Fig. 2.

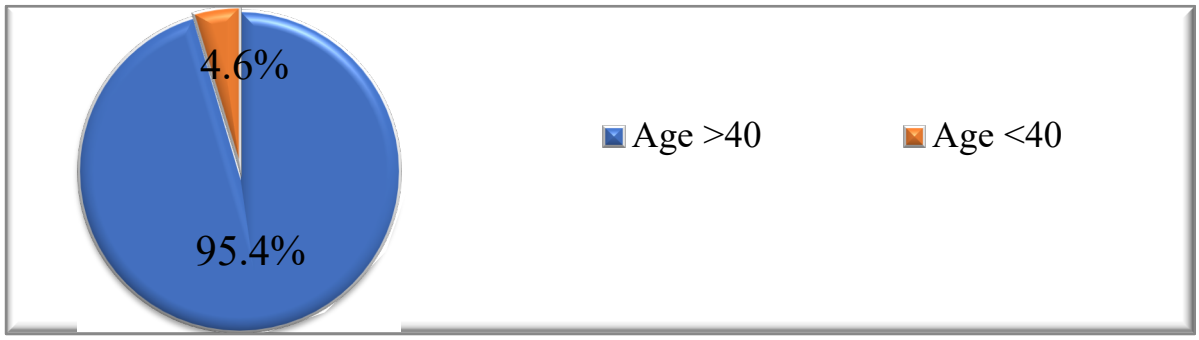

Fig. 2. Distribution of patients of the first group by age >40 and <40 years.

3. Data results according to the main diagnosis of the patients

The present study shows that a significantly higher proportion - 40 (90.9%) of the patients had a primary diagnosis of malignancy. In 4 patients (9.1%), the intake of BF was indicated by an underlying disease of osteoporosis.

Fig. 3. Distribution of patients from the first group according to the main diagnosis

4. Data results according to the type of the administered BF

When examining the patients according to the type of the administered BF, it was found that the administered BF with the highest frequency was Zoledronic acid - in 32 (72.7%) of the patients. Second place is taken by Zoledronic and Pamidronic acid in 5 (11.4%) patients. Alendronic acid and Ibandronic acid in 2 (4.5%) and Ibandronic acid in 2 (4.5%) of the studied patients followed in the same percentage. In the last place in distribution are Pamidronic acid in 1 patient (2.3%), Zoledronic and Alendronic acid in 1 (2.3%) and Zoledronic, Ibandronic and Pamidronic acid also in 1 patient (2.3%).

It was also established that in the largest percentage of cases Zoledronic acid was taken - in 32 (72.7%), followed by Zoledronic acid and another BF - in 16% (7 of the patients). In a significantly smaller percentage of cases with an equal number of patients, Ibandronic acid (4.5%, 2 patients) and Alendronic acid and Ibandronic acid (4.5%, 2 patients) and Pamidronic acid in 1 patient (2.3%).

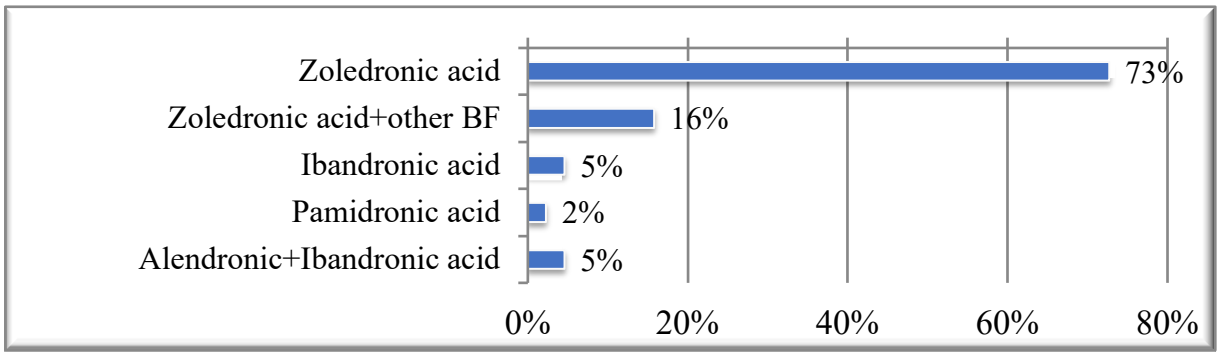

Fig. 4. Distribution of patients from the first group according to the type of BF taken

It was also found that in a significantly larger percentage - 88.5% of the cases, the BF administered was Zoledronic acid (alone or in combination with another drug from the BF group), compared to 11.5% in total for all other BF.

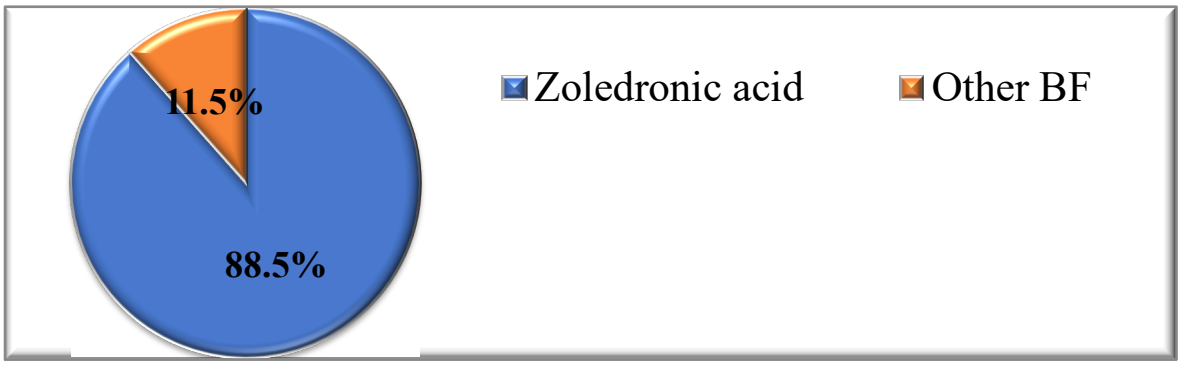

Fig. 5. Distribution of patients from the first group according to the type of BF introduced

5. Data results according to BF administration method

According to the method of introduction of BF into the body, we found the following distribution - in a significantly greater percentage of cases, BF was administered intravenously in 40 patients (90.1%), compared to 4 of the patients (9.1%), in which BF was administered orally.

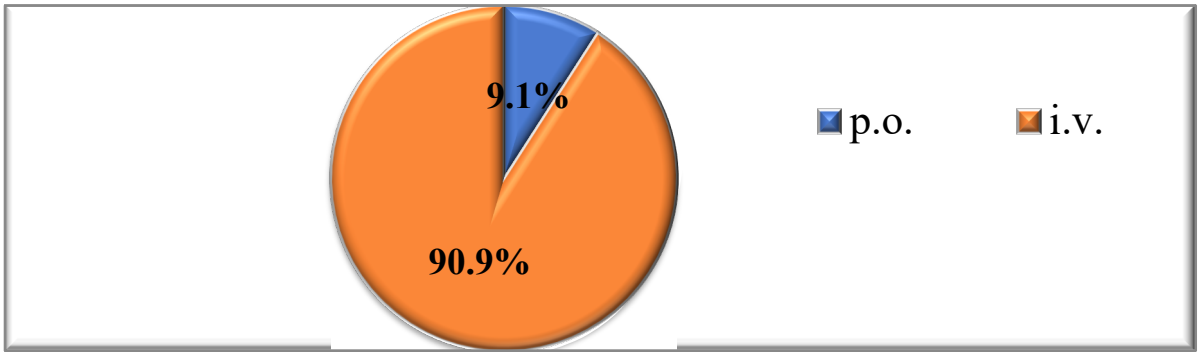

Fig. 6. Distribution of patients from the first group according to the method of administration of BF

6. Data results according to duration of BF intake

Our study showed a maximum value of the duration of BF 108 intake (in months), a minimum value of 8 months, an average value of 41.75 months, with a standard deviation of 27.1 months. The distribution is shown in the table below:

	Average value	Minimum value	Maximum value	Standard deviation
Duration of BF intake	41,75	8	108	27,08

Table 3. Distribution of cases according to the duration of BF intake in the patients of the first group

7. Results of the data according to the presence of previous surgical intervention or mechanical trauma

The examination of the clinical material shows that in a significantly higher percentage of cases - 39 (88.6%) of the patients before the appearance of BRONJ, a dentoalveolar surgical intervention (tooth extraction or placement of a dental implant) was carried out, compared to 5 (11.4%) of the patients with mechanical trauma from a removable prosthesis.

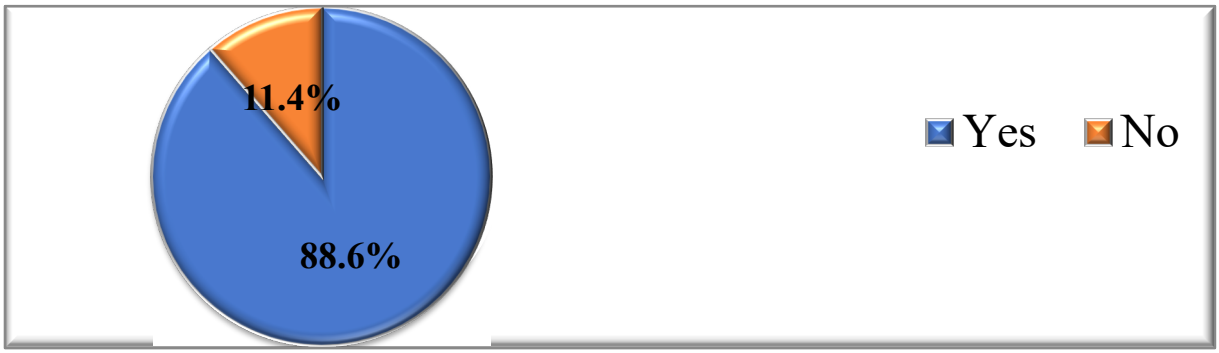

Fig. 7. Distribution of the patients of the first group according to the presence of previous surgical intervention or mechanical trauma

8. Data results according to the factor Time from the dentoalveolar surgical intervention

Analyzing the data according to the factor Time from the dentoalveolar surgical intervention (the time from the surgical intervention to the clinical manifestation of BRONJ), we found a minimum value of 2 months, a maximum value of 36 months, an average value of 8 months, with a standard deviation of 8.319.

	Mean	Minimal	Maximum	Standart deviation
TFSI	8	2	36	8,32

Table 4. Distribution of the patients of the first group according to the factor of time from the dentoalveolar surgical intervention.

II. Results on the second task - To study the clinical manifestations of BRONJ in the oral cavity - localization of BRONJ, clinical symptoms, stage of BRONJ, radiographic changes in the jaw bones of the studied patients

1. Data results according to the localization of BRONJ (depending on which of the jaw bones is affected - mandible, maxilla, or both).

The research carried out regarding the localization of BRONJ shows that in the largest percentage - in 28 patients (63.6%) the lower jaw is affected, followed by 12 patients (27.3%) with involvement of the upper jaw, and in the most - low degree - in 4 of the patients (9.1%) the disease affects the upper and lower jaws.

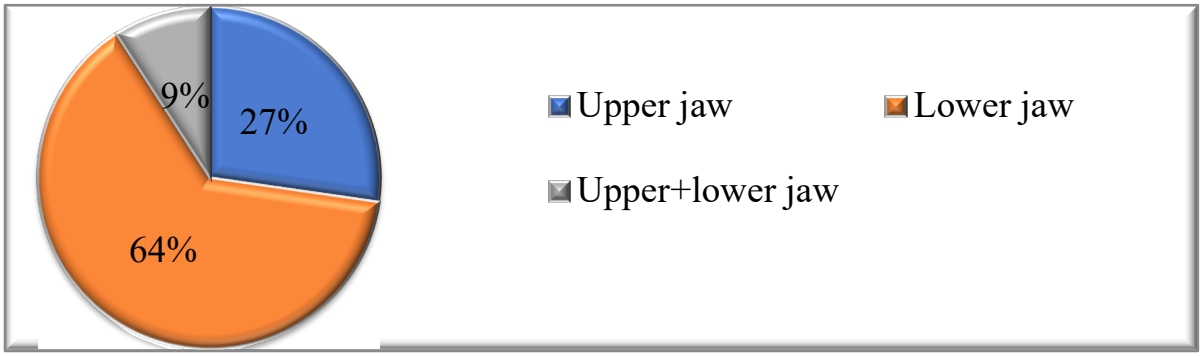

Fig. 8. Distribution of the patients of the first group according to the localization of BRONJ depending on which of the jaw bones is affected

2. Data results according to the localization of BRONJ (depending on which part of the jaw bones is affected - frontal, distal or both).

The most common localization in the studied group was the distal region of the jaw - in 34 (77.3%) patients. Next was the frontal region in 6 (13.6%) of the patients, and the lowest rate was observed in 4 of the patients (9.1%), in which both the frontal and distal regions of the jaw bones were affected.

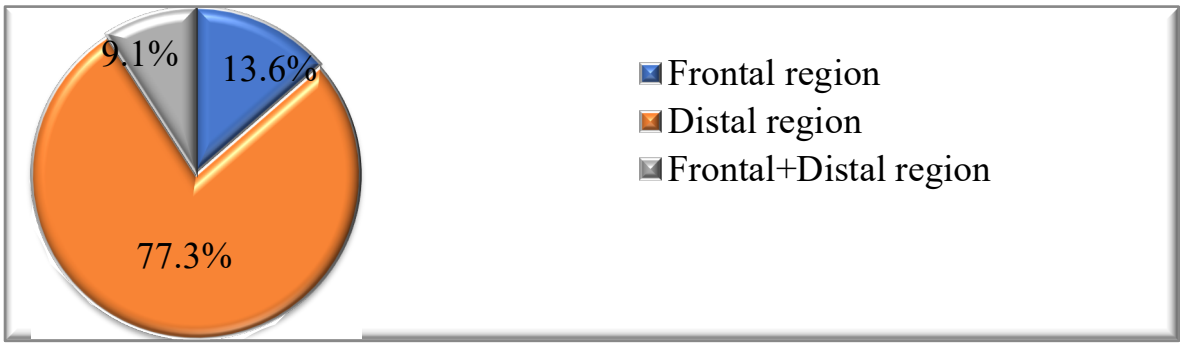

Fig. 9. Distribution of patients of the first group according to the localization of BRONJ depending on which part of the jaw bones is affected.

3. Data results according to the observed clinical symptoms

When examining the clinical symptoms that occur in our patients, it was found that non-specific symptoms and clinical findings were found in all 44 patients (100%). Exposed necrotic bone was observed in 43 (97.7% of patients), the percentage of patients with pain was also high - 39 of patients (88.6%) and the presence of purulent exudate (the same), closely followed by 38 of patients (86.4%), in which erythema of the surrounding tissues was established. The percentage of patients with extraoral fistula (4 of the patients) is significantly lower (9.1%), the percentage of patients with oroantral communication is also low (4.6% - 2 of the patients), and the last place in terms of frequency is osteolysis outside the lower border of the mandible, which was observed in only one patient (2.3%).

4. Data results according to the stage of BRONJ at the time of the initial diagnose of the patients

When examining the patients in relation to the stage in which they were at the time of diagnosis, it was found that in the monitored group, the frequency of patients in stage II was the highest - 33 (75%). In second place are the patients in stage III - 6 (13.6%), followed by those in stage I - 4 of the patients (9.1%). Only one of the studied patients (2.3%) was diagnosed at stage 0.

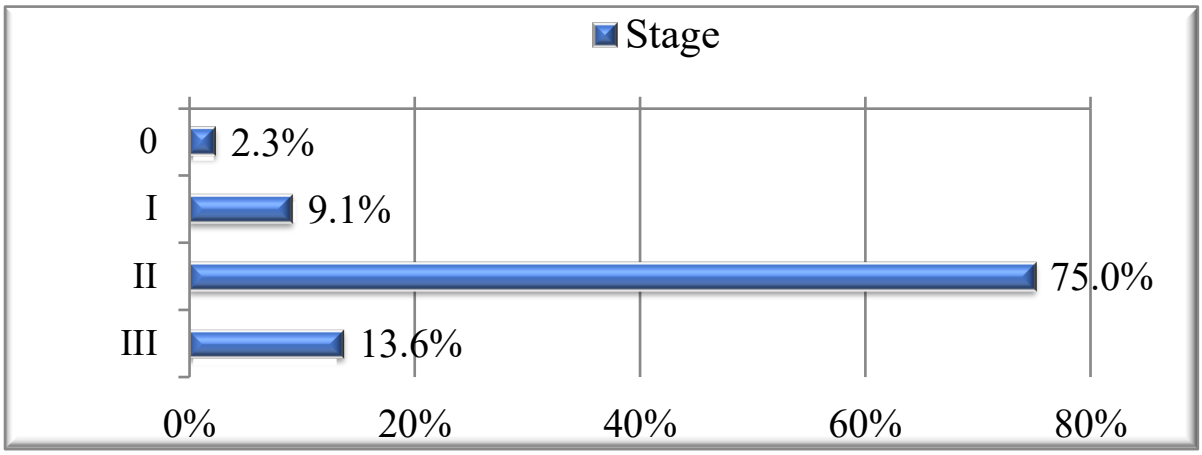

Fig. 10. Distribution of patients of the first group according to the stage of BRONJ, at the moment when the patients were diagnosed

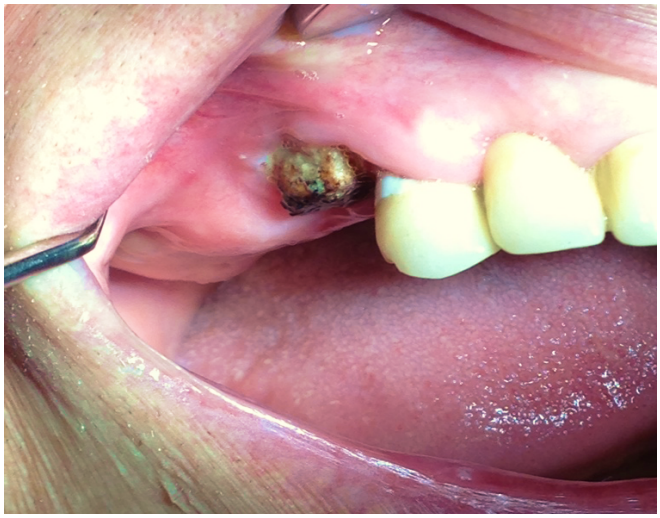

Photo 1. Patient P.G. age 72 with a primary diagnosis of prostate carcinoma with bone metastases, on Zometa therapy in the first stage of BRONJ

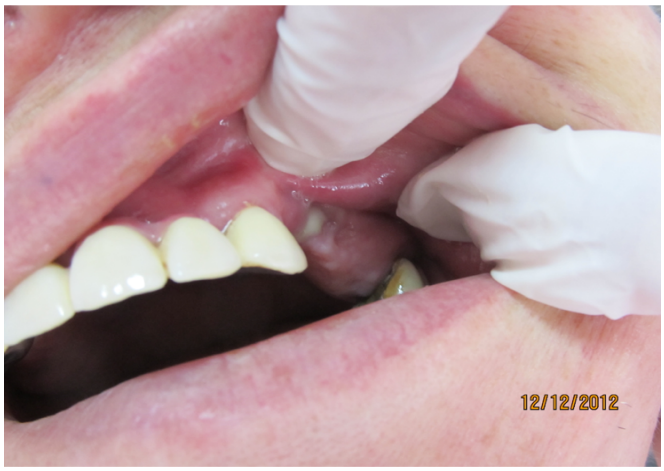

Photo 2. Patient Ya. L., 59 years old. with a primary diagnosis of lung carcinoma with bone metastases, on Zometa therapy in the second stage of BRONJ development

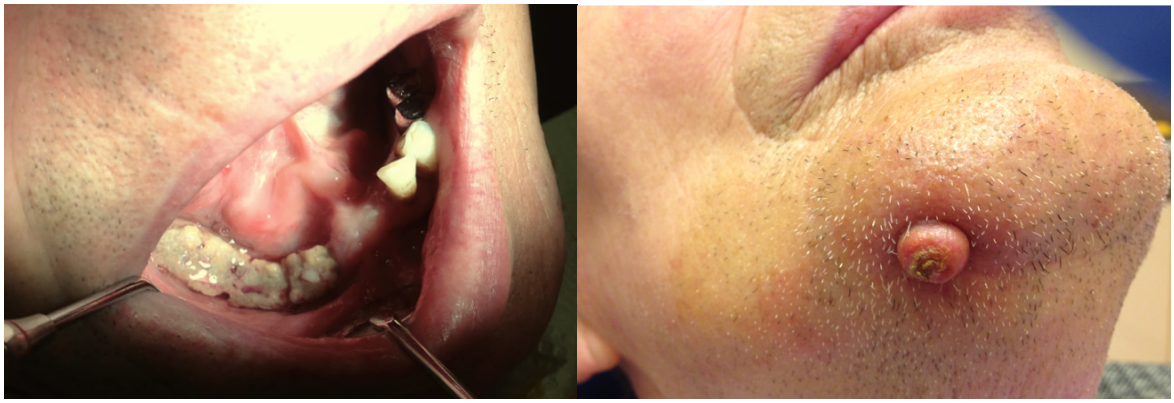

Photo 3 and 4. Patient J.D. age 71 with a primary diagnosis of prostate carcinoma with bone metastases, on Zometa therapy in the third stage of BRONJ with extraoral skin fistula

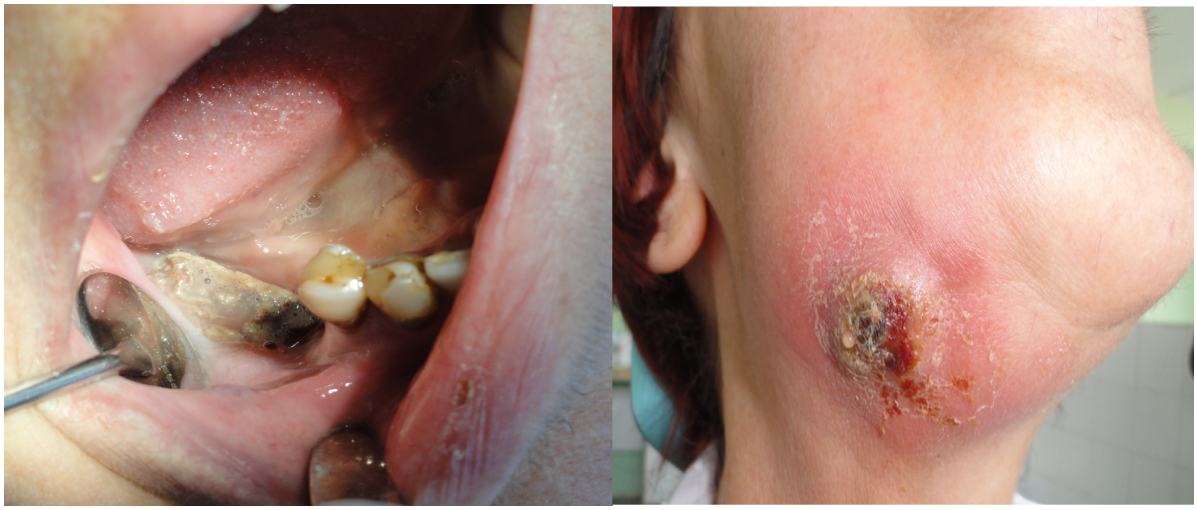

Photo 5 and 6. Patient C.V., 68 y. o.. with a primary diagnosis of breast carcinoma with bone metastases, on Zometa therapy in the third stage of BRONJ, the extraoral skin fistula is also visible.

5. Data results according to the radiographic finding.

In the analysis of the data, it was found that the percentage of patients with the presence of osteolysis and osteosclerosis prevailed significantly - 31 (70.5%) of the patients, compared to those with the presence of osteolysis, osteosclerosis and a formed sequestrum - 13 patients (29, 5%).

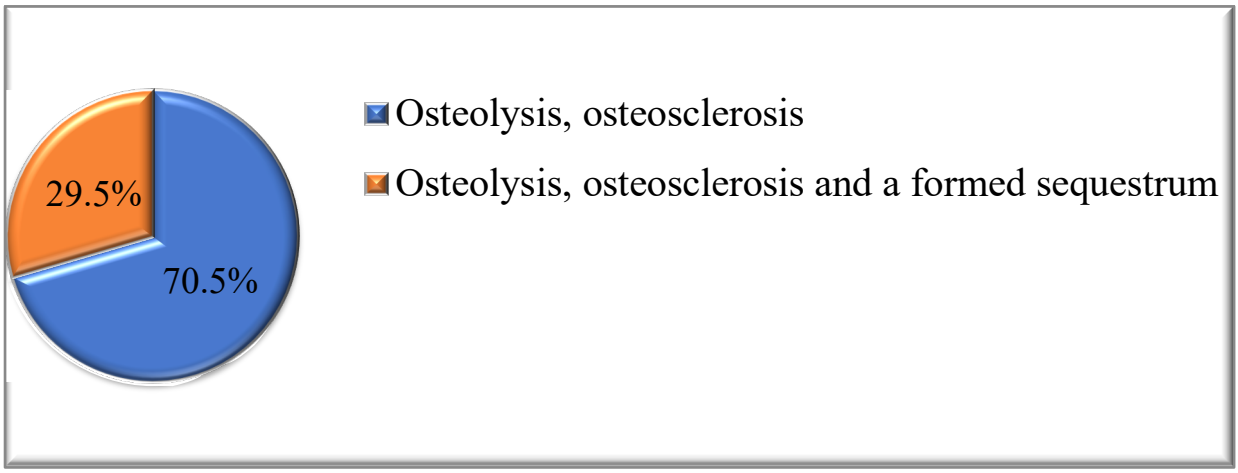

Fig. 11. Distribution of patients from the first group according to the radiographic finding.

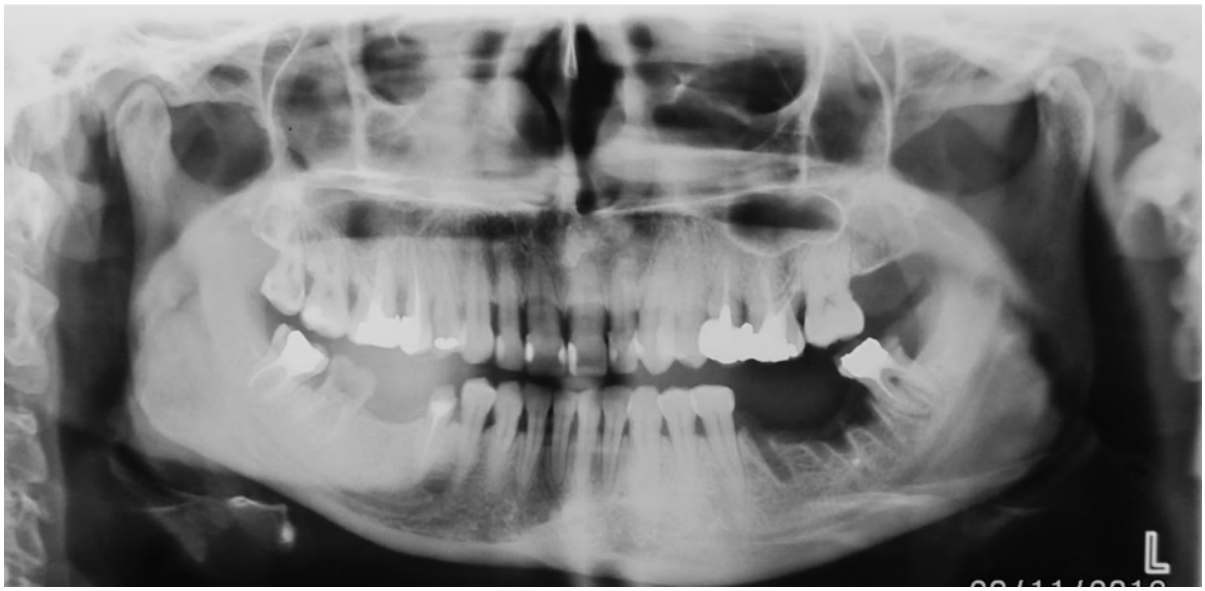

Photo 7. Patient N.I. 36 years old, primary diagnosis of breast carcinoma with bone metastases, on Zometa therapy, radiographic findings of osteolysis and osteosclerosis

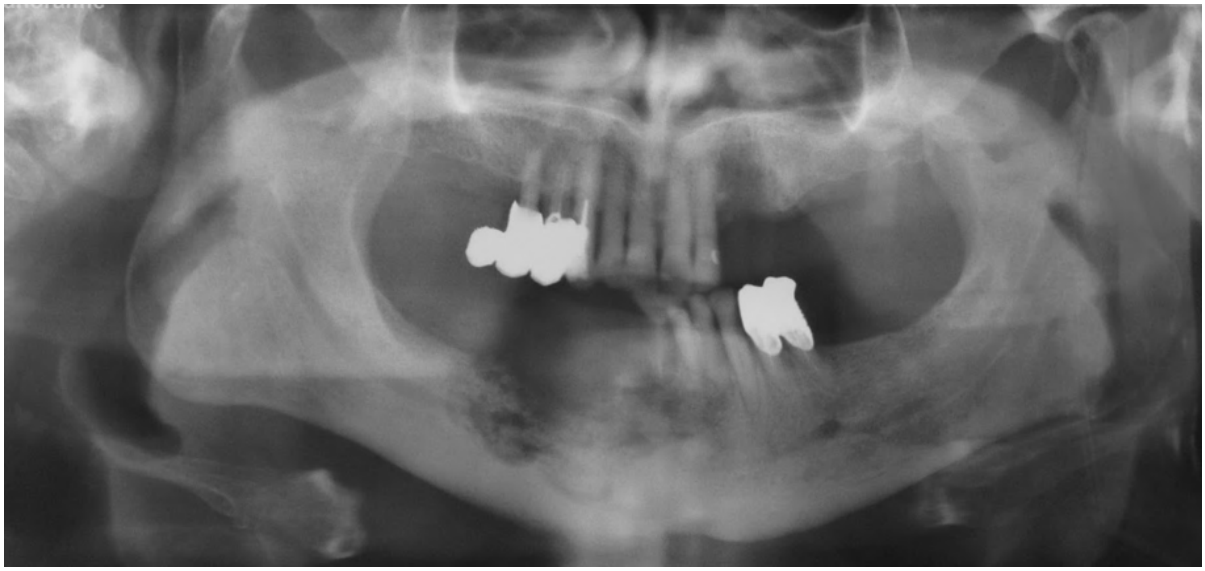

Photo 8. Patient J.D. at the age of 71 with a primary diagnosis of prostate carcinoma with bone metastases, on Zometa therapy in the third stage of BRONJ with radiographic findings of osteolysis and osteosclerosis and formed bony sequestrum.

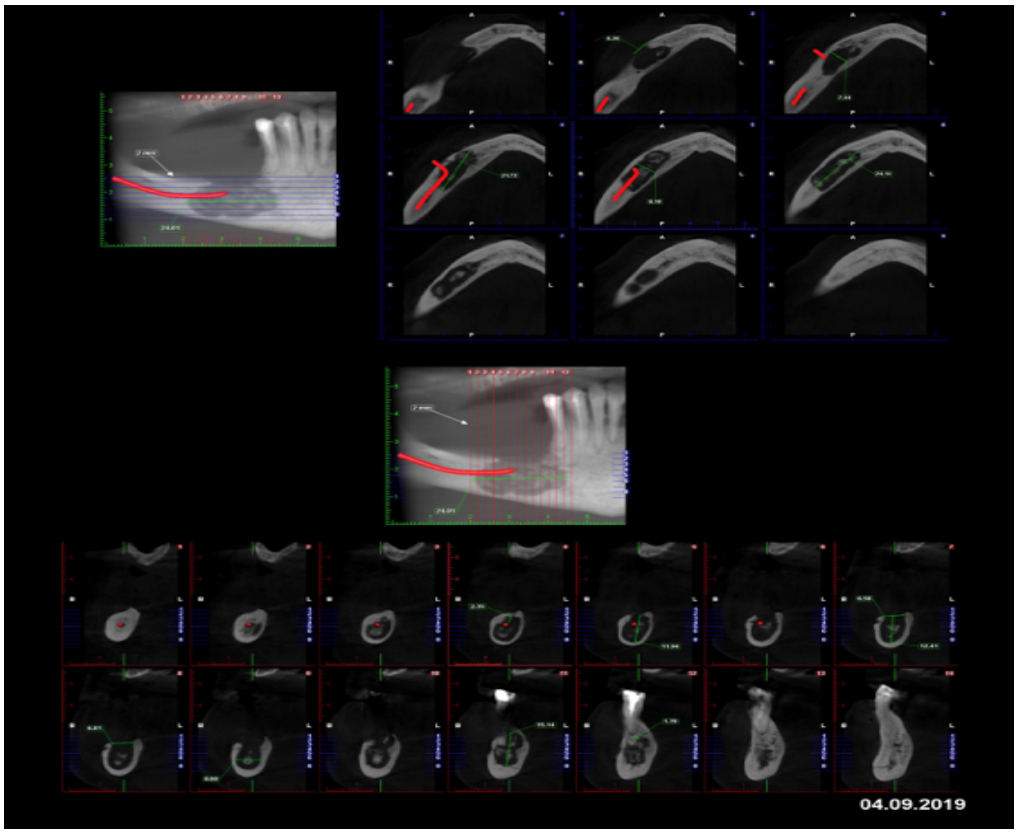

Photo 9. Patient C.V., 68 years old. with a primary diagnosis of breast carcinoma with bone metastases, on therapy with Zometa in the third stage of BRONJ development, with radiographic findings of osteolysis and osteosclerosis and formed bony sequestrums.

III. Results on the third task. To investigate the effect of the performed conservative treatment (antibiotic and cleaning of necrotic tissues-debridement)

1. Data results according to surgical treatment performed

When examining the distribution of patients with regard to the surgical treatment performed, we found that the percentage distribution in the three groups was similar - 15 (34.1%) of the patients did not undergo surgical treatment, 13 (29.5%) of the patients underwent sequestrectomy and in 16 patients (36.4%) surgical debridement was performed.

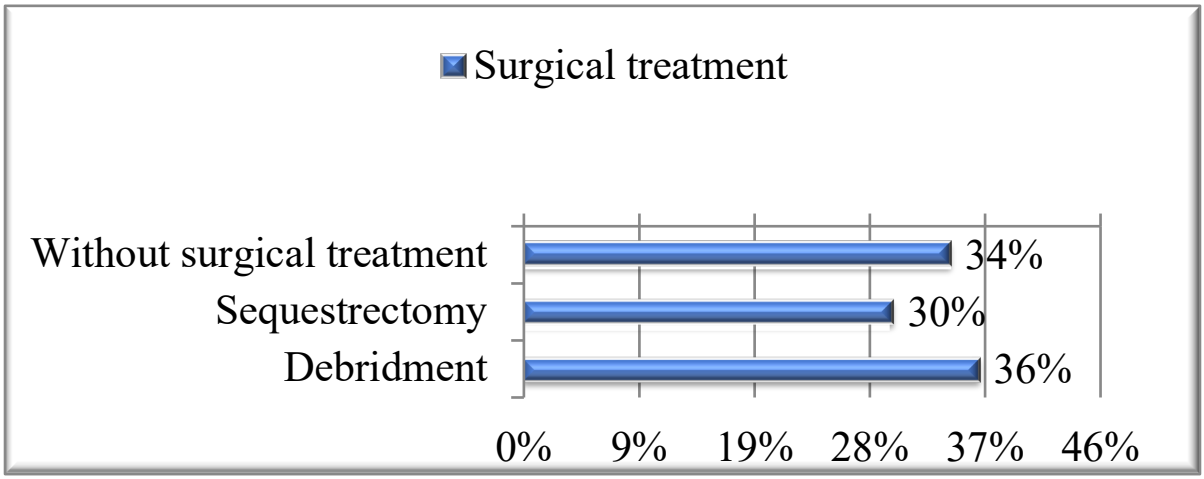

Fig. 12. Distribution of patients from the first group according to the performed surgical treatment.

2. Data results according to the medical treatment carried out

According to the medical treatment carried out, the patients are distributed as follows: an antibiotic from the penicillin group was most often administered - in 32 patients (72.7%), followed by 0.2% chlorhexidine solution in 5 of the patients (11.4%) , in third place, the results for taking Lincosamide are close - in 4 patients (9.1%), followed by 2 of the patients (4.5%) - an antibiotic from the group of Cephalosporins and only in 1 patient (2.3%) Tetracycline was administered.

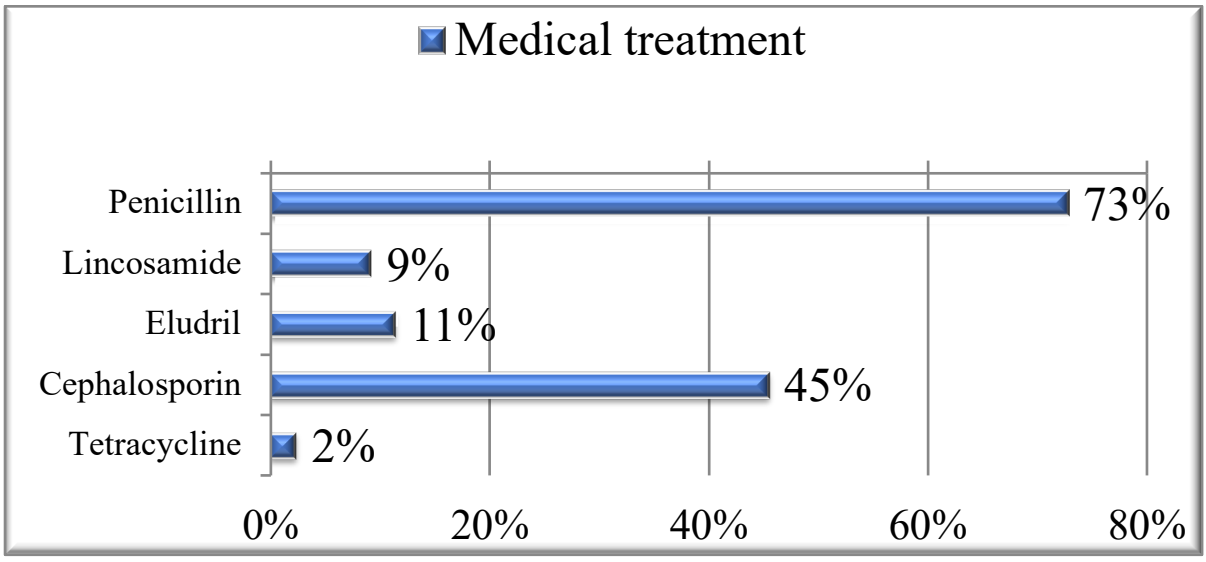

Fig. 13. Distribution of patients from the first group according to the administered medical treatment

3. Data results according to the performed surgical and medical treatment.

Our study showed that of the examined patients, a higher percentage of 29 (65.9%) were treated surgically and medically, compared to 15 (34.1%) in which only medical treatment was administered.

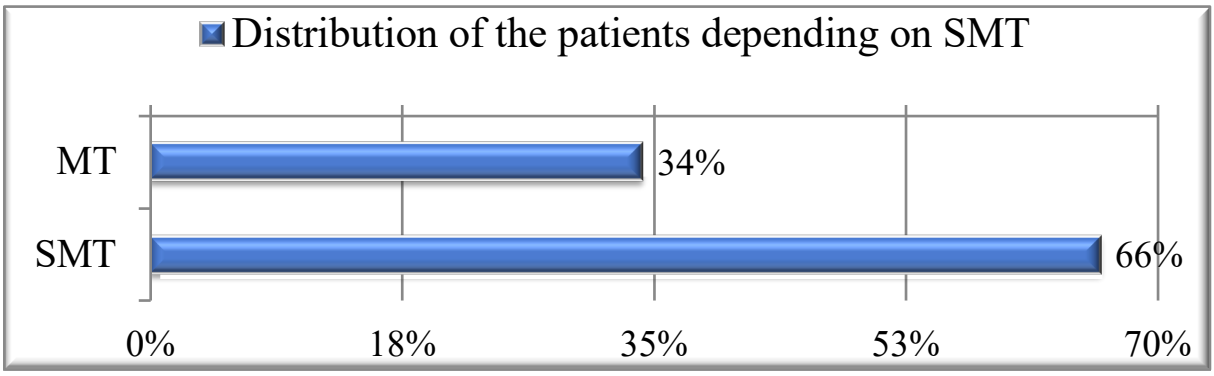

Fig. 14. Distribution of patients from the first group according to the performed surgical and medical treatment.

4. Data results according to the development of the disease (BRONJ) after 1 month.

With regard to the development of BRONJ at a follow-up examination after 1 month, we found the following distribution: in the first place with the highest percentage - in 26 (43%) of the patients, the disease was stationed, in second place followed the patients in whom a clinical improvement of the disease was observed - 15 (34.1%) of the patients, in the third place

in 2 of the patients (4.5%) there was disease progression, and finally only in 1 patient (2.3%) - remission.

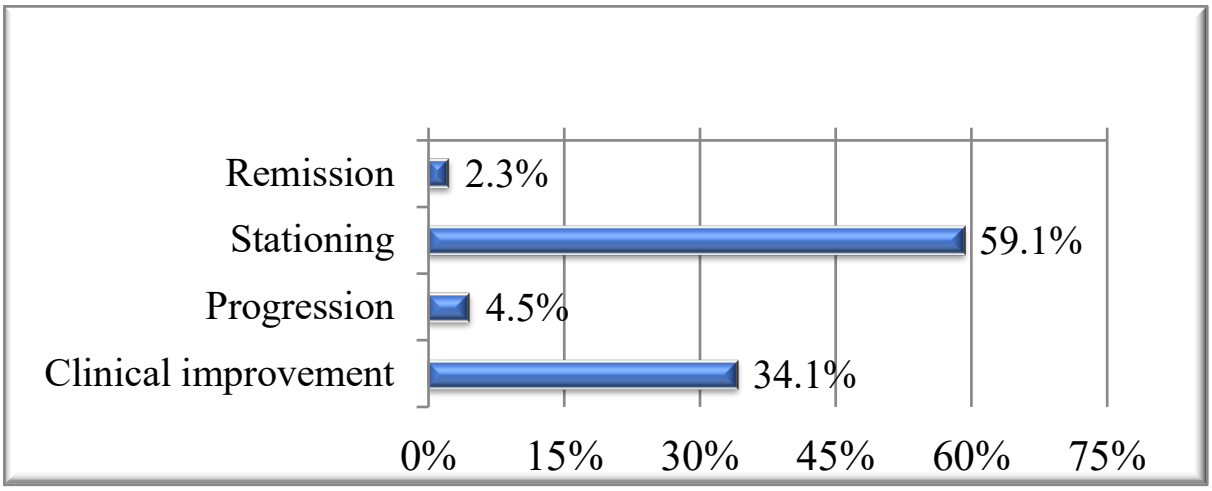

Fig. 15. Distribution of patients of the first group according to the development of the disease (BRONJ) after 1 month.

5. Data results according to the development of the disease (BRONJ) after 6 months.

Of the patients examined by us regarding the development of the disease after 6 months, we found that hospitalization was most often observed - in 20 (45.5%) of the examined patients, in second place were the patients with clinical improvement - in 11 (25%) of the patients, progression - in 7 (15.9%) of the patients and remission in 6 (13.6%), occupy third and fourth place with a close distribution percentage.

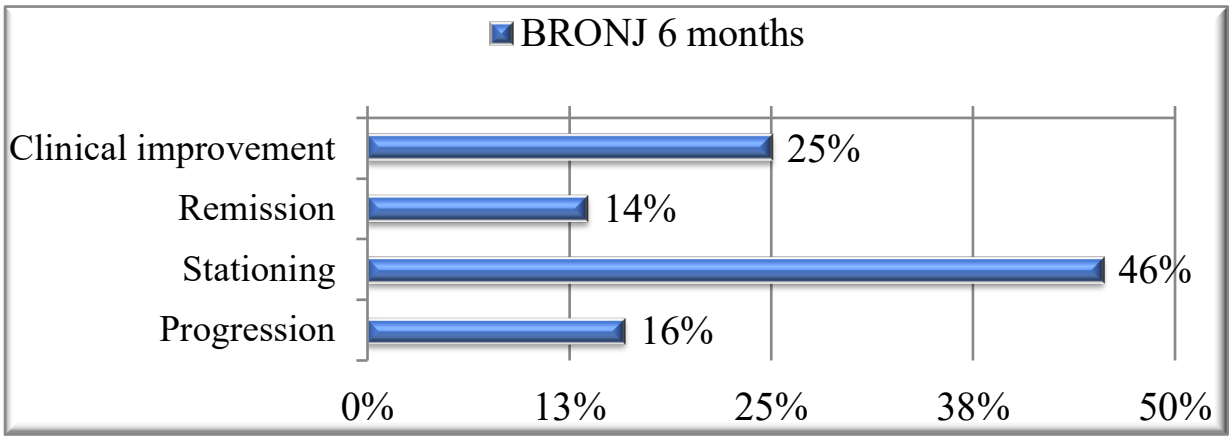

Fig. 16. Distribution of patients of the first group according to the development of the disease (BRONJ) after 6 months.

6. Results regarding the outcome of the treatment at the 1st and 6th month in sequestrectomy.

Sequestrectomy was applied to 13 of the examined patients. When considering the results regarding the outcome of the treatment in the 1st month with this method, we found that the highest share was occupied by the patients in whom we observed a regression of the disease - 76.9% (10 patients). In the second place, with a significantly lower percentage were the patients in whom stationing occurred - 15.4% (2 of the patients), followed by 1 patient (7.7%), in whom disease progression occurred and remission of the disease was not observed in any of the patients.

Taking into account the results of the 6th month of treatment, again in terms of its outcome, it was found that in the first place, with the highest percentage are the patients in whom remission of the disease occurs - 46.2% (6 patients), in the second place patients in which regression occurs - 38.5% (5 patients), and in the same number of patients (one) we observe stationing (7.7%) and progression (7.7%) of the disease.

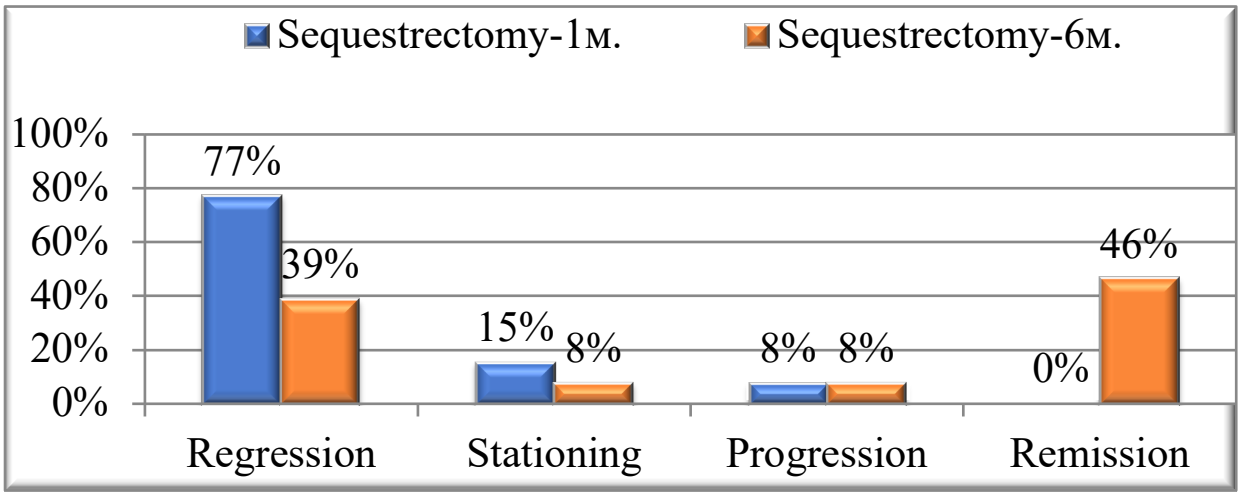

Fig. 17. Distribution of the patients from the first group according to the outcome of the treatment at the 1st and 6th month in sequestrectomy.

Using the statistical method of statistical hypothesis testing for the difference of two proportions, it was found that:

- In the sequestrectomy treatment method, when comparing the results of the treatment at the first and sixth months of its application, there is a statistically significant difference ($p=0.0236<0.05$) in the outcome of the treatment regression - a statistically significant decrease in the number of patients at the 6th month compared to those at the first month.
- The difference regarding the outcome of the treatment remission is also statistically significant ($p=0.0008<0.05$) - there is a significant increase in the number of patients

with the outcome of the treatment remission on the 6th month, compared to that established on the 1st month of the applied treatment.

- No statistically significant difference was found regarding the outcome of the treatment, stationing (p=0.2696>0.05) and progression (p=0.5>0.05) at the first and sixth months when applying the sequestrectomy treatment method.

7. Results regarding the outcome of the treatment at the 1st and 6th months with debridement.

Treatment method debridement was applied to 16 of the examined patients.

The results recorded in the first month of the applied treatment show that with this method the highest percentage (62.5%, 10 patients) takes stationing as the outcome of the treatment, the next place with a significantly lower percentage is regression (25%, 4 of the patients) and the last two places are occupied by progression (6.3%) and remission (6.3%) in one of the patients.

When reporting the results regarding the outcome of the treatment at the sixth month, we found a similar distribution of the results compared to those at the 1st month of the applied treatment. The highest share is occupied by patients in whom we observe stationing - 50% (in 8 of the patients), in second place are patients in which regression occurs - 31.3% (5 patients), in third place are patients with progression of the disease-12.5% (2 of the patients) and in the last place are the patients in whom we observe remission-6.3% (one patient).

When applying a treatment method of debridement, no statistically significant difference was found regarding the outcome of the treatment: regression (p=0.3475>0.05), stationing (p=0.238>0.05), progression (0.2721>0 .05) and remission (p=0.5>0.05) at the first and sixth months of treatment.

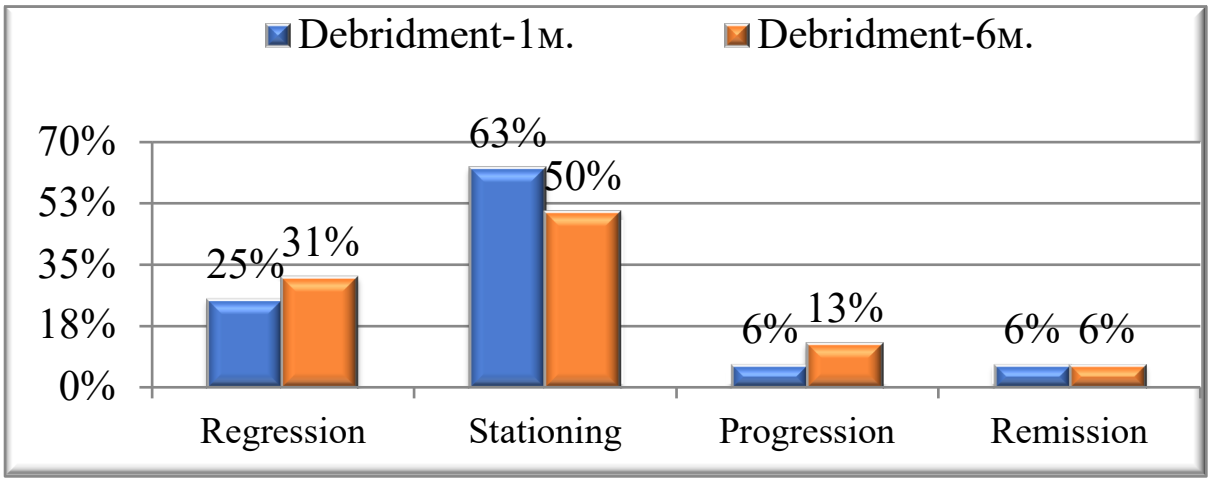

Fig. 18. Distribution of the patients from the first group according to the outcome of the treatment at the 1st and 6th month of debridement.

8. Results regarding the outcome of the treatment at the 1st and 6th months of drug treatment.

Medical treatment was applied in 15 of the studied patients.

When reporting the results of the first month of the applied medical treatment, we found the following results: stationing was observed in the highest percentage (86.7%) of the patients studied by us (in 13 of the patients). A significantly lower percentage distribution was observed in terms of regression-6.7% (1 patient) and progression-6.7% of the disease. Remission did not occur in any of the patients studied by us.

Taking into account the results of the sixth month of the applied treatment, we found that here again the first place in the distribution of stationing of the disease is retained - 73.3% (11 patients), progression of BRONJ takes second place with 20% (3 patients) and third place is regression-6.7% (in one of the patients). No remission occurred in any of the patients examined by us - 0%.

With regard to the method of medical treatment: we did not find a statistically significant difference in terms of treatment outcome regression ($p=0.5>0.05$), stationing ($p=0.1806>0.05$), progression ($0.1414> 0.05$) and remission ($p=0.5>0.05$) at the first and sixth months of treatment.

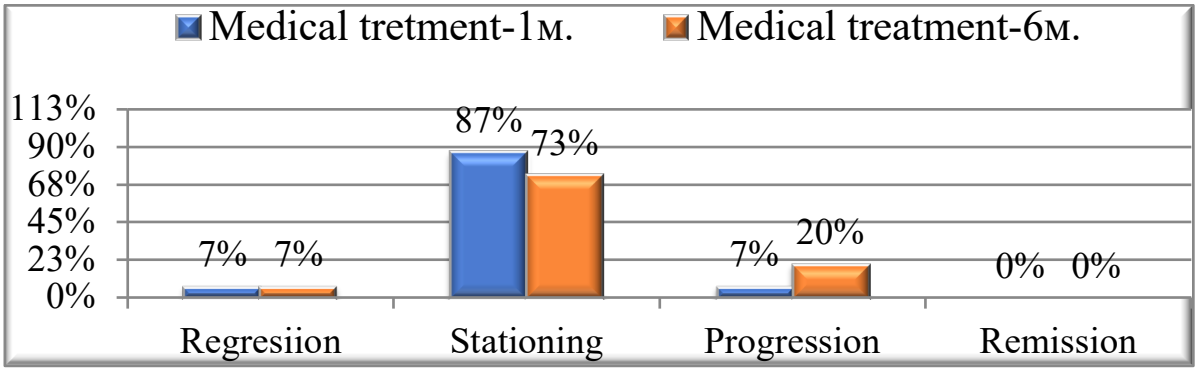

Fig 19. Distribution of the patients from the first group according to the outcome of the treatment at the 1st and 6th months of medical treatment.

9. Comparison of the outcome of the treatment methods Sequestrectomy and Debridement+Medical treatment at the 1st and 6th months

When comparing the results of the treatment outcome of the first month in the Sequestrectomy and Debridement+Medical treatment groups, we found a statistically significant difference in terms of treatment outcome regression ($p=0.0001<0.05$) and stationing ($p=0.0002 <0.05$). Regarding treatment outcome progression ($p=0.4409>0.05$) and remission ($p=0.2562>0.05$) no statistically significant difference was found.

Indicator A	Medication+Debridement	Sequestrectomy	$P(z > z_0)$
regression	0,16129	0,76923	0,0001
stationing	0,74194	0,15385	0,0002
progression	0,06452	0,0769	0,4409
remission	0,03226	0,0000	0,2562

Table 5. Comparison of the results of the treatment outcome of the first month in the Sequestrectomy and Debridement+Medication treatment groups.

When comparing the two groups regarding the outcome of the treatment at the 6th month, we found that the outcome of the treatment stationing prevailed in the medication+debridement group (77.4%), significantly more, compared to stationing in the other group we studied (Sequestrectomy- 7.7%). A significantly higher percentage of patients in the sequestrectomy group achieved disease remission (46.2%), compared to remission in the medication+debridement group (3.2%). Patients with regression as an outcome of the disease were in a higher percentage in the Sequestrectomy group (38.5%) compared to those in the medication+debridement group (19.3%). With regard to progression as a result of BRONJ treatment, the results in the two groups compared were as follows: 16.1% in the medication + debridement group and 7.7% in the sequestrectomy group.

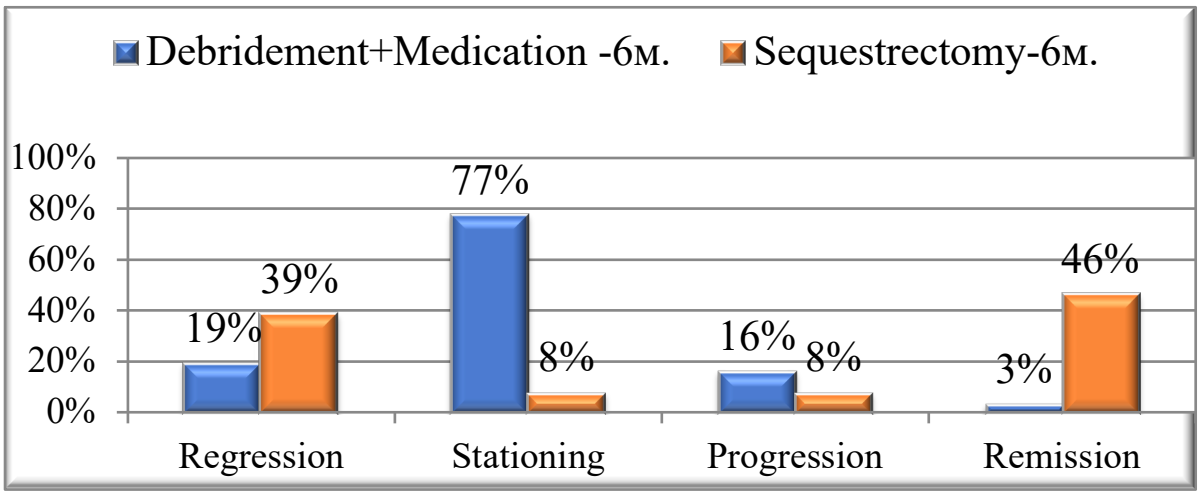

Fig. 20. Comparison of the results of the treatment outcome at the sixth month in the Sequestrectomy and Debridement+Medication treatment groups.

IV. Results on the fourth task. To investigate, to follow up cases of development of a healing process or necrosis in patients undergoing therapy with bisphosphonates in connection with malignant diseases or osteoporosis, examining the duration of reception, the time from the surgical intervention, the age of the patient as factors influencing the radiographic finding and the outcome of BRONJ treatment

1. Analysis of the relationship between the duration of BF intake and the outcome of the BRONJ treatment, reported at a follow-up examination one month after it in the first group of patients.

The method of logistic regression was used, with the help of which we found that the factor of duration of BF intake had an effect on the outcome of the treatment reported in the first month after it, since the p-level=0.0368<0.05.

Through the built logistic model, it is possible to predict the probability of BRONJ progression in the first month of the treatment. The statistical analysis carried out shows that as the duration of BF intake increases, so does the probability of disease progression, detected during the patient's examination in the first month after the applied treatment.

The plot of the change in the probability of admission duration is presented in the figure below.

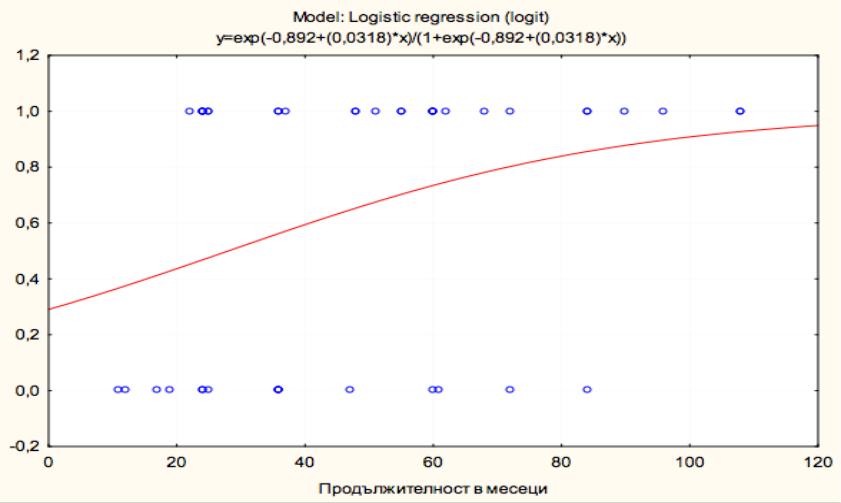

Fig. 21. Change in the probability of progression of BRONJ-1m. depending on the values of the duration of treatment.

2. Analysis of the dependence between the factors Time from the surgical intervention (TFSI) and the outcome of the treatment established 1 month after it in the first group of patients.

The logistic regression model used showed that TFSI had an effect on treatment outcome reported at the first month after it, because p-value 0.03<0.05. The coefficient B1 is positive /0.122/ and as can be seen from the graph below it follows:

As the values of the factor of limitation of surgical intervention (TFSI) increase, the probability of progression of the disease, established at the examination of the patient in the first month after the applied treatment, grows.

The graph of the change in the probability of progression of BRONJ-1 m. depending on the length of time of the surgical intervention is presented in the figure below:

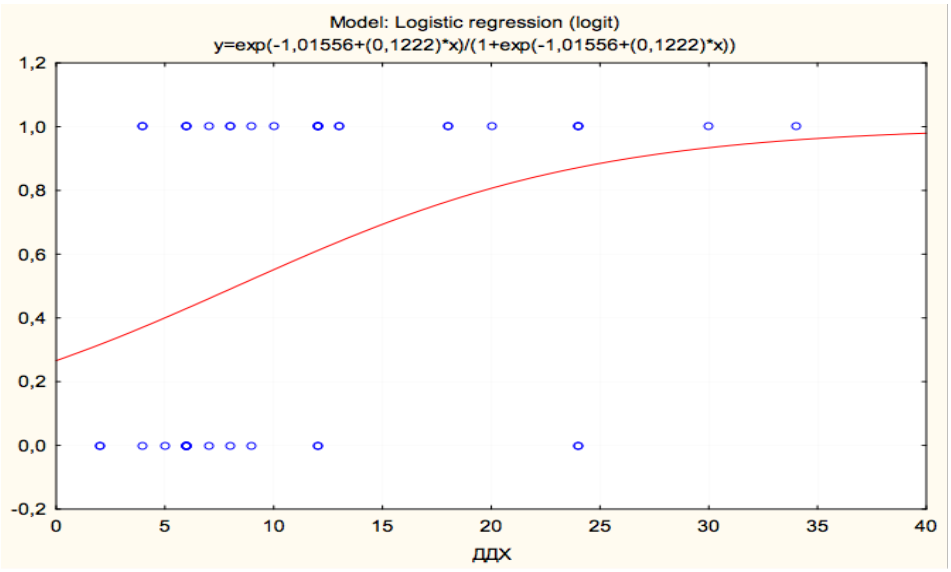

Fig. 22. Change in the probability of progression of BRONJ-1m. depending on the TFSI values.

3. Analysis of the dependence between the factor Age of the patient and the outcome of the treatment reported in the first month after it in the first group of patients.

A logistic regression model was used to establish a relationship between the factor Age and the outcome of the treatment, reported at the first month after it. It was found that age was not a prognostic factor for BRONJ-1m (p=0.4807685>0.05)

However, the trend of the relationship is clear (B1=0.02137>0): As age increases, the probability of disease progression at 1 month increases.

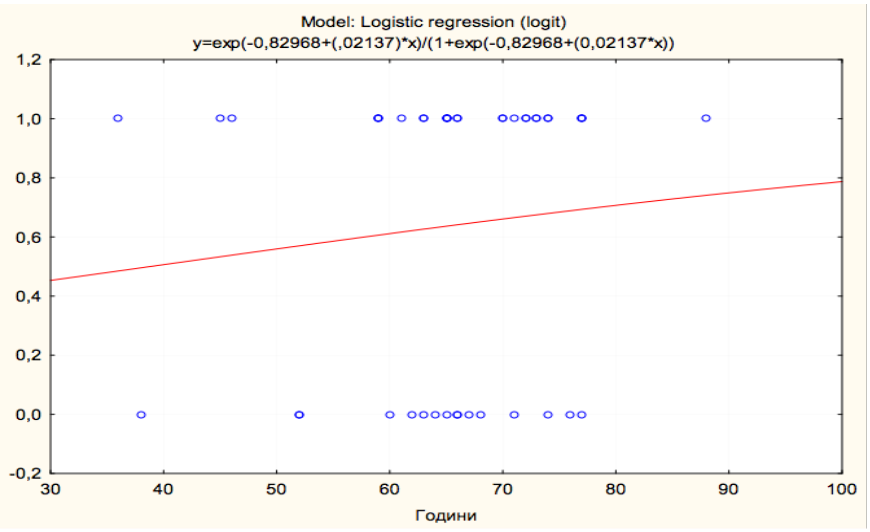

Fig. 23. Change in the probability of progression of BRONJ-1m. depending on the values of the patient's age factor.

4. Analysis of the dependence between the factors time from the surgical intervention (TFSI) and the outcome of the treatment established 6 months after it in the first group of patients.

The logistic regression model used showed that the factor time from the surgical intervention (TFSI) had an effect on the outcome of the treatment reported at the sixth month after it, because p-value 0.02<0.05. The coefficient B1 is positive /0.094/ and as can be seen from the graph below it follows:

As the values of the factor of time from the surgical intervention (TFSI) increase, the probability of code 2 of BRONJ-6m increases. i.e. for progression.

The graph of the change in the probability of progression of BRONJ, established at the sixth month of the applied treatment, depending on the TFSI is presented in the figure below.

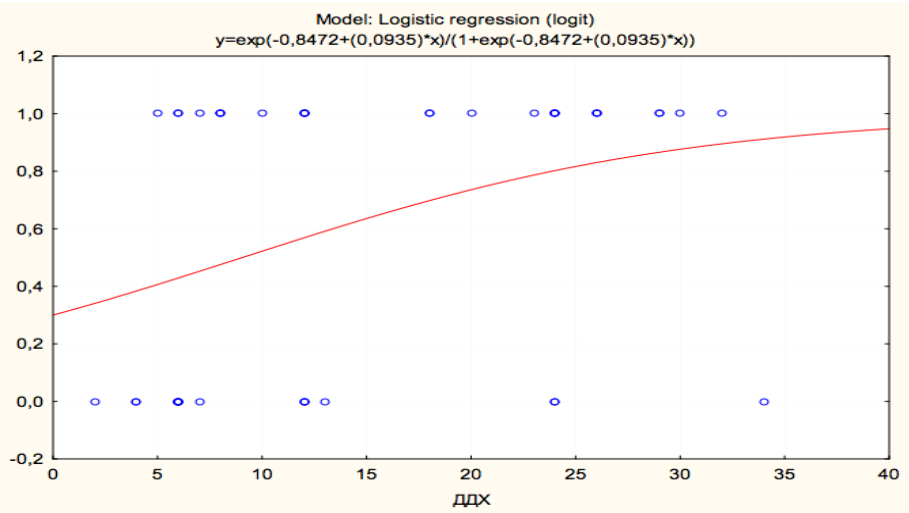

Fig. 24. Change in the probability of progression of BRONJ-6m. depending on the values of the factor time from the surgical intervention.

5. Analysis of the dependence between the factors duration of BF treatment and BRONJ-6m. (outcome of the treatment established 6 months after it) in the first group of patients.

The logistic regression model used showed that the factor duration of BF treatment had an effect on the outcome of the treatment reported at the sixth month after it, because p-value 0.02<0.05. The coefficient B1 is positive /0.059/ and as can be seen from the graph below it follows:

As the values of the duration of BF treatment increase, the probability of code 2 on BRONJ-6m increases. i.e. for progression.

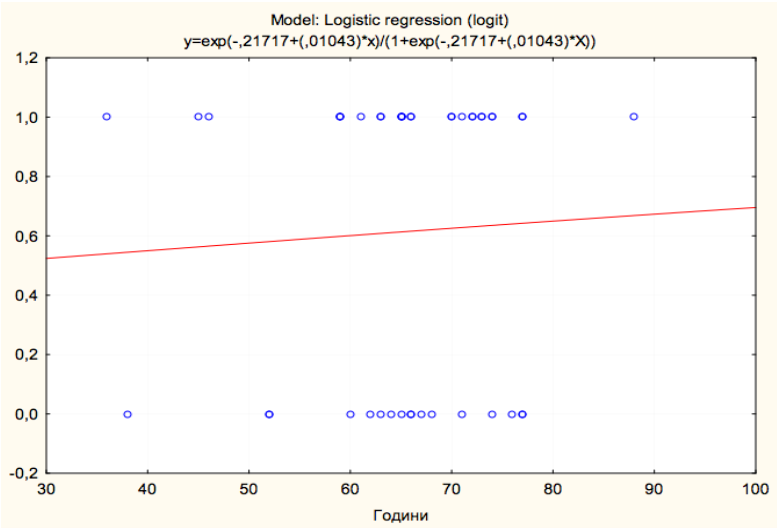

Fig. 25. Change in the probability of progression of BRONJ-6m. depending on the values of the duration of treatment.

6. Analysis of the dependence between the factors age of the patient and BRONJ-6m. (outcome of the treatment established 6 months after it) in the first group of patients.

The logistic regression model used showed that the age factor had no effect on the outcome of the treatment, reported at the sixth month after it.

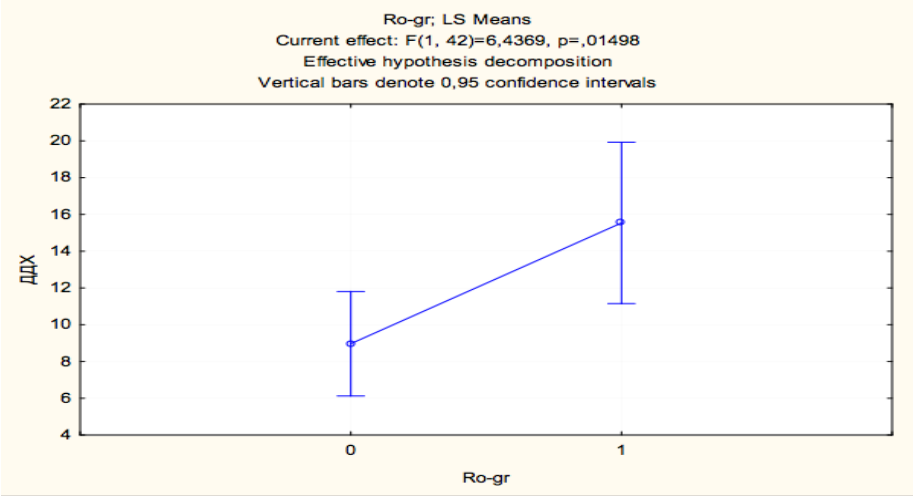

Fig. 26. Change in the probability of progression of BRONJ-6m. depending on the values of the patient's age factor.

7. Analysis of the relationship between the time from the surgical intervention and the X-ray data in the first group of patients (group of patients diagnosed with BRONJ).

Using the ANOVA method, we found that there was a statistically significant difference in the mean values for Time from the surgical intervention ($p=0.01498<0.05$) for the two types of Ro-gr results (0-osteolysis and osteosclerosis and 1-osteolysis, osteosclerosis and sequester formed).

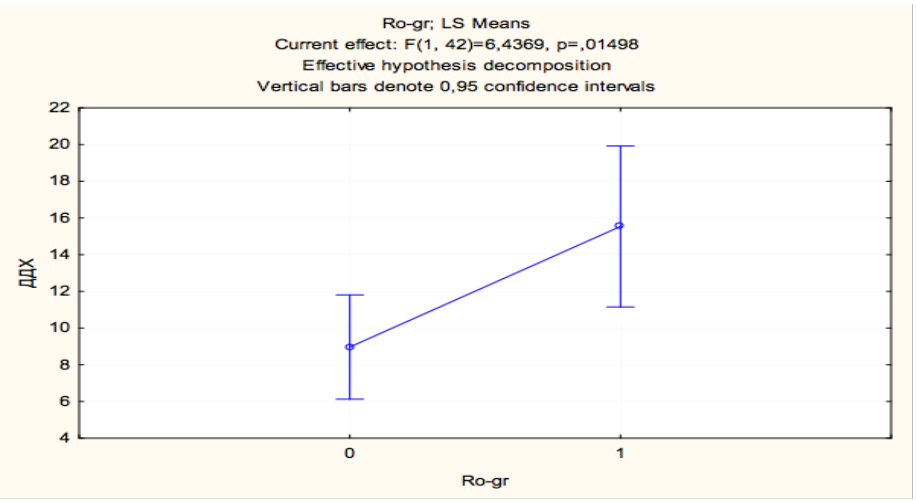

Fig. 27. Means and 95% Confidence Intervals of Time from the surgical intervention for the Two Different Radiographic Results.

There is a statistically significant difference in the mean values for TFSI (Time from Surgical Intervention) ($p=0.01498<0.05$) for both types of Ro-gr results.

From the obtained data, we can conclude that with a 95% confidence interval of TFSI and a mean value of TFSI 9 months, the probability of radiographic findings of osteolysis and osteosclerosis is greater, and at a 95% confidence interval of TFSI and a mean value of TFSI 15, 5 months, the radiographic finding is more likely to be osteolysis, osteosclerosis, and sequester formed. Therefore, we can use the TFSI factor as a factor influencing the probability of bone sequestrum formation ($p=0.01498<0.05$). We can also conclude that as the time elapsed from the dentoalveolar surgery to the diagnosis of the disease increases, the probability of radiographic finding of osteolysis, osteosclerosis and bone sequestration formation increases. As the mean values of this interval decrease, the likelihood of radiographic findings of osteolysis and osteosclerosis increases.

8. Data analysis regarding the relationship between radiographic findings and duration of BF intake.

Using a logistic regression model, we found that $B1=0.09936667>0$, and therefore, as the duration of BF intake increases, the probability of Ro-gr=1 also increases. A radiographic finding of osteolysis, osteosclerosis and a formed sequester is coded with a value of 1, and with a value of 0 - osteolysis and osteosclerosis.

Therefore, as the duration of BF intake increases, the likelihood of bone sequestration formation increases.

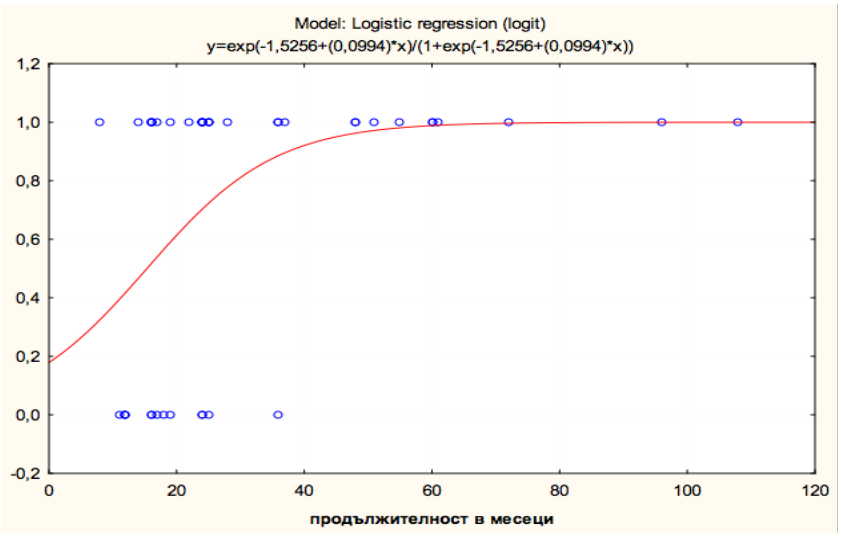

Fig. 28. Change in the probability of Ro-gr =1 depending on the values of the duration of treatment.

9. Analysis of the relationship between The period of time from the surgical intervention and stage in the second group of patients.

In the statistical analysis done using the ANOVA method, we found that the difference between stages 1 and 3 and 2 and 3 was statistically significant, but between 1 and 2 there was no statistically significant difference.

Based on the obtained results, we can conclude that with a 95% TFSI confidence interval and an average TFSI of 9.2-9.8 months, the probability that the patient is in the first or second stage of the disease is the same, and the probability to be in stage 3-less. With a TFSI 95% confidence interval and a TFSI median of 18 months, the probability of a patient being in stage 3 disease is greater compared to the probability of being in stages 1 and 2. We can conclude that with an increase in the average value of TFSI, the probability that the patient is in the third stage of the disease increases, and with a decrease in the average value of the TFSI, the probability that the patient is in stage 1 or 2 of BRONJ increases.

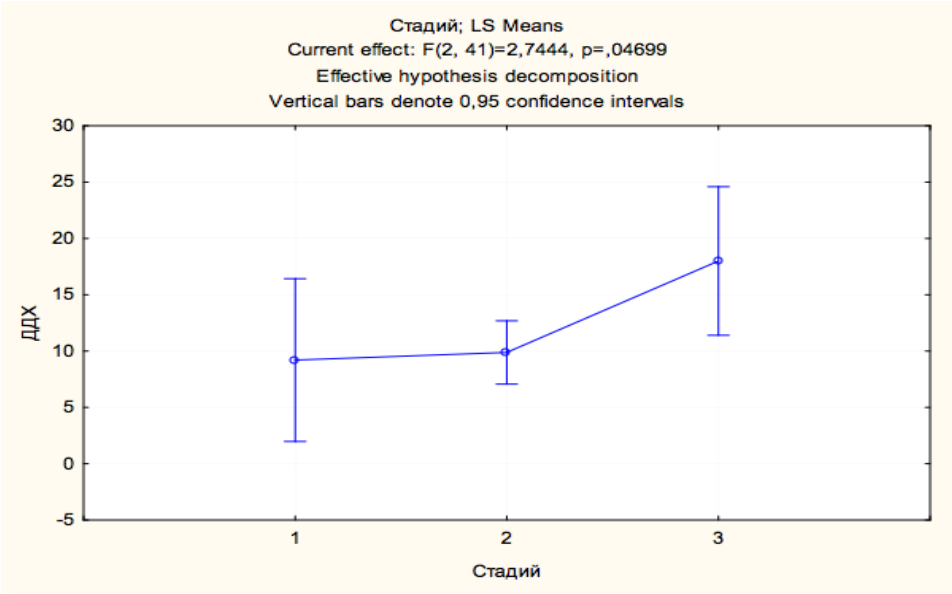

Fig. 29. Mean values and 95% confidence intervals of TFSI at different stages.

V. Results on the fifth task. To investigate the outcome of tooth extraction in patients on bisphosphonate therapy in the jaw quadrant without BRONJ

The study includes the patients of the second group in our study - patients undergoing bisphosphonate therapy (oral or intravenous), with indications for extraction of one or more teeth. In these patients, there is no clinical data on the development of BRONJ, in the quadrant of the intended extraction at the time of the primary examination. They are subject to surgical and medical treatment in outpatient settings. This group includes a total of 30 patients.

1. Results of the data according to the gender of the patients

Regarding the distribution of patients by gender, we found that 23 (76.7%) of the patients examined by us were women and 7 (23.3%) were men, and the difference between the sexes was statistically significant ($p<0.05$).

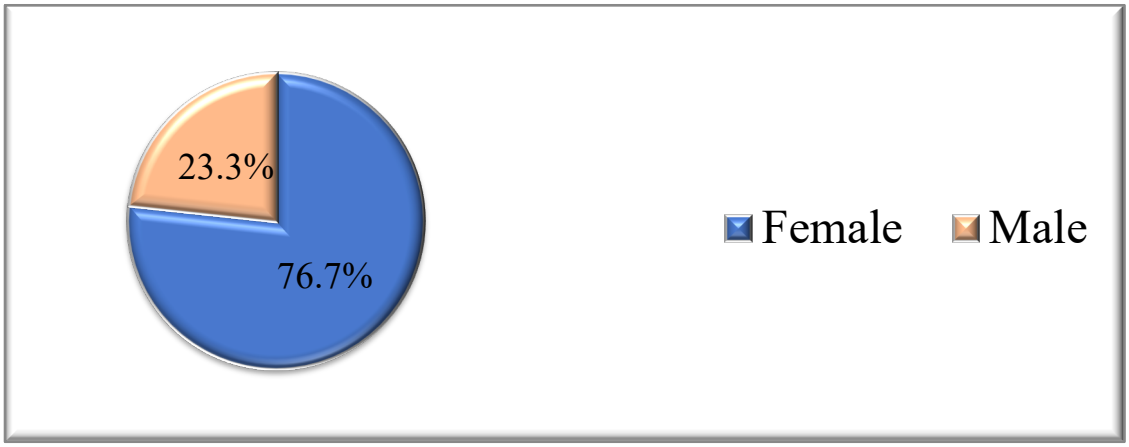

Fig. 30. Distribution of patients from the second group by gender

2. Results of the data according to the age of the patients included in the study.

Patients were divided into six age groups presented in Table 6.

Age group	**Number of patients**	**Percent**
30-40 years	3	10
41-50 years	1	3,333
51-60 years	4	13,333
61-70 years	15	50
71-80 years	6	20
81-90 years	1	3,333

Table. 6. Frequency distribution according to the variable Age in the group of 30 patients

From table 6, it can be seen that BRONJ occurs most often in the age between 61-70 years. There were 15 (50%) patients in this age group. The age between 71-80 years old patients is also highly represented (20%). The percentage distribution is lower in the age group 51-60 years (13.3%), followed by the group 31-40 years - 3 patients (10%). We observe 1 case (3.3%) of BRONJ in the 41-50 and 81-90 age groups. In the studied material, we did not find a case under the age of 30 years and over 91 years.

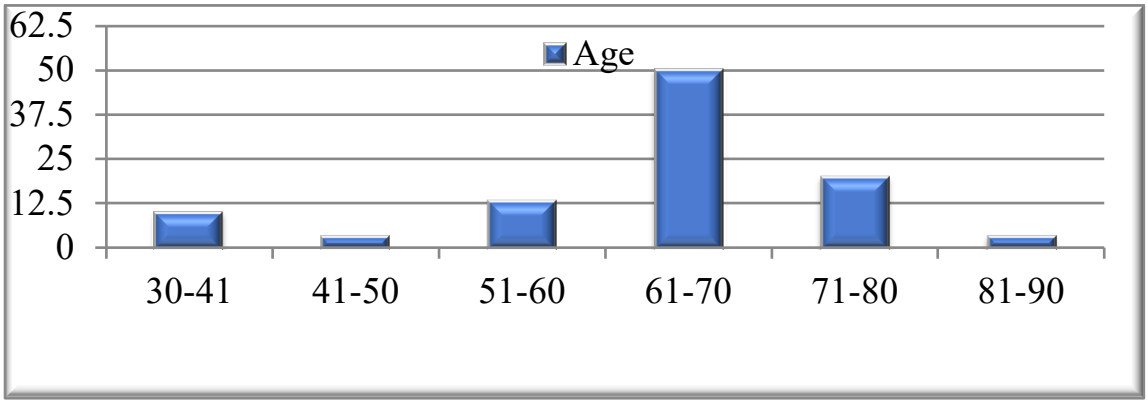

Fig. 31. Distribution of patients from the second group by Age

With regard to the age factor of patients with BRONJ, we found a minimum age of 30 years, a maximum age of 83 years, an average value of 63 years, with a standard deviation of 12.84.

3. Results of the data according to the main diagnosis of the patients

The present study showed that 16 (53.3%) of the patients had a primary diagnosis of malignancy. In 14 patients (46.7%), the intake of BF was indicated by an underlying disease of osteoporosis.

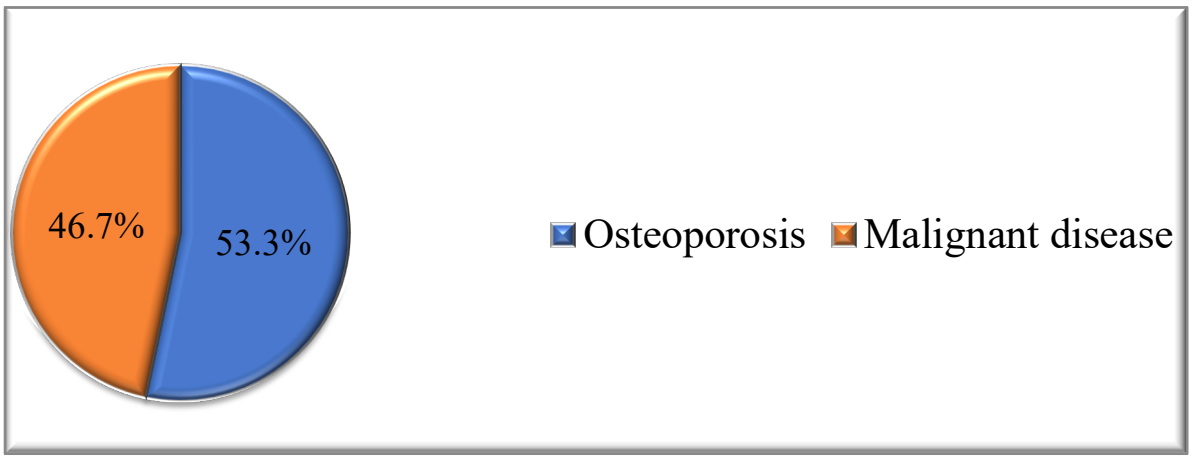

Fig 32. Distribution of patients from the second group according to the main diagnosis

4. Data results according to the type of administered BF.

When examining the patients according to the type of BF administered, it was found that the BF with the highest frequency was Zoledronic acid - in 17 (56.7%) of the patients. Second place was taken by Ibandronic acid in 7 (23.3%) patients. Alendronic acid followed in 5 (16.7%) and Alendronic + Ibandronic acid in last place in distribution in 1 (3.3%) of the examined patients.

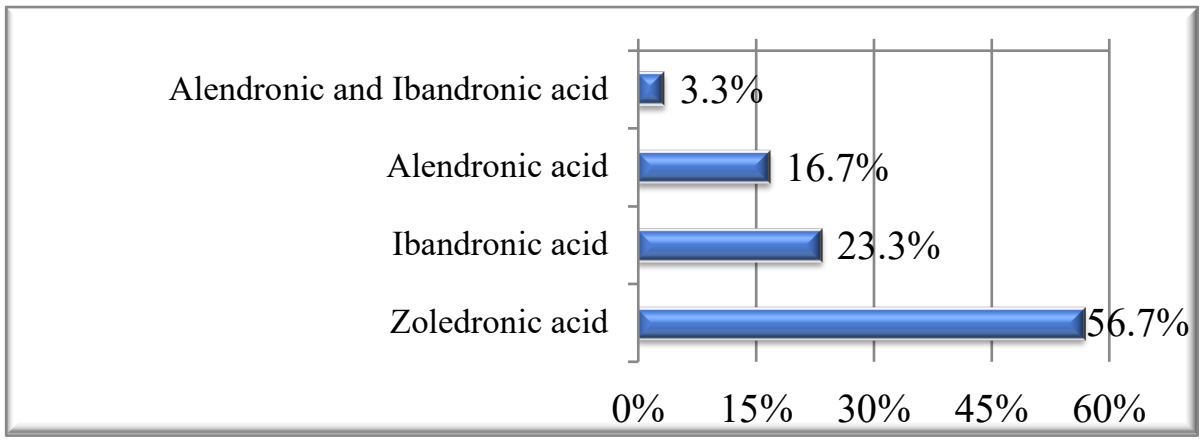

Fig. 33. Distribution of patients from the second group according to the type of BF

5. Data results according to the method of intake of BF

According to the method of introduction of BF into the body, we found close distribution values - BF was introduced intravenously in 17 patients (56.7%), compared to 13 of the patients (43.3%), in whom BF was introduced orally.

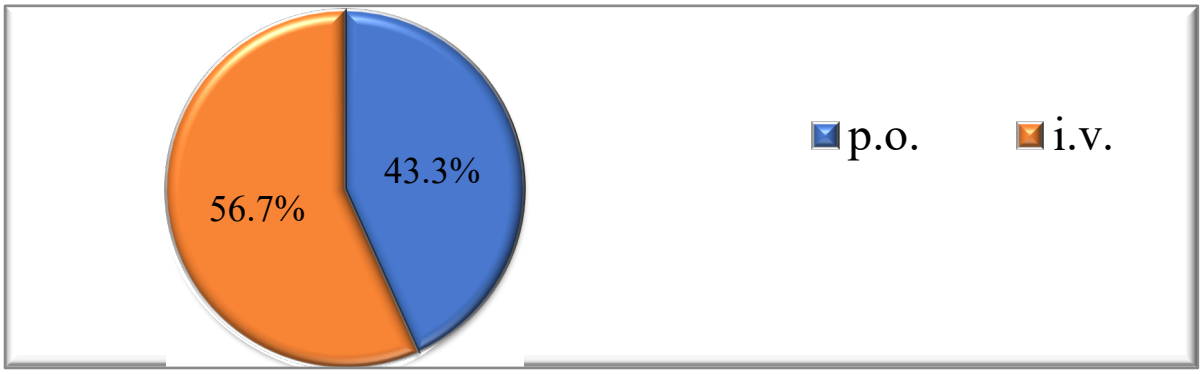

Fig. 34. Distribution of cases from the second group according to the method of introduction of BF

6. Data results according to duration of BF intake

Our study showed a maximum value of the duration of BF intake 157 (in months), a minimum - 2 months, an average value - 42.23 months, with a standard deviation of 41.47 months. The distribution is shown in the table below:

	Mean	**Minimum**	**Maximum**	**Standard Deviation**
Duration	42,23	2	157	41,47

Table 7. Distribution of cases according to the duration of BF reception

7. Results of the data according to the presence of BRONJ before extraction.

7 (23.3%) of the patients had a BRONJ involving another quadrant before extraction and 23 (76.7%) of the patients had no BRONJ before the extraction.

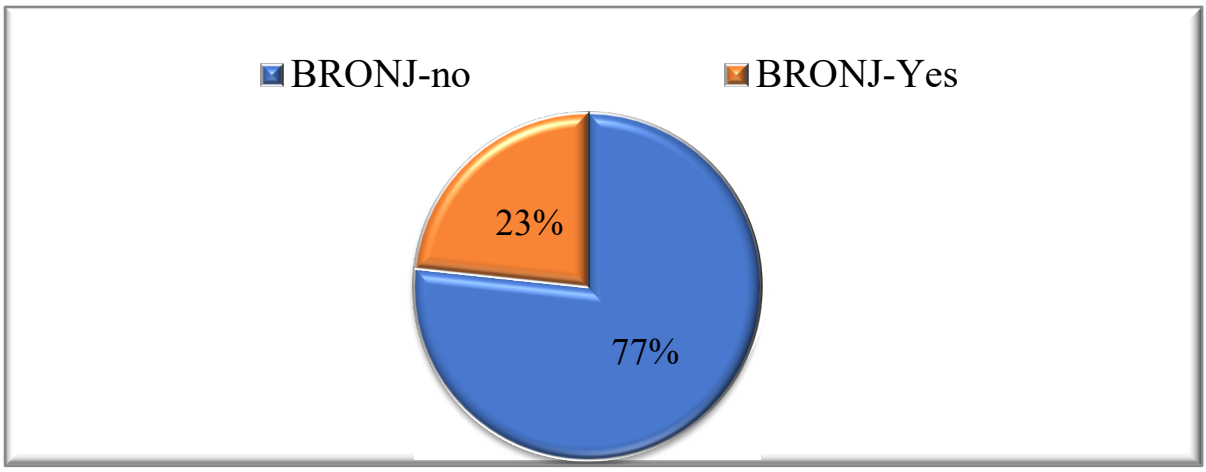

Fig. 35. Distribution of cases according to the presence or absence of BRONJ before tooth extraction

8. Data results according to the diagnosis of the tooth to be extracted.

In the largest percentage of cases - 21 (70% of patients) the diagnosis of the tooth subject to extraction is Periodontitis chronica granulomatosa diffusa/localisata. Next is the diagnosis of Parodontitis chronica generalisata - 7 of the patients (23.3%), in 1 patient (3.3%) - Dens semiretinens, as well as 1 patient with a diagnosis of Cysta radicularis (3.3%).

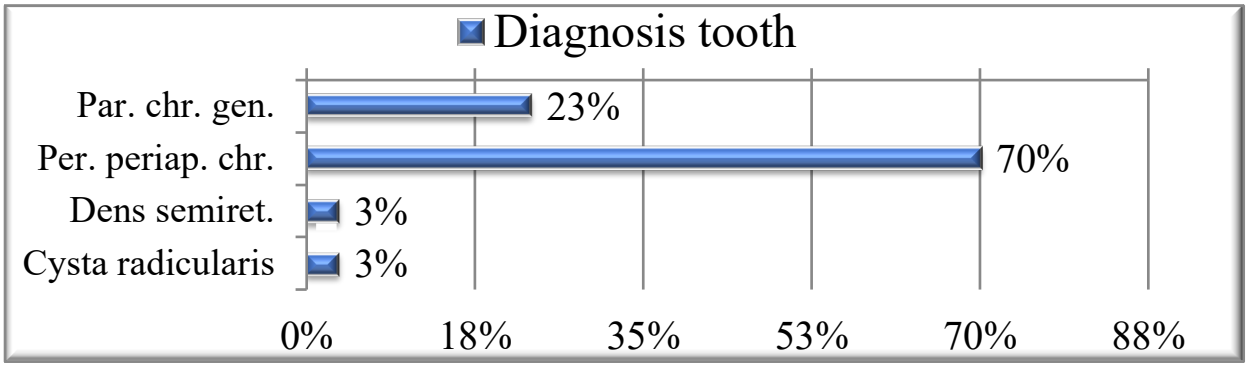

Fig. 36. Distribution of cases according to the diagnosis of the tooth subject to extraction

9. Data results according to the jaw on which the teeth to be extracted are located.

According to the jaw on which the teeth subject to extraction are located, the distribution is as follows: in 8 patients (26.7%) the teeth are located in the lower jaw, in 17 patients (56.7%) in the upper jaw and in 5 patients (16.7%) were extracted teeth of the lower and upper jaw.

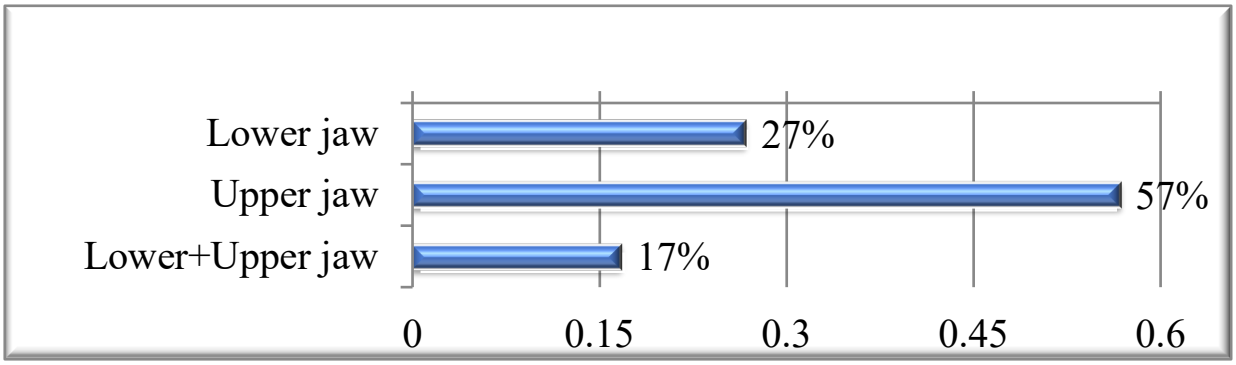

Fig. 37. Distribution of cases according to the jaw on which the teeth subject to extraction are located.

10. Results of the data according to the area of the jaw on which the teeth subject to extraction are located.

According to the area of the jaw in which the teeth subject to extraction are located, we found the following distribution: in 9 of the patients (30%) teeth located in frontal and distal region of the jaw, in 6 of the patients (20%) the extracted teeth were in the frontal region and in 15 (50%) in the distal region of the jaw.

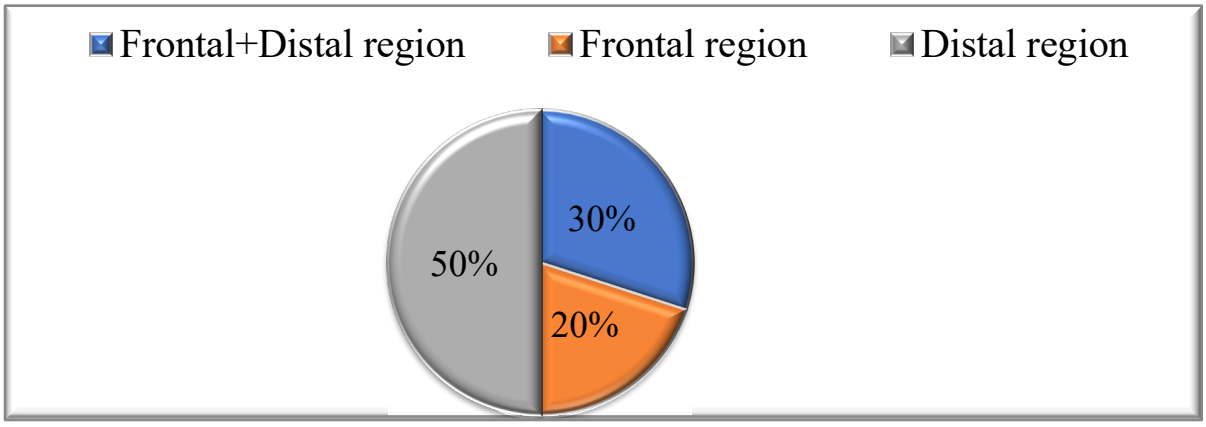

Fig. 38. Distribution of cases according to the area of the jaw in which the teeth subject to extraction are located.

11. Results of the data according to the type and duration of the antibiotic taken during the antibiotic prophylaxis.

Only 3 of the patients (10%) received Lincosamide and a significantly greater percentage of the patients-27 (90% of the patients) received Penicillin.

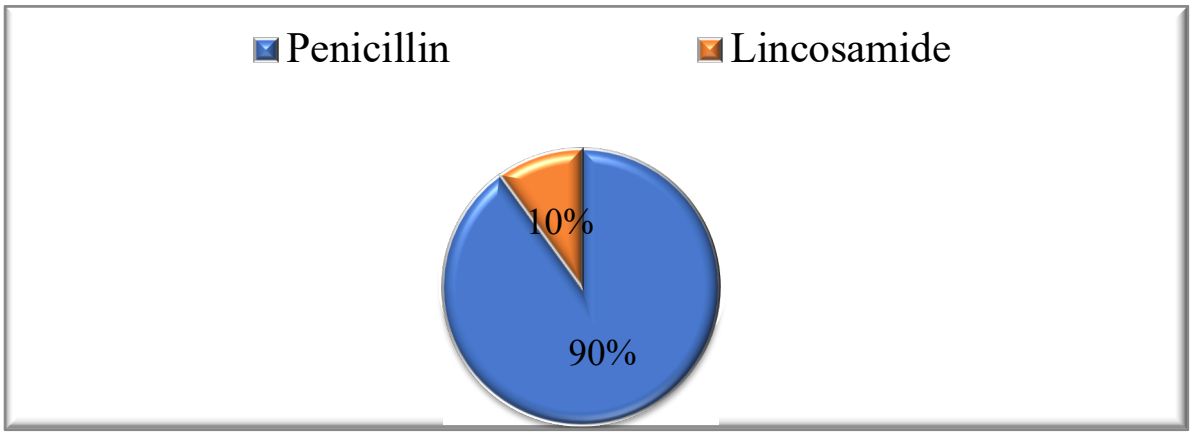

Fig. 39. Distribution of cases from the second group according to the type of antibiotic taken for antibiotic prophylaxis.

Regarding the duration of antibiotic intake, we found an average value of 14.7 days, a minimum duration of intake of 7 days and a maximum of 21 days.

12. Data results by treatment outcome

Regarding the outcome of the treatment, we found that in a significantly larger part - 28 of the patients (93.3%) after the extraction, a healing process occurred and in 2 (6.7%) of the patients, BRONJ developed.

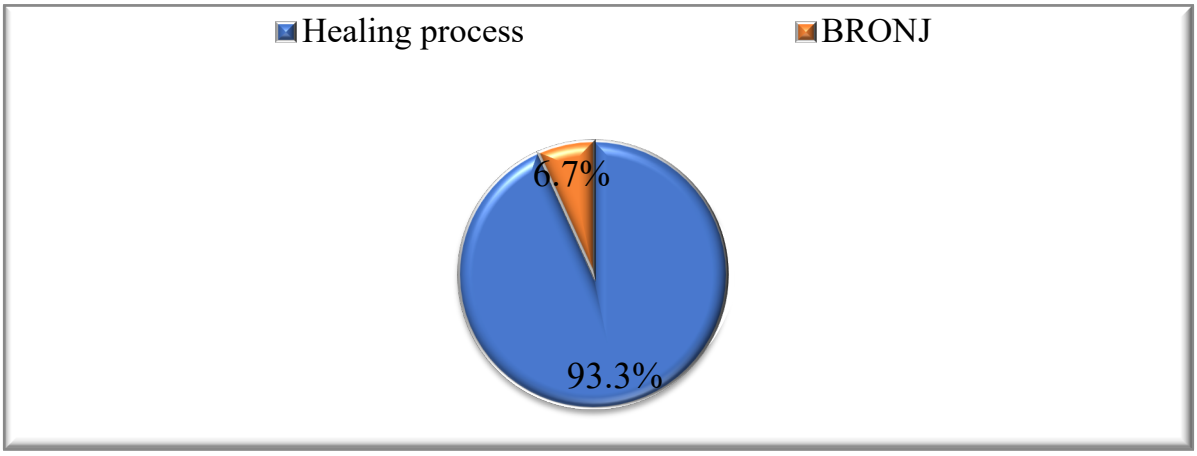

Fig. 40. Distribution of cases from the second group according to treatment outcome.

Discussion

I. Discussion on the first task

1. Age and gender of the studied contingent

Findings based on the results:

1. The gender distribution male:female is 1.1:0.9, and the difference between the sexes is not statistically significant ($p>0.05$).

2. The disease is most common in the 61-70 years old group. We found no case under 30 years of age and over 91 years of age.

3. BRONJ is a disease of adulthood with an average age of 62 years.

4. The percentage of patients over 40 years old is significantly higher - 95.4%, compared to 4.6% for patients with BRONJ under the age of 40 years.

Our results coincide with the data from the literature on the absence of a statistically significant difference between the sexes as a demographic factor that is relevant to the development of BRONJ.

According to Badros A et al., Hoff AO et al., Bamias A et al., Kastritis E et al. and American Association of Oral and Maxillofacial Surgeons gender is not statistically significantly associated with BRONJ.

Some authors, however, report a preferential involvement of female patients -73-87% of all studied patients with BRONJ. We found no such dependence in our study.

According to the AAOMS, the higher rate of this complication in women is more likely a reflection of the underlying disease necessitating BF intake (i.e., osteoporosis, breast carcinoma).

From the analysis of the distribution of cases by age groups, it can be seen that BRONJ is a disease of adults. The frequency of the disease increases with age. A peak is established in the 61-70 years old group and remains high for the 71-80 years old as well. The average age of the studied contingent in our study is 62 years and varies between 36 and 88 years.

A number of studies have linked advanced age with BRONJ, which is also shown in our study. This may be due to the slowing down of restorative and healing processes in elderly people. Also, in older patients, the complications of caries and periodontal diseases increase and so the need to perform dentoalveolar surgical manipulations, and the percentage of patients using removable dentures increases. Dentoalveolar surgery and trauma from removable dentures are considered risk factors for the development of BRONJ. In addition, advanced age may be associated with a longer period of BF intake due to a longer course of the underlying disease. That is why we cannot consider advanced age as a predictive factor for the

development of BRONJ on its own. More extensive research is needed to establish the role of age as a factor in the development of BRONJ.

According to Badros et al., the risk of developing BRONJ increases with each additional year of follow-up and with increasing of the age of the patient.

We observe a significant decrease in the frequency of BRONJ in 81-90 years old patients. This is most likely due to genetic or lifestyle factors and associated comorbidity. In this group, we found only 1 patient (2.27%) - an 88-year-old man in the third stage.

In the group that we studied, the cases with young people < 40 years occupy 4.55% (2 patients - a woman aged 36 and a man aged 38).

In our group, the youngest patient was a 36-year-old woman with BRONJ localized in the left distal region in the mandible after extraction of tooth 36. The disease was diagnosed by us in the second stage, 12 months after the appearance of the first symptoms and signs. Ignorance of the clinical manifestation of the disease has led to a delay in diagnosis and incorrect treatment.

We did not find development of BRONJ in the age of less than 30 years. In this age group, BFs are used to treat diseases such as Osteogenesis imperfecta. Our results are consistent with those published so far in the literature. Despite the long-term use of BF, no cases of BRONJ have been identified in children and young patients (up to 24 years).

2. Basic diagnosis of the patients

Findings based on the results

2. We found the main diagnosis of malignant disease in a significantly higher proportion - 40 (90.9%)

3. Osteoporosis was the main disease of 4 patients (9.1%).

Data analysis showed that the difference in underlying disease was statistically significant (K-S $d=0.53180$, $p<0.01$). Therefore, the main diagnosis of the patient's malignant disease is a risk factor for the development of BRONJ, compared to the main disease of osteoporosis.

Our results are close to those published in the literature to date.

According to a number of authors, the frequency of BRONJ is significantly higher in patients who undergo BF therapy due to the underlying disease multiple myeloma, prostate carcinoma, breast carcinoma. Patients treated for benign bone diseases such as osteoporosis, osteogenesis imperfecta show a relatively low incidence of BRONJ. This may be due to the

lack of oncological treatment and the fact that a relatively low cumulative dose of BF is sufficient to achieve a therapeutic effect.

In the osteoporotic patient population, the incidence of ONJ is estimated to be 0.001% to 0.01%, slightly higher than the incidence in the general population.

AAOMS in 2014 suggest that two parameters should be taken into account when interpreting the expected frequency of MRONJ: the indications for the therapy and the types of treatment. Therapeutic indications are grouped into two categories: osteoporosis and osteopenia or malignant process. The authors concluded that, compared with patients with malignant disease, the risk of ONJ in osteoporotic patients treated with antiresorptive drugs was about 100 times lower.

3. Type of the used BF

Findings based on the results

1. The largest percentage -72.7% of patients are on Zoledronic acid therapy
2. The percentage of Zoledronic acid combined with another BF is also high - 15.8%
3. Ibandronic acid was taken by 4.5% of patients
4. Alendronic and Ibandronic acid were taken by 4.5% of patients
5. The percentage of patients treated with Pamidronic acid is the lowest -2.2%.

This percentage distribution is close to results published in the literature.

According to Boonyapakorn et al. the type of BF taken may play a role in the occurrence of BRONJ. As the action potential of BF increases, so does the risk of developing BRONJ. Zoledronate, Pamidronate (i.v.) and Alendronate (p.o.) were administered in the largest number of reported cases of patients with BRONJ.

Other studies have shown that patients who have ever received zoledronate had a 4.5- to 28-fold increase in the relative risk of developing BRONJ.

Otto et al. reported the following percentage distribution, depending on the BF used - with the greatest frequency - Zoledronat (47.6%), Zoledronat combined with another BF (24.6%), i.v. administered Pamidronate (15.1%), i.v. Ibandronate (7.1%), 5.6%-combination of intravenous BFs, 3.2%- oral BFs- Risedronate and Alendronate.

According to a study by Sook-Bin Woo, 94% of patients who developed BRONJ were treated with Pamidronate and Zoledronic acid. In our country, this percentage reaches 92.9%. When comparing BFs administered intravenously, the one with the strongest potential of action, Zoledronate, is more often associated with the occurrence of BRONJ, compared to the one with a lower potential, Pamidronate.

According to our results, Zoledronat (72.7%) had the highest risk of developing BF, followed by Zoledronat combined with another BF (15.8%), Ibandronic acid (4.5%), Alendronic acid and Ibandronic acid acid (4.5%), Pamidronic acid (2.2%) ($p<0.01$).

4. Method of administration of BF

Findings based on the results

1. In a significantly greater percentage of cases, BF was administered intravenously - in 40 patients (90.1%), compared to 4 of the patients (9.1%) in whom BF was administered orally.

2. Therefore, the intravenous intake of BF dominates significantly over the oral intake and is a risk factor for the development of BRONJ ($p<0.01$).

Our results are close to those described in the literature. Otto et al. found that 96.8% of their studied patients with BRONJ had a clinical history of intravenous BF, with only 3.2% taking BF orally.

A number of authors reported a frequency of intravenous BF in patients with BRONJ, close to that found in our study - a frequency higher than 90%. This is most likely due to the fact that the bioavailability of intravenous BF derivatives in the body is approximately 100 times higher than that of oral BFs.

According to other authors, the two risk factors of greatest importance for the development of BRONJ are the intravenous intake of BF and dentoalveolar procedures.

5. Duration of the BF intake

Findings based on the results

1. The maximum value of the duration of BF intake in our study was 108 months,
2. The minimum value of the duration of BF reception is 8 months,
3. The mean is 41.75 months, with a standard deviation of 27.1 months

A number of authors found that the intake of BF for a long period of time is associated with an increased risk of developing BRONJ.

In his study, Kos found a mean duration of BF intake of -34 months and Bamias et al. 35 months, which is lower compared to our results (41.75 months).

Migliorati et al. also found a lower mean duration of i.v. admission of BF, in which BRONJ develops, of 25 months, compared to our study.

Yoshiga et al. studied 52 patients and found that the mean duration of BF administration until the onset of BRONJ was 41.6 months, as in our study.

A study by Otto S. et al. showed that the average duration of the period from the initiation of BF therapy to the diagnosis of BRONJ was 38.9 months, values close to our study.

According to Marx et al. the most critical factor for the development of BRONJ in patients taking oral BF is the duration of the BF intake. He defines a duration of admission over 3 years as critical for the development of BRONJ.

We found a higher value for the minimum duration of BF intake that leads to the development of BRONJ compared to Vahtsevanos et al., who stated that the development of BRONJ is very unlikely if BF intake is shorter than 6 months.

Other authors found a greater value of the minimum duration of BF intake at which BRONJ develops – 12-13 months, compared to our results (8 months).

6. Presence of previous surgical intervention or mechanical trauma

Findings based on the results

1. Dentoalveolar surgical intervention is a risk factor for the development of BRONJ. 88.6% of patients underwent dentoalveolar surgical intervention (tooth extraction or placement of a dental implant), and 11.4% of patients had mechanical trauma from a removable prosthesis.

Our results are similar to those of Hess L. et al., who found that 88.9% of patients taking oral BFs reported a dental procedure preceding the appearance of BRONJ.

Other authors found a lower percentage (data vary between 50-77%) of development of BRONJ after dentoalveolar surgical intervention:

Boonyapakorn et al. found spontaneous occurrence of BRONJ in 23% of the studied patients on intravenous BF therapy, and in the remaining 77%-development of BRONJ after tooth extraction. According to Kos, this percentage reaches 78%.

Sven Otto et al. reported that the frequency of dental procedures preceding the development of BRONJ was 63.6% (including tooth extractions or extractions combined with endodontic or periodontal procedures, or decubitus injuries.

Another study involving patients taking oral BFs showed that 50% of cases of BRONJ occur spontaneously, the remaining 50% - as a result of a dental procedure - 40% after tooth extraction, 6.7% - after placement of a dental implant and 3.3%-after taking a palatal connective tissue graft.

According to the AAOMS, dentoalveolar surgery is a major risk factor for the development of MRONJ, citing studies in which dental extractions were performed in 52-61% of patients with MRONJ. In the absence of sufficient data, the committee considered that the risk of ONJ after placement of dental implants and endodontic or periodontal procedures that

require bone exposure and manipulation is comparable to the risk associated with tooth extraction.

According to another study, there is a plausible relationship between dental extractions and the development of BRONJ in cancer patients.

In view of the presented facts, the question arises as to whether the intake of BF itself is a sufficient condition for the development of BRONJ. Although necrosis can occur spontaneously, in the greater percentage of cases it is associated with trauma from dentoalveolar surgery (88.6% in our study) or mechanical trauma from a removable prosthesis (11.4% in the present study). A number of authors raise the question of the role of infection in the pathogenesis of BRONJ, but most likely it does not lead to the development of the disease if there is no exposed bone. The exposure of the alveolar bone during dentoalveolar surgery creates an open door for microorganisms, bacterial invasion and the development of infection. This may explain the correlation we found between BRONJ and dental surgical interventions.

7. Period of time from the surgical intervention

Findings based on the results

1. The minimum amount of time from the surgical intervention to the clinical manifestation of BRONJ is 2 months,

2. The maximum value of the TFSI is 36 months,

3. The mean is 8 months, with a standard deviation of 8.319.

The 8-month mean value we found in our study is greater than that published by some authors to date. Woo found a time interval of 1 to 3 months between the occurrence of the risk event (tooth extraction, lesions due to an unstable prosthesis) and the patient's admission to a specialized department due to the appearance of symptoms (pain).

A retrospective study conducted in 2015 on a cohort of 72 patients in Munich found a time interval of 4–6 months between the triggering event and osteonecrosis.

Lesclous et al. found that the interval between surgery and diagnosis of ONJ varied from 2 to 6 months.

Other authors have published results close to ours. A study conducted in China on patients with breast carcinoma with bone metastases treated with zoledronic acid showed an average of 8.58 months between tooth extraction and the onset of osteonecrosis.

II. Discussion on the second task

1. Localization of BRONJ (depending on which of the jaw bones is affected - mandible, maxilla or both).

Findings based on the results

1. The lower jaw is most frequently affected - 63.6%

2. The upper jaw is affected in 27.3% of patients with BRONJ.

3. The lowest frequency is the simultaneous involvement of the upper and lower jaws - 9.1%.

Our results are similar to those of studies published in the literature, with the highest percentage of involvement of the mandible, followed by the maxilla, and the least common involvement of both jaws.

Ruggiero et al. studied 63 patients with BRONJ and found that the lower jaw was affected in 63% and the upper jaw in 38%. In another study of his, he reported that the ratio of the incidence of mandibular involvement to the incidence of maxillary involvement was 2:1.

Marx et al. studied 119 patients and reported the following distribution: 68.1% mandible, 27.7% maxilla, 4.2% in both jaws.

Sook-Bin Woo et al. summarized 368 published cases of BRONJ in which the upper jaw was affected in 65%, the lower jaw in 26%, and both jaws in 9%.

Boonyapakorn et al. reported that the lower jaw was affected in 59% of cases, the upper jaw in 27% and both jaws in 14%.

Otto et al found the following frequency distribution regarding the localization of BRONJ - in 70.6% the mandible was affected, in 18.3% - the maxilla and in 11.1% - both jaws.

In a study by Lesclous et al. 54% of cases of ONJ occur in the mandible, 43% in the maxilla and 3% in both jaws.

In the cited literature, the frequency of involvement of the lower jaw is from 59-70.6%, for the upper jaw the frequency ranges from 18.3-38% and involvement of both jaws is observed in 4.2-14%, results close to our research.

Bone turnover in alveolar bones is enhanced, leading to a greater probability of incorporating BF into their structure, compared to other skeletal bones. Bone metabolism in alveolar bone is thought to be more enhanced than that of long bones (~10 times that of the tibia and 3-5 times that of the inferior margin of the mandible), making it more susceptible to agents affecting remodeling.

This, as well as the presence of teeth in these bones, which may be a gateway for infection, may explain the exclusive involvement of the upper and lower jaws by BRONJ. In addition, the oral mucosa is thin and susceptible to injuries caused by, for example, dentures.

Consistent with studies reported in the literature, we found that BRONJ most commonly affects the mandible. This is because the mandible, like other bones such as the femur, is surrounded by cortical bone, but the teeth located within this bone provide a pathway

for microorganisms to penetrate from the periodontal space into the bone marrow. A possible explanation for the preferential involvement of the mandible is that the maxilla has an abundant blood supply that is greater than in the mandible. The results of another study using the bone scintigraphy method showed that the bone metabolism of the intact mandible was affected by long-term administration of BF.

2. Localization of BRONJ (depending on which part of the jaw bones is affected - frontal, distal or both).

Findings, based on the results

1. Most often BRONJ affects the distal parts of the jaws (in 77.3% of cases)

2. The frontal region is affected in 13.6%

3. The rarest is the simultaneous involvement of the frontal and distal sections of the jaw bones (in 9.1% of cases).

Data from the literature overlap with our results.

Regarding the site affected by the necrosis, Otto et al. found that predilection sites for the development of BRONJ are the molar and premolar areas of both jaws.

According to a study by Thumbigere-Math et al. the distal parts of the mandible are indicated as the most frequently affected area by BRONJ.

Marx et al. found that the most frequently affected region was the distal part of the mandible, in the area of the molars (65.5%), followed by the distal part of the maxilla (22.7%).

The increased accumulation of BF in the jaw bones, as well as the greater mechanical forces to which these bones are subjected, may explain why the distal regions of the maxilla and mandible (which are exposed to the greatest loading forces) are more frequently affected. The structure and blood supply of the jawbones in these areas (dense compact bone, less cancellous bone, fewer blood vessels) may also be relevant to the more frequent involvement of the distal areas by BRONJ.

3. Stage of BRONJ, at the time when patients are diagnosed

Findings, based on the results

1. The largest percentage of patients - 75% - were diagnosed in the II stage of the disease.

2. 13.6% of patients were diagnosed in stage III

3. 9.1% of patients are in stage I

4. Only 2.3% are diagnosed at stage 0

Our results are similar to those reported in the literature.

Filleull et al. analyzed the data of 2400 cases of BRONJ, publishing information on the staging of 572 patients. Of these, as in our study, in the largest percentage of cases -66% patients were in stage II, followed by 18% of patients in stage III and 16% in stage I.

In a study by Shibahara et al. involving 4,797 patients, the results were similar - 61.4% of the studied patients were in stage II, but the percentage of patients in stage I (20.7%) compared to those in stage III (16.8%) was greater.

Wutzl et al. also published a distribution close to ours - 61.2% of patients were in stage II, 22.5% - in stage III and 16.3% - in stage I.

Graziani et al. found the highest frequency of patients in stage II - 60%, followed by those in stage I with 28% and in stage III were 12% of the 374 examined patients.

Andriani et al. studied 55 patients on bisphosphonate therapy and obtained results close to ours - the highest percentage were patients diagnosed in stage II - 83.8%, followed by those in stage III - 9% and lastly were patients in stage I - 7.3 %.

One of the main clinical symptoms of BRONJ is the presence of exposed nonvital bone. It may be preceded by undefined pain or discomfort in the affected area. Inflammation and superimposed infection are seen in advanced cases and are the leading causes of the symptomatic manifestations of BRONJ.

According to our research, it is precisely at the symptomatic manifestations of the disease (exposed necrotic bone, accompanied by pain, suppuration and discomfort in the affected area) that patients seek help and are diagnosed (75% in stage II and 13.6% in stage III). This distribution shows us that a very small percentage of patients seek help in the early stages of the disease, which speaks of insufficient awareness and ignorance of the early symptoms of BRONJ by patients.

Both in our study and in the literature, the largest number of patients were diagnosed in stage II. This is the stage in which the majority of clinical symptoms are manifested - the presence of exposed necrotic bone or a fistula on probing of which reaches bone associated with infection, accompanied by pain and erythema in the area of exposed bone with or without drainage of purulent exudate.

4. Radiographic finding.

Findings, based on the results

1. Osteolysis and osteosclerosis were detected radiographically in a significantly higher percentage - 70.5% of patients

2. A formed bony sequestrum, along with osteosclerosis and osteolysis, is observed radiographically in 29.5% of cases.

The most common radiographic findings in the literature were bone sclerosis and osteolysis, similar to other studies.

Simpione et al. found a higher percentage of cases with bony sequestrums formed (52.4%) compared to our results. Osteosclerosis was observed in only 28.6% of patients.

The presence of osteosclerosis in clinically symptomatic areas of the jaws has been described as a frequent tomographic finding in both early and advanced forms of osteonecrosis.

In addition to sclerosis, osteolysis and sequestrum formation were frequent findings in stage I and II, and very common in stage III BRONJ. According to other authors, these well-recognized tomographic features are mainly associated with advanced stages of this disease, where sequestrum formation and periosteal reaction predominate.

III. Discussion on the third task

1. Treatment carried out - surgical and medication treatment

Findings based on the results

1. No surgical treatment was performed in 15 (34.1%) of the patients

2. Sequestrectomy was performed in 13 (29.5%) of the patients

3. Surgical debridement was performed in 16 patients (36.4%).

4. A higher percentage of patients - 29 (65.9%) were treated surgically and medically, compared to 15 (34.1%) who received only medication treatment.

2. Development of the disease (BRONJ) after 1 month.

Findings based on the results

1. In the first place with the highest percentage - in 26 (43%) of the patients there is stationing of the disease

2. In second place are the patients in whom clinical improvement of the disease is observed - 15 (34.1%) of the patients,

3. Thirdly, 2 of the patients (4.5%) had disease progression

4. Finally - only in 1 patient (2.3%) - remission.

3. Development of the disease (BRONJ) after 6 months.

Findings based on the results

1. Stationing was most often observed - in 20 (45.5%) of the examined patients,

2. In second place are the patients with clinical improvement - in 11 (25%) of the patients,

3. Progression - in 7 (15.9%) of the patients and

4. Remission in 6 (13.6%), occupy the third and fourth place with a close distribution percentage.

Our results regarding remission of the disease are much lower than the results published in the literature.

Hayashida et al. reported that a healing process was achieved in a high percentage of patients who underwent surgical treatment - 76.7% of 361 patients with stage II BRONJ treated surgically were cured, but only 25.2% of patients treated conservatively were cured.

In the literature, conservative treatment of BRONJ has been described as partially successful, with a healing process reported in only 50% of cases, especially in stages 2 and 3. In comparison, surgical treatment has led to favorable results in more than 80% of patients.

Eguchi et al. reported that surgical treatment was successful in 89.3% of patients, compared to patients treated conservatively—only 33.3% of them were cured.

However, the comparison between the results of different therapies is complicated, due to the multifactorial nature of this disease and the lack of homogeneity in the studied groups regarding these factors.

4. Outcome of the treatment at the 1st and 6th months with sequestrectomy.

Findings based on the results

On the first month of treatment

1. The highest share is occupied by the patients in whom we observed regression of the disease - 76.9% (10 patients).

2. Stationing - in second place, with a significantly lower percentage - 15.4% (2 of the patients)

3. Disease progression occurred in one patient (7.7%)

4. Remission of the disease was not observed in any of the studied patients.

On the 6th month of treatment

1. First of all, with the highest percentage are the patients in whom remission of the disease occurs - 46.2% (6 patients),

2. In second place are the patients in which we observed regression - 38.5% (5 patients),

3. In the same number of patients (one) we observed stationing (7.7%) and progression (7.7%) of the disease.

4. With the sequestrectomy method of treatment, when comparing the results of the treatment at the first and sixth months of its application, there is a statistically significant difference ($p=0.0236<0.05$) at the outcome of the treatment ***regression*** - a statistically

significant decrease in the number was found of patients at the 6th month, compared to those at the first month.

5. The difference regarding the outcome of the treatment ***remission*** is also statistically significant ($p=0.0008<0.05$) - a significant increase in the number of patients with the outcome of the treatment remission on the 6th month, compared to that established on 1st month of applied treatment.

6. No statistically significant difference was found regarding the outcome of the treatment stationing ($p=0.2696>0.05$) and progression ($p=0.5>0.05$) in the first and sixth months when applying a treatment method sequestrectomy.

In the literature, the results of treatment with the sequestrectomy method differ from ours, as a healing process is observed in a significantly higher percentage of patients.

Ferlito et al. applied the method in 94 patients and achieved a healing process in 100% of the operated patients. Junquera et al. obtained the same results-remission in 100% of patients who underwent sequestrectomy.

Hoefer et al. achieved a healing process in 70% of the 46 patients after treatment with the sequestrectomy method.

Andriani et al. reported a healing process of their patients in 66.6% of cases, clinical improvement in 16.7% and progression or no change of the disease in 16.7% of the patients they studied, in which they applied the method of sequestrectomy combined with antibiotic treatment.

Close to our results were obtained by Wultz et al., who achieved a healing process in 58.5% of the examined patients after sequestrectomy.

Considering the results of the publications included in our review, the success rate of surgical treatment of BRONJ varies between 58.5-100%. This difference in the results can be explained by the different surgical techniques, the lack of homogeneity regarding the accompanying characteristics and risk factors of the studied patients (type of BF; duration of BF therapy; presence of additional risk factors and localization of lesions), the lack of well-defined success criteria and additional treatments (antibiotics, antiseptics) performed. Furthermore, to facilitate future research on this topic, it would be particularly important to unify the success criteria.

5. Outcome of the treatment on the 1st and 6th months with debridement.

Findings based on the results

On the first month of treatment

1. The highest percentage (62.5%, 10 patients) is stationing as an outcome of the treatment

2. With a significantly lower percentage is regression (25%, 4 of the patients)

3. The last two places are occupied by progression (6.3%) and remission (6.3%) in one of the patients.

On the sixth month of treatment

1. The highest share is occupied by patients in whom we observe stationing - 50% (in 8 of the patients)

2. In second place are the patients who experienced regression - 31.3% (5 patients),

3. In third place are patients with disease progression - 12.5% (2 of the patients)

4. In the last place are the patients in whom we observe remission - 6.3% (one patient).

5. When applying a treatment method debridement, no statistically significant difference was found regarding the outcome of the treatment: regression ($p=0.3475>0.05$), stationing ($p=0.238>0.05$), progression ($0.2721 >0.05$) and remission ($p=0.5>0.05$) on the first and sixth months of the treatment.

The results published in the literature regarding the outcome of this treatment modality differ significantly from ours. A number of authors emphasize the important role of debridement in the treatment concept of BRONJ, suggesting an overall success rate in the range of 50–100%. Again, the lack of well-defined criteria for treatment success contributes to the wide variation in results published in the literature.

Graziani et al. examined 374 patients, in 65.4% applied the debridement method and achieved remission in 49% of cases.

Andriani et al. achieve a healing process in 45.5% of the patients they examined, improvement in 40.9% and progression or no change in 13.6% of patients.

6. Outcome of the treatment on the 1st and 6th month with medication treatment.

Findings based on the results

On the first month of the applied treatment

1. Stationing was observed in the highest percentage (86.7%) of the patients examined by us (in 13 of the patients).

2. A significantly lower percentage was observed in terms of regression-6.7% (1 patient) and progression-6.7% of the disease.

3. Remission did not occur in any of the examined patients.

On the sixth month of the applied treatment

1. First place in distribution takes the stationing of the disease-73.3% (11 patients)

2. Progression of BRONJ takes second place with 20% (3 patients)

3. In third place is regression-6.7% (in one of the patients).

4. No remission occurred in any of the studied patients.

5. With regard to the method of medical treatment, we did not find a statistically significant difference in terms of treatment outcome regression ($p=0.5>0.05$), stationing ($p=0.1806>0.05$), progression ($0.1414>0.05$) and remission ($p=0.5>0.05$) at the first and sixth months of treatment.

We did not find remission in any of the patients who received drug treatment alone. Some authors published results according to which 10.5% of the patients they treated had a healing process, 52.6% improved, and 39.6% had no improvement or disease progression. Other authors published results with much higher success rates of medical treatment of BRONJ, from 33.3% to 84.6% and 91.5%. In these studies, however, the small number of observed patients (20-26, below the statistically necessary number for reliability of the results) is striking.

The routine usage of antibiotics (both preoperative and postoperative) and antiseptic mouthwashes, usually with chlorhexidine digluconate 0.2%, is recommended by the majority of authors. Bacteria play an important role in the pathophysiology of BRONJ and appear to be directly involved in the development of necrotic lesions and in the inhibition of epithelial regeneration on exposed bone. Once extensive lesions of the jawbones develop, systemic antibiotics cannot reach the affected area, possibly because of the lack of vascularization. Indeed, Junquera et al. concluded that patients with advanced BRONJ will not improve when treated with antibiotics alone, as lesion progression will occur. However, it seems that conservative treatment is effective in the initial stages of the disease (stage 0 and stage I). Nicolau-Galitis et al. and Fortuna et al. achieve respectively 91.5% and 84.6% success rates with this approach. From our experience, we find that antibiotic treatment is insufficient to achieve remission in patients, but can achieve disease stabilization and can be used as symptomatic treatment to influence symptoms in cases of exacerbation.

7. Comparison of the outcome of the treatment methods Sequestrectomy and Debridement+Medication treatment on the 1st and 6th months

Findings based on the results

Outcome on the first month of treatment

1. In the Sequestrectomy and Debridement+Medication treatment groups, we found a statistically significant difference regarding the outcome of treatment regression ($p=0.0001<0.05$) and stationing ($p=0.0002<0.05$).

2. Regarding the outcome of the treatment, progression ($p=0.4409>0.05$) and remission ($p=0.2562>0.05$), no statistically significant difference was found.

3. In the Sequestrectomy group, we found a significantly higher percentage of patients with regression of the disease (76.9%), compared to regression in the medication+debridement group (16.1%).

4. Stationing as an outcome of the treatment in the first month prevails in the medication+debridement group (74.2%) significantly more, compared to stationing in the other group studied by us (Sequestrectomy-15.4%).

5. Regarding the progression as a result of the treatment of BRONJ, the results in the two compared groups are close - 6.5% in the medication+debridement group and 7.7% in the Sequestrectomy group.

6. The results are also close without a statistically significant difference and in terms of the outcome of the treatment in the first month, remission 3.2% in the medication+debridement group and 0% in the sequestrectomy group.

Outcome of the treatment at the sixth month

1. A statistically significant difference was found regarding the outcome of treatment remission ($p=0.0002<0.05$) and stationing ($p=0.0008<0.05$).

2. There is no statistically significant difference between the two compared groups in the outcome of treatment progression ($p=0.2284>0.05$) and regression ($p=0.0909>0.05$).

3. Stationing prevails in the medication+debridement group (77.4%), significantly more, compared to stationing in the other group studied by us (Sequestrectomy-7.7%).

4. A significantly higher percentage of patients in the Sequestrectomy group experienced remission of the disease (46.2%), compared to remission in the medication+debridement group (3.2%).

5. Patients with regression as an outcome of the disease were in a higher percentage in the Sequestrectomy group (38.5%), compared to those in the medication+debridement group (19.3%).

6. Regarding the progression as a result of the treatment of BRONJ, the results in the two compared groups were as follows: 16.1% in the medication + debridement group and 7.7% in the Sequestrectomy group.

We consider successful the treatment in which remission of the disease is established for a long-term period (on the 6th month of treatment). Comparing the two groups, we found a tenfold higher percentage of patients who achieved remission in the group treated with Sequestrectomy compared to those treated conservatively (medication + debridement).

Regression (transition to a lower stage of BRONJ) can also be accepted as a favorable result as an outcome of the disease, but we do not observe a complete cure of the patients at the 6th month examination. Again, the Sequestrectomy method has a twice higher result compared to medication + debridement.

Regression and stationing of the disease can be considered a failure in treatment. From the percentage distribution, we see that these two treatment outcomes significantly prevail in the conservative treatment methods - in the medication + debridement group - twice as much in terms of disease progression and ten times higher result, in terms of stationing, as an outcome of the treatment.

Treatment strategies of BRONJ are controversial, especially in the early stage of the disease. AAOMS presented disease staging criteria and treatment methods in the American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw, published in 2014. When treating patients in stages I and II, they recommend conservative treatment - taking antibiotics and gargling with 0.12% chlorhexidine. When there are concerns about bacterial colonization due to the formation of sequestrums, a surgical procedure for their selective removal is recommended. Many authors who agree with the AAOMS treatment recommendations have published evidence for the effectiveness of conservative treatment.

A large number of authors, however, have recently pointed out the positive effect of resection of the affected area, which is expected to rapidly relieve symptoms.

Hayashida et al. reported that a healing process was achieved in a high percentage of patients who underwent surgical treatment - 76.7% of 361 patients with stage II BRONJ treated surgically were cured, but only 25.2% of patients treated conservatively achieved healing process.

Eguchi et al. reported that surgical treatment was successful in 89.3% of patients, compared to patients treated conservatively-only 33.3% of them were cured.

IV. Discussion on the fourth task

1. Dependence between the duration of BF intake and the outcome of the treatment in the 1st and 6th months.

Findings based on the results

• As the duration of BF intake increases, so does the probability of disease progression, detected at the patient's examination, both at the first and at the sixth month after the treatment.

Our results are similar to those of other authors published in the literature to date. According to Choi et al. and AAOMS factors best known to be associated with MRONJ

treatment outcomes are duration of use of antiangiogenic or antiresorptive agents and type of drug.

Details of the ways in which medications affect the incidence of MRONJ are provided in the American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw in 2014. In general, the incidence of MRONJ increased with increasing duration of drug administration.

2. Dependence between the factors time from the surgical intervention (TFSI) and outcome of the treatment established 1 and 6 months after it.

Findings based on the results

• As TFSI values increase, the probability of BRONJ progression increases, both at the first and at the sixth month of the applied treatment

When analyzing the results, we found a relationship between the factors TFSI (time from the surgical intervention) and treatment outcome established 1 month after it, as well as between TFSI (time from the surgical intervention) and treatment outcome established 6 months after it. As the time elapsed from the surgical intervention on the alveolar bone (extraction or placement of a dental implant) to the diagnosis of BRONJ increases, the probability of disease progression at 1 and 6 months after diagnosis increases. We did not find such a relationship in the literature.

3. Dependence between the Age factor and the outcome of the treatment, established 1 and 6 months after it.

Findings based on the results

• The patient's age factor is not a prognostic factor and does not influence the outcome of the disease at the 1st and 6th months.

Our results are similar to those of Nisi et al., not finding any positive correlation between worsening of BRONJ stage and increasing of patients' age, unlike other reports in the literature; i.e. increased risk of BRONJ with increasing of the patients' age. According to Badros et al., the risk of developing BRONJ increases with each additional year of follow-up and with increasing of the patients' age.

We found no results showing a relationship between the age of the patient and the outcome of BRONJ treatment.

4. Dependence between the time from the surgical intervention (TFSI) and the X-ray data in the first group of patients (group of patients diagnosed with BRONJ).

Findings based on the results

1. As the time elapsed from the dentoalveolar surgery to the diagnosis of the disease increases, the probability of radiographic findings of osteolysis, osteosclerosis, and bony sequestrum formation increases.

2. As the mean values of this interval decrease, the probability of radiographic findings of osteolysis and osteosclerosis increases.

3. The factor **time from the surgical intervention (TFSI)** can be used as a prognostic factor for the probability of bony sequestrum formation

5. Dependence between the radiographic findings and the duration of BF intake in the first group of patients.

Findings based on the results

• As the duration of BF intake increases, the likelihood of bony sequestrum formation increases.

In the literature, we found no studies concerning the relationship between the radiographic finding and the duration of BF intake, as well as the relationship between the radiographic finding and the history of dentoalveolar surgery.

Several authors have concluded that advanced forms of BRONJ may present with increased bone density, periosteal reactions, and bony sequestrums and have associated the stage of BRONJ with the likelihood of bony sequestrum formation.

A recent study shows that the results from the radiographic examination of the internal structure of the bone lesions obtained at the primary examination are related to the outcome of the conservative treatment of BRONJ. The time required for healing in patients with a radiographic finding of "bony sequestrum" is less and we can expect a more favorable progression of the disease. Radiographic finding "Sclerosis" and "Normal bone" are associated with lesions with a longer healing period.

Our results allow us to predict the outcome of the patients' treatment and to choose an appropriate treatment method according to the duration of BF intake and the history of dentoalveolar surgery.

6. Dependence between the time from the surgical intervention (TFSI) and stage in the first group of patients.

Findings based on the results

1. As the average value of TFSI increases, the probability that the patient is in the third stage of the disease increases

2. As the average value of TFSI decreases, the probability that the patient is in stage 1 or 2 of BRONJ increases.

3. The factor time from the surgical intervention (TFSI) is prognostic regarding the stage of the patient's disease.

In the literature, we found studies that showed an association between the duration of treatment with BF and the likelihood of advanced stage (stage 3) of the patient. Results have been published showing that the number of stage 3 patients was significantly higher in patients treated for longer than 5 years with both low- and high-dose BF.

We did not find any studies that linked patients' stage with the elapsed time from the dentoalveolar surgery. The stage of the patient is one of the factors we take into account when choosing a treatment method. Our results can allow us to predict the stage in which the patient will be and help us in the choice of a treatment strategy.

V. Discussion on the fifth task

1. Age and gender of the studied contingent

Findings based on the results:

1. The gender distribution of men: women is 1:3.3, and the difference between the sexes is statistically significant ($p>0.05$). In the two patients who developed BRONJ, the gender distribution was 1:1.

2. The largest number of patients examined by us are in the group of 61-70 years old. Both patients (100%) who developed BRONJ after extraction were in this group, with a mean age of 65.5 years. We found no cases under 30 years of age and over 91 years of age.

Some authors report a preferential involvement of female patients -73%, 87% of all studied patients with BRONJ. According to the AAOMS, the higher rate of this complication in women is more likely a reflection of the underlying disease necessitating BF intake (e.g., osteoporosis, breast carcinoma).

We also believe that the greater percentage of female patients and the age distribution is related to the frequency of occurrence of the underlying disease necessitating the use of BF in these groups.

2. Basic diagnosis of the patients

Findings based on the results:

1. We established a primary diagnosis of malignancy in 14 (46.7%) patients

2. Osteoporosis was found in 16 (53.3%) patients

3. Malignancy (multiple myeloma) was the main diagnosis in both patients who developed BRONJ (100%).

3. Type of introduced BF

Findings based on the results:

1. Zoledronic acid was introduced with the highest frequency - in 17 (56.7%) of the patients.

2. Second place is occupied by Ibandronic acid - in 7 (23.3%) patients.

3. Alendronic acid was taken by 5 (16.7%) patients

4. Alendronic + Ibandronic acid in 1 (3.3%) of the examined patients is in the last place in terms of distribution.

5. Zoledronic acid was a BF taken by both patients (100%) who developed BRONJ

4. Method of BF intake

Findings based on the results:

1. BF was administered intravenously in 17 patients (56.7%)

2. BF was administered orally in 13 of the patients (43.3%).

3. BF was administered intravenously in both patients who developed BRONJ (100%).

5. Duration of BF intake

Findings based on the results:

1. Maximum duration of BF intake is 157 (in months),

2. Minimum duration of BF intake is 2 months,

3. The average value of the duration of BF admission is 42.23 months, with a standard deviation of 41.47 months.

4. The average value of the duration of BF intake in the two patients who developed BRONJ was 84 months, about twice that of the patients in the second group

6. Presence of BRONJ before extraction.

Findings based on the results:

1. In 7 (23.3%) of the patients there was a BRONJ involving another quadrant before the extraction

2. In 23 (76.7%) of the patients, there was no BRONJ before the extraction

3. BRONJ involving another quadrant before extraction was present in both patients who developed BRONJ (100%).

7. Diagnosis of the tooth to be extracted.

Findings based on the results:

1. Periodontitis chronica granulomatosa diffusa/localisata was found in the largest percentage of cases - 21 (70% of patients)

2. Periodontitis chronica generalisata in 7 of the patients (23.3%)

3. Dens semiretinens - in 1 patient (3.3%)

4. Cysta radicularis in 1 patient (3.3%)

5. Parodontitis chronica generalisata was the diagnosis necessitating tooth extraction in both patients who developed BRONJ after extraction (100%).

8. Jaw on which the teeth subject to extraction are located.

Findings based on the results:

1. The teeth subject to extraction are located on the lower jaw in 8 patients (26.7%)

2. In 17 patients (56.7%) they are located on the upper jaw

3. In 5 patients (16.7%) teeth of the lower and upper jaw were extracted.

4. In one patient (50%) teeth were extracted on the upper jaw, in the other (50%) the teeth were located on the lower jaw

9. Section of the jaw on which the teeth subject to extraction are located.

Findings based on the results:

1. The largest number of teeth were extracted in the distal part of the jaw - in 15 patients (50%).
2. In 9 of the patients (30%), teeth located in the frontal and distal part of the jaw were extracted
3. In 6 of the patients (20%), the extracted teeth were in the frontal area
4. In both patients (100%) who developed BRONJ, the extracted teeth were located in the distal region.

10. Type and duration of antibiotic intake for the purposes of antibiotic prophylaxis.

Findings based on the results:

1. A significantly greater percentage-27 (90% of patients) took an antibiotic from the Penicillin group.
2. 3 of the patients (10%) were taking Lincosamide
3. Regarding the duration of antibiotic intake, we found an average value of 14.7 days, a minimum duration of intake of 14 days and a maximum of 21 days.

4. Both patients (100%) who developed BRONJ were taking an antibiotic from the penicillin group with an average duration of 17.5 months.

In the literature, the risk factors for the development of BRONJ are divided into three main groups: 1) those related to the intake of BF 2) systemic factors and 3) local risk factors. In the present study, we found that in the two patients who developed BRONJ in relation to the administered BF, it was zoledronic acid administered intravenously, with a mean duration of administration of 84 months. Regarding the systemic factors in both patients, we established a primary diagnosis of malignancy (multiple myeloma), and taking into account the local risk factors in both patients - the diagnosis of the extracted teeth was Parodontitis chronica generalisata, the patients had developed BRONJ in another quadrant, before the extraction and the extracted teeth are located in the distal part of the jaw. Due to the limited sample size, however, to draw definitive conclusions regarding the role of various potential risk factors considered in the literature, further studies that include a larger number of patients will be needed.

11. Treatment outcome

Findings based on the results

1. The incidence of BRONJ in the extraction protocol applied by us is relatively low - 2 (6.7%) of the patients examined by us and 3 (3.8%) of the teeth extracted by us

The majority of patients tolerated the operation well, the healing process was smooth, and there were no complaints at the time of the last examination. Two patients developed complications in the healing process of the extraction wound.

The total number of extracted teeth was 78. Of these, 75 (96.2%) underwent a healing process and 3 teeth (3.8%) developed BRONJ.

The first patient who developed BRONJ was S.M. - male, 62 years old. with a primary diagnosis of multiple myeloma. He has been on monthly Zometa IV treatment for 60 months. The reason for the extraction of teeth 16 and 26 (upper jaw, distal region) was chronic generalized periodontitis. The patient was diagnosed with BRONJ in the fourth quadrant, distal section-II stage.

The second patient who developed BRONJ was D.S. -woman, 69 years old. She has been on monthly intravenous Zometa treatment for 108 months because of Multiple Myeloma. She had an extraction of tooth 45 (lower jaw, distal section), the reason for the extraction was chronic generalized periodontitis. The patient was diagnosed with BRONJ in the third quadrant distal section-II stage.

After tooth extraction, antibiotic treatment with Augmentin 1g, 2g daily, divided into two doses, lasting 14 days in the first patient and 21 days in the second patient, was carried out

in both patients. At the control examinations at the first and sixth month after the extractions of both patients, we found an unsatisfactory healing process, the extraction wounds were partially covered with epithelium and the presence of exposed necrotic bone was found. There were no complaints from the patients - they did not report the presence of pain, erythema, purulent exudate. In both patients, the development of BRONJ stage I was detected.

Several protocols have been published in the literature dealing with risk assessment and tooth extraction behavior of patients taking BF. However, the recommendations are somewhat contradictory. Therefore, the main purpose of this study was to prove whether the recommendations published by AAOMS and the German Oral and Maxillofacial Surgery Society, regularly applied in our clinical practice, are applicable and successful in this group of patients.

The results of this study confirm that the extraction protocol we used is reliable, with a low probability of developing osteonecrotic lesions although 46.7% of the patients are in high-risk group with malignant underlying disease receiving intravenous bisphosphonate treatment and we also included some patients with already developed BRONJ in other quadrants of the jawbones.

From the literature, we selected studies with an extraction protocol similar to ours in a second group of patients and found the following: Lodi et al. reported that of their study of 23 patients on BF treatment in whom 38 teeth were extracted, none developed ONJ during a follow-up period of 15 months. Schubert et al. performed extractions in 36 patients, 1 of whom (2.7%) developed ONJ. Otto et al. extracted 216 teeth in 72 patients, of which 5 patients (6.9%) developed BRONJ (3.2% of extracted teeth).

Kato et al. performed extractions on 20 patients in whom he extracted 62 teeth and reported the development of osteonecrosis in 4 of them (20% of patients and 6.4% of extracted teeth).

Vescovi et al. studied 126 patients who performed extractions using the Nd:YAG laser in the treatment. Of the patients he studied and a follow-up period of >12 months, no patient developed ONJ.

Sanchís et al. performed extractions on 34 patients in whom he extracted 62 teeth and reported the development of osteonecrosis in 9 of them (26.5% of patients and 14.5% of extracted teeth).

Our results are close to those of a number of authors - Lodi et al., Schubert et al., Vescovi et al. and Otto et al.

Compared to the studies of Kato et al. and Sanchís et al., we obtain a lower rate of BRONJ development after our dental extractions.

Tooth extractions and dentoalveolar surgical procedures in patients taking bisphosphonates are of increasing clinical importance in the field of dentistry, as well as in oral and maxillofacial surgery. Currently, dentoalveolar surgery is considered a major risk factor for the development of BRONJ. According to the AAOMS, dentoalveolar surgery is a major risk factor for the development of BRONJ, citing studies with dental extraction performed in 52–61% of patients with BRONJ. Our study also shows that in 88.6% of the patients of the first group, a dentoalveolar surgical intervention (tooth extraction or placement of a dental implant) was performed. A number of authors recommend that tooth extraction and other procedures that lead to direct involvement of bone to be avoided. Recently, however, the number of authors who define as the main risk factor for the development of BRONJ the infection of dental origin, and not the surgical intervention itself is increasing.

A number of authors recommend that teeth with a poor prognosis should be extracted to prevent the development of ONJ as a result of infection of dental origin.

Also, prolonged antibiotic treatment and complex dental rehabilitation may not be possible in cancer patients and in patients with compromised health.

Taking in mind these considerations we can perform the extraction prophylaxis in teeth, the cause of infection in the jawbones, which cannot be treated conservatively, assessing the risk of developing BRONJ.

There are differing opinions regarding discontinuation of BF therapy in patients with BRONJ. Some authors include this in the treatment approach in these patients. Dentists, oncologists, and oral surgeons should carefully evaluate the risks and benefits of discontinuing BF before and after invasive dental procedures. Discontinuation of BF may expose patients to malignancy-related hypercalcemia, failure to control bone metastases, and progression of osteoporosis. For cancer patients, the therapeutic effects of BF are of great benefit as they control pain and the likelihood of pathologic fractures. Discontinuation of i.v. BF does not provide short-term benefits. According to Wutzl A. et al. discontinuation of BF does not affect long-term outcomes after oral surgical procedures in terms of occurrence or worsening of BRONJ. If systemic conditions permit, long-term cessation of BF may contribute to the stabilization of established foci of BRONJ, reducing the risk of developing new foci and relieving clinical symptoms. According to other authors, there is no absolute reason for discontinuing BF therapy due to the long half-life and high efficiency of BF in stabilizing bone metastases. The patients from the first group studied by us did not cease BF treatment before and after the extraction.

Conclusion

BRONJ is a disease that most often affects the group of 61-70 years old, and we did not find a case under the age of 30 years and over 91 years.

The disease affects both sexes, with a male:female ratio of 1.1:0.9.

After discovering the disease in 2003. by Robert E. Marx, a large number of studies have been published in the literature that aim to identify risk factors for the occurrence of BRONJ.

Using the method of descriptive statistics, we found that in the group we studied the distal part of the mandible was at increased risk and most often affected. Most often, the disease is associated with intravenous Zoledronate intake for a long period of time (the average value of the duration of BF intake in our study was 41.75 months), and the intake of drugs from the BF group is indicated for the treatment of a malignant disease (bone metastases, multiple myeloma). It should be emphasized that BRONJ occurs most often after tooth extraction or dentoalveolar surgery, when the surgical protocol for tooth extraction in patients on BF therapy is not followed.

In the literature, the results of different treatment methods - conservative or surgical - are also widely discussed, looking for the most effective treatment strategy for the disease. The results published so far in the literature are contradictory. Our study showed that BRONJ is a difficult to treat disease with a protracted course.

Because of the well-known difficulties in the treatment of this disease, we investigated some important prognostic factors that have a significant impact on the outcome of therapy. The question of the prognosis of the outcome of the treatment of BRONJ in relation to the diversity of the individual clinical manifestations of the disease has not been resolved to date.

Using the statistical method univariate logistic regression to model the dependence of a qualitative two-outcome variable, we found that duration of BF intake and the period of time elapsed from the dentoalveolar surgery (time from intervention to onset of symptoms of bisphosphonate osteonecrosis) were major prognostic factors regarding the likelihood of disease progression. The age of the patient is not a prognostic factor and does not influence the outcome of the disease, which was established by standardized control examinations conducted in accordance with the methodology used by us on the 1st and 6th months of the applied treatment. Thus, this mathematical model gives valuable information about the course of the disease in relation to these two prognostic factors and can be used in the planned control of the patients' condition. This statistical methodology could also be useful in conducting multicenter studies with an expansion of the scope of clinical cases.

When choosing a treatment strategy to help clinicians, the information we reached with the help of the statistical method Anova analysis would be useful, namely that the factors duration of BF intake and the period of time elapsed from the dentoalveolar surgery are prognostic factors regarding the probability of formation of bony sequestrum. Another important conclusion we reached is that the period of time elapsed from the dentoalveolar surgery is prognostic regarding the stage of the patient's disease. The presence of a bony sequestrum and the stage of the patient's disease have a decisive importance for the choice of treatment approach.

In the literature, we found opposition of the authors and the results obtained by them regarding conservative treatment methods. Using the statistical method Statistical hypothesis testing for the difference of two proportions /of two relative frequencies/, we made a comparison of the outcome of the treatment after applying the Sequestrectomy methods and a conservative method of treatment (medication treatment and debridement). We found a relatively higher rate of success in the treatment of the patients examined by us when the Sequestrectomy method was applied, compared to those in which the conservative method (medication treatment and debridement) was applied. From our study, we can conclude that antibiotic treatment itself is insufficient to achieve remission in patients, but it can lead to disease stabilization and can be used as symptomatic treatment to influence the clinical symptoms during exacerbation.

The prevention of the disease and the application of a precisely and clearly defined approach when conducting dentoalveolar surgical intervention are of utmost importance to prevent the occurrence, as well as to influence the development and/or progression of BRONJ. Therefore, we investigated treatment outcomes with our protocol, finding a low incidence of disease and reliability and predictability in treatment outcome with our treatment strategy.

As a conclusion, we can say that BRONJ is a multifactorial disease, it is difficult to be treated and is with an unclear prognosis. Knowing the factors influencing the onset of the disease, as well as those influencing the outcome of its treatment, is of utmost importance when choosing a treatment strategy. Prevention of the disease and prevention of its development is of primary importance for clinicians from various specialties related to the initiation and choice of BF therapy, the control of occurrence of complications in the jawbones and the corresponding treatment. In this sense, interdisciplinary collaboration between medical and dental specialists is of leading importance for the prevention and control of the consequences of therapy with bisphosphonates, and this is particularly significant for the outpatient dental practice, in which the first symptoms of necrobiotic changes in the jaw bones are detected. It

can be successfully applied using a clearly defined protocol when performing dentoalveolar surgical intervention in patients treated with drugs from the bisphosphonate group.

Findings

1. BRONJ mainly affects patients in the age group of 61-70 years (average age 62 years), and in the present study no cases were found under the age of 30 years and over 91 years. The disease affects both sexes, with a male:female ratio of 1.1:0.9.

2. Patients undergoing bisphosphonate drug therapy for malignancy have a higher risk of developing BRONJ compared to those receiving bisphosphonates for the treatment of osteoporosis.

3. The type of bisphosphonate, the method of BF intake and the duration of BF administration have a significant impact on the occurrence of the disease. Zoledronat has the highest risk of developing BRONJ, followed by Zoledronat combined with another bisphosphonate, Ibandronic acid, Alendronic and Ibandronic acid, Pamidronic acid.

4. Intravenous administration of bisphosphonates is associated with a higher risk of developing BRONJ compared to oral administration. Taking bisphosphonates for a long period of time was also associated with an increased risk of developing BRONJ, with the mean duration of bisphosphonate intake in our study being 41.75 months.

5. Dentoalveolar surgical intervention is also a major factor in the development of BRONJ, and the average time from the surgical intervention to the clinical appearance of BRONJ is 8 months.

6. In terms of localization, the distal areas of the mandible are at increased risk of BRONJ occurrence.

7. Patients most often seek medical help and are diagnosed with the symptomatic manifestations of the disease in the II and III stages of the disease. A very small percentage of them seek medical help in stages 0 and I, which speaks of insufficient awareness and ignorance of the early symptoms of BRONJ.

8. The most common radiographic findings are bone sclerosis and osteolysis. A formed sequestrum, together with osteosclerosis and osteolysis is observed radiographically in approximately 1/3 of cases.

9. With regard to the development of the disease, in the present study we found during the clinical examinations of the first and sixth months after the primary diagnosis and the treatment measures carried out, that in the first place with the highest percentage of patients is stationing of the disease, followed by the patients in which clinical improvement is observed, in the third place there is disease progression and in the last place - remission. BRONJ is a hard-to-treat disease with a protracted course.

10. A relatively higher rate of success in treatment is found when applying the "Sequestrectomy" method, compared to the Conservative method (medication treatment and debridement).

11. The duration of BF intake and the period of time from the dentoalveolar surgical intervention are important prognostic factors regarding the probability of disease progression after the applied treatment, as well as in the formation of bone sequestration. The age of the patient is not a prognostic factor and does not influence the outcome of the disease.

12. Regarding the surgical technique - atraumatic surgical intervention, smoothing of the sharp bony edges and closure of the extraction wound, combined with antibiotic prophylaxis is the recommended approach with a known risk of developing BRONJ in the extraction of teeth unsuitable for conservative treatment in patients undergoing oral and/or intravenous bisphosphonate treatment.

9. Contributions:

Scientific Applied Contributions:

1. For the first time in our country, through logistic-regression analyses, the correlation between the prognostic factors "duration of bisphosphonate intake" and "time from the dentoalveolar surgery" and the time interval until the manifestation of the symptoms of the disease, its progression and/or its recurrence is proven.

2. For the first time in our country, a comparative analysis is being made between the results of conservative treatment (antibiotics and cleaning of necrotic tissues - debridement) and sequestrectomy in terms of the development of the disease.

Contributions of a confirmatory nature:

3. Our research has a confirmatory nature regarding the influence of some risk factors related to demographic and clinical characteristics - age, sex, type of the main disease, the presence of a previous surgical intervention, type of administered bisphosphonate, duration of administration, medicinal form of application (parenteral, oral).

4. The results regarding the clinical manifestations of BRONJ in the oral cavity established in our study are also of a confirmatory nature.

5. The present study confirms and complements the treatment strategies described in the world literature regarding the rules for tooth extraction in patients on bisphosphonate therapy in the quadrant of the jaw without necrosis, with the recommendation to follow the clearly defined and described in the dissertation surgical protocol.

List of scientific publications

1. Илиева Б., Свещаров В. Съвременна концепция относно Бисфосфонат-асоцииранатa остеонекроза на челюстните кости-клиника, стадиране, параклиника, превенция. Дентална медицина, том 104, 2/2022, 137-142.

2. Ilieva B, Prodanova K., Svechtarov V. The period of time from the surgical intervention as a predictive factor on the outcome of the treatment of Bisphosphonate-Associated Osteonecrosis of the Jaws. Medinform 2024, Vol. 11 (1), issue 1, p: 1753-1800.

3. Ilieva B, Prodanova K., Svechtarov V. Prediction of bisphosphonate-associated osteonecrosis of the jaws in Bulgarian patients using logistic regression. International Journal of Applied Mathematics Volume 36 No. 6 2023, 815-827, ISSN: 1311-1728 (printed version); ISSN: 1314-8060 (on-line version). doi: http://dx.doi.org/10.12732/ijam.v36i6.6

Participation in scientific events:

1. IX Scientific Congress of SRK at BZS Sofia 30.11-01.12.2019 Lecturer on the topic "Bisphosphonate-associated osteonecrosis of the jaw bones (BAONJ) - etiology, risk factors, clinical picture, prevention and treatment.".
2. XIII Scientific Congress of SRK of BZS, Sofia 17-18.02.2024. Lecturer on the topic "Modern concepts regarding the medication-related osteonecrosis of the jawbones and the role of the dentist in its prevention."