10.1053.paor.2000.0227 available online at http://www.idealibrary.com on IDEAL

ARTICLE

Possibilities of Preventing Osteoradionecrosis During Complex Therapy of Tumors of the Oral Cavity

Zsolt NÉMETH,[1] András SOMOGYI,[2] Zoltán TAKÁCSI-NAGY,[2] József BARABÁS,[1]
György NÉMETH,[2] György SZABÓ[1]

[1]Department of Oral and Maxillofacial Surgery, [2]Department of Radiotherapy, Semmelweis University, Budapest

In recent years, there has been a dramatic increase in the number of tumors of the head and neck. Their successful treatment is one of the greatest challenges for physicians dealing with oncotherapy. An organic part of the complex therapy is preoperative or postoperative irradiation. Application of this is accompanied by a lower risk of recurrences, and by a higher proportion of cured patients. Unfortunately, irradiation also has a disadvantage: the development of osteoradionecrosis, a special form of osteomyelitis, in some patients (mainly in those cases where irradiation occurs after bone resection or after partial removal of the periosteum). Once the clinical picture of this irradiation complication has developed, its treatment is very difficult. A significant result or complete freedom from complaints can be attained only rarely. Attention must therefore be focussed primarily on prevention, and the oral surgeon, the oncoradiologist and the patient too can all do much to help prevent the occurrence of osteoradionecrosis. Through coupling of an up-to-date, functional surgical attitude with knowledge relating to modern radiology and radiation physics, the way may be opened to forestall this complication that is so difficult to cure. (Pathology Oncology Research Vol 6, No 1, 53–58, 2000)

Keywords: Tumors of the oral cavity, mandibular resection, radiotherapy, osteoradionecrosis, prevention

Introduction

One of the integral components of the complex treatment of tumors of the head and neck is irradiation of the affected region. As a complication of such treatment, osteoradionecrosis may develop in a small proportion of the irradiated patients. When the treatment involves tumors of the oral cavity, osteoradionecrosis can occur predominantly in the mandible (90%), but also in the maxilla (10%), and rarely in other facial bones.[9] Since the process affects the mandible in the vast majority of the cases, the present paper does not deal with disease forms affecting the maxilla or other facial bones.

In our experience, an inflammatory process subsequent to irradiation is most frequent in the region of the molars; more rarely, it starts from the regions of the incisors or the ramus. As a result of the process, extensive osteonecrosis may develop, with the possibility of a pathological fracture, and finally a fistula leading to the neck, and the emergence of a septic state.[9,16] The danger of the development of osteoradionecrosis is greatest in the 12 months following the treatment; there is subsequently an exponential decrease in its probability, but the danger persists throughout the lifetime of the treated patient.[18]

The vascular anatomic features of the mandible mean that its blood supply is essentially poorer than that of bones at other sites in man. Because of its bone structure and the teeth situated in it, it reacts much more sensitively than any other bone tissue to irradiation. Profound changes occur in the soft parts too; radiomucositis may be observed in the mucosa, with obliterating endarteritis and fibrosis in the deeper layers of the tissue, an osteoblast deficiency in the bone, and osteocyte destruction.[9,17]

Osteoradionecrosis was first described by Regaud in 1922.[19] Its exact pathogenesis remained unknown for a long time, and numerous misconceptions arose regarding its cause. In 1970, Meyer mentioned a triad that is characteristically associated with the development of the clinical picture: irradiation, trauma and inflammation.[15] Happonen ascribed the process to a mixed pathogenic microflora of the oral cavity, emphasizing that Actinomyces and Candida strains fea-

Received: Sept 16, 1999; *accepted:* Dec 10, 1999

Correspondence: Dr. Zsolt NÉMETH, Semmelweis University, Department of Oral and Maxillofacial Surgery, Mária u. 52., H-1085 Budapest, Hungary; Tel: +36-1-2660-457; fax: +36-1-2660-456

 1219-4956/00/010053+06 $ 12.00/0

ture as pathogens in all cases.[6] Other authors stressed the roles of Streptococcus mutant and Lactobacillus strains.[5,12]

The currently most widely accepted theory was put forward by Marx in 1983. His investigations demonstrated that the primary cause was not the superinfection of the irradiated bone, but the irradiation-elicited intraosseal ischaemia, multiple embolization, extensive tissue hypoxia and secondary cell destruction. The decrease in the number of cells was considered to be connected with the damage to the bone marrow and the periosteum, and with the decrease in the number of osteoblasts.[13] The studies by Jones first revealed that irradiation is also followed by a substantial decrease in the number of osteoclasts. This was attributed to the damage to the medulla, and to the vascular obstruction. Importance was attached to the observations that the osteoclasts were not capable of phagocytizing the irradiated bone tissue, and that the osteoblast deficiency led to a secondary osteoclast deficiency. It was held that an essential role was also naturally played in the process by the secondary infection of the damaged bone, which could occur via a mucosal defect caused by the radiomucositis, or more rarely via a haematogenic pathway.[11]

This conception was supported by the observations of Bras. He made a comparison of the bone tissue from mandibles resected because of osteoradionecrosis with that from patients who had also been irradiated, but in whom this complication had not developed, and who had died for other reasons. His histopathological examinations confirmed that partial or total obstruction of the inferior alveolar artery leads to ischaemic osteonecrosis.[4]

According to Marx, we may speak of osteoradionecrosis in all cases in which the mandible becomes free towards the oral cavity following irradiation, no tumor can be detected in the oral cavity, and conservative treatment does not result in healing within 3 months. Naturally, there is also a disease form in which the characteristic clinical signs appear even though the intraoral mucosa is intact. Marx classified post-irradiation osteomyelitis as a spontaneous phenomenon in 30% of the cases, and as of post-traumatic origin in 70%.[9]

Possibilities of treatment

Although osteoradionecrosis occurs as a complication in only a small proportion of irradiated patients, its treatment poses a considerable problem. The conservative treatment modes include medication (locally or systemically administered antibiotics), hyperbaric oxygen therapy[14,24] or the local application of fluorine-containing pastes. Hyperbaric oxygen increases oxygen supply in hypoxic tissue, thus inducing fibroblastic proliferation and capillary formation. HBO could be given at 2.5-2.8 atmosphere absolute pressure (ATA) for 90-120 minutes, once per day. The patients should receive 5-10 treatments pre and postoperatively.[1] The available surgical methods are excochleation, sequestrotomy, mandibular resection and reconstruction (grafting of alloplastic materials and vascularized bone). One of the preconditions of successful surgical treatment is early recognition, but this can not be ensured with the currently available imaging procedures.[22] In spite of the fact there are numerous possibilities for the treatment of osteoradionecrosis, the very poor indices relating to healing stimulate us to devote much more attention to the prevention of these serious complications of irradiation.

Possibilities of prevention

Prevention of the development of osteoradionecrosis demands the collaboration of the surgeon, the oncoradiologist and the patient.

It is the task of the stomato-oncological team to decide on the sequence of therapy, to direct the patient to the appropriate place, to verify any tumor histologically and to perform a thorough examination of the patient. Unfortunately, when osteoradionecrosis has already developed, the possibilities for collaboration are somewhat limited. Traditionally, it happens that these latter patients are usually cared for in the unit where the operation was performed, without collaborative consultation.

Correct irradiation is possible only in units that are equipped with up-to-date instrumentation and where the specialist staff are appropriately well trained. The expense involved means that the number of such modern radiation therapy centres in Hungary is very limited. Accordingly, it rarely occurs that high-level maxillofacial surgery and high-level radiology are to be found within one institution, and patients are therefore exposed too often to the risk of osteoradionecrosis and their systematic, joint examinations and follow-up are not solved.

It follows logically from the nature of the disease that the oncoradiologist is striving to achieve prevention, whereas the operating surgeon is concerned both with prevention and with the treatment of the already developed disease. Let us consider what each can do, and when to prevent the disease from developing.

The following questions can arise for the oncotherapists in connection with the irradiation and with the mandibular surgery:

When and what type of surgery can be performed on the mandible after irradiation?

How can it be established which parts of the mandible are affected by the irradiation?

After what time can dental surgical interventions be carried out?

If mandibular osteotomy was performed to facilitate removal of the tumor, but without resection, when can postoperation irradiation be begun?

Is irradiation possible after removal of the periosteum of the corticalis, block or segment resection or after reconstruction with a metal plate or ceramics?

What is the maximum dose that can be tolerated by the bone?

Can irradiation be performed years or decades after the primary operation in the event of head or neck tumors in other locations?

Possibilities of a surgical solution to prevent osteoradionecrosis

Before surgery or irradiation, it is of fundamental importance to access the dental status of the patient and to bring the dentition into a good condition. In the course of irradiation, the hard tissues of the teeth undergo extensive damage. As regards the process, predisposing effects may be exerted by a diminished function of the salivary glands, a decrease in the quantity of saliva excreted, or a change in its composition. Since dental surgical interventions (extraction, sculpting, resection, etc.) are contraindicated during irradiation and in the following year, it is the duty of the surgeon to ensure that necessary dental preservation treatment should be carried out before, or at the latest during surgery. In the event of complaints during this year, treatment such as trepanation, root treatment or filling should be performed rather than extraction.

Another important task during surgery is to maintain as far as possible the integrity of the bone, and to leave the periosteum intact. An effort must be made not to bare the mandible; if this is nevertheless necessary for surgical technical reasons, then after the intervention it should be covered in several layers with tissues with a good blood supply. The predominant cause of the development of osteoradionecrosis is well known to be the deterioration of the circulation of the mandible and the adjacent tissues after irradiation. If the blood supply of the bone and the soft parts in its environment are damaged even during the operation, the risk of development of the clinical picture may be multiplied.

A further problem arises if the tumor adheres strongly to the periosteum or even affects the bone. In such cases, the periosteum may have to be removed, together with part of the mandible itself too, in the form of a block or segment resection. The blood supply of the mandible is clearly damaged in these cases, so that the safety of postoperative irradiation is automatically open to question.

Operations interrupting the continuity of the mandible involve the necessity of immediate reconstruction. Functional and aesthetic rehabilitation nowadays comprises just as much a part of complex tumor therapy as the surgery, the irradiation, the cytostatic treatment or the psychological care of the patient.

Reconstruction may be carried out with the use of alloplastic materials (metal plates, ceramics or plastics) and/or grafting of bone taken from some other region of the body. It is a general rule that bone not possessing its own blood supply can be utilized for free mandibular replacement only under sterile conditions and, since a connection arises between the oral cavity and the surface of the mandible in a large majority of the operations, this procedure may be employed only in secondary surgery. One exception is free bone grafting involving a vascular stem. In these cases, a satisfactory result (undisturbed wound healing) is observed even if the grafted bone comes into direct contact with the flora of the oral cavity in the course of the operation. During primary surgery (if the mandible is resected), reconstruction is performed with a metal plate or by the simultaneous implantation of a metal plate and ceramics, with the proviso that, after about 1 year, in the event of a tumor-free state, a final replacement is achieved with the aid of bone grafting.

If bone substitution is nevertheless carried out during primary surgery, this can be done with „living“ bone. Bone with its own blood supply is much more resistant to infection, and the danger of necrosis and demarcation is much lower.[7,20,21] Following irradiation, surgery must in all cases be performed only under protection with broad-spectrum antibiotics.

In order to remove the tumor (without bone resection), mandibular osteotomy is performed (to expose tumors in the floor of the mouth or at the root of the tongue), and the operation is followed by stable osteosynthesis with a metal plate and screws. Irradiation of the patient is justified in this case, and also after mandibular reconstruction with a metal plate and Al_2O_3 ceramics. The scattering of the radiation on the metal parts, and the excess radiation loading of the parts around the plate, are negligible. There is also a risk of the development of osteoradionecrosis after surgery in which the integrity of the bone and the blood supply of the mandible are maintained and the periosteum is spared, but irradiation is indicated by the histological type ad the location of the tumor.

We have observed that mandibular osteotomies performed in the midline lead to far fewer complications than when the transmandibular approach occurs via the corpus. The difference clearly results from the fact that median osteotomy does not cause a profound deterioration in the mandibular blood supply.

By 6 months after the treatment, the irradiated tissues have regained their normal function. [10] However, surgery must be carried out earlier in all cases. The patient is therefore of necessity exposed to a risk, and it is the task of the operator to assess this.

Possibilities for the oncoradiologist to prevent osteoradionecrosis

The probability of osteoradionecrosis can be minimized if special attention is paid in the course of the planning and performance of the irradiation to exclusion of the mandible from the target volume as far as possible, and to ensuring that the bone is subjected to the lowest possible dose. This can currently be achieved with the greatest reliability following the most modern, CT-guided, 3D irradiation planning, with conformal irradiation via a Multi-Leaf-Collimator.

The essence of the procedure is that serial CT images are taken at 2-mm intervals of the target volume to be irradiated (tumor + safety zone). On every individual CT image, the target volume is denoted. On this basis, the computerised irradiation program builds up the target volume in 3D, and the result can be rotated at will on the screen, and viewed from all angles. With a similar technique, images are also produced of the adjacent critical organs that are to be protected from the irradiation (e.g. the eyeball, the spinal cord, or in our case the mandible). Depending on the number of fields via which the radiation treatment is administered, a corresponding number of field forms of various shapes are created with the aid of the multi-leaf collimator. The shape of the field faithfully follows the shape of the target volume from the direction of the main radiation beam (the beam's eye view). This technique guarantees the optimum dose distribution, and thus the radiation loading of the unnecessarily irradiated healthy tissues can be minimized. In this way, it can be achieved that only the absolutely necessary bone tissue should be irradiated, e.g. in the case of tumors extending to the bone.

The dose that can be tolerated by the bone tissue depends on the nature of the radiation applied, on its fractionation, and on the dose per fraction.

If bone resection should nevertheless become necessary after irradiation, the extent of the bone tissue irradiated (e.g. a mandibular segment) can be established exactly by means of MR examinations.[2,8] The irradiated part appears on the images as an area of enhanced sclerosis (in T2). In this case, however, preliminary consultations must be held with the radiotherapist in all cases, as regards the extent of the applied irradiation field. Naturally, in such a case the resection lines must lie outside the irradiated area. If, in the interest of a better cosmetic result and a more facile reconstruction, less bone is removed and the resection line is led through the irradiated area, then newer and newer surgery will subsequently become unavoidable because of the necrosis of the resection edges.[23] It is to be noted that, whereas the same dose of radiation reached the mandible on both sides when the traditional techniques were employed, only the affected side is subjected to irradiation when the treatment is applied by means of the multi-leaf collimator.

The radiation therapy should be provided, if possible, with an ultrapotential radiation source (telecobalt source and linear accelerator) since the amount of radiation absorbed by the bone tissue is then less than for radiation of lower energy.

Because of the steep fall in dose, irradiation with interstitial (after-loading) brachytherapy is similarly suitable for the avoidance of osteoradionecrosis. Via this method, by appropriate location of the implants and by means of the X-ray pictures of this (these clearly demonstrate the spatial relationship of the implanted catheters and the critical organ, in this case the mandible), the computerized planning system allows selection of the reference points so that the radiation affecting the bone should be minimized, or even eliminated.[3]

In the 3D procedure, in brachytherapy, and in irradiation with an ultrapotential source or even with heavy particles such as neutrons (among the most modern techniques), the primary point is the location of the tumor: the risk of the development of osteoradionecrosis can not be completely avoided either for tumors destroying the bone or for tumors in the vicinity of the bone. Similarly as in surgical interventions, the primary aim is the most radical extirpation of the tumor, so that the prevention of complications can only be secondary.

Duties of the patient

The patient too must collaborate in the prevention of osteoradionecrosis. Besides regular participation in the oral surgical and oncoradiological control examinations, he or she must devote particular care to the cleanliness of the teeth and to maintaining a healthy parodontium. Minor dental interventions with a preserving aim, depurations and periodontal treatments may always be performed without delay, but in all cases it is recommended to learn the opinion of the treatment physician in advance. In order to maintain the appropriate oral hygiene, it is recommended to use a chlorhexidine-containing toothpaste and oral rinse: only these ensure effective defence against plaque formation and secondary periodontal diseases, which may play a deciding role in superinfection of the bone which is in a damaged condition following irradiation. In the event of a complaint, the patient must turn immediately to the treatment physician.

Case report

A 45-year-old male, was admitted to our Department because of an extensive tumor ($T_3N_{2b}M_0$) that infiltrated the tongue and the posterior third of the sublingual region on the left side. The case history extended back over 6 months. On admission, the patient complained of pain in the region of the tumor, and of difficulty in swallowing. The mandible was not affected by the tumor. The long-term case history included hyperthyroidism. Histological examination confirmed squamous cell carcinoma. Clinical and ultrasonographic and CT examinations revealed multiple lymphadenomegaly on the same side, in the regions of the prevascular, retrovascular, subdigastric and parajugular lymph nodes. Other laboratory findings were not indicative of pathological changes. With regard to the euthyroid condition and the result of the cervical ultrasonographic exami-

Figure 1. Intraoral view

Figure 2. Extraoral view

nation (negative thyroid), the requested internal consultation did not recommend treatment or pre-treatment.

The patient underwent a full examination. The state of his poor dentition was improved, and the calculus was removed. In view of the extent of the primary process and the cervical status, preoperative intra-arterial cytostatic treatment was begun, and this led to a significant remission. For 10 days, the patient received a 24-hour perfusion of 60 mg Bleomycine and 150 mg Methotrexate, 150 mg Cisplatin intra-arterially, together with 2250 mg Elobromol (DBD) and 1.5 mg Vincristin systemically. The patient tolerated this treatment well: the blood picture was stable throughout and no side-effects were observed. Surgery was performed 10 days after completion of the treatment: tumor exstirpation, with extensive functional cervical dissection on the left side. Histological examination of the surgical preparations demonstrated only reactive hyperplasia in the cervical lymph nodes; the resection edges were negative for tumor. The tumor did not affect the bone, and the mandibular periosteum remained intact during surgery. Following a problem-free postoperative period, the patient was discharged.

With regard to the length of the case history and to the extent and location of the primary tumor, postoperative irradiation was recommended. The patient participated in 60 Gy telecobalt irradiation 1 month after surgery. 1 year following the irradiation, it became necessary to extract the left lower 4 and 5 teeth in consequence of the unsatisfactory oral hygiene and the damage caused to the dental substance by the irradiation. This intervention was performed under protection with Dalacin C (Clindamycin) in a daily oral dose of 1200 mg, for 21 days, started 3 days before the intervention.

The extraction wounds healed sluggishly or not at all. Alveolitis developed, followed by abscessing osteoradionecrosis (osteomyelitis) extending between the soft parts of the vestibule and the submandibular region. Because of the tissue necrosis, a fistulous, wide dermal defect developed towards the neck (*Figure 1-2*). Following bacteriological sampling and resistance testing, a high dose of Clindamycin was administered intravenously. Although the process stabilized, the necrotic mandible did not display any tendency towards regeneration.

23 months after the first operation, mandibular resection was carried out from the angle on the left side to the midline, and reconstruction was performed with a vascularized osteomyocutaneous flap obtained from the iliac crest (*Figure 3*). The bone used for the replacement was fixed to the mandible with a metal plate and screws. Oral Clin-

Figure 3. Postoperative view

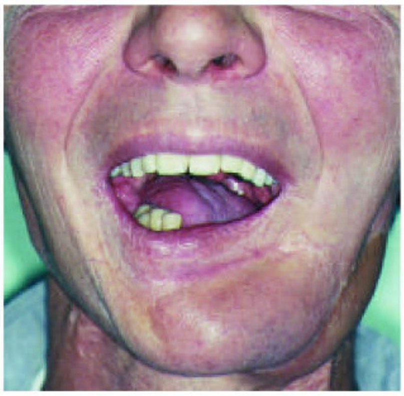

Figure 4. One year after operation

Figure 5. One year after operation

damycin treatment was continued in the postoperative period. The wound healing was undisturbed. Since surgery (12 months), the patient has been free of complaints (*Figure 4-5*). As a residual symptom, mention should be made of a minor limitation of mouth opening. Prosthetic rehabilitation is in process.

Conclusions

The causes and pathomechanism of the development of osteoradionecrosis have been discussed. In the light of the inducing factors ad on the basis of experience acquired during the treatment of tumor patients, consideration is given to the possibility of preventing this serious complication. An indication is provided as to how the various medical teams (and himself or herself the patient too) can contribute by various means to reducing the likelihood of occurrence of this disease form. A case report is presented to illustrate the development of osteoradionecrosis and the possibilities for its treatment.

References

1. *Aitasalo K, Niinikoski J, Grenman R, et al:* A modified protocol for early treatment of osteomyelitis and osteoradionecrosis of the mandible. Head-Neck 20:411-417, 1988.
2. *Bachmann G, Rossler R, Klett R, et al:* The role of magnetic resonance imaging and scintigraphy in the diagnosis of pathologic changes of the mandible after radiation therapy. Int J Oral Maxilofac Surg 25:189-195, 1996.
3. *Behar RA, Martin PJ, Fee WE, et al:* Irridium-192 interstitial implant and external beam radiation therapy in the management of squamous cell carcinomas of the tonsil and soft palate. Int J Radiat Oncol Biol Physics 28:221-227, 1994.
4. *Bras J, Jonge de HKT, Merkesteyn JPR:* Osteoradionecrosis of the mandible: pathogenesis. Amer J Otolaryngology 11:244-250, 1990.
5. *Epstein JB, Mc Bride BC, Stevenson-Moore P, et al:* The efficacy of chlorhexidine gel in reduction os Streptocossus mutans and Lactobacillis species in patients treated with radiation therapy. Oral Surgery, Oral Medicine, Oral Pathology 71:172-178, 1991.
6. *Happonen RR, Viander M, Pelliniemi L, et al:* Actinomyces israelii in osteoradionecrosis of the jaws. Histopathologic and immunocytochemical study of five cases. Oral Surgery, Oral Medicine, Oral Pathology 55:580-588, 1983.
7. *Hartmann A, Almeling M, Carl UM:* Hyperbaric oxygenation (HBO) in the treatment of radiogenic side effects. Strahlenther Oncol 172:641-648, 1996.
8. *Hermans R, Fossion E, Ioannides C, et al:* CT findings in osteoradionecrosis of the mandible. Skeletal Radiol 25:31-36, 1988.
9. *Horiot JC, Bone MC, Ibrahim E, et al:* Systemic dental management in head and neck irradiation. Int J Radiat Oncol Biol Physics 7:1025-1029, 1981.
10. *Jesse RH, Fletcher GH, Lindberg RD, et al:* Cancer of the head and neck. In Cancer Patient Care at M.D. Anderson Hospital and Tumor Institute, ed. by Clark RL and Howe CD Chicago, Yearbook Medical Publishers, Inc. 92-93, 1976.
11. *Jones SJ, Boyde A, Ali NN:* The resorption of biological and non-biological substrates by cultured avian and mammation osteoclasts. J Anatomy Embriology 170:247-256, 1984.
12. *Keene HJ, Fleming TJ:* Prevalence of caries associated micraflora after radiotherapy in patients with cancer of the head and neck. Oral Surgery, Oral Medicine, Oral Pathology 64:421-426, 1987.
13. *Marx RE:* Osteoradionecrosis: A new concept of its pathophysiology. J Oral Maxillofacial Surgery 41:283-288, 1983.
14. *McKenzie MR, Wong FLW Epstein JB, et al:* Hyperbaric oxygen and postradiation osteonecrosis of the mandible. Oral Oncology, European J Cancer 29B:201-207, 1993.
15. *Meyer I:* Infectious diseases of the jaw. J Oral Surgery 28:17-26, 1970
16. *Morton ME:* Osteoradionecrosis : A study of the incidence in the North West of England. Br J Oral Maxillofacial Surgery 24: 323-331, 1986
17. *Murray CG, Herson J, Daly TE, et al:* Radiation necrosis of the mandible: A 10 year study. Part I. Factors Influencing the onset of necrosis. Int J Radiat Oncol Biol Physics 6:543-548, 1980.
18. *Murray CG, Herson J, Daly TE, et al:* Radiation necrosis of the mandible: A 10 year study. Part II. Dental factors; Onset, duration and management of necrosis. Int J Radiat Oncol Biol Physics 6:549-553, 1980.
19. *Regaud C:* Sin la necrose des os attrens par un processus cancereux et traites par les radiations. Compt Rend Soc De Biol 87: 427, 1922.
20. *Santamaria E, Wei FC, Chen HC:* Fibula osteoseptocutaneous flap for reconstruction of osteoradionecrosis of the mandible. Plast Reconstr Surg 101:921-929, 1998.
21. *Shaha AR, Cordeiro PG, Hidalgo DA, et al:* Resection and immediate microvascular reconstruction in the management of osteoradionecrosis of the mandible. Head-Neck 19:406-11, 1997.
22. *Szabó G, Kovács Á, Dõri F:* Behandlung der Osteoradionekrose im Unterkieferbereich. Septische Mund-Kiefer-Gesichtschirurgie, Band XXIX. Georg Thieme Verlag, Stuttgart, New York 138-140, 1984.
23. *Szabó G, Németh G, Le van Tach, et al:* Az alsó állcsont helyreállításának szempontjai sugárkezelés után. Magyar Radiológia 58:9-17, 1984.
24. *van Merkesteyn JPR, Bakker DJ, Borgmeijer-Hoelen AMMJ:* Hyperbaric oxygen treatment of osteoradionecrosis of the mandible. Experience in 29 patients. Oral Surgery, Oral Medicine, Oral Pathology 80:12-16, 1995.