Aus der Klinik und Poliklinik für Mund-, Kiefer- und Gesichtschirurgie

der Ludwig-Maximilians-Universität München

Direktor: Prof. Dr. med. Dr. med. dent. Michael Ehrenfeld

Clinical presentation and risk factors of osteoradionecrosis

Dissertation

zum Erwerb des Doktorgrades der Zahnheilkunde

an der Medizinischen Fakultät der

Ludwig-Maximilians-Universität zu München

vorgelegt von

Aristeidis Chronopoulos

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Athen, Griechenland

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Mit Genehmigung der Medizinischen Fakultät

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To my parents with deep gratitude

Contents

Abstract

Clinical presentation and risk factors of osteoradionecrosis

Introduction: Osteoradionecrosis (ORN) of the jaws is defined as exposed irradiated bone that fails to heal over a period of 3 months without the evidence of a persisting or recurrent tumor. In the previous decades, numerous factors were associated with the risk of ORN development and severity.

Aims: The purposes of this study were to present the data of the patients that were treated for ORN in the Department of Oral and Maxillofacial Surgery in Munich (LMU), to detect factors that contributed to the onset of ORN, to identify risk factors associated with the severity of ORN and finally, to delineate and correlate these factors with the personal, health and treatment characteristics of the patients.

Material and Methods: A retrospective study was conducted during the period from January 2003 until December 2012 that included all ORN cases having been treated in the Department of Oral and Maxillofacial Surgery in Munich (LMU). The total sample was categorized in three groups according to stage and several variables were evaluated in an attempt to identify possible correlations between them and the necrosis severity.

Results: One hundred and fifty three cases of ORN were documented. Among them, 23 (15.1%) cases were stage I, 31 (20.2%) were stage II and 99 (64.7%) were stage III and all localised in the mandible. There was a predominance of the disease in the posterior region when compared to the anterior region. The majority of cases was addicted to alcohol and tobacco abuse and was suffering from Diabetes Mellitus (DM). All cases were treated with RT and 80.4% of them with concomitant chemotherapy. The initial tumor was predominantly located in the floor of the mouth, the tongue and the pharynx. Approximately two thirds of the cases occured either after dental treatment or due to a local pathological condition. Logistic regression analysis identified Diabetes Mellitus (OR: 4.955, 95% Cl: 1.965-12.495), active smoking (OR: 13.542, 95% Cl: 2.085-87.947), excessive alcohol consumption (OR: 5.428, 95% Cl: 1.622-18.171) and dental treatment/ local pathological condition (OR: 0.237, 95% Cl: 0.086-0.655) as significant predictors for stage III necrosis. Tumor

size (T) ($p<0.001$), stage of the tumor (UICC) ($p=0.001$), concomitant chemotherapy ($p<0.001$), dental examination and treatment prior to RT ($p<0.001$) and the different causes of ORN ($p=0.03$) were statistically significantly associated with the severity of ORN.

Conclusion: The aforementioned factors are predictive of ORN severity and can guide its prophylaxis and management. Based on these findings, prospective studies should be conducted in order to better understand risk factors associated with the development, severity and pathophysiology of ORN and improve treatment strategies for this complication of RT.

Zusammenfassung

Klinische Präsentation und Risikofaktoren der Osteoradionekrose

Einleitung: Die Osteoradionekrose (ORN) der Kiefer ist definiert als freilegender bestrahlter Knochen, der über einen Zeitraum von 3 Monaten nicht ausheilt, ohne Nachweis eines bestehenden oder rezidivierenden Tumors. In den letzten Jahrzehnten wurden zahlreiche Faktoren mit dem Risiko der Entwicklung einer ORN und ihrem Schweregrad assoziiert.

Ziele: Die Ziele dieser Studie waren die Daten von Patienten, die wegen einer ORN in der Klinik für Mund-, Kiefer- und Gesichtschirurgie der LMU in München behandelt wurden, zu präsentieren, die Faktoren die zur Manifestation der ORN beigetragen haben, zu erkennen, die Risikofaktoren, die mit dem Schweregrad der ORN verbunden sind zu ermitteln und schließlich diese Faktoren mit der allgemeinen Gesundheits- und Behandlungscharakteristik der Patienten zu korrelieren.

Material und Methoden: Eine retrospektive Studie wurde durchgeführt, um alle Fälle, die wegen einer ORN in der Klinik für Mund-, Kiefer- und Gesichtschirurgie der LMU in München im Zeitraum von Januar 2003 bis Dezember 2012 behandelt wurden, zu erfassen. Die Gesamtgruppe wurde gemäß den Erkrankungsstadien entsprechend in drei Gruppen eingeteilt und verschiedene Variablen wurden ausgewertet, um zu untersuchen, ob eine Korrelation zwischen ihnen und dem Schweregrad der Nekrose besteht.

Ergebnisse: Einhundertdreiundfünfzig Fälle einer ORN wurden dokumentiert. Von ihnen entsprachen 23 (15.1%) Stadium I, 31 (20.2%) Stadium II und 99 (64.7%) Stadium III. Alle entwickelten sich im Unterkiefer. Es zeigte sich ein Vorherrschen der ORN im posterioren Anteil des Unterkiefers. Bei der Mehrzahl der Fälle lag Alkohol- und Tabakmissbrauch sowie ein Diabetes Mellitus (DM) vor. Alle Fälle wurden mit Strahlentherapie und 80.4% von ihnen mit Radio-Chemotherapie behandelt. Die Mehrheit der ursprünglichen Tumoren war im Mundboden-, Zungen- und Rachenraum lokalisiert. Zwei Drittel der Fälle waren auf eine spezifische Ursache, einschließlich zahnärztlich chirurgischer Behandlungen oder einen lokalen pathologischen Zustand zurückzuführen. Die logistische Regressionsanalyse

identifizierte Diabetes Mellitus (OR: 4.955, 95% Cl: 1.965-12.495), das aktive Rauchen (OR: 13.542, 95% Cl: 2.085-87.947), übermäßigen Alkoholkonsum (OR: 5.428, 95% Cl: 1.622-18.171) und chirurgische Zahnbehandlungen/lokale pathologische Zustände (OR: 0.237, 95% Cl: 0.086-0.655) als signifikante Prädiktoren für das Stadium III der Nekrose. Die Tumorgröße (T) ($p<0.001$), das Tumorstadium (UICC) ($p=0.001$), die gleichzeitige Chemotherapie ($p<0.001$), die zahnärztliche Untersuchung und Behandlung vor der Strahlentherapie ($p<0.001$) und die auslösenden Ereignisse der Osteoradionekrose ($p=0.03$) waren mit der Schwere der Osteoradionekrosen statistisch signifikant verbunden.

Zusammenfassung: Die oben genannten Faktoren sind prädiktiv für die Schwere der ORN und können zu einer Optimierung ihrer Prophylaxe und Therapie führen. Auf Basis dieser Erkenntnisse sollten prospektive Studien durchgeführt werden, um die Risikofaktoren für die Entwicklung von ORN, deren Schweregrad sowie Pathophysiologie besser zu verstehen und die Fähigkeit diese Komplikation zu behandeln, zu verbessern.

General Part

Chapter 1

Oropharyngeal cancer

Oropharyngeal cancers (OPCs) are defined as tumors of the oral mucosa, upper and lower alveolar process, hard palate, anterior two-thirds of the tongue, floor of the mouth, lips, larynx, pharynx, sinus maxillary and salivary glands (Schwenzer & Ehrenfeld 2011).

OPCs consist major health concerns nowadays since oral cancer is the sixth most common cancer worldwide (Moore et al. 2000, Howlader et al. 2010). Incidences vary widely across geographical areas. The United Kingdom is demonstrating a relatively low incidence of 3500 cases annually. In parts of South East Asia like India a third of all male cancers originate in the oral cavity (Sunny et al. 2004). In the United States, about 30.000 new cases of OPC are diagnosed every year and they cause more than 8.000 deaths. About 26% of new OPC patients do not survive the first year after diagnosis and the 5-year survival rate of 52% has not improved for several years (Edwards at al. 2002). The vast majority of these cancers (85%) are squamous cell carcinomas and the remaining 15% are distributed among salivary gland, lymphoid and sarcomatous tumors (Peleg & Lopez 2006). The incidence of OPCs in Germany is 2% among all malignancies (3.3% males, 1.4% females). The mean age of occurrence of OPCs is 61 years for males and 63 years for females (Schwenzer & Ehrenfeld 2011).

Several extrinsic and intrinsic risk factors contribute to the development of OPC. These include age, ethnicity, gender, habitual use of tobacco and alcohol, viral infections, bad oral hygiene and plaque, bacterial colonization, chronic infections and chronic mechanical irritation (Schwenzer & Ehrenfeld 2011). Fifty different potential carcinogens have been identified in tobacco, implicating smoking a significant risk factor for oral cancer (McDowell 2006). The synergistic effect of tobacco and alcohol results in 13-fold increased risk for developing oral cancer compared to either tobacco or alcohol use alone (Castellsague et al. 2004). Etiological factors like tobacco and alcohol consumption, as well as betel nut chewing, may be the reason for the geographical variations that were mentioned above (IARC 1985). Infection with

human papilloma virus (HPV) has also been identified as a potential risk factor for high incidence of OPCs in non-smokers. However, a relationship with oral cavity cancer is not yet established (Pintos et al. 2008).

The great majority of OPCs are diagnosed in individuals over 65 years (Silverman 2001) and males are 2 to 4 times more likely to develop oral cancer than women (McDowell 2006). With advancing age, there is a tendency for prolonged exposure of oral tissues to potential carcinogens, and aging cells may be more susceptible to DNA damage (McDowell 2006). The unusual rise of oral cancer in younger individuals and women without obvious risk factors has not been yet fully clarified. HPV is considered a probable cause. It is involved in the development of oral squamous cell carcinoma and is also associated with 30–40% of oral epithelial dysplasia and cancerous lesions (Schantz & Yu 2002, Kreimer et al. 2005).

Chapter 2

Staging

Clinical staging of malignant tumors is based on the TNM classification which was introduced in 1931 by the Swiss radiologists Schinz and Zuppinger and since then has been constantly revised in order to be adjusted to the latest clinical findings (Aggelopoulos & Alexandridis 2004, Schwenzer & Ehrenfeld 2011).

T: describes size of the original (primary) tumor and whether it has invaded nearby tissue,

N: describes nearby (regional) lymph nodes that are involved,

M: describes distant metastasis.

Although there are tumors that they don't have a TNM classification such as brain tumors, most of the common tumors have their own TNM classification. For example the TNM classification for the OPCs is as follows:

Based on tumor size are distinguished:

- Tx: Tumor cannot be evaluated
- Tis: Carcinoma in situ
- T0: No signs of tumor
- T1: Small tumor (≤ 2 cm)
- T2: Bigger tumor (>2cm)
- T3: Tumor reaches organ boundary (or >4cm)
- T4: Tumor invades adjacent structures (for example bone, soft tissues of the neck)

The lymph node involvement includes:

- Nx: Lymph nodes cannot be evaluated
- N0: Tumor cells absent from regional lymph nodes
- N1: Regional lymph node metastasis present

- N2: Extensive unilateral or bilateral lymph node metastasis (for example the neck)
- N3: More distant or numerous regional lymph nodes metastasis (>6cm or fixed)

Distant metastasis includes:

- M0: No distant metastasis
- M1: Metastasis to distant organs

Based on TNM classification the Union Internationale Contre le Cancer (UICC) developed and maintained a globally recognized standard (Staging) for classifying the extent of a cancer's spread. Both TNM classification and Staging system are also used by the American Joint Committee on Cancer (AJCC) and the International Federation of Gynecology and Obstetrics (FIGO). Staging system is presented in the following table:

Table 1: Staging system UICC

Stage	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3 T2 T3	N0 N1 N1	M0 M0 M0
Stage IVA	T4 T4 Any T	N0 N1 N2	M0 M0 M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Chapter 3

Treatment of oropharyngeal cancers

Treatment of OPCs needs a multifaceted approach and is divided into:

- Curative therapy which means healing of tumor disease
- Palliative therapy which means no healing of tumor disease but malignancy and the associated consequences like functional disability and pain become more bearable for the patient (Aggelopoulos & Alexandridis 2004, Schwenzer & Ehrenfeld 2011).

Treatment involves surgery, chemotherapy, radiation therapy (RT), immunotherapy, monoclonal antibody therapy or a combination of these. The choice of therapy depends on the location and grade of tumor and stage of the disease, as well as the general state of the patient (performance status) (Aggelopoulos & Alexandridis 2004, Schwenzer & Ehrenfeld 2011, Turner et al. 2013). Early tumors (T1 and T2) are well managed with surgery or radiotherapy (RT). In many cases RT has the advantage of causing less impairment than surgical treatment. Moreover, RT is the alternative for patients with larger tumors who are unfit or do not want to undergo surgery (Turner et al. 1996). A number of experimental cancer treatments are also under development (Aggelopoulos & Alexandridis 2004, Schwenzer & Ehrenfeld 2011, Turner et al. 2013).

Goal of the treatment should be the complete removal of cancer without damage to the rest of the body. Sometimes this can be accomplished by surgery. However, its effectiveness is often limited due to the propensity of the cancers to invade adjacent tissues or to spread to distant sites by microscopic metastasis. On the other hand, chemotherapy and RT can unfortunately have a negative effect on normal cells (Aggelopoulos & Alexandridis 2004, Schwenzer & Ehrenfeld 2011). Despite their complications, two-thirds of patients with OPCs with local or regionally advanced disease are usually treated with both surgery and RT or with multimodality treatment (incorporating RT and chemotherapy) (Sciubba & Goldenberg 2006).

In spite of advances in treatment techniques of OPCs, there is still a high rate of acute and chronic oral complications that significantly affect the survival rate of patients (Sonis et al. 1978).

3.1 Chemotherapy

Chemotherapy consists of palliative chemotherapy, use of alkylating agents, plant alkaloids, antitumor antibiotics and toposiomerase inhibitors. Chemotherapy is used to treat cancers which are too large or have spread too far and can not be treated by surgery alone (Turner et al. 2013). The aim of the chemotherapy is to fight the tumor with local (local chemotherapy) or systemic (systemic chemotherapy) medicine, delay its development and relieve the patients of any symptoms. In cases of OPCs systemic chemotherapy is preferred. Substances which are usually used include 5-Fluoruracil (5-FU), Vincristin, Cisplatin, Carboplatin, Paclitaxel, Docetaxel, Methotrexate, Ifosfamide and Bleomycin (Schwenzer & Ehrenfeld 2011, Turner et al. 2013). These agents are used either alone as a monotherapy or in combination.

Some forms of chemotherapy target all cells that divide rapidly and are not specific to cancer cells. However, some degree of specificity may come from the inability of many cancer cells to repair DNA damage, while normal cells generally can. Hence, chemotherapy has the potential to harm healthy tissue, especially tissues with a high repair rate (e.g. intestinal lining). These cells usually repair themselves after chemotherapy. It also affects the gastrointestinal tract, leads to leukocyte reduction and sickness. Sometimes the complications might be severe and cause termination of the therapy (Aggelopoulos & Alexandridis 2004, Schwenzer & Ehrenfeld 2011).

3.2 Radiotherapy

Radiation therapy, radiotherapy or radiation oncology is the medical use of ionizing radiation as part of cancer treatment to control or kill malignant cells (Lee et al. 2012). RT may be curative in some cases, but it may also be used as part of the adjuvant therapy in order to prevent tumor recurrence after surgery or to remove a primary malignant tumor (for example early stages of breast cancer).

RT has the ability to control cell growth. Ionizing radiation damages DNA of cancerous tissues and leads to cellular death. This damage is caused by one of two

types of energy, photon or charged particle. In order to spare normal tissues such as skin or organs, through which radiation will pass, shaped radiation beams are aimed from several angles of exposure to intersect at the tumor. This provides a much larger absorbed dose there, than in surrounding healthy tissue. Apart from the tumor, radiation fields may also include draining lymph nodes if they are clinically or radiologically involved with the tumor, or if there is suspicion of subclinical malignant spread. Inclusion of normal tissue around the tumor is necessary since uncertainties can be caused by internal movement and movement of external skin marks relative to tumor position (Harrison et al. 2002, Bucci et al. 2005, Lutz et al. 2011).

3.2.1 Dose and fractionation

The amount of radiation used in photon RT is called dose and is measured in gray (Gy). It varies and depends on type and stage of the tumor. For curative cases the dose for a solid epithelial tumor ranges from 60 to 80 Gy, while for lymphomas this dose varies from 20 to 40 Gy. Many factors are considered by radiation oncologists when selecting the dose. These include patient comorbidities, silmutaneous chemotherapy and period of RT (before or after surgery) (Harrison et al. 2002, Lutz et al. 2011).

Delivery parameters of dose are determined during treatment planning. This is performed on computers using specialized treatment planning software. The radiation oncologist will design a plan that delivers a uniform prescription dose to the tumor and minimizes the dose to surrounding healthy tissues (Lutz et al. 2011).

The total dose delivered to patient is fractionated for several reasons. First of all normal cells have time to recover between fractions while tumor cells are less efficient. Then fractionation allows tumor cells, which were in a relatively radio-resistant phase of the cell cycle during one treatment, to cycle into a sensitive phase of the cycle before the next fraction is given, improving tumor cell kill. Fractionation programmes differ between therapy centers and oncologists. In Europe the typical fractionation schedule is 1.8-2 Gy per day, five days a week. In some cases two fractions per day are used at the end of the treatment. This schedule is known as concomitant boost regimen or hyperfractionation and is used on tumors which regenerate more quickly when they are smaller such as head and neck tumors (Mendenhall et al. 2003, Lutz et al. 2011, Lee et al. 2012).

A fractionation schedule increasingly used today is the hypofractionation. In this schedule the total dose is divided into large doses. The idea behind this is to minimize the possibility of cancer recover by not giving the cells enough time to reproduce and also exploit the unique biological radiation sensitivity of some tumors (Ferguson & Stevens 2007, Lee et al. 2012). Another well known fractionation schedule is Continuous Hyperfractionated Accelerated RT (CHART) which consists of three smaller fractions per day. In this approach a shorter duration of the therapy without reduction of total dose is achieved. A six-hour interval between fractions is important in order to allow time for normal tissues to repair (Ferguson & Stevens 2007). An alternative fractionation schedule, used to treat breast cancer is the Accelerated Partial Breast Irradiation (APBI). It involves two high-dose fractions per day for five days, compared to whole breast irradiation, in which a single, smaller fraction is given five times a week over a six-to-seven-week period (Ferguson & Stevens 2007, Lee et al. 2012).

3.2.2 Types of radiation therapy

RT is divided into three groups:

- External beam RT (EBRT or XRT) or teletherapy
- Brachytherapy or sealed source RT
- Systemic radioisotope therapy or unsealed source RT

The main difference between these types is the position of radiation source; external is outside the body, brachytherapy uses sealed radioactive sources placed in the area under treatment and systemic radioisotopes are given by infusion or oral ingestion (Ferguson & Stevens 2007, Turner et al. 2013).

EBRT includes three types:

1. Conventional EBRT which is delivered via two-dimensional beams using linear accelerator machines
2. Stereotactic radiation which uses focused radiation beams targeting a well-defined tumor using extremely detailed imaging scans

3. Virtual simulation, 3- dimensional conformal RT (3D-CRT) and intensity-modulated RT (IMRT)

Particle therapy is a special sort of EBRT. According to this treatment energetic ionizing particles (protons or heavier ions) are directed at the target tumor. The advantage of this special therapy is that less energy is deposited into healthy tissue which surrounds the target area (Turner et al. 2013).

Technical advances in RT and its delivery aim to address the tumor mass aggressively, while normal surrounding tissue is injured as little as possible (Hall & Wuu 2003, Galvin et al. 2004, Bucci et al. 2005). They include gamma knife, CyberKnife, linear accelerator X knife, IMRT, 3D-CRT and particle therapy. New radioisotopes such as cesium-137 and iridium-192 have replaced the initial radium sources improving systemic therapy (Ferguson & Stevens 2007). Positron emission tomography scans (PET-scan) lead to exact localization of the tumor, relative to proximal normal tissues. With use of 3D-CRT and IMRT, target volumes and critical normal tissues can be identified with accuracy. The 3D reconstruction of the patients' anatomy enable the oncologist to get better diagnostic information about extension of tumor and its relation to normal tissues and develop a three dimensional treatment planning. With use of sophisticated computer software and hardware an accurate positioning of the patient is permitted (Hall & Wuu 2003, Galvin et al. 2004, Bucci et al. 2005, Ferguson & Stevens 2007). Another innovation in RT is the spacers. They decrease the exposure of normal tissues (for example lingual mandible) and minimize the incidence of complications after RT (Masahiko et al. 1988). These new innovations in addition to changes in fractionation patterns (hyperfractionation, accelerated fractionation) enable patients to profit from RT with minimal physical damage.

Chapter 4

Complications after chemotherapy and radiotherapy

Ionizing radiation used for head and neck tumors affects oral mucosa, salivary glands, bone, dentition, masticatory musculature and also changes the quality and quantity of saliva, vascularity and oxygenation of bone and tissues and mucosal quality (Andrews & Griffiths 2001, Sciubba & Goldenberg 2006). As a result a number of complications can emerge after RT and chemotherapy (Koga et al. 2008a, Khojastepour et al. 2013, Turner et al. 2013). These complications can be divided into two groups (Table 2).

Table 2: Acute and chronic complications of RT (Andrews & Griffiths 2001, Sciubba & Goldenberg 2006, Koga et al. 2008a, Chrcanovic et al. 2010a, Khojastepour et al. 2013, Turner et al. 2013)

Acute complications	Chronic complications
Oral mucositis	Mucosal fibrosis and atrophy
Infection: fungal, bacterial	Salivary gland dysfunction: xerostomia, dental caries
Salivary gland dysfunction: sialadenitis, xerostomia	Soft- tissue necrosis
Taste dysfunction	Osteoradionecrosis (ORN)
	Taste dysfunction: dysgeusia, ageusia
	Muscular fibrosis, cutaneous fibrosis or trismus
	Infections: fungal, bacterial

Other complications mentioned in the literature include microvascular alteration, local discomfort, oedema and periodontal attachment loss (Andrews & Griffiths 2001, Koga et al. 2008a, Chrcanovic et al. 2010a, Khojastepour et al. 2013). Reduction of mandibular cortex's width and inferior alveolar canal's dimensions are considered among postirradiation effects, which may be predictive of the risk of ORN

(Khojastepour et al. 2013). In severe cases, even death can occur (Marx & Johnson 1987). Acute complications persist during treatment but resolve within the first weeks after completion of the treatment (Fischer & Epstein 2008). On the other hand, chronic complications prolong after treatment and result in lifelong morbidity. Oral complications after chemotherapy are of short duration (weeks to months), whereas complications after RT are more severe and serious (Turner et al. 2013).

Several factors contribute to complications after RT. These include trauma to oral tissues during normal oral function and high cellular turnover rates of oral mucosa. As a result 90-100% of patients whose irradiation fields include the oral cavity will develop some degree of oral complications (Herrstedt 2000). The severity of complications is related also to several factors such as the dose and frequency of radiation as well as the volume of irradiated tissue and simultaneous use of RT and chemotherapy (Sciubba & Goldenberg 2006). Complications increase as the dose increases; the use of fractionation and the exposure of the patient to lower doses, reduce the side effects. Other factors that increase the severity of complications include preirradiation bone surgery, bad oral hygiene, alcohol and tobacco abuse and dental extractions after RT (Khojastepour et al. 2013).

4.1 Oral mucositis

Oral mucositis is an acute complication after RT, chemotherapy or a combination of both treatments. Oral mucositis is a result of direct contact between radiation and oral epithelium. Chemotherapy-induced mucositis depends on several factors such as patient's age, degree of stomatotoxicity of the chemotherapeutic agent and preexisting oral conditions (Sonis 1998, Nishimura et al. 2012). Cinical characteristics include erythema, mucosal ulceration, oropharyngeal pain, and speech difficulties (Turner et al. 2013). About 80% of patients who take radiation will develop mucositis, with onset usually one week after start of the therapy (Kielbassa et al. 2006). It persists for two to three weeks after completion of RT (Million & Cassisi 1984, Dreizen 1990). Four weeks after end of the treatment, 90-95 % of the patients show complete healing of mucositis and sore throat is absent or minimal. Scarring may also develop (Million & Cassisi 1984, Epstein & Klasser 2006, Mosel et al. 2011, Nishimura et al. 2012).

Free radicals released by therapeutic agents cause a direct injury to the oral epithelium and can lead to this complication (Sonis 1998, Fischer & Epstein 2008). Mucous cells of the oral cavity, pharynx and larynx have a high turnover rate and low radiation resistance and respond early to radiation. Doses which are fractionated (for example 2 Gy/day) lead to the development of mucosal erythema within one week (Million & Cassisi 1984). This erythema is caused due to a thinning of the epithelium and vascular dilation, inflammation and oedema of submucosa (Brown et al. 1975). As RT continues mucosa becomes denuded, with ulcerations and is covered with fibrinous exudates. The result is pain, burning and discomfort especially during eating. Depending on the extent of treatment fields, involvement of pharyngeal mucosa may produce difficulties in swallowing and speech (Dreizen 1990).

Several attempts have been made to manage oral mucositis. Cryotherapy by sucking on ice chips before therapy has been used to reduce blood flow and stomatotoxic effects of chemotherapy (Cascinu et al. 1994). Use of granulocyte-macrophage colony stimulating factor, granulocyte colony stimulating factor and keratinocyte growth factor to improve local immune response and accelerate wound healing have also produced some beneficial effects (Hejna et al. 2001, Ryu et al. 2007). Poor oral hygiene, irritation from ill-fitting prosthesis and defective restorations can exacerbate oral ulcerations. Consequently, pre-therapy dental consultation to eliminate these potential risk factors will reduce oral morbidity (Sonis 1998). Use of chlorhexidine gluconate as an antimicrobial rinse may be beneficial by reducing oral microbial load and secondary infection. Topical application of lidocaine, benzocaine, or rinsing the mouth with a solution consisting of diphenhydramine, milk of magnesia, and a local anesthetic have beneficial palliative effects in oral mucositis patients. In severe cases, it may be necessary to administer systemic anti-inflammatory agents and opioid analgesics (Mosel et al. 2011). Many locally applied drugs have also been investigated to prevent or treat mucositis, which include sucralfate, vitamin E, chlorhexidine, anti-inflammatory substances, cytokines, alprostadil and dinoprostone, multidrug topical mouth rinses, folinic acid, and allopurinol (Herrstedt 2000).

4.2 Infections

The risk for oral infections is increased during and after therapy of OPCs because oral microbial flora is altered by myelosuppression and oral cleansing property of saliva is diminished by reduced salivary flow.

Fungal: Candida is a normal oral commensal in 34–68% of healthy individuals. Nevertheless, candidiasis is one of the most frequent oral infections during OPC therapy (Pyykönen et al. 1986, Ship et al. 2007, Fischer & Epstein 2008). Clinically, oral candidiasis presents as a removable white pseudomembrane or erythematous patch on the tongue, palate and labial commissures (Turner et al. 2013). It causes taste alterations, mucosal soreness and oral burning sensations. Heavy accumulations of candida may dislodge causing esophagitis, fungemia and pose aspiration risk to the patient. In rare circumstances, more invasive fungal organisms like mucormycosis and aspergillosis may affect myelosuppressed individuals and spread to the underlying bone.

Two different forms of candidiasis can be distinguished: the acute form and the chronic form. The acute form is expressed as an erythema and burning sensation of the oral mucosa and may be mistaken for radiation mucositis. However, if erythema occurs bilaterally and symmetrically, in areas not within the radiation fields, candidiasis should be considered (Epstein et al. 1993). Fungal colonies may also be seen. In chronic forms of candidiasis, infection most commonly occurs in mouth corners or beneath prostheses (Dreizen 1990).

Topical antifungal therapy is very effective (Epstein et al. 2002). Persistent or systemic spread of fungal infections can be controlled with systemic antifungal treatment. Systemic fungal infections are responsible for one third of deaths in immunocompromised patients (Epstein et al. 2002). As a result it is often necessary to administer prophylactic antifungals to reduce morbidity and mortality during OPC therapy.

Viral: The most common cause of a viral infection in patients, who are treated for OPCs with chemotherapy and RT, is reactivation of latent herpes simplex virus type-1 (HSV) (Schubert 1991, Mosel et al. 2011). Appearance in the oral cavity is atypical; it may become life threatening. In contrast to oral mucositis which occurs early, HSV

lesions generally appear about 18 days after initiation of therapy. Viral cultures are the most useful diagnostic tools for HSV infections. Seropositive OPC patients usually receive prophylactic treatment with acyclovir, an inhibitor of viral thymidine kinase (Epstein & Stevenson-Moore 2001, Lerman et al. 2008). Valacyclovir and famciclovir are alternative drugs with better bioavailability than acyclovir. In cases of acyclovir-resistant HSV infections, other therapeutic options like foscarnet or cidofovir are recommended (Lerman et al. 2008).

Bacterial: Bacterial infections often arise from mucosal, gingival or odontogenic sources. Poor oral hygiene and hyposalivation increase oral microbial load thereby disrupting the balance of oral flora. Gram-positive organisms predominantly colonize oral cavity; but during OPC therapy, the inability to mount appropriate inflammatory response allows other pathogenic organisms to flourish leading to various opportunistic infections (Lee et al. 2011, Mosel et al. 2011). Conventional signs and symptoms of bacterial infections such as swelling, suppuration, and erythema may be muted or absent due to immune suppression.

4.3 Hyposalivation and xerostomia

Decreased salivary flow or hyposalivation is a common complication of OPC therapy. It is caused due to damage to salivary glands and presents as progressive xerostomia (dry mouth) (Mossman et al. 1982, Mossman 1983, Turner et al. 2013). Salivary flow can be decreased by about 50–60% in patients who undergo chemotherapy and by those who receive up to 20 Gy RT (Sweeney et al. 1997, Vissink et al. 2003b). The glandular architecture is replaced by ductal remnants and loose fibrous connective tissue which is moderately infiltrated with lymphocytes and plasma cells. This progressive glandular atrophy, fibrosis and reduced salivary output begin shortly after initial exposure and intensify thereafter (Kaplan 1985).

Hyposalivation is usually reversible depending on the dose of radiation received. Only 2.25 Gy has been shown to cause a 50 per cent reduction in the resting flow rate within 24 hours (Edgar & Mullane 1996). If all salivary glands are included in the treatment field, the result is viscous saliva (Million & Cassisi 1984) and salivation may be reduced by as much as 93% (Beumer et al. 1979a). When total dose is greater than 50 Gy and the salivary gland is in the field of radiation, hyposalivation is

irreversible (Eneroth et al. 1972, Vissink et al. 1988). By comparison, the cumulative dose used to treat head and neck solid tumours often exceeds 60 Gy, which can provoke the loss of at least 80 per cent of salivary gland function (Mossman 1983). Patients have difficulties to speak, smell, taste, chew or swallow and are more susceptible to oral infections, dental caries and periodontal diseases (Fischer & Epstein 2008). Composition and physiological functions of saliva are also affected, thereby reducing saliva buffering capacity, antimicrobial activity and ability to re-mineralize damaged tooth enamel (Sonis et al. 1978). The oral mucosa is friable and susceptible to trauma, inflammation, and irritation (Fischer & Epstein 2008). The oral microbial population shifts to acidogenic microflora and increased concentrations of streptococcus mutans, lactobacillus and candida. As a result, patients become more susceptible to dental caries and opportunistic infections (Garcia et al. 2009).

With advances in RT, an attempt is made to minimize these complications. If both parotid glands are spared during RT, then most of the patients report a little or no difference in quality and quantity of saliva and minimal long-term reduction in saliva is seen (Johnson & Moore 1983, Million & Cassisi 1984). If the upper limit of radiation field lies below the submental region, there is minimal long term reduction in salivary flow (Mossman et al. 1982). IMRT has been effective in reducing salivary gland damage and xerostomia (Jabbari et al. 2005). Fractionated radiation allows delivery of radiation to the tumor region at doses that allow normal tissue to repair sub-lethal DNA damage before the next dose is administered (Vissink et al. 2003b). Introduction of Amifostine, a radioprotective drug administered prior to RT has been very effective in minimizing hyposalivation during OPC therapy (Wasserman et al. 2005, Sasse et al. 2006, Bardet et al. 2011).

The management of hyposalivation includes the stimulation of the salivary gland during treatment in order to preserve salivary function by reducing glandular damage. Sucrose-free lemon drops or sugarless gum are nonpharmacologic agents used to stimulate salivary flow during and after RT. Use of cholinergic agonists like pilocarpine and cevimeline is also beneficial in stimulating salivary flow from residual glandular tissue (Gornitsky et al. 2004, Chambers et al. 2007). In cases of minimal residual salivary function, saliva substitutes can also be prescribed. Recently,

acupuncture has been shown to promote recovery from xerostomia in head and neck cancer patients treated with radiation (Garcia et al. 2009).

4.4 Oedema, fibrosis, trismus and pain

During the post-radiation period, scarring, fibrosis and oedema begin to appear. Although lymphatic channels are thought to be relatively radioresistant, radiation-induced fibrosis impairs the patency of lymphatic and venous channels, resulting in lymphatic and venous obstruction. Oedema is prominent in the submental region, after the irradiation for anterior tongue and floor of mouth carcinoma and compromises tongue mobility and salivary control, incommoding denture wearing and speech articulation. Patients complain also for tongue and cheek biting. Furthermore, presence of fibrosis and oedema makes the detection of early recurrent lesions more difficult. Severity of oedema varies from day to day and from the time of the day (worse on waking and early morning) (Andrews & Griffiths 2001).

5–38% of patients develop trismus after treatment for head-and-neck cancer (Sciubba & Goldenberg 2006). Patients who have been previously irradiated, those who receive both surgery and RT, and those who are being treated for a recurrence, are at higher risk of trismus than those receiving their first treatment. Trismus will cause damage and fibrosis of mastication muscles and also degenerative problems in the temporomandibular joint. These degenerative problems could mimic arthritic changes, and could be accompanied by inflammation and pain. If the symptoms are left untreated, degenerative processes will continue and become permanent (Sciubba & Goldenberg 2006).

Clinically, trismus manifests as a slowly evolving inability to open the mouth to enable normal function. The mouth opening will be restricted, painless, and could be noted most readily during the first year after treatment. Speech articulation will not be adversely affected in most instances, but eating is often made difficult because of the restricted range of motion in all jaw movements. Restriction of mouth opening can result in compromised oral hygiene, which is particularly important in patients who also have radiation-induced xerostomia (Buchbinder et al. 1993, Sciubba & Goldenberg 2006).

Use of high-energy radiography beams and sophisticated multiple-field techniques can reduce the dose of radiaton to the temporomandibular joint and mastication muscles. The physicians should be able to identify the early signs of trismus. A simple test is the so-called three finger test. In this test, the patient is asked to insert three fingers into the mouth. Management of trismus includes also passive and active physiotherapy with simple and special devices. These include aggregated tongue blades or forced opening with finger pressure several times per day, as well as the use of more elaborate dynamic opening systems (such as TheraBite®) which are thought to be more efficient (Sciubba & Goldenberg 2006). Spastic reactions that cause abnormal jaw muscle closure can be controlled with botulinum toxin injections (Clark 2003, Stubblefield et al. 2010).

Neuropathic pain (25% of OPC patients) and neurosensory abnormalities can cause complications during the OPCs therapy. The reason for neuropathic pain is tumor invasion in peripheral or central nervous system or as a consequence of the treatment (Marchettini et al. 2001). Surgical resection of the tumor can also stretch or transect adjacent nerves causing neuropathic pain (Clark & Ram 2008). Management of the pain is achieved with use of pharmacologic agents such as anticonvulsants, antidepressants, local anesthetics, and N-methyl-D-aspartate receptor blockers (Baron et al. 2010).

4.5 Taste dysfunction

Alteration of taste sensation occurs as a result of the direct effect of radiation on taste buds and due to changes in the saliva (Mossman 1986, Nelson 1998, Spielman 1998). Dryness and damage to the taste buds caused by radiation lead to dysgeusia or ageusia and cause anorexia and malaise since interest in food is lost (Silverman 1990). In severe cases, reduction in the oral intake of fluids and nutrients can lead to dehydration and malnutrition (Mosel et al. 2011). This development may necessitate hospitalization to provide intravenous fluids or parenteral hyperalimentation (Andrews & Griffiths 2001).

In most instances, taste acuity is partially restored 20-60 days after RT and gradually returns to normal or near-normal levels within one year after RT (Conger 1973, Tomita & Osaki 1990). There is usually no need for treatment. Prevention of taste loss

can best be accomplished through direct shielding of healthy tissue or placement of these tissues outside the radiation field by means of shielding or repositioning prostheses. As taste loss can result in weight loss, it is important to have a dietary counseling (Lees 1999, Erkurt et al. 2000). Level of hyposalivation is also important, since insufficient moistening and lubrication of oral tissues and food have a major negative impact on food intake and the ability of a patient to eat (Epstein et al. 1999a). Some patients may be left with residual hypogeusia after RT. Zinc supplements are reported to be helpful in increasing taste acuity in such patients. The acceleration of taste improvement in the post-RT period is probably of more benefit than the preservation of taste during RT (Vissink et al. 2003a).

4.6 Radiation caries

Radiation caries is a highly destructive form of dental caries with rapid onset and progression (Vissink et al. 2003b, Kielbassa et al. 2006). Lesions start on the labial surface at the cervical areas of teeth, including mandibular anterior teeth, which are usually very resistant to caries in nonirradiated populations. Dental caries can begin to develop as early as 3–6 months after treatment and progresses to complete destruction of all teeth over a period of 3–5 years (Jham et al. 2008). The developing tooth buds can also be destroyed if irradiated prior to mineralization. RT can also increase the severity of dental developmental disturbances induced by chemotherapy (Cubukcu et al. 2012, Turner et al. 2013).

Radiation caries are categorized based on clinical and radiographic features. Type 1 radiation caries is widespread superficial caries, type 2 is caries of the cementum and dentin at the cervical region and type 3 is dark pigmentation of the entire crown; combinations of these features may occur (Aguiar et al. 2009).

Although a lot of investigators attribute radiation caries to the direct effects of radiation on teeth, others point to xerostomia, changes in salivary pH or alterations in microbial, chemical, immunological and dietary parameters (Vissink et al. 2003b, Kielbassa et al. 2006, Turner et al. 2013). The high incidence of radiation caries and its progression to the tooth cervix, which is seldom affected, is assigned to drastic reduction in salivation (Dreizen et al. 1977a, Pyykönen et al. 1986). As mechanical rinsing of teeth and buffering capacity of saliva are reduced (Brown et al. 1975),

saliva no longer protects teeth, and caries can attack any tooth surface. Adverse changes in the oral flora as a result of radiation constitute another important factor promoting caries. The number of S. mutans and Lactobacillus increase at expense of the less cariogenic S. sanguis, Neisseria and Fusobacterium (Brown et al. 1975). Although the immunological response of saliva against these micro-organisms improves, this effect is cancelled out by the low saliva secretion (Brown et al. 1975, Pyykönen et al. 1986). Nevertheless, the most likely cause of radiation caries appears to be a combination of those factors as well as the patient's preirradiation susceptibility to caries, degree of postirradiation gingival recession, level of patient's oral hygiene maintained, and intrairradiation dietary changes (Hayward et al. 1969).

Until nowadays there are few reports of basic research on the topic of prevention and therapy of radiation caries. It is important to eliminate potential sources of dental infection prior to OPCs therapy (Lee et al. 2011, Mosel et al. 2011). A preventive caries program consisting of daily oral hygiene and daily topical 1.0% NaF gel application by means of custom-designed fluoride carriers, developed by Daly and Drane (1976) at the M.D. Anderson Cancer Center at Houston, TX (USA), has been studied extensively and forms the basis for the majority of other studies (Kielbassa et al. 2006). This programme dramatically reduced caries incidence and was also successful in arresting existing lesions, regardless of cariogenecity of the patients' diet (Dreizen et al. 1977a, Dreizen et al. 1977b). On the basis of a more than- 10-year experience with 935 head and neck cancer patients, Horiot et al. (1983) proved that this protocol was a highly reliable method for prevention of radiation caries. He also proved that the use of a toothpaste with a high fluoride content (3.0% NaF) twice a day was a good alternative, provided its pre-requisites (higher level of compliance) were well-understood by both clinician and patient. Because hyposalivation is irreversible in the majority of head and neck irradiation patients, application of fluoride must be continued indefinitely, regardless of chemical formulation and application method; otherwise caries will develop within months. Finally, since radiation caries is a lifelong threat to patients who have received radiation treatment for head and neck cancer, there is a lifelong need for meticulous oral hygiene and frequent fluoride applications to these patients (Vissink et al. 2003a).

Chapter 5

Prevention of complications before, during and after radiation therapy

5.1 Before radiotherapy

Oral problems which are associated with RT can be prevented or minimized through optimal management. A consultation with a dental team which has experience in care of patients with OPCs should be completed before onset of therapy (Simon & Roberts 1991, Carl 1993). Poor oral hygiene, broken teeth, defective restorations and periodontal disease, are likely to cause complications during and after a course of RT. A thorough radiographic examination is also essential in order to determine the presence of inflammatory periapical abnormalities, periodontal status, other dental disease and tumour invasion of bone. A panoramic radiograph thus periapical or bitewing films (or both) are compulsory for pre-RT dental assessments. Communication with the patient's physician regarding timing, nature and features of RT is also essential (Hancock et al. 2003).

Teeth with periodontitis and bone loss may become exacerbated during OPC therapy resulting in local and systemic complications (Epstein & Stevenson-Moore 2001). Direct radiation injury to periodontal structures will compromise vascular supply, cause destruction of more periodontal tissues and promote bacterial invasion (Fujita et al. 1986, Chambers et al. 2007). Chemotherapy causes neutropenia, neutrophil dysfunction and impaired inflammatory response, which further delay tissue healing and a consequent loss of more periodontal tissues (Galler et al. 1992, Epstein et al. 1998). It is important to assess the periodontal status of teeth and tissues within the field of radiation prior to therapy (Epstein & Stevenson-Moore 2001, Chrcanovic et al. 2010b). All teeth, but especially those which are located within the radiation fields, should be closely evaluated. A study in the UK showed that only 11.2% of patients who reported regular visits in a general dentist before diagnosis of oral cancer

were considered to have no dental conditions that required treatment before RT (Lizi 1992).

Factors considered when estimating pre-RT dental status, include general condition of patient's dentition (caries, periapical status, inflammatory periapical abnormalities), previous dental care, current oral hygiene, urgency of cancer treatment, planned therapy (radiation fields and dose) and prognosis of cancer therapy (cure or palliation). The dental management strategy should be more aggressive for patients with limited previous dental care, poor oral hygiene and evidence of past dental or periodontal disease (Hancock et al. 2003).

5.2 During radiotherapy

An increased monitoring of the oral cavity should be done during RT so as to decrease the severity of side effects. The patient's self-care procedures should include frequent brushing with a soft-bristled toothbrush and fluoride toothpaste or gel to help prevent plaque accumulation and demineralization or caries of teeth (Carl 1993). The patient should be motivated to follow stringent plaque control. Dental health guidelines include: tooth brushing and dentifrice, mouth rinsing and flossing, fluoride supplementation with a fluoride gel, topical antimicrobial rinses such as Chlorhexidine 0,12 %, care of dentures during and after RT and care of lips and mouth. Use of dentures should be discontinued during and for a few weeks after RT in order to allow the radiation mucositis to heal (Turner et al. 2013).

5.3 After radiotherapy

After the end of RT, acute oral complications usually begin to resolve. Patients should continue to follow an oral health self-care programm in order to keep teeth and gums healthy and make the repair of any residual oral damage easier. Oral exercises should be continued or introduced to reduce the risk or severity of trismus. Furthermore, dietary counselling sessions may be appropriate for patients who must make long-term dietary adaptations to accommodate permanent changes to their oral cavity produced by surgery and radiation. Competition of patients to support groups can also be a useful adjunct to patients' return to optimal functioning. Long-term management and close follow-up of patients after RT is obligatory. Finally, a frequent and careful

examination to detect signs of recurrence or new primary malignant lesions is compulsory (Hancock et al. 2003).

Chapter 6

Osteoradionecrosis

ORN is a devastating complication of RT in head and neck cancer. It was first described by Regaud (1922) and remains a clinical challenge until nowadays. Through the years several attemps have been made in order to best define ORN. Ewing (1926) was the first to use the term "radiation osteitis" to describe changes in bone after RT. In the following years several terms have been used to name these changes in bone such as radiation osteitis, ORN and avascular bone necrosis (Jereczek–Fossa & Orecchia 2002). In 1974 Guttenberg proposed the term "septic ORN of the mandible" to describe the stage of necrosis when irradiated bone becomes superficially infected ending up in high risk of involvement of deeper structures (Guttenberg 1974).

In 1983 Marx defines ORN as "an area greater than 1 cm of exposed bone in a field of irradiation that had failed to show any evidence of healing for at least 6 months" (Marx 1983b). He also mentioned that there is only superficial contamination and no interstitial infection. In 1987 Marx and Johnson proposed the following definition for ORN: "exposure of nonviable bone, which fails to heal without intervention" (Marx & Johnson 1987). Epstein et al. (1987b) defined ORN as "an ulceration or necrosis of the mucous membrane, with exposure of necrotic bone for more than 3 months". Widmark et al. (1989) describe ORN as "a nonhealing mucosal or cutaneous ulcer with denuded bone, lasting for more than 3 months". Together with Marx, they exclude conditions with necrotic bone but with an intact mucosa and skin. On the other hand, Store and Bosysen (2000) mention that not all cases of ORN involve exposed bone, but radiological evidence can be found in all cases. In 1997, Wong et al. define ORN as "a slow-healing radiation-induced ischemic necrosis of variable extent occurring in the absence of local primary tumor necrosis, recurrence or metastatic disease" (Wong et al. 1997).

According to the most recent literature ORN of the jaws is defined as exposed irradiated bone that fails to heal over a period of 3 months without evidence of persisting or recurrent tumor (Marx 1983a, Marx & Johnson 1987, London et al.

1998, Teng & Futran 2005, Pitak- Arnnop et al. 2008, Khojastepour et al. 2013). At the time of diagnosis it might involve the bone superficially or deeply; it might be a process that progresses slowly or it might be in an active progressive state which can lead to a pathologic fracture (Thorn et al. 2000). The clinical consequences include pain, numbness, trismus, dysphagia, orocutaneous fistulae, pathological fractures, and local or systemic infections (Monnier et al. 2011).

Taking into account all the above definitions the majority of authors agree to the following points (Wong et al. 1997, Chrcanovic et al. 2010a):

1. Affected bone should have been irradiated.
2. There should be absence of recurrent tumor.
3. Mucosal breakdown or failure of healing should occur, resulting in bone exposure.
4. Overlying bone should be “dead”.
5. Presences of pathologic fracture, fistulation or cellulitis are not necessary in order to diagnose ORN.

The duration of bone exposure has also been an issue of great controversy. Some authors do not comment on time of exposure (Epstein et al. 1992). Other authors recommend a 2-month period of exposed bone before diagnosis (Beumer et al. 1979b, Hutchinson et al. 1990, Tobias & Thomas 1996), or even 3 (Morrish et al. 1981, Beumer et al. 1983a, Harris 1992) and 6 months (Marx 1983a, Marx 1983b). There are also cases where a late diagnosis is present. Berger and Symington (1990) reported two late presentations: one 45 years after a radium implant and the other 38 years after external beam treatment.

Generally, a too short waiting period can lead to over-diagnosis as mucosal radionecrosis can occur without ORN. Moreover, any surgery and/or extraction performed, usually can take up to 1 month to heal. On the other hand, long periods such as 6 months are difficult to establish at clinical practice, and some intervention before this time is certainly needed. For these reasons it is proposed that the bone exposure should be of at least 3 months (Chrcanovic et al. 2010a).

6.1 Epidemiology

According to literature the average age of patients with ORN is over 55 years (Grötz et al. 2001a, Reuther et al. 2003, Pitak-Arnnop et al. 2008, Almazrooa & Woo 2009). Mandibular ORN is predominant when compared to maxilla (ratio between mandible and maxilla is 24:1) (Perrier & Moeller 1994).

Incidence of ORN varies in the literature. This variability is probably due to differences in study populations, observation periods, and existence of pretreatment dental assessment and dental management of cohorts. In the literature, incidence of ORN in head and neck–irradiated population was estimated to be 4.74-37.5% (Watson & Scarborough 1938, MacComb 1962, Grant & Fletcher 1966, Daly et al. 1972, Bedwinek et al. 1976, Murray et al. 1980b, Morrish et al. 1981, Epstein et al. 1987a, Withers et al. 1995, Reuther et al. 2003). Incidence decreased since 1990s (Berger & Bensadoun 2010). Recent studies show a decrease in incidence to <5%. This is attributed to the advent of megavoltage RT, improved dental preventive care, and improved radiation techniques including 3D-CRT and IMRT (Jereczek-Fossa & Orecchia 2002, Reuther et al. 2003, Studer et al. 2004). Clayman (1997) found an overall incidence of 11.8% before 1968 and 5.4% thereafter when megavoltage therapy became available. Wahl (2006) described a reduction in the incidence of ORN from 11.8% before 1968 to 5.4% from 1968-1992, and after 1997 to approximately 3%. Recently, Lee et al. (2009) found that the frequency of ORN among 198 patients with either oral cavity or OPCs treated with radiation between the years 1990 and 2000 was 6.6%.

Although most authors report an incidence rate between 5-15% (Khojastepour et al. 2013), rates as low as 0.4% and as high as 56% are also found in the literature (Jereczek-Fossa & Orecchia 2002, Reuther et al. 2003, Mendenhall 2004). In up to 20% of patients where ORN persists and does not respond to aggressive treatment, bone damage is caused in fact by recurrent disease or a second primary tumour (Hao et al. 1999, Thorn et al. 2000).

6.2 Classification of osteoradionecrosis

Several staging or scoring systems of ORN have been proposed. These systems are based on response to hyperbaric oxygen (HBO) therapy, degree of bone damage, clinical–radiological findings, length of bone exposure through the overlying skin or mucosa, and treatment needed.

Coffin (1983) divided ORN cases in two groups: minor and major. Minor form was considered to be a series of small sequestra which separate spontaneously after varying periods of weeks or months. These small areas can be seen clinically but cannot be demonstrated radiologically. Major form was defined as necrosis occuring to an extent that involves entire thickness of the jaw, and a pathological fracture is inevitable. This form can be obviously seen radiologically and is extremely rare in the maxilla.

Morton and Simpson (1986) subdivided ORN into three groups 'minor', 'moderate' and 'major'. Minor ORN consisted of ulceration with exposed bone and a history of bony spicules which healed spontaneously over a period of months. Moderate cases consisted of exposed bone and small sequestra limited in nature and healing spontaneously with conservative treatment within 6 to 12 months. Major ORN consisted of large areas of exposed bone, with formation of large sequestra, possible fracture and sinus formation. These cases often progressed rapidly, lasting in excess of 1 year and often requiring radical treatment.

In 1983 Marx proposed a new staging system for ORN which is used until nowadays. Advantages of this protocol include selection of patients who are able to respond to less aggressive treatments, use of minimum HBO exposure, resolve of the disease process, and preparation of patients' tissues for reconstruction without further HBO (Peleg & Lopez 2006).

According to this protocol if patient exhibits exposed bone in a field of radiation that has failed to heal for at least 6 months, and does not have a pathologic fracture, cutaneous fistula, or bony osteolysis to the inferior border, he or she enters stage I. In stage I, all patients receive 30 sessions of HBO at 2.4 ATA for 90 minutes at depth. After these 30 sessions, patients that respond to HBO alone (stage I responder) do so by demonstrating a softening of the radiated tissues and spontaneous sequestration of

exposed bone with formation of granulation tissue. Each so-called stage I responder undergoes an additional 10 HBO sessions and is then allowed to heal completely. Those patients who have not progressed after 30 sessions of HBO are advanced to stage II. This group represents patients with an amount of nonviable bone in excess of that capable of resorption and sequestration from HBO-induced angiogenesis alone. The nonviable bone requires surgical debridement in a manner so as not to compromise blood supply of adjacent viable, but radiation-damaged, bone. Stage II patient therefore undergoes transoral resection with limited soft tissue reflection. Surgical treatment includes extraction of involved dentition and a noncontinuity bone resection to clinically bleeding bone. Wound flaps are closed primarily and patient is given 10 postsurgical sessions of HBO. Tissues that heal without complication are challenged with prosthesis, as tissues in stage I responders. Tissues that dehisce and show additional exposed bone are advanced to stage III. Stage III patients represent those with a great quantity of nonviable bone and/or soft tissue unable to be managed by HBO-induced angiogenesis alone or HBO combined with local sequestrectomy. In addition to 30 presurgical HBO treatments, each stage III patient requires a continuity resection, stabilization, 10 postsurgical sessions of HBO, and plans for later (usually 3 months) reconstruction (stage III-R). Stage III patients are therefore those who fail to respond in stage I and stage II and those who present initially with a pathologic fracture, cutaneous fistula, or osteolysis to the inferior border (Marx 1983a, Peleg & Lopez 2006).

In 1987 Epstein et al. support a new staging system for ORN (Epstein et al. 1987a). In this system three different stages are distinguished based on clinical findings and not on response to HBO. Stage I represents healed, resolved ORN. Pathologic fracture may have occurred (Stage Ib), but the patient will have been reconstructed to provide continuity of the jaw. Stage II includes patients with chronic (>three months), persistent ORN. Lesion is not tender, remains stable in size, and neurologic symptoms of paresthesia and anesthesia, if present, are not progressive. The patient is either pain free or discomfort is well controlled. Patients may have a pathologic fracture (Stage IIb) and compromised jaw function; however symptoms are stable. In stage III, patient with progressive, active ORN manifest signs and symptoms of continuing disease. Resolution of the necrotic lesion and reversion to Stage I disease is goal of the treatment.

The scoring system proposed by Glanzmann and Gratz (1995) is focused on length of bone exposure and necessity of treatment. Clayman (1997) used a classification of ORN related to the overlying mucosa being intact or not. Clayman uses the term type I for cases in which bone lysis occurs under intact gingiva or mucosa and type II for a more aggressive type, called radiation osteomyelitis. In the latter type soft tissues break down, exposing the bone to saliva, and causing secondary contamination. It is suggested that type I cases heal with conservative therapy, while type II do not heal.

In 2000 Store and Boysen introduced a new classification for ORN. It is based on presence or absence of clinical and radiological signs. In this system 4 different stages are distinguished: 0=mucosal defects only, I=radiological evidence of necrotic bone with intact mucosa, II=positive radiographic findings with denuded bone intraorally, III=clinically exposed radionecrotic bone, verified by imaging techniques, along with skin fistulae and infection (Store and Boysen 2000).

The Marx staging system is the one used until today, although it relates to use of and response to HBO. The staging system of Epstein et al. (1987a) is an improvement, but is focused on the presence or absence of a pathologic fracture (Schwartz & Kagan 2002). Under this rationale two new similar staging systems are designed which are simple, memorable and do not rely for the classification on any knowledge of clinical progress or response to treatment (Shaw & Dhanda 2011). These are the system of Schwartz and Kagan (2002) and the system of Notani et al. (2003). According to the system of Notani et al. patients are divided into grades I, II and III based on the extent of the ORN lesion. Grade I is defined as ORN confined to alveolar bone. Grade II is ORN limited to alveolar bone and/or the mandible above the level of mandibular alveolar canal. Grade III is ORN that extends to the mandible under the level of mandibular alveolar canal and ORN with a skin fistula and/or a pathologic fracture.

6.3 Infected osteoradionecrosis

Infection is a dreaded complication after ORN occurs. It is regarded as the most serious complication of ORN with a markedly increased risk for sepsis, bone fracture, severe impairment of quality of life and is called infected osteoradionecrosis (IORN) (Guttenberg 1974, Thiel 1989). Patients may have pain and fever. They also present with fistula and signs of inflammation of the surrounding mucosa or skin.

Several mechanisms contribute to the development of IORN. The damage of salivary glands through ionizing radiation, leads to salivary gland dysfunction and xerostomia. As a result sufficient saliva is not produced, which plays a crucial role in oral clearance, physiological bacterial microenvironment and the maintenance of mucosal integrity. The result is an increased predisposition to infections (Andrews & Griffiths 2001).

Several studies showed particularly high numbers of IORN cases positive for several microorganisms (Happonen et al. 1983, Andrews & Griffiths 2001, Annane et al. 2004, Store et al. 2005, Hansen et al. 2006a). Significant increases have been noted for Streptococcus mutans and Lactobacillus species as well as Actinomyces (Andrews & Griffiths 2001). Among them, Actinomyces spp. was detected by several techniques in tissues from IORN patients since RT makes a favorable environment for this microorganism to flourish due to bone tissue alterations (Happonen et al. 1983, Curi et al. 2000a, Store et al. 2005, Hansen et al. 2006a). Studies of Curi et al. (2000a) and Hansen et al. (2006b) demonstrate that the overall prognosis of ORN is worsened in the presence of Actinomyces. Histological studies of IORN patients revealed that Actinomyces occurred in necrotic bone tissue and not in the oral mucosa or at the site of fistula (Hansen et al. 2006a). These organisms are involved in chronic, nonhealing inflammatory processes and purulent discharge, common characteristics of IORN. These bacteria are also associated with prolonged treatment duration (Hansen et al. 2006a). Moreover, in the study of Curi et al. (2000a) patients with actinomycosis infection had significantly longer treatment period than those without infection.

It was then debated whether detection of Actinomyces, which are normal inhabitants of the oral microflora, could be due to contamination or could be of importance in pathogenesis and course of the disease. In his study, Store et al. (2005) detected Actinomyces spp. by DNA–DNA hybridization in deep medullary bone specimens of patients suffering from ORN. Since these specimens had been obtained from areas completely covered by mucoperiostium, the authors suggested that the bacteria do not represent contaminants.

6.4 Clinical symptoms and diagnosis

Diagnosis of ORN is based on clinical signs and symptoms. They include ulceration or necrosis of the mucosa with exposure of necrotic bone for longer than 3 months. Other symptoms include pain, trismus and suppuration in the area (Baker 1983, Epstein et al. 1987a, Nakatsuka et al. 1996, Shaha et al. 1997, Oh et al. 2009). Associated symptoms are neurologic symptoms such as pain, dysesthesia or anesthesia. Other symptoms such as fetor oris, dysgeusia and food impaction in the area are usually seen. Exposure of rough and irregular bone can result in physical irritation of adjacent tissues. Progression of ORN may lead to pathological fractures, intraoral or extraoral fistulae and local or systemic infection. Difficulties in mouth opening, mastication and speech arise frequently (Epstein et al. 1987, Jacobson et al. 2010, Mücke et al. 2011a, Mücke 2011b). In patients treated with EBRT osseous alterations usually appear in the body of mandible (premolar and molar regions) whereas in those managed with brachytherapy, on the lingual or buccal surface (Hermans et al. 1996).

Diagnosis of septic ORN appears to be easier. Primary symptom in this case is marked pain. A thorough clinical examination will reveal intra- or extraoral draining fistulae, ulcerations of the mucous membrane, exposed devitalized bone, hemorrhages, cellulitis or pathologic fractures. However, final diagnosis will be given through a biopsy in order to exclude metastatic cancer (Guttenberg 1974).

6.5 Radiological findings

Many radiological techniques can be used in order to detect ORN. They include radiographs, computer tomography (CT) scans, magnetic resonance imaging (MRI), Doppler ultrasound, nuclear medicine and near infrared spectroscopy (Chrcanovic et al. 2010a).

Radiology is not very helpful in early stages of ORN (Miles 1992) and even in its advanced stages it does not necessarily relate to imaging features (Niebel & Neeman 1957, MacDougall et al. 1963, Guttenberg 1974). In plain radiographs normal bone may be associated with large areas of exposed non-viable bone; conversely, if a small area is exposed the disease may spread into normal bone (Epstein et al. 1992). The described radiographic features range from normal appearance, to localized osteolytic

areas, extensive osteolytic areas, sequestra and fracture. Sockets after extraction of teeth will often remain visible for longer than twelve months after surgery. The most definitive radiographic alteration in early disease is that of increased radiodensity, followed by osteolysis in the affected area as well as a mixed radio-opaque radiolucent lesion, with radiolucent areas representing bone destruction (Guttenberg 1974).

The cheapest and readily available image is orthopantomogram (OPT), which can be supplemented with other extraoral or intraoral radiographs. ORN shows an undefined radiolucency without sclerotic demarcation which surrounds necrotic zone, but radiopaque areas can be identified when bone sequestra are formed. The visibility of ORN in OPTs requires a substantial alteration in mineral content and extensive involvement of bone, which only occurs in later stages (Epstein et al. 1987b). Ardran (1951) noted that a 30% loss of bone mineral content is necessary before any radiographic change can be seen.

Although CT scans have similar limitations like traditional radiographs (Tobias & Thomas 1996), they show osseous abnormalities such as focal lytic areas, cortical interruptions and loss of the spongiosa trabeculation on the symptomatic side, frequently accompanied by soft tissue thickening. Such a picture may cause difficulties in differential diagnosis between ORN and recurrent tumour (Hermans et al. 1996). In MRI with gadolinium administration an abnormal marrow signal, cortical destruction and slight to mild irregular enhancement is demonstrated (Fujita et al. 1991, Rabin et al. 1996, Store et al. 2000, Yoshioka et al. 2000). Advantages of MRI include excellent tissue contrast and high spatial resolution (Bachmann et al. 1996).

Bone scintigraphy permits estimation of extension and location of the lesion. It shows high sensitivity (up to 100%) but low specificity (about 60%) for diagnosis of ORN (Bachmann et al. 1996). Scintigraphy using 99mTc-marked diphosphonates (99mTc-MDP) allows highly sensitive depiction of mandibular lesions due to their altered phosphate metabolism. It can identify pathophysiologic changes in bone earlier than conventional radiography since scan changes reflect osteoblastic activity and good blood flow (Alexander 1976). Disadvantages of the method include low spatial resolution and overprojection by soft tissues, but they can be overtaken with use of single photon emission computerized tomography (SPECT) (Bachmann et al. 1996).

Finally, Positron Emission Tomography (PET) has been advocated as being able to differentiate between ORN and tumor recurrence (Minn et al. 1993).

6.6 Histopathological findings

Histologic findings of ORN include endarteritis, hyperemia, hyalinization, cellular loss, hypovascularization, thrombosis and fibrosis (Mainous & Hart 1975, Marx 1984, Marx & Johnson 1987). Some of these radiation effects, such as hyperemia, acute cellular loss and thrombosis are evident in the early phase, and other effects like hypovascularization and fibrosis occur 6-12 months after end of RT (Marx & Johnson 1987). ORN is also characterized by destruction of osteocytes, marrow stem cells and blood vessels, resulting in absence of osteoblasts from bone margins, empty marrow spaces, marrow fibrosis, necrotic blood vessels and lack of new osteoid (Murray et al. 1980b, Marx & Tursun 2012). Atrophic bone changes resemble those combined with atrophic changes of skin or mucous membranes (Howland et al. 1975).

A histologic specimen of ORN of mandible shows bone with regular trabeculae but without osteoblastic activity. Marrow is replaced by sparsely cellular fibrous tissue admixed focally with bone debris. In addition, the specimen demonstrates a lack of inflammatory cells. In comparison, chronic osteomyelitis usually shows bone with irregular trabeculae due to osteoblastic and osteoclastic activity and bone marrow replaced by fibrous tissue. Moreover, inflammatory cells may be detected histologically in a chronic osteomyelitis (Reuther et al. 2003).

6.7 Pathogenesis of osteoradionecrosis

Over the past 80 years a lot of theories have been proposed about pathogenesis of ORN with consequent implications for its treatment (Khojastepour et al. 2013).

In 1970, Meyer proposed a theory about pathogenesis of ORN (Meyer 1970). He hypothesized that osteonecrosis is a result of radiation injury to the bone and soft tissue followed by trauma (eg, tooth extraction or ridge irritation) and secondary infection (classic triad of radiation, trauma and infection). The vascular compromise induced by radiation sensitized bone to bacterial infiltration. Based on these findings he recommended operative debridement of necrotic bone and use of antibiotics as therapy. In 1976 Bump et al. mentioned that sepsis of devitalized bone produces a

virulent form of osteomyelitis with extensive tissue destruction (Bump et al. 1976). Titterington (1971) also mentioned that ORN is “an osteomyelitis secondary to irradiation”. Other authors stressed the role of Actinomyces, Candida, Streptococcus mutans and lactobacillus strains in pathogenesis of ORN (Haponnen et al. 1983, Keene & Fleming 1987, Epstein et al. 1991).

However, there was little pathologic evidence to support Meyer’s hypothesis. He did not demonstrate through cultures or tissue sections a spread of osteomyelitis and microorganisms throughout the bone. He did not demonstrate septic destruction in avascular tissue, which cannot mount an inflammatory response (Marx 1983a). In the majority of ORN tissue specimens, bacterial infection and inflammation were absent and many cases did not continue as sepsis. Moreover, new studies (Pappas 1969, Beumer & Curtis 1979c, Rohrer et al. 1979) gave impetus to new ingestigations with respect to pathogenesis of ORN.

As a result in 1983 Marx proposed a new biologic model for ORN (Marx 1983a). He suggested that ORN is not a primary infection of irradiated bone since bacteria were present only on the surface of bone and not within the bone. Radiation induced endarteritis, produced a vascular injury causing the bone and overlying soft tissue to become hypovascular, hypocellular, and hypoxic (the so-called “three H hypothesis”). In hypoxic, hypocellular, and hypovascular irradiated tissue, the ability to replace normal collagen loss or normal cellular loss is severely compromised or nonexistent. The result is a breakdown unrelated to microorganisms but related more to the degree of original radiation damage and rate of normal or induced cellular death and collagen lysis. Indeed, the role of trauma in initiation of ORN can now be seen as a single quantum of collagen lysis and induced cellular death. Mucosa in the irradiated area is thinner and more susceptible to mechanical injury and breakdown through eating, teeth brushing, hot food, poor oral hygiene and by effects of tobacco and alcohol (Vanderpuye & Goldson 2000). The wound which is created has an oxygen requirement and a demand for the basic elements of tissue repair that are beyond the capabilities of local tissue to provide. Furthermore, the incidences of ORN unrelated to trauma are consistent with a pathogenesis that does not necessarily include direct trauma as the etiologic agent. More likely, spontaneous ORN results, when mucosal breakdown or even breakdown of skin is due to tissue’s inability to keep up with

cellular turnover and collagen synthesis. It is related to use of implant sources and higher total radiation doses. Once any wound is created, it would be unrealistic to expect effective healing, considering the greatly increased demands for oxygen, energy, and nutrition in a tissue that could not maintain itself at its former level of metabolic demand (Marx 1983a). The mechanism is generally seen as an inability of both soft and hard tissue to keep up with cellular turnover and collagen synthesis (Epstein et al. 1987a). Sequence is as follows: (a) radiation, (b) hypoxic-hypovascular-hypocellular tissue ("three H" principle), (c) tissue breakdown (cellular death and collagen lysis exceed synthesis and cellular replication), and (d) nonhealing wound (a wound in which energy, oxygen, and metabolic demands exceed supply) (Marx 1983a, Oh et al. 2009).

Marx et al. (1985) advocated for use of prophylactic and therapeutic HBO therapy in an effort to stimulate monocyte and fibroblast growth and increase the expression of vascular endothelial growth factor with secondary angiogenesis. After comparing antibiotic-treated versus HBO-treated radiated patients undergoing dental extractions, concluded that HBO therapy significantly lowered the risk of developing ORN. As a result, aim of treatment should be the reverse of hypoxia and the increase of vascularity and cellularity of tissues (Marx 1983a, Vudiniabola et al. 2000).

However, there are few studies duplicating Marx's results (Pasquier et al. 2004, Wahl 2006). A recent randomized, controlled, double-blind trial reported no preventive benefit in a HBO treated group undergoing extractions. In this study, there was actually an increased risk of ORN in patients receiving prophylactic HBO (Annane et al. 2004, Mendenhall 2004). In 2004, Assael hypothesized that ORN occurs by the same mechanism as other types of osteonecrosis (eg, bisphosphonate-related osteonecrosis) and results from decreased osteoclastic bone resorption (Assael 2004), a mechanism that was also proposed previously from Jones and Boyde (1984) and supported by Bras et al. (1990). Increased subperiosteal bone deposition in ORN specimens and thickening of the jaw in radiated zones support this theory. Without osteoclasts to resorb the nonviable, radiated bone, healing is impaired (Al- Nawas et al. 2004). However, there is contradictory evidence to suggest that bisphosphonates may promote healing in patients with ORN (Delanian et al. 2005). Store et al. (2005)

used DNA hybridization and showed that bacteria may in fact play a fundamental role in pathogenesis of ORN, supporting Meyer's original hypothesis.

Another question that has also been an issue of controversy over the years is if ORN occurs primarily due to necrosis of bone or enveloping tissues. Store and Larheim (1999) confimed the existence of an initial central bone necrosis following radiation, with loss of the spongiosa, thinning and penetration of the cortex. This may explain the very special pathological pattern found in stage I cases, with radiological evidence of bone necrosis, even to the degree of a spontaneous fracture, still with full mucosal coverage (Store et al. 2000).

A current theory proposes that ORN occurs by a radiation-induced fibroatrophic mechanism. In particular progression of ORN may be due to activation and dysregulation of fibroblastic activity that secondarily leads to necrosis of microvessels, local ischemia, and tissue loss. In the theory of Delanian (Delanian & Lefaix 2005, Delanian et al. 2011) ORN lesions are ultimately caused by an imbalance of bone resorption and bone deposition. Bone atrophy occurs in the setting of extensive fibrosis. Combination of osteoblast death, failure of osteoblast repopulation, and excessive proliferation of myofibroblasts results in bony matrix being replaced by fibrous tissue. Three distinct phases are seen (Vozenin-Brotons et al. 2003): the initial pre-fibrotic phase in which changes in endothelial cells predominate, together with the acute inflammatory response; the constitutive organised phase in which abnormal fibroblastic activity predominates, and there is disorganisation of the extracellular matrix and the late fibroatrophic phase, when attempted tissue remodeling occurs with formation of fragile healed tissues that carry a serious inherent risk of late reactivated inflammation in the event of local injury.

After RT, endothelial cells are injured, both from direct damage by radiation and from indirect damage by radiation-generated reactive oxygen species or free radicals. Injured endothelial cells produce chemotactic cytokines that trigger an acute inflammatory response and then generate a further release of reactive oxygen species from polymorphs and other phagocytes (Dambrain 1993). Destruction of endothelial cells, coupled with vascular thrombosis, leads to necrosis of microvessels, local ischaemia and tissue loss. Loss of natural endothelial cell barrier allows seepage of various cytokines that cause fibroblasts to become myofibroblasts. These

myofibroblasts are characterised by unusually high rates of proliferation, secretion of abnormal products of the extracellular matrix and a reduced ability to degrade such components. Combination of osteoblasts' death after irradiation, failure of osteoblasts to repopulate and excessive proliferation of myofibroblasts results in reduction in bony matrix and replacement with fibrous tissues. Ultimately, myofibroblasts undergo apoptosis, and even decades after RT, bone remains paucicellular, poorly vascularised and fibrosed (Riley 1994).

In this case, resection of devascularized tissue would be insufficient to counteract the perturbations of bone metabolism. Such a mechanism may explain the possibility for ORN to persist and progress even after extensive mandible resection. Even if the surgeon notes vascularized margins after completion of resection, impaired functioning of fibroblasts, osteoclasts, and osteoblasts would continue on to exacerbate ORN progression (Zaghi et al. 2012). New antioxidant agents such as pentoxifylline and tocopherol have emerged on the basis of this theory as possible adjuvant treatments for ORN with promising results (Delanian & Lefaix 2004).

Chapter 7

Risk factors of osteoradionecrosis

Numerous factors in the literature are associated with the risk of developing ORN. These include total radiation dose, brachytherapy, fractionation, poor oral hygiene, alcohol, tobacco use, dental extractions, tumor size and location, staging (Morrish et al. 1981, Kluth et al. 1988, Jereczek-Fossa & Orecchia 2002, Reuther et al. 2003, Niewald et al. 2013). They can be divided into three main groups (Jereczek-Fossa & Orecchia 2002):

1. Treatment-related factors (total dose, photon energy, brachytherapy, field size, fraction size, volume of the mandible irradiated)
2. Patient-related factors (periodontitis, preirradiation bone surgery, bad oral hygiene, alcohol and tobacco abuse, bone inflammation, dental extraction after RT)
3. Tumor-related factors (size of tumor, stage, anatomic tumor site, proximity of tumor to bone)

Some of these factors are related with high risk of developing ORN whereas others with lower risk depending on population of each study and other parameters. For example optimization of nutritional status, use of steroids and limitation of total radiation dose minimize the risk of ORN (Goldwasser et al. 2007), while diabetes mellitus (DM), advanced primary tumor, alcohol and tobacco abuse are related with higher risk of ORN (Vanderpuye & Goldson 2000, Oh et al. 2009).

According to the cause two different types of ORN can be distinguished: spontaneous and posttraumatic (Marx 1983a). These types are influenced from the different factors mentioned above and occurrence varies in different studies. For example Marx reported that 70% of ORN were posttraumatic (Horiot et al. 1981, Marx 1983a) whereas Hao et al. (1999) mentioned that 81% of patients had ORN due to iatrogenic cause. Spontaneous ORN is associated with doses higher as 60 Gy and its occurrence is decreased to the rate 6% or less due to use of newer techniques of radiation (3D-CRT, IMRT) (Vissink et al. 2003b, Studer et al. 2004).

7.1 Technique of radiation

Type of RT plays a significant role in the occurrence of ORN. The previous use of megavoltage and cobalt units during RT resulted in high accumulated doses to bone and higher incidence of ORN (Shaw & Butterworth 2011). Since the introduction of higher-energy RT, incidence of ORN has decreased from 10.31% to 6.28%. In the study of Meyer (1970) 5% of the patients treated with orthovoltage developed ORN while only 1-1.5% developed it with use of supravoltage.

Risk of developing ORN is greatest when an interstitial implant is used as sole radiaton source (brachytherapy), less with combination technique and lowest with external beam alone. When the implant is close to the bone, the adjacent bone receives a high dose of radiation and is particularly susceptible to necrosis whereas bone far from implant preserves biologic activity. As distance from the implant increases, there is a rapid fall in radiation. For these reasons severity and extent of necrosis associated with an implant are less marked in these patients than those treated with EBRT (Murray et al. 1980b). As a result brachytherapy will cause more localized cases of grade I and II ORN, while damage caused by external RT is uniform within the radiation field resulting in extensive cases of grade III ORN (Notani et al. 2003).

During the last years, new radiation techniques like IMRT and 3D-CRT were also studied by authors. IMRT reduces dose delivered to salivary glands and the rate of xerostomia, as well as other radiation related toxicities, providing superior target volume dose homogeneity and sparing of organs at risks. Many authors have mentioned the superiority of IMRT in reducing incidence and severity of ORN (Studer et al. 2006, Ben-David et al. 2007, Ahmed et al. 2009, Peterson et al. 2010, Gomez et al. 2011, Bhide et al. 2012, Gevorgyan et al. 2013, Tsai et al. 2013). Although encouraging, these results need further validation with longer follow-up.

7.2 Fractionation

The fractionation schedule mostly used nowadays is described as 1.8-2.0 Gy once daily, 5 days a week, over 4-8 weeks (Mendenhall et al. 2003). Changes in this fractionation schedule are connected with higher or lower incidence of ORN. Since 1991, the increasing use of hyperfractionation and concomitant boost with better dose

homogeneity as well as moderately accelerated fractionated irradiation with modern techniques of three-dimensional conformal irradiation result in a lower risk of ORN (Studer et al. 2004). Many authors report lower incidence of ORN with use of hyperfractionation and accelerated fractionation with dose reduction, an expected finding due to total dose reduction (Parsons et al. 1988, Pigott et al. 1993, Mak et al. 1995, Dische et al. 1997, Gwozdz et al. 1997, Fu et al. 2000, Mendenhall et al. 2000, Ang et al. 2001, Fallai et al. 2006, Skladowski et al. 2006, Cummings et al. 2007, Suwinski et al. 2008, Nabil & Samman 2012). Niewald et al. (2013) report in their study an increase in the frequency of ORN from 8.6% to 22.9% in patients treated with conventionally fractionated RT and hyperfractionated RT with higher total dose respectively.

When using hyperfractionation, an interfraction interval >4.5 h is important. Niewald et al. (1996) showed an increase in the incidence of ORN (22.9%) after hyperfractionation with an interfraction interval of < 4.5 h. According to the study of Studer et al. (2004) as well as data of Mendenhall et al. (2000), Parsons et al. (1988) and Fu et al. (2000), the risk of ORN is <5% after a total dose between 72 and 80 Gy and an interfraction interval of 6h.

7.3 Dose of radiation

Results of different studies concerning total radiation dose given to patients are controversial. Some authors concluded that there was no association between radiation dose the patient received and stage of necrosis (Store & Boysen 2000) or that high dosage alone does not increase the risk of ORN (Kluth et al. 1988). The reason is that mandible shows a tolerance to irradiation doses ranging from 60 to 72 Gy (Emami et al. 1991). Other authors propose and most of them agree that the higher the radiation dose the higher the risk of ORN (Beumer et al. 1972, Murray et al. 1980a, Murray et al. 1980b, Morrish et al. 1981, Beumer et al. 1983a, Beumer et al. 1984, Withers et al. 1995, Reuther et al. 2003, Chang et al. 2007, Lee et al. 2009, Gomez et al. 2011). Although most of ORN cases occur in the upper level of therapeutic doses, few can develop after lower dose of radiation (Kluth et al. 1988, Curi & Dib 1997).

Bedwinek et al. (1976) reported no cases of ORN at a radiation dose of 60 Gy or lower. Curi & Dib (1997) reported that 95.2% of the patients with ORN had received a radiation dose of 50 Gy or higher. Thorn et al. (2000) reported that 93% of ORN cases received a radiation dose of 64–68 Gy; Wong et al. (1997) reported that percentage of surgical removal was high for ORN that developed at >65 Gy. Goldwasser et al. (2007) concluded that patients receiving a radiation dose above 66 Gy increased the risk of developing ORN by almost 11-fold. Other authors mention that an increase of radiation dose alone can not lead to increase in the incidence of ORN but its occurence is related to the synergic effect of radiation, fractionation and volume of irradiated tissue (Lozza et al. 1997, Jereczek-Fossa & Orecchia 2002, Reuther et al. 2003, Studer et al. 2006, Ben-David et al. 2007, Nabil & Samman 2011).

The dose of radiation influences also the occurrence of spontaneous and trauma-induced ORN. Spontaneously occurring ORN is dose dependent (>60 Gy) and relates to the extent of radiation exposure (Marx & Johnson 1987, Glanzmann & Gratz 1995), whereas trauma-induced ORN is more dependent on traumatic dental events such as periodontal disease, postirradiation teeth extraction, poor oral hygiene and inadequate denture irritation (Marx 1983b, Marx & Johnson 1987, Curi & Dib 1997, Thorn et al. 2000). Patients receiving higher radiation doses would therefore be more likely to develop spontaneously occurring ORN, whereas patients receiving lower doses would need trauma in the radiated tissue to initiate development of ORN (Thorn et al. 2000).

7.4 Volume of irradiated tissues

A correlation between the incidence of bone necrosis and the volume of irradiated mandible has been reported since many years (Beumer et al. 1984). Recent studies (Withers et al. 1988) of volume effect (based on field area rather than actual volume) in patients with oral cavity and oropharyngeal tumours were not able to demonstrate an increase in acute or late normal tissue injury with increasing treatment volume. Some previous analyses (Grant & Fletcher 1966, Shukovsky & Fletcher 1973, Spanos et al. 1976) of this relationship suggested that volume does influence normal tissue injury. Turner et al. (1996) proved that increasing target volume for doses less than 55 Gy is a risk factor for ORN. It is therefore suggested that volume of irradiated tissue

together with radiation dose influence the incidence of ORN (Lozza et al. 1997, Reuther et al. 2003, Studer et al. 2006, Ben-David et al. 2007).

7.5 Combination of radiotherapy with chemotherapy

Chemoradiation therapy (CRT) is used in patients with positive margins or with evidence of extracapsular spread (Bernier et al. 2005). Also patients who are not suitable for surgery receive CRT as definitive treatment unless contraindicated. Chemotherapy is likely to weaken local immune response by damaging cellular immune system (Reuther et al. 2003).

The synergic effect of CRT as a risk factor of ORN is also studied with different results (Nabil & Samman 2012). Some authors report higher incidence of ORN when CRT was used, (Hao et al. 1999, Jeremic et al. 2000, Denis et al. 2003, Cooper et al. 2004, Budach et al. 2005, Semrau et al. 2006, Stenson et al. 2010) others when RT was used alone (Brizel et al. 1998, Huguenin et al. 2004, Racadot et al. 2008) whereas some authors reported no difference (Corvo et al. 2001, Fallai et al. 2006). Turner et al. (1996) proved that synchronous treatment with RT and Methotrexate chemotherapy is a significant prognostic factor for the development of ORN.

7.6 Anatomy and localization of the tumor

Anatomy of the bone is also a risk factor of ORN as mandibular ORN is much more common than ORN of the maxilla (Morrish et al. 1981, Beumer et al. 1984, Eggert et al. 1985, Kluth et al. 1988, Curi & Dib 1997, Thorn et al. 2000). The posterior molar region of the mandible is more affected than the anterior (Bras et al. 1990, Mounsey et al. 1995, Thorn et al. 2000, Reuther et al. 2003). The reasons proposed to explain this phenomenon are different. The mandible has a restricted localized blood supply, which is often completely within the radiation field, whereas the maxilla has many anastomoses located outside the area of irradiation (Cowgiel 1960, Hoffmeister et al. 1969, Beumer et al. 1984, Thorn et al. 2000, Reuther et al. 2003). Moreover, the difference between bone density of maxilla and mandible, with mandible absorbing more amount of radiation may also explain the higher incidence of mandibular ORN (Cheng & Wang 1974, Mainous & Hart 1975, Morrish et al. 1981, Vanderpuye & Goldson 2000, Lambade et al. 2013). Posterior areas of mandible are almost always

included in the RT of both oropharynx and regional lymph nodes (Epstein et al. 1987b, Thorn et al. 2000), as well as in the boosted RT fields. They also undergo maximal load during mastication and are often subjected to dental extractions (Jereczek-Fossa & Orecchia 2002).

Localization of the initial tumor is mentioned as a risk factor of ORN. Generally, tumors of oral cavity or oropharyngeal region result in a higher incidence rate of ORN because of the inclusion of the mandible in the radiation field (Nabil & Samman 2012). Patients with tumors related to the mandible have five times greater risk of developing ORN than those with anatomic sites other than the mandible (Murray et al. 1980b). Oral cavity tumors, especially tumors of the tongue, floor of mouth, alveolar ridge or retromolar region contribute to higher risk for developing ORN after irradiation (Watson & Scarborough 1938, Curi & Dib 1997, Evensen et al. 2002, Notani et al. 2003, Reuther et al. 2003, van den Broek et al. 2006), since mandibular bone is directly involved in radiation fields and almost always an aggressive and radical surgical approach for tumor resection is needed (Curi & Dib 1997). On the other hand, tumors of sinonasal or nasopharyngeal areas present a higher risk for developing ORN in the maxilla (Tong et al. 1999, Cheng et al. 2006, Homma et al. 2009), if any, because the maxilla is more resistant to ORN (Nabil & Samman 2012). Patients in whom RT portals include only the angle or ramus of mandible, like pharyngeal or laryngeal cancers, have a lower likelihood of developing ORN (Ferguson & Stevens 2007). When the primary tumor is adjacent to or is overlying bone, the risk of ORN is increased (Rohrer et al. 1979, Murray et al. 1980b, Tobias & Thomas 1996).

7.7 Stage of tumor

It has been reported that risk of developing ORN is greater in patients with advanced stage tumor (Bedwinek et al. 1976, Kluth et al. 1988, Reuther et al. 2003, Oh et al. 2009, Tsai et al. 2013) and tumor invasion to adjacent bone (Murray et al. 1980c, Morrish et al. 1981, Epstein et al. 1987b). Turner et al. (1996) proved that bone involvement at the time of presentation, independent of tumor size and nodal stage, is related with higher incidence of ORN. The study of Curi and Dib (1997) concluded to the same result.

7.8 Alcohol and tobacco use

Tobacco and alcohol abuse is clearly identified as a risk factor for ORN by many studies (Kluth et al. 1988, Schratter-Sahn et al. 1991, Glanzmann & Gratz 1995, Curi & Dib 1997, Thorn et al. 2000, Reuther et al. 2003, Shimizutani et al. 2005, Katsura et al. 2008, Tsai et al. 2013). In their study, Oh et al. (2009) showed that in patients with ORN who continued to smoke or consume alcohol, failure of conservative ORN management and ultimate requirement for surgical resection were more likely. Their mode of action is unexplained. Vasoconstriction which occurs owing to smoking may enhance the occurrence of mandibular hypovascularisation after RT (Katsura et al. 2008). Furthermore, they probably potentiate the combined effects of other negative factors such as poor oral hygiene. Taking into account the above, encouragement of patients to quit smoking and alcohol consume is considered to be very important for the prevention of ORN.

7.9 Dental status and oral health

Occurrence and severity of ORN does not only depend on the extent of radiation damage to bone, but also on patient's dental health (Nabil & Samman 2012). It is known that risk of developing ORN is increased in patients with poor oral health because more traumatic dental events are to be expected to these patients (Carl et al. 1972, Regezi et al. 1976, Murray et al. 1980b, Murray et al. 1980c, Beumer et al. 1984, Kluth et al. 1988, Bachmann et al. 1996, Katsura et al. 2008).This is further supported by findings that edentulous patients are at a lower risk of developing ORN (Murray et al. 1980b).

Katsura et al. (2008) proved that oral health conditions that increased the risk of ORN were periodontal pocket depth >5mm, dental plaque score >40% alveolar bone loss >60% and a grade 3 radiographic periodontal status. Niewald et al. (2013) support that number of carious teeth and odontogenic cysts are significant prognostic factors for the occurrence of ORN. Murray et al. (1980a & 1980c) and Beumer et al. (1984) found a positive association between periodontal dental disease and occurrence of ORN. It can be concluded that periodontal disease should be eradicated before irradiation of oral tissues and the patient should eliminate plaque with correct tooth brushing technique in order to avoid spontaneous ORN cases. Finally, the importance

of good oral health and good dental management should be emphasized to patients undergoing radiation for head and neck cancer.

7.10 Trauma before and after radiotherapy

Trauma can be delivered to tissues in several ways; local trauma due to dentures or other reasons and surgically due to teeth extractions and major surgery related to treatment of the malignancy itself. Although until the 1970s and 1980s trauma was proposed as initiating factor of ORN, its role was since then questioned as many patients developed ORN without having evidence of previous trauma (Bedwinek et al. 1976, Marx 1983a, Epstein et al. 1987b).

7.10.1 Tooth extraction

Tooth extractions play a crucial role in the pathogenesis of ORN (Hansen et al. 2006a) and they are proposed as the most common cause of trauma-induced ORN of the jaws in 60-89% of the cases (Murray et al. 1980a, Marx & Johnson 1987). The pathogenetic mechanism can be described as follows: a wound due to surgical procedure (dental extraction) requires protein syntheses which are obtained by cellular activity and vascular events (Maxymiw et al. 1991). Ionizing radiation promotes irreversible cellular and vascular damage resulting in hypoxic, hypocellular and hypovascular tissue. This fact can drastically affect the reparation process (Beumer et al. 1976, Beumer et al. 1983a, Beumer et al. 1983b, Beumer et al. 1984, Koga et al. 2008a). Results regarding effect of tooth extraction to the occurrence of ORN are controversial. The highest incidence of ORN is observed in patients who have had extractions immediately before or immediately after RT (Epstein et al. 1987b) and after extractions of posterior mandibular teeth with roots lying below the mylohyoid line (Teng & Futran 2005).

Regarding ORN cases related to extractions performed before RT, most studies show low incidence: Bedwinek et al. (1976) found 6.3% ORN cases, Regezi et al. (1976) 2% after 311 dental extractions (49 patients), Epstein et al. (1987b) 5.4% in 454 exodontias (92 patients), Sulaiman et al. (2003) 2.6% in 300 teeth removed in 77 patients, Oh et al. (2004) 1.8% in 55 patients submitted to 99 extractions of third molars and Koga et al. (2008b) 0.5% in 1647 teeth removed in 363 patients. Interestingly, Starcke and Shannon (1977) and Makkonen et al. (1987) evaluated 515

exodontias (62 patients) and 45 exodontias (10 patients) respectively and there were no ORN cases related to dental extractions executed before irradiation. On the other hand, Carl et al. (1973), Beumer et al. (1983a), Sulaiman et al. (2003) and Chang et al. (2007) observed higher risk of ORN in dental extractions performed before RT compared with preservation of teeth.

Considering extractions performed after RT, in the study of Koga et al. (2008b) from 57 patients only 1 developed ORN (1.7%). This rate is lower than the 9.1% encountered by Horiot et al. (1981), 7.1% found in 42 patients submitted to 137 dental extractions by Epstein et al. (1987b), and 20.0% noted after extraction of 7 third molars in 5 patients by Oh et al. (2004). Furthermore, Sulaiman et al. (2003) observed 1.8% ORN rates in 330 exodontias (107 patients). In several other studies postirradiation dental extractions are associated with high rates of ORN (Beumer et al. 1972, Morrish et al. 1981, Beumer et al. 1984, Marx & Johnson 1987, Thorn et al. 2000). However, Regezi et al. (1976), Makkonen et al. (1987), and Maxymiw et al. (1991) evaluated 10, 25, and 72 patients submitted to 23, 88, and 126 dental extractions, respectively, and there was no case of ORN related to dental extractions after head and neck irradiation. Other studies show similar results between dental extractions before and after RT (Epstein et al. 1987b, Reuther et al. 2003).

Healing time after extractions until onset of RT is also a theme of great controversy among authors. Some of them propose that healing time is necessary for oral mucosa to recover and exposed bone to be completely covered before RT. This time should range from 10 to 21 days (Wildermuth & Cantril 1953, Stein et al. 1957, Shearer 1967, Gehrig 1969, Hayward et al. 1969, Beumer et al. 1979b, Murray et al. 1980c, Beumer et al. 1983a, Coffin 1983, Epstein et al. 1987a, Marx & Johnson 1987, Maxymiw et al. 1991, Tobias & Thomas 1996, Curi & Dib 1997, Koga et al. 2008b). The proposition of this time interval comes from experimental work which has shown that it takes 3 weeks for osteoid to form in the sockets and epithelial repair to be complete after extractions (Peterson et al. 2010). Surgical extractions or extractions performed on old people require longer time for healing (Wildermuth & Cantril 1953, Beumer et al. 1972). Other authors (Starcke & Shannon 1977, Epstein et al. 1987b) report that healing time is not a statistically significant factor in the development of ORN or that calculations of healing time should take into consideration radiation

dose, location and status of tumor and extent and type of any surgical procedures performed (Daly et al. 1972). Generally, repairing time should not be extended for a long period that compromises oncologic treatment and prognosis (Beumer et al. 1983a, Epstein et al. 1987b, Marx & Johnson 1987, Maxymiw et al. 1991, Tong et al. 1999, Reuther et al. 2003).

Concerning all the above the question is when to extract teeth, before, during or after RT. The worst moment for a tooth extraction is considered to be during RT, but the common belief to delay extractions after RT, in anticipation of tissue recovery with time, is wrong (Marx & Johnson 1987). All teeth that are severely diseased should be extracted at the pre-RT appointment (Chrcanovic et al. 2010b). After RT there is a 5-6 month period of tissue repair and healing before the onset of progressive fibrosis and loss of vascularity. This phase is a much safer time to do necessary extractions in order to decrease the chances of ORN (Marx & Johnson 1987).

Finally, most recent data show a downward trend of ORN risk after extractions (Nabil & Samman 2011). This finding together with that of Thorn et al. (2000) who found that out of 80 patients only 1 developed ORN outside the radiation field, indicates a great benefit of new radiation delivery and planning techniques such as IMRT and 3D-CRT (Studer et al. 2006, Ben-David et al. 2007). Their ability to exclude jaws from radiation field could eliminate the risk of ORN. Moreover, extractions outside the radiation field can be performed safely.

7.10.2 Placement of implants

Placement of implants is also mentioned as a risk factor for developing ORN in the literature. Many changes in the irradiated bone increase the risk of ORN from implant placement (Nishimura et al. 1998). Rohrer et al. (1979) found that osteocytes in the direct path of irradiation are killed in both outer lamellar and Haversian bone. Blood vessels of Haversian canals may become obliterated and periosteum loses cellularity, vascularity, and osteoid formation. King et al. (1979) reported a reduced vascular patency in irradiated bone at 1 year after irradiation. Hematopoietic proliferation becomes sparse in the bone marrow and sinusoids become irregular in configuration and distribution (Knospe et al. 1966). Late effects of irradiation may result in the catabolic processes of bone exceeding anabolic processes, which eventually lead to a net reduction in the mineral content of irradiated bone (Finston et al. 1966).

Many authors mention different success rates and risk of bone necrosis after implant placement with or without use of HBO therapy (Granström et al. 1993, Taylor and Worthington 1993, Franzen et al. 1995, Arcuri et al. 1997). It is generally accepted that the risk of ORN should be considered when the region of placement is in the treatment field (Nishimura et al. 1998). It is relatively safe to place implants in irradiated mandibular sites if the dose is less than 55 Gy (Morrish et al. 1981, Beumer et al. 1983). In patients irradiated with more than 65 Gy, a course of HBO is recommended (Granström et al. 1992). Other factors such as dose per fraction, tissue response to irradiation and general health of patient should also be considered.

7.10.3 Surgery related to tumor therapy

Another source of trauma is resection surgery, which includes the field of irradiation, and certainly reduces blood supply to the area. Mandibulotomy or mandibulectomy prior to RT are mentioned to be significant risk factors in the occurrence of ORN (Marx & Johnson 1987, Celik et al. 2002, Lee et al. 2009, Monnier et al. 2011). Findings of other authors demonstrate that the more radical the resection of mandible during surgical therapy of tumor was, the sooner ORN occurred (Murray et al. 1980a, Marx & Johnson 1987, Reuther et al. 2003).

7.10.4 Trauma due to denture

Dentures may cause mucosal irritation and ulceration leading to ORN (Daly et al. 1972). As a result it is important to avoid irritation from prosthetic appliances (Rankow and Weissman 1971). Some studies have recommended only mucosa-supported prostheses (Curtis et al. 1976), others only implant-supported (Weischer and Mohr 1999) and others implant- and tissue-supported prostheses.

Most patients can tolerate prosthesis without risk of bone necrosis. During RT the patient should wear dentures only for meals (Jansma et al. 1992a & 1992b, Mainous & Boyne 1974). Great care must be exercised in fabrication of dentures and in post insertion period. All patients must be followed regularly to ensure continued excellence of function and tissue relationship of their prostheses. In most maxillofacial centers the standard interval between irradiation and construction of dentures is 9 months to one year (Beumer et al. 1979b), but this time varies widely, depending on the individual. It has been suggested that six months is the average time required for irradiated tissues to return to as nearly normal a state as possible (Clark &

Howe 1976). This would seem a reasonable minimal interval to wait before commencing prosthodontic procedures.

7.11 Time interval between radiation and occurrence of osteoradionecrosis

Time interval between RT and onset of ORN varies in different studies and may influence the severity of ORN (Rathy et al. 2013). Occurrence of ORN varies from one month to 14 years after RT (Morrish et al. 1981, Curi & Dib 1997, Epstein et al. 1997, Reuther et al. 2003, Studer et al. 2004, Sciubba & Goldenberg 2006, Studer et al. 2006, Almazrooa & Woo 2009, Nabil & Samman 2011), but risk remains until the end of patient's natural life (MacComb 1962). Most of cases occur during the first postradiotherapeutic year (MacComb 1962, Beumer et al. 1972, Daly & Drane 1972, Starcke & Shannon 1977, Murray et al. 1980a & 1980b, Beumer et al. 1984, Epstein et al. 1987a, Kluth et al. 1988). Other authors mention that the majority of cases occur within 3 years after RT (Gowgiel 1960, Marx & Johnson 1987, Clayman 1997, Thorn et al. 2000, Notani et al. 2003, Chang et al. 2007).

The later ORN develops and the higher the dose radiation dose, the more it progresses (Notani et al. 2003). The explanation is a reduction in biologic activity which develops irreversibly with time after RT (Bedwinek et al. 1976, Larson et al. 1983, Marx 1983a & 1983b, Epstein et al. 1987a). This means that ORN which develops early may have still more biologic activity to heal sponataneously and lesion will be localized. On the other hand, late-onset may have less biologic activity and lesion will become serious.

Marx and Johnson (1987) observed that most spontaneous presentations of ORN occurred between 6 months and 2 years after RT, whereas the risk of developing trauma-induced ORN lasts indefinitely. This is also shown by other authors (Epstein et al. 1987a, Curi & Dib 1997, Thorn et al. 2000). Thorn et al. (2000) discovered that most late-onset ORN incidents were trauma-induced with the latest being 16 years after RT. Marx and Johnson (1987) found a bimodal peak of incidence relating to trauma-induced ORN and showed that the second peak starts after 2 years and peaks at 5 years. This peak is probably due to the increasing number of patients needing extraction due to tooth breakdown a few years after RT.

Chapter 8

Treatment of osteoradionecrosis

Although many reports have been published on the management of ORN, it remains a difficult and challenging problem. Various different treatment methods of ORN have been reported (Guttenberg 1974, Beumer et al. 1984, Nakatsuka et al. 1996, Shaha et al. 1997, Aitasalo et al. 1998, Oh et al. 2009) depending on several factors such as presentation of necrotic lesion, response to conservative nonsurgical therapy, general health of the patient, prognosis for successful management of the cancer, wishes of the patient, dose of irradiation and time interval after RT (Epstein et al. 1987a, Kawahara et al. 1987, Notani et al. 2003).

Management of ORN includes medical and surgical intervention. Medical management is the conservative treatment and includes oral care, local debridement, ultrasonography, or HBO. Surgical management includes resection of the necrotic bone with reconstruction and is indicated if conservative therapy does not resolve the pathologic condition (Guttenberg 1974) or in late stages of ORN which include fistula, fracture and a large area of exposed bone (Hao et al. 1999, Lambade et al. 2013). Some investigators agree that initial treatment of ORN should be conservative, since failure of this course can always be followed with a more radical approach (Niebel & Neeman 1957, MacComb 1962, Hahn & Gorgill 1966). Others believe that a radical approach should be instituted at initial diagnosis (MacDougall et al. 1963, Marchetta et al. 1967). Most of the authors advocate a treatment approach according to stage of necrosis (Jacobson et al. 2010, Gevorgyan et al. 2013).

Conservative treatment is usually used for almost all patients; however, the ultimate need for radical resection after conservative treatment is reported to be as high as 70% to 83% (Bedwinek et al. 1976, Larson et al. 1983, Marx 1983a & 1983b). Protocols combining surgery and HBO have shown success rates 15-90% (D'Souza et al. 2007, Shaw & Dhanda 2011, Shaw & Butterworth 2011) but are also denoted as being impractical by other authors because of costs and time (Epstein et al. 1987b, Wong et

al. 1997). Recent studies have shown good results with use of stem cells in order to promote healing (Thom et al. 2006).

8.1 Conservative treatment

Conservative nonoperative management is usually recommended, especially in case of early and localized lesions or a lesion that is not progressing with minimal symptoms. Conservative surgical management can also be useful in some cases (Guttenberg 1974, Beumer et al. 1984, Nakatsuka et al. 1996, Shaha et al. 1997, Aitasalo et al. 1998, Oh et al. 2009). Conservative treatment includes nonoperative (for example improvement of oral hygiene, antibiotics, and analgesics) and surgical management (for example debridement and sequestrectomy), as well as HBO therapy.

During conservative management, local irritants such as alcohol, tobacco, smoking, and ill-fitting dentures should be avoided, and regular dental visit are advised. Initial approach should be with medication and local wound care only (Chrcanovic et al. 2010b). Oral hygiene is essential, including use of 0.2% aqueous chlorhexidine mouthwashes after meals (Scully & Epstein 1996) and constant saline mouthwashes. Debris should be washed or irrigated away and sequestra should be allowed to separate spontaneously or gently removed, since any surgical interference may encourage extension of necrotic process. Other authors state that if sequestration is present the decision should be surgical removal and in this case success rate is 75% (Wong et al. 1997, Lambade et al. 2013). Curi and Dib (1997) advocate sequestrectomy when a sequestrum is identified by radiologic techniques.

Analgesics and antiinflamatory drugs are prescribed when necessary (increasing signs and symptoms of pain, discomfort, etc.). Although ORN is not primarily an infectious process and tissues are hypovascular, limiting the success of systemic antimicrobial agents, tetracyclines have been recommended because of their selective uptake by bone (Rankow & Weissman 1971, Coffin 1983, Store & Granström 1999, Teng & Futran 2005). However, access to avascular bone is questionable, making tetracycline inactive. Penicillin has also been used, because of involvement of oral bacteria in the superficial contamination (Daly et al. 1972, Marx et al. 1985). Unacid is also an effective antibiotic in the prophylaxis and treatment of ORN (Heibel et al. 2005). Metronidazole 200 mg, three times daily or other broad spectrum antimicrobials can

also be given in cases of severe infection or where anaerobes are implicated (Beumer et al. 1983b, Marx 1984, Harris 1992).

Conservative strategies have been reported by authors to spare patients resection in 77-96% (Rankow & Weissman 1971, Beumer et al. 1984, Epstein et al. 1987a). If complete resolution is not achieved, asymptomatically preserved function may still be acceptable especially in patients with advancing age or those who wish to avoid surgery (Epstein et al. 1987a). For some patients, surgery is inappropriate, and they are more appropriately treated with conservative measures because of age and poor health.

8.1.1 Hyberbaric oxygen therapy

HBO therapy is the intermittent, usually daily, inhalation of 100 per cent oxygen at a pressure greater than one atmosphere absolute (ATA) (Clanci & Sato 1994). Thus, it is a means of increasing dose of oxygen dissolved in plasma and delivered to tissues. HBO treatment developed from studies carried out by U.S. Navy medicine units investigating management of decompression sickness and arterial gas embolism. HBO Committee of the Undersea and Hyperbaric Medical Society currently recommend HBO for several uses, including air and gas embolism, carbon monoxide poisoning, clostridial myonecrosis, refractory osteomyelitis, ORN and others (Jamil et al. 2000, Coulthard et al. 2003).

HBO reduces hypoxia within affected tissues, stimulates angiogenesis in hypovascular tissues and improves fibroblastic cellular density. It limits the amount of nonviable tissue to be surgically removed, enhances wound healing and prepares tissues for reconstruction (Shaha et al. 1997, Grime & Bryson 2001). The mechanism of action of HBO has been shown to enhance phagocytic ability of leucocytes (Hunt & Pai 1972), stimulate fibroblast growth, increase collagen formation and promote growth of new capillaries (Knighton et al. 1981). It is also inhibitory to aerobic and anaerobic bacteria and bacterial toxin formation (Mader et al. 1980).

Clinically it is used to treat various forms of chronic radiation tissue injury producing a favorable response in terms of relief of pain, elimination of extraoral sinus tracts, return of osseous union in areas of pathologic fractures, and rapid dissolution of sequestra without suppuration, so that further loss of hard and soft tissues is kept to a

minimum (Mainous & Boyne 1974). It supports wound flaps and grafts placed into irradiated tissue to improve function and relieve pain (Myers & Marx 1990, Steckeler et al. 1994). HBO therapy represents a more conservative approach in management of ORN and enhances the probability of total rehabilitation (Mainous & Boyne 1974). Numerous authors recommend the use of HBO prior to surgical therapy for ORN. It may also be used prophylactically in patients who require dental extractions and are at high risk for developing ORN (David et al. 2001).

HBO is delivered by sessions within a hyperbaric chamber, which may range from a small monoplace chamber for one patient to a multiplace chamber which holds several patients and an attendant. A single HBO session for ORN treatment commonly consists of patient breathing 100 per cent pure oxygen at 2-2.4 atmospheres for 90-120 minutes. Usually treatments occur on a daily basis, five to six days per week, until the required number of sessions is completed (Davis et al. 1979, Vudiniabola et al. 1999). The guideline used for dental extractions after RT usually consists of 20-30 sessions before the procedure and 10 after tooth removal (Marx et al. 1985, Dhanda et al. 2009). At least 20 to 30 mm Hg of wound PO_2 is needed to increase oxygen to hypoxic tissues (Davis et al. 1979). 30 dives of HBO result in a mean increment of 50-86 % of transmucosal oxygen in hypoxic tissues (Thorn et al. 1997). Other protocols are also designed for irradiated patients requiring implant treatment (Granström et al. 1993). Patients receiving more than 60 Gy and in need for extraction of mandibular teeth within the irradiated field appear to benefit most (Nabil & Samman 2011).

Toxic effects are usually observed in central nervous system (Koga et al. 2008a) and main contraindications against employment of HBO are some drugs, non-treated pneumothorax, neuritis, some forms of pulmonary disease, smoker's emphysema, active viral infections (Giebfried et al. 1986, Vudiniabola et al. 2000, Chavez & Adkinson 2001), as well as some certain chemotherapeutic agents like bleomycin, cispatin and adriamycin (Vanderpuye & Goldson 2000). The only absolute contra-indications to HBO are optic neuritis, and existing neoplasia (Wood & Liggins 1996). Although HBO may stimulate malignant growth (Feldmeir 2004), it is not contraindicated in patients with treated neoplasia (Marx & Ames 1982). HBO may be of use pre- and postoperatively in patients with neoplasia both in primary and delayed

reconstruction cases. Side effects of HBO are uncommon but include transient myopia (Kaur et al. 2009), seizures, and otic or pulmonary barotraumas, the latter potentially leading to air embolism (Vudiniabola et al. 1999, Chavez & Adkinson 2001, Bessereau & Annane 2010). Concern has been expressed that HBO may exacerbate a variety of autoimmune and immunosuppressive disorders, and viremia (Giebfried et al. 1986), but there is little supporting evidence. Relative contraindications to HBO therapy include upper respiratory tract infection, chronic sinusitis, epilepsy, chronic obstructive airways disease, high fevers, a history of spontaneous pneumothorax or thoracic or ear surgery, arterial air embolism, oxygen toxicity seizure, pulmonary oxygen toxicity, acute pulmonary edema, viral infections, congenital spherocytosis, a history of optic neuritis, and claustrophobia (Giebfried et al. 1986, Scully & Epstein 1996, Leach et al. 1998, London et al. 1998, Vudiniabola et al. 1999). Further limitations include limited availability, especially outside main cities and cost of the treatment (Vudiniabola et al. 1999).

Many animal studies (Hamblen 1968, Yablon and Crucss 1968, Wada & Iwa 1970) and clinical reports about use of HBO exist until nowadays, yet there is controversy about its effectiveness. In 1973, Greenwood & Gilchrist reported for first time the benefits of HBO on wound healing in postradiation patients (Greenwood & Gilchrist 1973). Since then, several authors have reported beneficial effects of HBO in management of ORN of jaws. In 1975, Mainous & Hart treated 14 cases of refractory mandible ORN with HBO and hemimandibulectomy, with complete resolution of all cases (Mainous & Hart 1975). In 1978, Farmer et al. studied the use of HBO and found resolution in 54% and improvement in 23% of patients (Farmer et al. 1978). In 1981, Mansfield et al. treated 12 patients with refractory ORN of mandible with HBO therapy, resulting in complete healing in 11 cases (Mansfield et al. 1981). In 1983, Marx reported successful resolution in all of 58 cases of ORN using HBO in combination with surgery (Marx 1983b) and in 1984 Beumer et al. found HBO helpful in treatment of large areas of ORN when combined with surgical sequestrectomy (Beumer et al. 1984). McKenzie et al. (1993) published treatment with HBO of postradiation ORN of the mandible in 26 patients and concluded that resolution occurred in 69% (18 of 26) of the patients, improvement occurred in 12% (3 of 26) of the patients but 19% (5 of 26) of the patients did not show any improvement. Merkesteyn et al. (1995) reported a combination of surgical

debridement, antimicrobial therapy and HBO in 27 patients and concluded that 20 (69%) had completely healed after this treatment. Epstein et al. (1997) reported the results of a long-term follow-up study with the same group of patients previously published by McKenzie et al (1993). Of the 20 patients followed, 12 had completely healed, improvement had occurred in two patients and five of the patients still had chronic persistent ORN. Neovius et al. (1997) reported results on treatment with HBO after surgery in irradiated head and neck in 15 consecutive patients and compared them with a group of patients treated without HBO. The authors concluded that 12 out of 15 patients treated with HBO had healed completely and that only seven of 15 patients with similar signs of ORN had healed after therapy without HBO. In the study of Curi et al. (2000b) complete healing was achieved in 14 of 18 patients who were treated with HBO. Similar encouraging results were published by many other authors (Hart & Mainous 1976, Cronje 1998, Feldmeier & Hampson 2002, Hampson et al. 2012).

Although benefits of adjunctive HBO therapy in irradiated tissues have been demonstrated in a series of reports, some authors do not agree with use of HBO for treatment of ORN (Epstein et al. 1987a, Wong et al. 1997). In a retrospective study of 28 patients with mandibular ORN managed by conservative measures only, Wong et al. (1997) showed that 14 patients had complete healing. A previous study (Curi & Dib 1997), in which 104 patients with ORN were treated with conservative approaches (local debridement/gentle sequestrum removal), supports this statement, since it resulted in healing of 42.3% of patients. Reports of several other authors indicate that most cases of ORN can be managed successfully without HBO (Daly & Drane 1972, Beumer et al. 1984, Marciani & Ownby 1986, Harris 1992, Schwartz & Kagan 2002, Annane et al. 2004, Besserau & Annane 2010, Pitak-Arnoop et al. 2010). There is also insufficient information to show that use of HBO reduces the incidence of ORN in irradiated patients requiring tooth extraction or implant therapy (Schoen et al. 2007, Fritz et al. 2010).

In conclusion, HBO alone cannot heal ORN wounds (Epstein et al. 1987b, Granström et al. 1992, Van Merkesteyn et al. 1995). HBO without aggressive surgical management would not resolve disease progress in most cases. Only ‘mild’ cases of ORN can be cured with HBO, and severe cases will need surgery to remove dead

bone (McKenzie et al. 1993, Mounsey et al. 1995). Postoperative HBO cannot be treatment of choice if operation fails to treat ORN (Maier et al. 2000). Purpose of hyperbaric therapy is to prepare patient for surgical debridement and appropriate grafting, not try to rescue poor results following inappropriate use of surgery in the treatment of ORN (Grime & Bryson 2001). Finally, there is need for greater quality research into the value of HBO for prevention of ORN (Shaw & Butterworth 2011); there is also a need for randomized controlled clinical trials to determine effectiveness of HBO in irradiated patients who require dental extractions or implant therapy (Coulthard et al. 2003).

8.1.2 Ultrasound therapy

Ultrasound therapy is a conservative alternative therapy to HBO. Ultrasound increases angiogenesis and stimulates collagen and production of bone (Harris 1992). Ultrasound may be valuable in treatment of delayed unions, in callus maturation after distraction, and in treatment of ORN (Schortinghuis et al. 2003). According to a study conducted by Harris (1992), a regimen of ultrasound with local debridement and metronidazole has proved to be an effective and practicable treatment for ORN, achieving healing in ten out of 21 cases (48 %) without surgery. He also proposed a protocol for ultrasound in treatment of ORN. This includes 40–50 sessions of 10 min each until healing is complete.

8.2 Surgical treatment

Surgery is recommended in cases of extensive ORN with intractable pain, severe trismus, multiple discharging fistulae, a large area of exposed necrotic bone, or a coexistent fracture (Zarem & Carr 1983, Koka et al. 1990, Shaha et al. 1997, Hao et al. 1999, Maier et al. 2000). In cases of no response to conservative treatments intensive care is usually required for a long period, and sometimes the result is progressive destruction and pathologic mandibular fracture. In these cases, radical resection of mandible is needed (Guttenberg 1974, Marx 1983b, Beumer et al. 1984, Nakatsuka et al. 1996, Shaha et al. 1997, Aitasalo et al. 1998, Oh et al. 2009). Until inception of intraoral approach to mandibular resection for ORN, extraoral route had been utilized with a great degree of morbidity and mortality (Marchetta et al. 1967).

Surgical therapy of ORN includes removal of small sequestra, radical sequestrectomy alveolectomy with primary closure or hemimandibulectomy, closure of orocutaneous fistulae and local or microvascular free flap reconstruction (Chrcanovic et al. 2010b). Immediate reconstruction using a fibular free graft, scapular osteocutaneous flap, a free serratus anterior/rib flap or vascularized iliac crest flap provides excellent functional and cosmetic results (Ioannides et al. 1994, Nakatsuka et al. 1996, Chang et al. 2001). Promising results have also been observed with free omental transfer (Kobayashi et al. 2000).

In his study Oh et al. (2009) concluded that radical resection of necrotic and infected bone is the most valuable treatment in terms of successful outcome of therapy. Criteria for determining the extent of mandible resection involve a preoperative estimation with a CT or MRI and intraoperative assessment of bone vascularity by examining for presence of osseous bleeding from margins of resection (Buchbinder & Hilaire 2006, Curi et al. 2007, Suh et al. 2010). Newer techniques include measurement of partial pressure of oxygen (PO_2) with Eppendorf fine needle probe (Meuer and Meyer 2006) and intraoperative tetracycline bone fluorescence (Pautke et al. 2010). Simply resecting grossly necrotic bone does not ensure curability of ORN, and further studies are needed to prevent ORN and its morbidity. However, until nowadays there is no better approach in assessing resection margins. It can be argued that a more aggressive surgical approach including a hemimandibulectomy plus condylectomy in unilateral ORN cases and near-total mandibulectomy in bilaterally affected mandibles may be the only way to minimize recurrence. However, this more aggressive approach may produce unforeseen morbidities in speech and swallowing function (Zaghi et al. 2012).

The concept of wide radical resection of affected bone with immediate reconstruction has gained wide acceptance in the literature and seems therapy of choice in advanced ORN of the jaws especially in mandible (Curi & Dib 1997, Shaha et al. 1997, Celik et al. 2002, Schwartz & Kagan 2002, Wei et al. 2003, Curi et al. 2007, Hirsch et al. 2008, Oh et al. 2009). Many authors reported a positive effect on the quality of life of these patients regarding reduction in pain and improvement of form and function (Koka et al. 1990, Curi and Dib 1997, Celik et al. 2002, Curi et al. 2007). Reconstruction of resected mandible needs to be performed using a nonirradiated flap.

This will provide an improved blood supply to the region, promoting healing and perhaps enhancing viability of the remaining bone that might be marginally involved with ORN (Baker 1983).

Soft tissue reconstruction alone, either as a pedicled or free flap, can be performed. These procedures have the disadvantage that they require secondary bone grafting to obtain bony restoration (Baker 1983, Nakatsuka et al. 1996). Although fibular free flap is described as a very safe and reliable option for reconstruction, failure and complication rate varies between 8.7 and 20 % (Chang et al. 2001, Curi et al. 2007, Hirsch et al. 2008, Mücke et al. 2013) flap loss, and 21–43 % (Gal et al. 2003, Hirsch et al. 2008) overall complications. In classes 2 and 3 of ORN, the use of microvascular free flaps provides safe results with a high quality outcome of reconstruction (Curi and Dib 1997, Shaha et al. 1997, Celik et al. 2002, Schwartz & Kagan 2002, Curi et al. 2007, Hirsch et al. 2008, Wei et al. 2003).

The optimal reconstruction, particularly for a long segment of bone, is a vascularized composite flap, such as fibular, scapular, iliac crest, or radius bone (Nakatsuka et al. 1996, Shaha et al. 1997). Mandibular reconstruction with a fibula flap is an elegant solution to restore anatomic arch, oral functions and facial esthetics (Bodard et al. 2011). Although the use of bony flaps like free fibular or iliac crest flaps is perfect for full rehabilitation, these are more demanding procedures and may not be as successful as soft tissue only flaps (Mücke et al. 2013). In contrast, local wound closure after wound debridement, demonstrates a high rate of failure (Mücke et al. 2013).

In general, patients with adequate soft tissue volume and quality (limited fibrosis without contraction where proper wound closure and coverage of the plate can be achieved) can be resected transorally and stabilized with a reconstruction plate. Those with a quantitative soft tissue deficiency should be resected through a MacFee-type neck incision, and reconstructed with an immediate soft tissue myocutaneous flap like pectoralis major (Marx & Morales 1998), lattisimus dorsi, trapezius and sternocleidomastoid, which permits stabilization of bony segments with a reconstruction plate. Bony reconstruction (stage III-R) should be accomplished after about 3 months, with particulate bone and cancellous marrow graft harvested from posterior ilium or other part of the body (Peleg & Lopez 2006).

8.3 New treatment techniques

Recently, some authors propose the possibility of bone regeneration with use of platelets rich plasma (PRP) with promising results (Tözüm & Demiralp 2003, Boyapati & Wang 2006, Mannai 2006, Roukis et al. 2006, Rutkowski et al. 2007, Scala et al. 2007). PRP is the portion of blood containing the concentrate of platelets which are rich in mitogenic growth factors (GFs) such as platelet derived growth factors (PDGFs), transforming growth factor beta TGF-β, epidermal growth factor EGF, insulin like growth factor IGF and vascular endothelial growth factor VEGF. Growth factors entrapped within alpha granules in platelets corpuscles are released upon a process called 'platelets activation' that consists of bursting granules to release their GFs content. This occurs primarily by thrombin. Within their environment of release, such GFs play a crucial role in orchestrating the molecular cascade of healing. Benefit of the introduction of such a GF into a healing lesion might be emphasized especially in critical-size defects. A therapeutic advantage of PRP in this type of defect is introduction of the 'right' concentrated GFs that are missing for the healing process and their introduction in natural proportions necessary for a proper interaction to stimulate different pathways that ultimately lead to activation of gene expression and production of necessary proteins for healing (Kassolis et al. 2000, Van den Dolder et al. 2006). Use of PRP may reduce or eliminate the need for invasive procedures such as resection and reconstruction of mandible (Scala et al. 2010). However, it failed in some studies to show beneficial results (Batstone et al. 2012).

A new therapy focuses on the use of pentoxifylline and antioxidant alpha-tocopherol (vitamin E) pentoxyfiline (PENTO) (Kahenasa et al. 2012). PENTO was reported to be successful in healing superficial cases of radiation induced fibrosis, but was found to be insufficient for use alone in long standing ORN (Kahenasa et al. 2012). Delanian et al. (2005 & 2011) found that combination of Clodronate and PENTO was beneficial in severe cases of radiation induced fibroatrophic process inducing mandibular ORN but clodronate carries a potential risk of bisphosphonate-related osteonecrosis. All patients with a need of dental extractions could be given eight weeks of pentoxyfiline 400 mg twice daily with tocopherol 1.000 IU, starting a week before the procedure. If ORN developed, then they could be continued for a further six months with clodronate prescribed after three months if there has been no

appreciable response (Lyons & Ghazali 2008). Nevertheless, further controlled and randomized clinical trials are necessary in order to confirm the effectiveness of PENTO regimen in treatment of ORN (Kahenasa et al. 2012).

Chapter 9

Prevention of osteoradionecrosis

Improvements in RT that were mentioned above (3D-CRT, IMRT) aim to prevent complications after RT, especially ORN. In addition to these attempts a thorough, early pre-irradiation dental assessment and a dental care programme are also steps to this direction (Carl et al. 1972, Regezi et al. 1976, Makkonen et al. 1987, Kluth et al. 1988, Scully & Epstein 1996, Vudiniabola et al. 1999, Wahl 2006, Monnier et al. 2011). The aim is to identify the main factors that will likely increase the risk for ORN and take steps in order to control or eliminate as many factors as possible before RT begins (Stevenson- Moore 1990, Jansma et al. 1992b, Thorn et al. 2000, Schiodt & Hermund 2002). Primary goal should be to optimize the condition of patient's dentition, so that high risk procedures like extraction of teeth, apicoectomies, etc., will not have to be performed in the post-irradiation period (Beumer & Brady 1978, Beumer et al. 1979a, Beumer et al. 1979b, Stevenson-Moore 1990, Jansma et al. 1992b, Curi & Dib 1997, Tong et al. 1999, Thorn et al. 2000). An adequate time for treatment and healing must also be allowed before the onset of RT (Vanderpuye & Goldson 2000, Shaw & Butterworth 2011).

A trained dentist should evaluate the condition of teeth and associated tissues and should conduct a complete dental, oral and pharyngeal examination (Hayward et al. 1969, Coffin 1983). Necessary treatment should be administered at once so that RT will not be delayed unreasonably. During preirradiation period, the patient should receive restorative and periodontal therapy which is necessary and should be taught oral hygiene. Oral cavity should be examined and pressure points from removable dentures should be eliminated (Hellstein & Marek 2006). The decision to extract teeth or not must be left to a skilled oral surgeon who can evaluate each patient individually (Coffin 1983, Makkonen et al. 1987).

Whether to extract teeth before RT or not has been a thema of great controversy (Degnan 1964). Several factors such as individual characteristics of patients, tumor and oncological treatment and dental factors should be considered in order to take the

decision of performing preradiation extractions (Koga et al.2008a, Shaw & Butterworth 2011). Knowledge of radiation dose, modality of treatment, field of radiation, and tumor prognosis combined play an important role in clinical decision-making. Consideration is also given to preexisting periodontal condition of tooth or teeth in question and motivation of patient to follow a strict programme of oral hygiene (Murray et al. 1980c, Reuther et al. 2003, Sulaiman et al. 2003).

Results of published papers are controversial. Daland (1949) rendered the patient edentulous and so did Watson and Scarborough (1938) before the days of antibiotics. Some researchers have suggested that all teeth in the path of radiation should be removed (Del Regato 1939, Niebel & Neeman 1957, Robinson 1964). MacComb (1962) and Cook (1966) expressed the opinion that all teeth which would require extraction for dental reasons within one year after radiation should be extracted prior to irradiation. Other authors have reported that dental extractions which are associated with RT result in minimal complications (Wildermuth & Cantril 1953, Solomon et al. 1968). A very conservative attitude toward extractions was proposed by Paterson (1963), who advised that most teeth should be retained in spite of inevitable complications. Daly and Drane (1972) expressed the opinion that only teeth which are completely unsalvageable and would require extraction shortly after treatment, and those that would be the source of severe post irradiation complications if left in place, should be removed. Daly (1977) mentioned that extraction of totally decayed or periodontally involved teeth should be considered only if an adequate healing time (seven to ten days) was available. According to Beumer et al. (1984) all teeth with a questionable prognosis should be extracted. They also mentioned that dentition with significant periodontal deficiencies is difficult to maintain, and is quite susceptible to caries as well as periodontal infections after RT. Bruins et al. (1998) suggested a complex tooth-by-tooth algorithmus of extraction of teeth. Another school of thought proposes conservation of as many functional teeth as possible for the patient, provided that a continuous preventive, restorative and periodontal care is available (Tong et al. 1999).

Nowadays, extraction of teeth prior to RT is recommended for teeth with poor condition or poor prognosis (MacComb 1962, Morrish et al. 1981, Stevenson-Moore 1990, Jansma et al. 1992b, Thorn et al. 2000, Schiødt & Hermund, 2002, Koga et al.

2008a). Although in some cases a conservative approach is indicated, the less motivated the patient, the more aggressive one should be in extracting teeth before RT (Beumer et al. 1979a, Beumer et al. 1979b, Horiot et al. 1981, Jansma et al. 1992b, Epstein et al. 1999b, Epstein & Stevenson-Moore 2001). Teeth that are located in the high-dose radiation field should be extracted before RT if they are nonrestorable (Epstein 2001). Teeth that are likely to be nonfunctional or inaccessible after other extractions or due to cancer treatment effects should also be removed (Shaw & Butterworth 2011). Criteria for extraction of teeth before RT include moderate to advanced periodontal disease, periodontal pockets over 5-6mm (Schiodt & Hermund 2002), furcation involvement of grade 2 and mobility of grade 2 or more, extensive periapical root lesions, extensive decays, partially impacted teeth, and residual root tips not fully covered by bone (Murray et al. 1980a, Beumer et al. 1984, Jansma et al. 1992b, Sulaiman et al. 2003, Vissink et al. 2003a). Fully embedded teeth may not require removal if they are otherwise normal (Rothwell 1987, Mealey et al. 1994, Oh et al. 2004), but if they can provide an infectious pathway to the jaw bone and other problems they have to be extracted (Hayward et al. 1969). An indiscriminate extraction of all teeth is not idicated. Extractions of unrestorable, but asymptomatic teeth in pre-radiation visits or in the post-radiation period in patients with advanced or end-stage diseases are not advocated (Koga et al. 2008b). A minimum of 2 weeks should be allowed prior to onset of RT (Hayward et al. 1969, Epstein et al. 1987a, Marx & Johnson 1987, Berger et al. 1998) although there are studies where ORN developed 3 years after extraction of teeth (Chang et al. 2007).

The next phase of prevention of ORN includes the intrairradiation and postirradiation period. During this phase the patient's oral and dental health should not be overlooked. Patients should be followed up at regular intervals throughout their lifetime as septic ORN can occur at any time after RT. At each examination it must be determined whether there is a recurrent or new tumor or any degenerative change of teeth, bone, or oral soft tissue. Scaling measurement of the periodontal pocket depth and plaque index should be conducted once every 6 months and radiograph examination once every 12 months (Katsura et al. 2008). Acute dental diseases can be managed either with endodontic therapy or extraction of the affected teeth. This decision should be made on an individual basis depending upon patient‘s general condition and severity of dental problem (Guttenberg 1974). Dental extractions should

be delayed 9-12 months after completion of RT in order to reduce the risk of ORN (Vanderpuye & Goldson 2000). Postirradiation biopsies should also be avoided since trauma and secondary infection may lead to true necrosis (Howland et al. 1975).

In case of extractions most authors suggest that they should be performed with minimal trauma or atraumatically to reduce risk of developing ORN (Solomon et al. 1968, Kraut 1985, Epstein et al. 1987b, Schweiger 1987, Maxymiw et al. 1991, Tong et al. 1999, Lye et al. 2007, Kaur et al. 2009, Sulaiman et al. 2003). Atraumatic extraction is best described as limited mucoperiosteal disruption (Beumer et al. 1979b, Marciani & Ownby 1986, Maxymiw et al. 1991) and minimal bone injury. This can not be possible in difficult cases due to tooth-root morphology, impaction or deeply retained roots. The logic is to preserve integrity of periosteum, an important source of vascularity especially in impaired tissues (Beumer et al. 1979b). Alveoloplasty and suturing of socket are commonly performed to avoid ORN (Solomon et al. 1968, Rankow & Weissman 1971, Beumer et al. 1983b, Marx et al. 1985, Epstein et al. 1987b, Lambert et al. 1997, Carl & Ikner 1998, Tong et al. 1999, Chaux-Bodard et al. 2004, Lye et al. 2007). This procedure attempts to trim off sharp bony spicules and provide soft tissue coverage for the sockets to prevent bone exposure (Daly & Drane 1972, Bedwinek et al. 1976, Starcke & Shannon 1977). Niebel and Neeman (1957) suggested that alveoloplasty should be done to reduce clot size. Another reason is that alveolar ridge will not readily remodel in this compromised tissue resulting in an irregular ridge that would cause increased risk of bony exposure when wearing a denture in the future (Carl et al. 1973, Beumer & Frady 1978). Limiting the number of teeth extracted per session has been suggested to prevent ORN by avoiding overburdening the already limited blood supply (Carl et al. 1973, Beumer et al. 1983b, Maxymiw et al. 1991). Other less popular suggestions include avoiding lidocaine or adrenaline-containing local anesthesia (Maxymiw et al. 1991, Chaux-Bodard et al. 2004, Lye et al. 2007), use of a nasogastric tube during postoperative period (Horiot et al. 1983), elastic or orthodontic extraction (Niebel & Neeman 1957) and chlorhexidine mouthwash (Tong et al. 1999, Lye et al. 2007). Antibiotic prophylaxis is also part of preoperative preparation before extraction in irradiated population (Daly et al. 1972, Coffin 1983, Epstein et al. 1987b, Makkonen et al. 1987, Maxymiw et al. 1991, Costantino et al. 1995, Tobias & Thomas 1996, Tong et al. 1999, Kanatas et al. 2002, Sulaiman et al. 2003, Lyons & Ghazali 2008) since the incidence for post-

extraction ORN with use of antibiotics is 6% (Beumer & Seto 1981, Beumer et al. 1983a, Beumer et al. 1983b, Nabil & Samman 2011). Alternatives to tooth extraction for patients who have been irradiated to the jaws are treatment of infected teeth roots and grist to the level of gingiva (Hayward et al. 1969, Beumer & Seto 1981, Beumer et al. 1984) as well as exfoliation of hypermobile teeth (Hayward et al. 1969).

Attention should also be paid to dental care with efforts to ensure that caries is continuously and effectively prevented (Hayward et al. 1969, Daly & Drane 1972, Beumer et al. 1979b, Makkonen et al. 1987, Jolly 2004). In order to prevent occurrence of radiation caries, topical sodium fluoride gel should be applied daily to the remaining teeth for an indefinite period (Curi & Dib 1997, Jolly 2004, Chang et al. 2007). This procedure can be performed by the patient himself using a custom-made fluoride gel carrier. Application of 1% fluoride gel showed reduction in incidence of ORN from 35% to 24.5 % (Daly et al. 1972). A prospective French study showed also no case of post-dental extraction ORN in patients adhering to post–irradiation programme including five minutes daily application of fluoride gel and use of fluoride toothpaste (Horiot et al. 1983). As radiation-induced xerostomia is a causative factor of dental caries (Moller et al. 2004) and ORN, maintenance of a moist oral environment is crucial to prevent ORN (Jolly 2004). Patient with a dry mouth should avoid anything that further impairs salivation like drugs, tobacco and alcohol. They may benefit from dietary control, taking frequent sips of water and using artificial saliva (Scully & Porter 2001).

Patient's compliance plays also an important role in the prevention of ORN (Horiot et al. 1983, Perrier & Moeller 1994). Besides regular participation in the oral surgical and oncoradiological control examinations, patients must devote particular care to the cleanliness of teeth and to maintain a healthy parodontium. Minor dental interventions with a preserving aim, depurations and periodontal treatments may always be performed without delay, since unrestorable dental caries and moderate to severe periodontal disease are risk factors of ORN (Epstein & Stevenson-Moore 2001, Schiodt & Hermund 2002). In all cases it is recommended to learn the opinion of the treating physician in advance. Use of a chlorhexidine-containing toothpaste and oral rinse can ensure effective defence against plaque formation and secondary periodontal diseases, which may play a decisive role in superinfection of bone which is in a

damaged condition following irradiation (Calman 1991). In the event of complaints patients must turn immediately to the treating physician (Nemeth et al. 2000).

All the above mentioned measures can reduce likelihood of ORN by a factor of 3 (Grötz et al. 2001b). It can be concluded that it is important to prevent intraosseous infection by consistent pretherapeutic dental hygiene (Bast et al. 2013). This can be achieved by thorough explanations to patients for the importance of dental management and a “close follow-up” schedule (Jacobson et al. 2010).

SPECIFIC PART

Purpose of the study

Until nowadays, a great number of authors have studied the entity of ORN and risk factors for its occurrence. Several staging systems have been proposed to aid management of ORN. There exists also a wide spectrum of clinical and radiological manifestations of ORN. However, its treatment remains challenging despite multiple options proposed through the years.

A search of the literature (PubMed and MEDLINE Database, Cochrane Library) revealed a distinct lack of studies that identify factors associated specifically with the severity of mandibular ORN. The investigation of the severity is clinically extremely important, since the management of the severe cases differs considerably from that of early-stage disease. Clinical symptoms, radiological findings and prophylaxis protocols present a wide variance among the different stages of necrosis.

For these reasons, the purpose of this study is to find risk factors indicating the severity of ORN. More specifically it aims to:

i. describe the demographic data of patients that were treated for ORN,
ii. examine the tumor characteristics of these patients,
iii. investigate the oral status and symptomatology of these patients,
iv. detect factors that may have contributed to the onset of necrosis,
v. examine the frequency of areas where necrosis occurred,
vi. record the treatment methods of patients,
vii. identify risk factors associated with the severity of ORN and finally,
viii. delineate and correlate these factors with the general characteristics of the patients

The establishment of these factors would help to formulate appropriately aggressive prophylaxis and treatment strategies based on the severity of occurrence of ORN.

Chapter 10

Material and methods

A retrospective analysis of 115 patients who were diagnosed with ORN and were treated in the Department of Oral and Maxillofacial Surgery in Munich (LMU) in the period from January 2003 until December 2012 was conducted. These patients suffered from ORN once or more times during their life, either at the same or different areas from the initial outbreak. The study was approved by the Ethical Committee of the University of Munich (Project-Nr. 083-11).

ORN of the jaws was defined as exposed irradiated bone that fails to heal over a period of 3 months without evidence of persisting or recurrent tumor (Marx 1983a, Marx & Johnson 1987, London et al. 1998, Teng & Futran 2005, Pitak- Arnnop et al. 2008, Khojastepour et al. 2013).

Taking into account this definition inclusion criteria were the following:

- patients with head and neck tumors who had been treated with RT once or more times in their life,
- patients with denuded bone in the oral cavity for a period of more than 3 months,
- patients with no evidence of persisting or recurrent tumor,
- patients with no use of antiresorptive drugs (bisphosphonates or denosumab) before, during or after tumor therapy,
- patients with histologically proven ORN

Data were gathered by searching medical records of the patients, including files, letters, radiographic findings, histological examinations, photographs and operational reports. Data that were collected included:

1. personal data (age, gender),
2. health data (general health problems, smoking, alcohol consumption),
3. tumor data (localization, staging, means of therapy, dose of radiation, times of radiation),

4. oral health data (dental treatment before RT, dental treatment during or after RT)
5. information about symptomatology and factors that contributed to the onset of ORN
6. information about the methods of treatment conducted to these patients
7. information about the exact localization of necrosis to the jaws

All radiological examinations (OPT, CT, MRI) were thoroughly examined not only for general pathologic changes but also for abnormalities specific to ORN lesions. These included localized osteolytic areas, extensive osteolytic areas, sequestra, fractures, persistent sockets after tooth extraction and mixed radio-opaque radiolucent lesions.

Particular emphasis was given to the exact localization of necrosis. Localization was recorded after search in the medical files and was compared with data available on radiological examinations and photos. Affected regions were numbered according to the International Dental Scheme of Fédération Dentaire Internationale (FDI). A distinction between localization in maxilla and mandible was also conducted.

RT was categorized as: RT in head and neck region or RT in other parts of the body; metastasis in bone was differentiated from metastasis in other parts of the body. Smoking was recorded not only for active smokers at the time of the study conduction but also for those who had given the habit up after tumor therapy. The following symptoms were documented: exposure of bone, pain, swelling, inflammation, fistula, fracture, pus and inferior alveolar nerve hypesthesia. The treatment provided was divided into two groups: i) conservative including antibiotics, analgesics, debridement and sequestrectomy, and ii) surgical including radical sequestrectomy, alveolectomy with primary closure or hemimandibulectomy, closure of orocutaneous fistulae and local or microvascular free flap reconstruction.

Initially, the descriptive assessment of the data was carried out first by calculating observed values and relative frequencies over the entire patient population. Then the total sample was categorized in three groups (stages) based on the classification of Notani et al. (2003) (Table 3). Different variables were evaluated in an attempt to find a correlation between them and the severity of necrosis.

Table 3. Notani et al. classification of ORN after clinical examination and orthopantogram

Stage	Criteria
I	ORN confined to dentoalveolar bone
II	ORN limited to dentoalveolar bone or mandible above the inferior dental canal, or both
III	ORN involving the mandible below the inferior dental canal, or pathological fracture, or skin fistula

The variables were analyzed using the Statistical Package for the Social Sciences (IBM SPSS Statistics v.22, New York, NY, USA). Data analysis included descriptive statistics by analyzing observed values and frequencies. Association between categorical variables was tested for statistical significance using the chi-square test. The sample was then categorized in two groups. Group 1 consisted of stage III cases and group 2 included stage I and II cases. Those variables that demonstrated significant associations with the dependent variable 'stage of necrosis' were included in a binary logistic regression model in order to identify significant predictors for the stage III of necrosis. The level of significance was set in all cases at $p = 0.05$.

Chapter 11

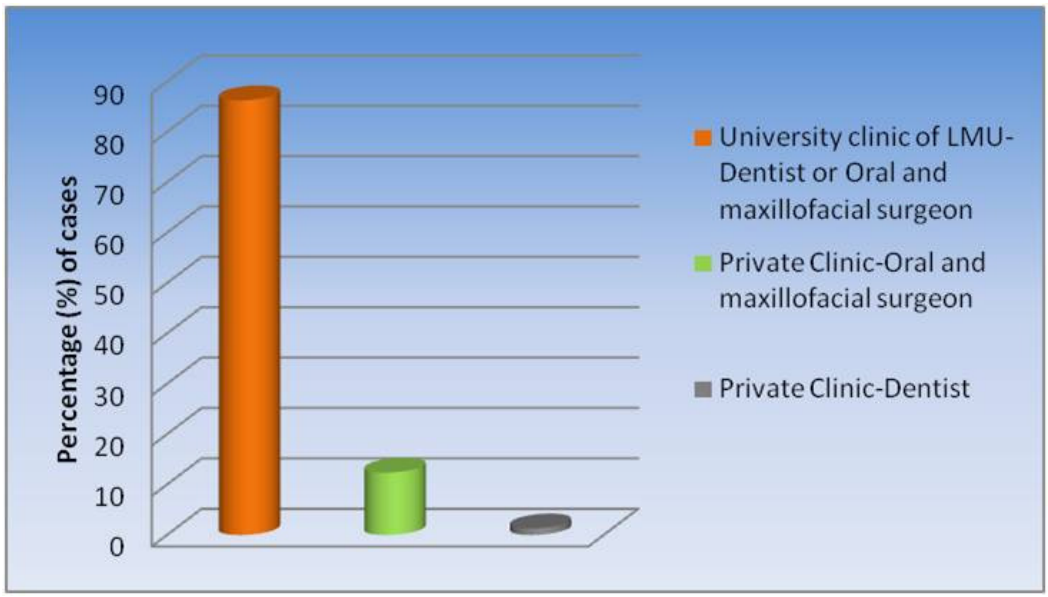
Results

Results were classified in the following categories: data regarding sample size, data regarding stage of necrosis, personal characteristics, general health characteristics, tumor-related characteristics, treatment-related characteristics, information about the oral health of patients and factors that contributed to the onset of ORN, information about symptomatology and localization of necrosis, information about treatment of necrosis and results of the logistic regression.

11.1 Data regarding sample size

One hundred fifteen patients were diagnosed with ORN and were treated in the Department of Oral and Maxillofacial Surgery in Munich (LMU) in the period from January 2003 until December 2012. From these patients 86 developed ORN once, 23 twice, 4 patients three times, 1 patient four times and 1 five times. The final sample consisted of 153 cases of ORN. Figure 1 shows the number of cases diagnosed in each institution.

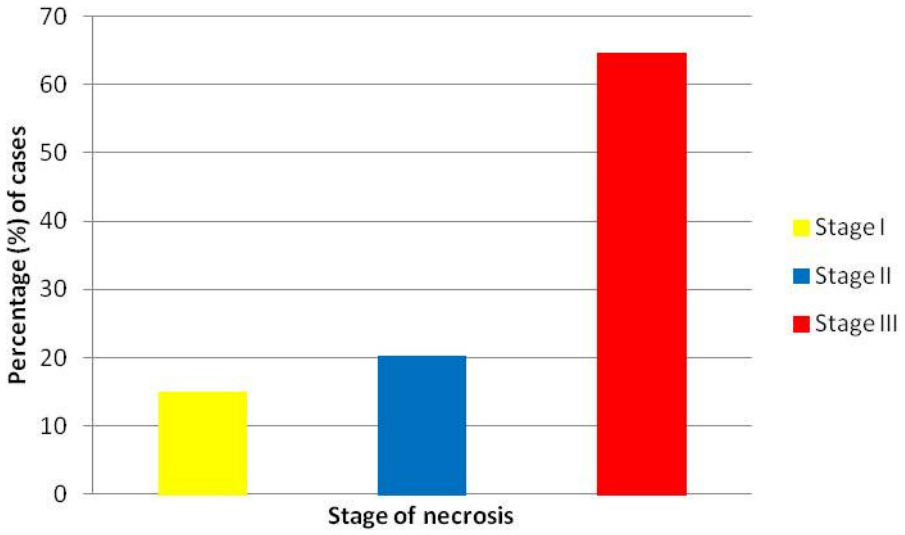
Figure1. Percentages (%) of cases being diagnosed in each institution



11.2 Data regarding stage of necrosis

One hundred percent of patients had mandibular ORN and none of them developed ORN of the maxilla. The distribution of cases according to the stage of ORN is shown in figure 2. Ninety-nine cases were stage III, followed by 31 stage II cases and 23 stage I cases.

Figure 2: Percentages (%) of cases by each stage of necrosis



11.3 Personal characteristics

Personal characteristics are shown in table 4. The mean age of cases at the time of occurrence of ORN was 60.68 years (SD=9.3). One hundred seventeen of the cases were male and 36 were female. Ninety-one of the cases were dead at the time when the study was completed.

Table 4 shows also the relationship between the variables and severity of necrosis. The difference in severity of mandibular ORN was not statistically significant between men and women (χ^2=1.65, p=0.44) and between the different age groups of the cases (χ^2=2.33, p=0,675).

11.4 General health characteristics

Table 5 shows the general health characteristics of the cases. There was a statistically significant association between the severity of ORN and DM (χ^2=51.96, p<0.001), active smoking (χ^2=85.81, p<0.001) and alcohol consumption (χ^2=73.71, p<0.001).

From the 23 cases that were referred as no smokers, 21 had never smoked and 2 were smokers in the past and had given up the habit after tumor diagnosis. The alcohol consumption was referred as positive when the patient was drinking more than the amount determined from American Heart Association as normal consumption.

Table 4. Personal characteristics by number (*N*) and percentages (%) of the cases and their distribution into 3 stages. Relationship between categorical variables and stage of necrosis (*P*-value)

Demographic factor	*N* (%)	Stage I *N* (%)	Stage II *N* (%)	Stage III *N* (%)	*P*-value*
Sex					
Male	117 (76.5)	18 (11.8)	21 (13.7)	78 (51.0)	0.44
Female	36 (23.5)	5 (3.3)	10 (6.5)	21 (13.7)	
Age					
≤55 years	36 (23.5)	5 (3.3)	8 (5.2)	23 (15.0)	0.675
56-65 years	76 (49.7)	14 (9.2)	16 (10.4)	46 (30.1)	
≥66 years	41 (26.8)	4 (2.6)	7 (4.6)	30 (19.6)	
Death					
Alive	62 (40.5)	11 (7.2)	11 (7.2)	40 (26.1)	
Dead	91 (59.5)	12 (7.8)	20 (13.1)	59 (38.6)	

*Chi-square test

11.5 Tumor-related characteristics

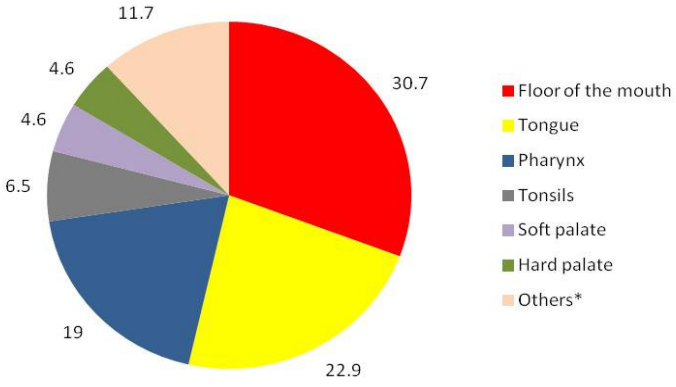
Figure 3 presents the initial tumor's site. Floor of the mouth, tongue and pharynx tumor comprised 111 cases of initial tumors. Table 6 outlines the tumor characteristics. Tumor size was detected from histological findings and stage was estimated according to the UICC system. Tumors were then divided into two groups according to their connection with the adjacent tissues (soft and hard tissues) and into four groups according to their localization regarding jaws (maxilla, mandible, oropharynx, other). A statistically significant association was found between size of tumor (χ^2=58.58, p<0.001) as well as stage of tumor (χ^2=23.54, p=0.001) and severity of ORN. There was no significant correlation between tumor connection with soft or hard tissues (χ^2=0.74, p=0.69) as well as tumor localization (χ^2=5.45, p=0.49) and the severity of necrosis.

Table 5. General health characteristics by number (*N*) and percentages (%) of the cases and their distribution into 3 stages. Relationship between categorical variables and stage of necrosis (*P*-value)

General health characteristic	*N* (%)	Stage I *N* (%)	Stage II *N* (%)	Stage III *N* (%)	*P*-value*
Diabetes mellitus (DM)					
Yes	92 (60.1)	0 (0.0)	14 (9.1)	78 (51.0)	<0.001
No	61 (39.9)	23 (15.0)	17 (11.2)	21 (13.7)	
Vessels disease					
Yes	90 (58.8)	14 (9.2)	21 (13.7)	55 (35.9)	0.47
No	63 (41.2)	9 (5.9)	10 (6.5)	44 (28.8)	
Rheumatic disorder					
Yes	7 (4.6)	0 (0.0)	1 (0.7)	6 (3.9)	0.42
No	146 (95.4)	23 (15.0)	30 (19.6)	93 (60.8)	
Active Smoking					
Yes	130 (85.0)	5 (3.3)	28 (18.3)	97 (63.4)	<0.001
No	23 (15.0)	18 (11.8)	3 (2.0)	2 (1.2)	
Alcohol					
Yes	117 (76.5)	2 (1.3)	23 (15.0)	92 (60.2)	<0.001
No	36 (23.5)	21 (13.7)	8 (5.2)	7 (4.6)	

*Chi-square test

Figure 3. Percentages (%) of cases in relation to initial tumor's site



*Others include tumors of salivary glands, body of the mandible, larynx, skin, throat, sinus maxillary, alveolar process and intermaxillary tumors

Table 6. Tumor characteristics by number (*N*) and percentages (%) of the cases and their distribution into 3 stages. Relationship between categorical variables and stage of necrosis (*P*-value)

Tumor characteristic	*N* (%)	Stage I *N* (%)	Stage II *N* (%)	Stage III *N* (%)	*P*-value*
Tumor size (T)					
1	24 (15.7)	3 (2.0)	9 (5.9)	12 (7.8)	<0.001
2	37 (24.2)	18 (11.8)	6 (3.9)	13 (8.5)	
3	30 (19.6)	0 (0.0)	10 (6.5)	20 (13.1)	
4	62 (40.5)	2 (1.3)	6 (3.9)	54 (35.3)	
Stage (UICC)					
I	20 (13.1)	2 (1.3)	7 (4.6)	11 (7.2)	0.001
II	12 (7.8)	4 (2.5)	3 (2.0)	5 (3.3)	
III	39 (25.5)	12 (7.8)	9 (5.9)	18 (11.8)	
IV	82 (53.6)	5 (3.3)	12 (7.8)	65 (42.5)	
Connection with tissues					
Soft	137 (89.5)	20 (13.1)	29 (19.0)	88 (57.4)	0.69
Hard	16 (10.5)	3 (2.0)	2 (1.3)	11 (7.2)	
Localization					
Maxilla	15 (9.8)	2 (1.3)	2 (1.3)	11 (7.2)	0.49
Mandible	91 (59.5)	13 (8.5)	17 (11.1)	61 (39.9)	
Oropharynx	41 (26.8)	6 (3.9)	12 (7.8)	23 (15.1)	
Other	6 (3.9)	2 (1.3)	0 (0.0)	4 (2.6)	

*Chi-square test

11.6 Treatment-related characteristics

Treatment data of the initial tumor are detailed in table 7. All 153 cases received one setting of RT. Among these 10 received also a second setting of RT and 3 received a third setting. Data regarding RT dose were available only for 138 cases. The mean dose at the first RT setting was 63.4 Gy (SD=6.8) and the mean age at the time of first RT setting was 54.5 years (SD=9.1). Eighty point four percent of the cases were treated also with chemotherapy and 10 out of 153 cases were treated also with RT in other parts of the body. A statistically significant correlation was found between the severity of ORN and treatment with chemotherapy (χ^2=1.87, p<0.001). There was no significant association between severity of ORN and times of RT (χ^2=2.14, p=0.71) as

well as dose at the first RT setting (χ^2=1.64, p=0.44), RT in other parts of the body (χ^2=0.72, p=0.70) and time between RT and occurrence of ORN (χ^2=5.57, p=0.47).

Table 7. Treatment characteristics of the initial tumor by number (*N*) and percentages (%) of the cases and their distribution into 3 stages. Relationship between categorical variables and stage of necrosis (*P*-value)

Treatment characteristic	*N* (%)	Stage I *N* (%)	Stage II *N* (%)	Stage III *N* (%)	*P*-value*
RT setting					
First	140 (91.5)	21 (13.7)	27 (17.6)	92 (60.2)	0.71
First and 1. adjuvant	10 (6.4)	1 (0.7)	3 (2.0)	6 (3.7)	
First and 2. adjuvant	3 (2.1)	1 (0.7)	1 (0.7)	1 (0.7)	
Dose at first RT setting ±					
≤60 Gy	62 (44.9)	10 (7.2)	15 (10.9)	37 (26.8)	0.44
>60 Gy	76 (55.1)	12 (8.7)	12 (8.7)	52 (37.7)	
Chemotherapy					
Yes	123 (80.4)	1 (0.7)	26 (17.0)	96 (62.7)	<0.001
No	30 (19.6)	22 (14.3)	5 (3.3)	3 (2.0)	
RT in other parts					
Yes	10 (6.5)	1 (0.7)	3 (2.0)	6 (3.8)	0.72
No	143 (93.5)	22 (14.4)	28 (18.3)	93 (60.8)	
Time between RT and occurrence of ORN ±					
0-3 years	55 (38.7)	12 (8.4)	9 (6.3)	34 (24.0)	0.47
3.1-6 years	40 (28.2)	3 (2.1)	10 (7.1)	27 (19.0)	
6.1-9 years	21 (14.8)	2 (1.5)	5 (3.5)	14 (9.8)	
>9 years	26 (18.3)	6 (4.3)	5 (3.5)	15 (10.5)	

*Chi-square test

±Number (*N*) and percentages (%) have been calculated with respect to the number of cases where data was available

11.7 Oral health condition before radiotherapy and factors that contributed to the onset of osteoradionecrosis

Table 8 shows the data regarding oral health condition of patients before RT and the factors that contributed to the onset of ORN. Fifty-six point nine percent of the cases did not undergo dental examination and treatment before RT. The difference in severity of ORN and dental examination and treatment before RT was statistically significant (χ^2=33.94, p<0.001).

In 59.5% of the cases there was an objective cause for the onset of ORN, whereas in 40.5% ORN occurred "spontaneously". The severity of necrosis was correlated with the occurrence of ORN either spontaneously or due to a specific factor (χ^2=11.99, p=0.002). Causes of ORN included many variables such as extraction of a tooth, implantation, denture irritation or even a local pathological condition such as marginal or apical periodontitis. For better analysis, these variables were divided into two groups in the present study. The first group was the dental treatment group including extraction, implantation and extraction combined with other dental treatment. The second group was the local pathological condition group including denture irritation, marginal periodontitis, impacted wisdom tooth and apical periodontitis. Fifty point five percent of stage III cases occurred spontaneously, whereas 47.8% of stage I and 41.9% of stage II were contributed to dental treatment in the region of necrosis (figure 4). The main cause in the dental treatment group (figure 5) was extraction of a tooth (85.6%) but the severity of ORN was not associated with the time of its occurrence (χ^2=5.20, p=0.52). The main cause in the local pathological condition group (figure 6) was marginal periodontitis (82.9%). Factors presented in figures 5 and 6 were also statistically significant associated with the severity of ORN (χ^2=31.15, p=0.03).

Table 8. Oral health condition before RT and factors that contributed to the onset of ORN by number (*N*) and percentages (%) of the cases and their distribution into 3 stages. Relationship between categorical variables and stage of necrosis (*P*-value)

Characteristics	*N* (%)	Stage I *N* (%)	Stage II *N* (%)	Stage III *N* (%)	*P*-value*
Dental examination & treatment before RT					
Yes	66 (43.1)	22 (14.3)	15 (9.8)	29 (19.0)	<0.001
No	87 (56.9)	1 (0.7)	15 (9.8)	71 (46.4)	
Occurrence of ORN					
Cause	91 (59.5)	19 (12.5)	23 (15.0)	49 (32.0)	0,002
Spontaneously	62 (40.5)	4 (2.6)	8 (5.2)	50 (32.7)	
Dental surgery					
No	97 (63.5)	12 (7.8)	18 (11.8)	67 (43.9)	0.52
Before RT	10 (6.5)	3 (2.0)	2 (1.3)	5 (3.2)	
After RT	40 (26.1)	8 (5.2)	9 (5.9)	23 (15.0)	
Unknown	6 (3.9)	0 (0.0)	2 (1.3)	4 (2.6)	

*Chi-square test

Figure 4. Percentages (%) of cases in relation to the type of occurrence of ORN and their distribution into 3 stages

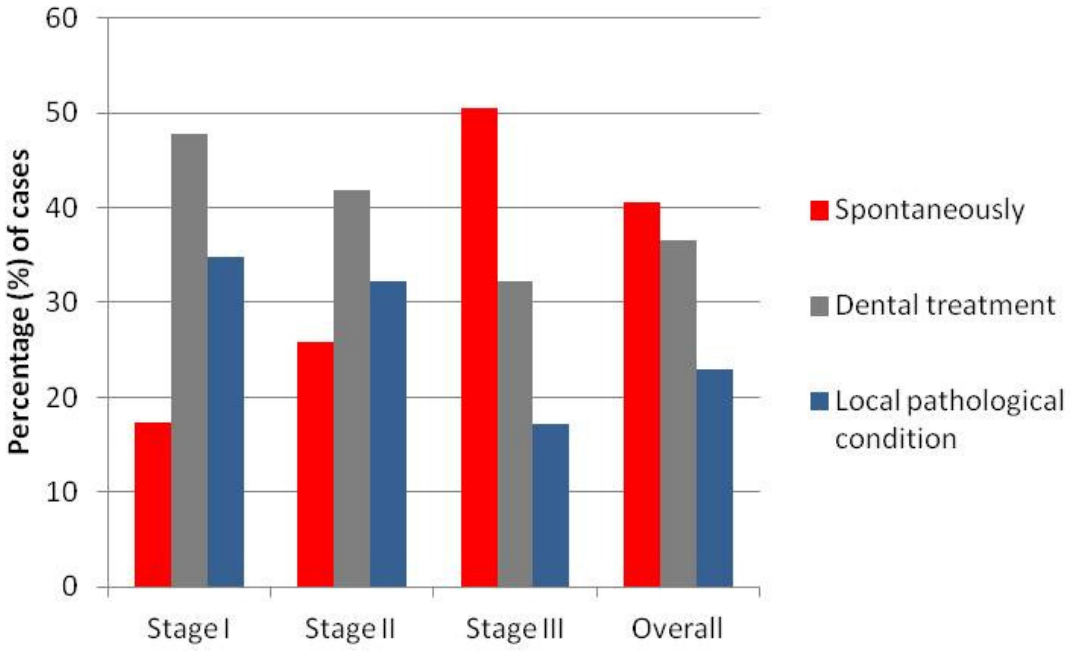
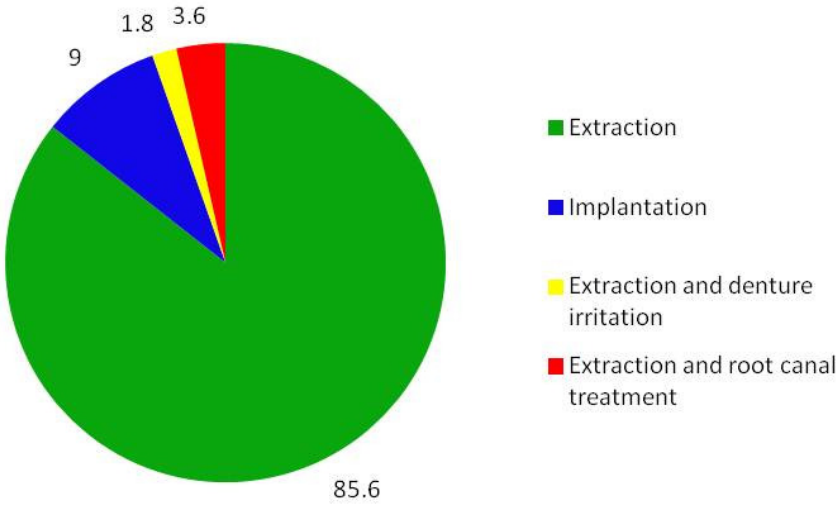
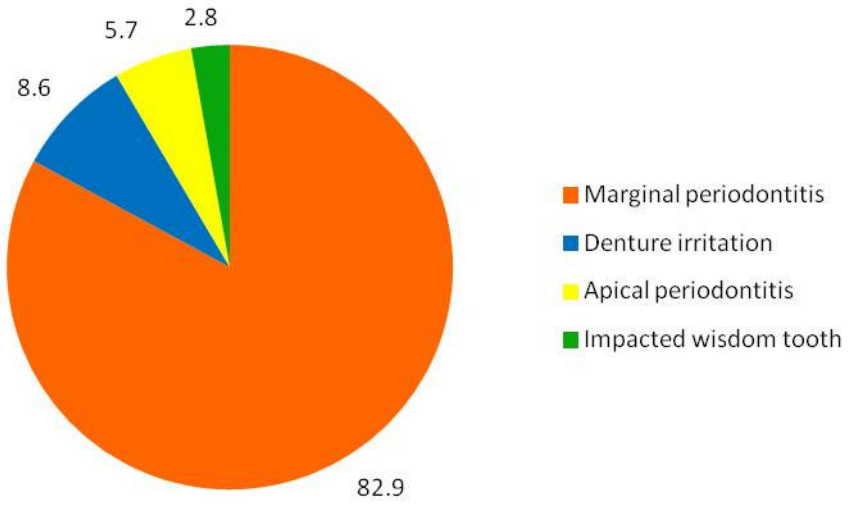


Figure 5. Percentages (%) of cases in relation to the type of dental treatment*



*Percentages (%) have been calculated with respect to the number of cases which occurred after dental treatment

Figure 6. Percentages (%) of cases in relation to the type of local pathological condition*



*Percentages (%) have been calculated with respect to the number of cases which occurred due to local pathological conditions

11.8 Symptomatology and treatment

Figure 7 shows the symptoms distributed into three stages. One hundred percent of the cases had exposure of bone. In 43.8% of the cases a fracture occurred, and 49.7% had a fistula. All of them were stage III cases. The main symptoms in stage II cases were inflammation (20.3% of the total), wound healing disorder (20.3% of the total), pain (19% of the total) and swelling (18.3% of the total). The majority of stage I cases were suffering from wound healing disorder (15% of the total) and pain (5.2% of the total). Twenty-one point six percent of the cases presented hypesthesia of the inferior alveolar nerve and all of them where stage III cases.

Treatment methods regarding stage of necrosis are presented in figure 8. Ninety-two point two percent of the cases independent of stage were treated surgical.

Figure 7. Percentages (%) of cases suffering from each symptom and their distribution into 3 stages

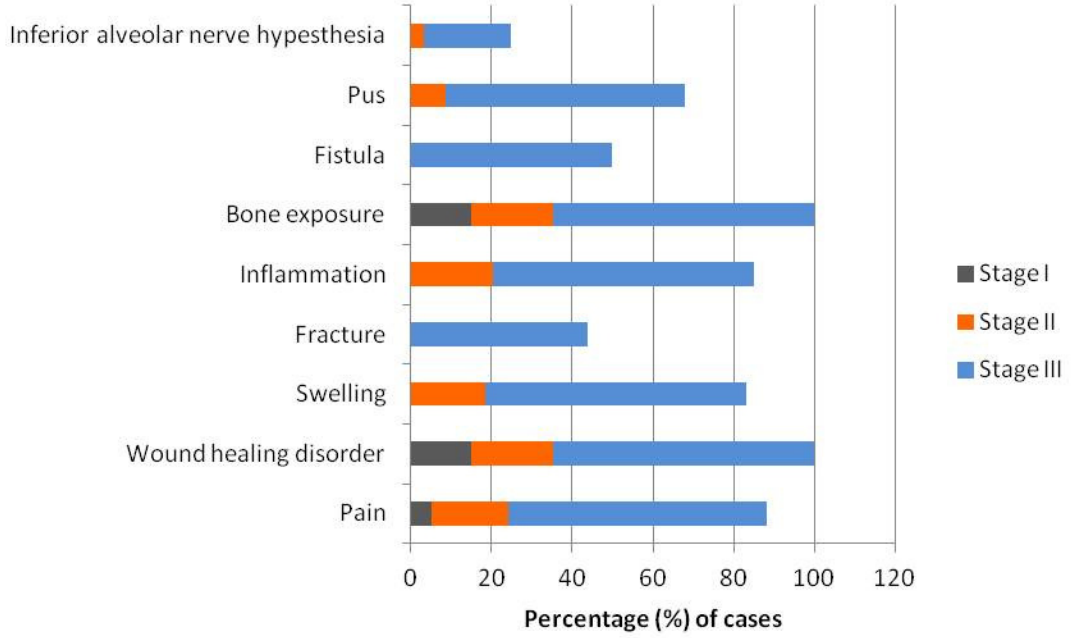
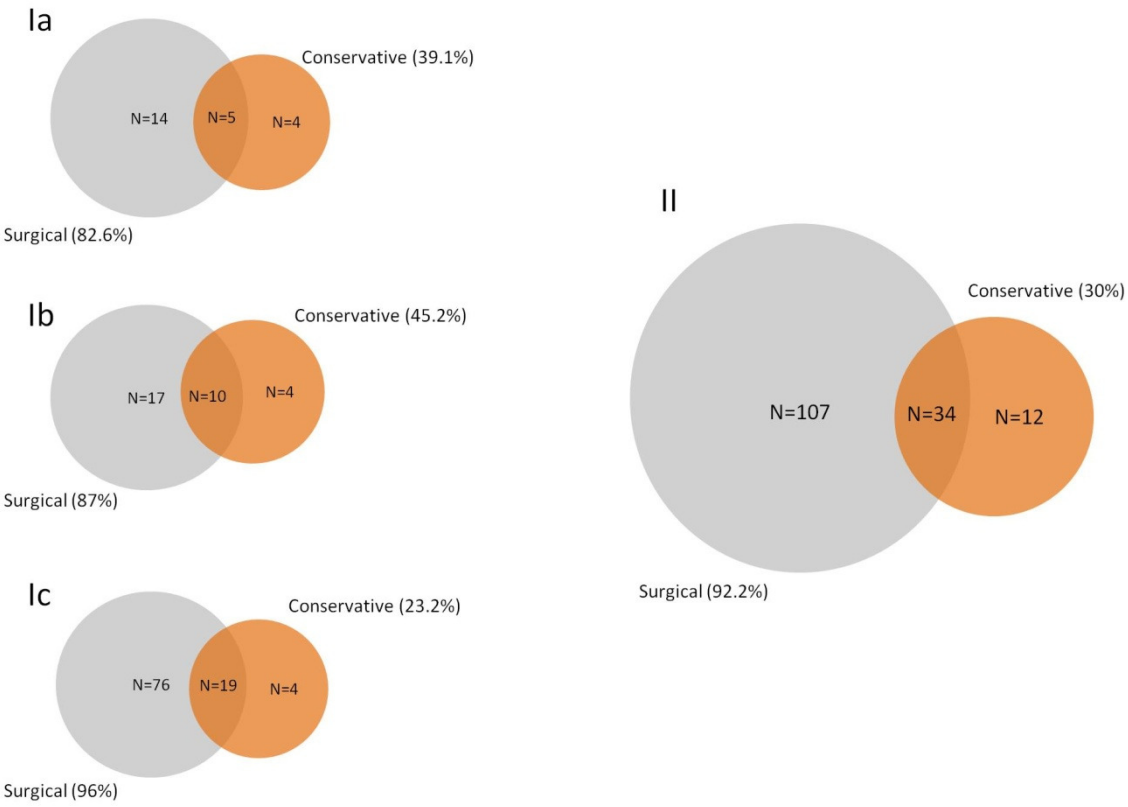


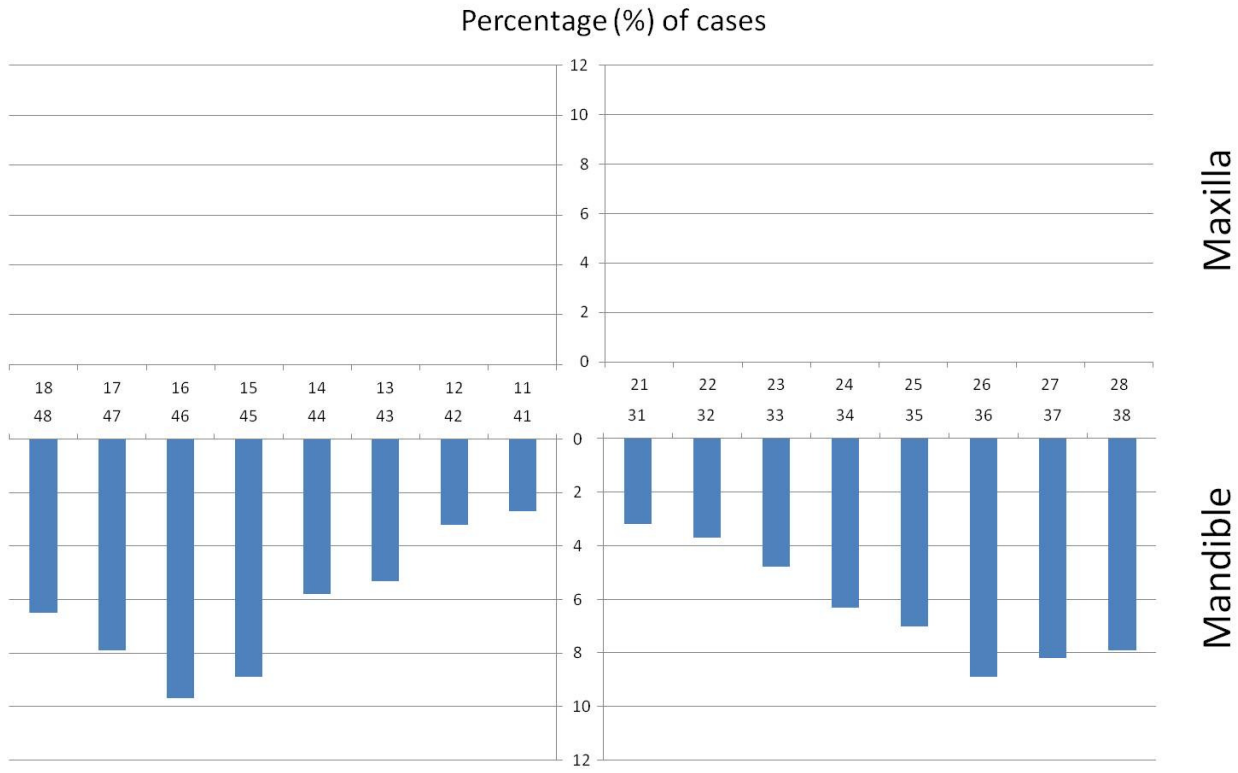
Figure 8. Number (*N*) of cases which have been treated by surgical and conservative treatment or both in each stage of osteonecrosis (Ia, Ib, Ic) and in all cases independent of stage (II). Percentage (%) of cases which have been treated by each method



11.9 Localization of necrosis

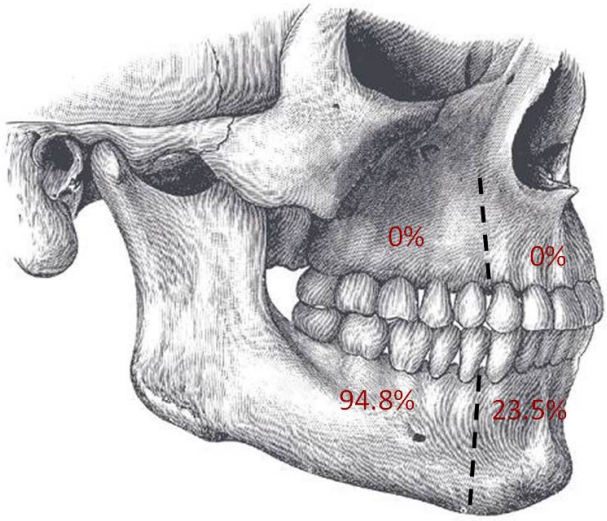
Figure 9 shows a detailed depiction of the areas of teeth that were affected. Affected regions were numbered according to the International Dental Scheme of FDI. One hundred percent of the cases occurred in the mandible and none of them in the maxilla. In 42.5% of cases right side (4.quadrant) of mandible was affected, in 35.9% left side (3. quadrant) and in 21.6% both sides. The distribution of cases into posterior and anterior region of mouth is shown in figure 10. Seventy-six point five percent of the cases occurred in the posterior region, 5.2% in the anterior and in 18.3% of the cases both posterior and anterior region were affected. However, there was no significant association between the severity of ORN and its localization in anterior or posterior region (χ^2=2.96, p=5.7).

Figure 9. Percentages (%) of the affected regions of the mouth according to the International Dental Scheme of FDI*



*Percentages (%) have been calculated with respect to the total number of times each region was affected

Figure 10. Percentages (%) of cases localized into anterior and posterior region of the jaws as well as upper and lower jaw



11.10 Results of the logistic regression

The forward stepwise logistic regression analysis revealed the following results:

- The cases that were suffering from DM were 4.955 times more likely (OR: 4.955, 95% Cl: 1.965-12.495) to develop stage III necrosis compared to those who were not suffering from the disease.
- The cases that were smoking were 13.542 times more likely (OR: 13.542, 95% Cl: 2.085-87.947) to develop stage III necrosis compared to those who were not smoking.
- The cases that were consuming more alcohol than the maximum permissible limit were 5.428 times more likely (OR: 5.428, 95% Cl: 1.622-18.171) to develop stage III necrosis compared to those who were not drinking.
- The cases in which ORN occurred spontaneously were less likely (OR: 0.237, 95% Cl: 0.086-0.655) to develop stage III necrosis compared to those in which ORN occurred due to dental treatment or local pathological condition (Table 9).

Table 9. Significant predictors for stage III of necrosis. Results of the forward stepwise logistic regression analysis*

Significant predictors	B (SE)	Exp (B)	95% Confidence level	*P*-value
DM	1.600	4.955	1.965-12.495	0.001
Smoking	2.606	13.542	2.085-87.947	0.006
Alcohol	1.692	5.428	1.622-18.171	0.006
Spontaneous ORN	-1.438	0.237	0.086-0.655	0.005
Constant	-2.919	0.054		0.004

*Variables that were inserted in the logistic regression analysis: 1. Stage of the tumor (UICC) (0: Stage I, 1: Stage II, 2: Stage III, 3: Stage 4), 2. DM (0: No, 1: Yes), 3. Active smoking (0: No, 1: Yes), 4. Alcohol consumption (0: No, 1: Yes), 5. Concomitant chemotherapy (0: No, 1: Yes), 6. Dental examination and treatment before RT (0: No, 1: Yes), 7. Occurrence of ORN (0: spontaneously, 1: due to dental treatment/ local pathological condition)

Chapter 12

Discussion

Several studies have already investigated the entity of ORN. The majority of them have addressed risk factors associated with causation of ORN (Morrish et al. 1981, Kluth et al. 1988, Jereczek-Fossa & Orecchia 2002, Reuther et al. 2003, Studer et al. 2006, Ben-David et al. 2007, Ahmed et al. 2009, Peterson et al. 2010, Gomez et al. 2011, Bhide et al. 2012, Niewald et al. 2013, Tsai et al. 2013). Only four studies were found regarding the severity of ORN (Store & Boysen 2000, Notani et al. 2003, Chopra et al. 2011, Gevorgyan et al. 2013). They either consisted of a small sample size (Gevorgyan et al. 2013) or focused on the severity of ORN proposing new classification systems or modalities of therapy (Store & Boysen 2000, Notani et al. 2003). Only Chopra et al. (2011) attempted to deal specifically with factors linked with disease severity.

The present study attempted to thoroughly investigate risk factors related to the severity of ORN. Its sample size (153 cases) is much higher compared to sample sizes from other similar studies (Chopra et al. 2011, Gevorgyan et al. 2013). Data was gathered through records of cases of ORN treated in the Department of Oral and Maxillofacial Surgery in Munich (LMU). Consequently, its reliance depended on accuracy of written record or recall of individuals (recall bias). Sometimes important data was either not available (dose of radiation, time between radiation and occurrence of ORN) or it was impossible to access important information due to restrictions by statute or institutional regulations. The lack of control group made the identification of differences in characteristics between patients who suffered from osteonecrosis and those who did not impossible, although both were exposed to radiation (Hess 2004).

In this study it was also impossible to conduct a multinomial logistic regression (MNL model) in order to identify significant predictors for each stage of necrosis. The reason is that a lot of warnings occurred and consequently the validity of the model was uncertain. For this reason, the sample was categorized as group 1: stage III cases

and group 2: stage I/II cases. A logistic regression was conducted in order to identify significant predictors for stage III of necrosis. This classification seems to be more appropriate because of the more aggressive management of the advanced disease.

On the other hand, advantages of the study include low cost and a high amount of information available for analysis at the time study was conducted. It was also feasible to study the occurrence of ORN without time cost although there is a long latency between exposure and disease in the case of ORN. Moreover, the results of this study can generate a hypothesis that can be tested in future prospectively with better results and improvements in quality of the study (Hess 2004).

12.1 Data regarding stage of necrosis

The majority of previous studies used the system of Marx in order to divide patients into stages (Marx 1983a). The staging system of Marx is based on use and response to HBO therapy which is not widely used as conservative therapy in the Department of Oral and Maxillofacial Surgery in Munich (LMU). The staging system of Epstein et al. (1987a) is also often used but is focused on the presence or absence of a pathologic fracture (Schwartz & Kagan 2002). Due to these limitations the staging system of Notani et al. (2003) was used in the present study. This staging system was chosen for multiple other reasons as well. It is based on the presence or absence of clinical and radiological signs, as opposed to other systems that are nonspecific with regard to site of involvement, and are based, at least in part, on patients' subjective interpretation. The classification is also based on pretreatment evaluation and not on treatment response or refractoriness, allowing for more accurate categorization. It is also simple and memorable.

In the present study the majority of cases were stage III (64.7%) followed by stage II (20.2%) and stage I (15.1%). This finding is in accordance with the published literature regarding the severity of ORN. In the study of Gevorgyan et al. (2013) 64.3% of patients were stage II and III, in the study of Notani et al. (2003) 85 out of 87 patients were diagnosed with stage II and III disease and in the study of Chopra et al. (2011) 89.0% of patients were suffering from stage II and III necrosis.

12.2 Localization of necrosis

In this study the mandible was involved in 100% of the cases, whereas no case was diagnosed in maxilla. These findings are concordant with results from other studies (Morrish et al. 1981, Beumer et al. 1984, Eggert et al. 1985, Kluth et al. 1988, Curi & Dib 1997, Store & Boysen 2000, Thorn et al. 2000, Notani et al. 2003, Chopra et al. 2011, Gevorgyan et al. 2013). There are many reasons which can explain this discrepancy. The mandible has a restricted localized blood supply, which is often completely within the radiation field, whereas the maxilla has many anastomoses located outside the area of irradiation (Cowgiel 1960, Hoffmeister et al. 1969, Beumer et al. 1984, Thorn et al. 2000, Reuther et al. 2003). Furthermore, bone density is different between maxilla and mandible and mandible absorbs more amount of radiation during RT (Cheng & Wang 1974, Mainous & Hart 1975, Morrish et al. 1981, Vanderpuye & Goldson 2000, Lambade et al. 2013).

The posterior region of teeth was affected in 94.8% of the cases whereas the anterior only in 23.5% of the cases, a finding in accordance to the literature (Bras et al. 1990, Mounsey et al. 1995, Thorn et al. 2000, Reuther et al. 2003). Posterior areas of mandible are almost always included in the radiation field during RT of both oropharynx and regional lymph nodes (Epstein et al. 1987b, Thorn et al. 2000), as well as in the boosted RT fields. They also undergo maximal load during mastication and are often subjected to dental extractions which can favor the occurrence of ORN (Jereczek-Fossa & Orecchia 2002). In this study, there was no significant association between severity of ORN and localization of necrosis in posterior and anterior teeth possibly due to the fact that the majority of affected areas were the posterior (94.8%). A higher sample size would be needed to highlight a possible association between the two variables. This was impossible in the present study as all cases of ORN treated in the Department of Oral and Maxillofacial Surgery in Munich (LMU) are included in the study.

12.3 Personal characteristics

The ratio of males to females in this study was 3.25:1 which is in accordance with the male predominance of this disease as reported in other studies (Epstein et al. 1987b, Curi & Dib 1997, Epstein et al. 1997, Curi et al. 2000a, Store & Boysen 2000, Notani

et al. 2003, Reuther et al. 2003, Goldwasser et al. 2007, Oh et al. 2009, Chopra et al. 2011, Monnier et al. 2011, Gevorgyan et al. 2013, Tsai et al. 2013). The reason for this finding is that males are two to four times more likely to develop oral cancer than women, as a result of increased alcohol and tobacco use in male patients (McDowell 2006). Therefore complications including ORN are more likely to emerge in men. The majority of cases were above 55 years old (76.5%) and most of them had stage III necrosis, a finding which is in accordance with a study by Epstein et al. (1997). The late onset of ORN can be attributed to the late occurrence of OPCs and their complications (over 60 years) (Silverman 2001). The reason is that oral tissues have a tendency of prolonged exposure to potential carcinogens with advancing age, and aging cells may be more susceptible to DNA damage. The result is in agreement with other studies (Curi et al. 2000a, Store & Boysen 2000, Goldwasser et al. 2007, Oh et al. 2009, Chopra et al. 2011, Monnier et al. 2011, Gevorgyan et al. 2013).

In accordance with literature, a statistically significant difference in severity of ORN with regard to sex as well as age at the time of diagnosis was not demonstrated (Chopra et al. 2011, Gevorgyan et al. 2013). This result can be attributed to the great superiority of men and also the small age variability in the sample size in the above mentioned studies.

12.4 General health characteristics

DM is related in the literature with higher risk of ORN (Vanderpuye & Goldson 2000, Oh et al. 2009) but is not correlated with the severity of ORN (Gevorgyan et al. 2013). In the present study, 60.1% of the cases were suffering from DM. A remarkable point is that none of these patients was suffering from stage I necrosis but all of them from stage II and III with the majority of them (n=78) suffering from stage III osteonecrosis. DM was also identified as a significant predictor for stage III of necrosis.

DM is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. It is divided into two groups: DM type 1 (insulin-dependent) and DM type 2 (non insulin-dependent). Wound healing is slowed and can also worsen rapidly when the patient is diabetic. There are several factors that influence and worsen wound healing in a diabetic patient. These include elevated blood glucose

levels which narrow blood vessels as well as poor circulation due to narrowed blood vessels which leads to decreased blood flow and oxygen to a wound. The elevated blood sugar level decreases the function of red blood cells that carry nutrients to the tissue resulting in lower efficiency of white blood cells to fight an infection. Without sufficient nutrients and oxygen a wound heals slowly. Moreover, DM lowers the efficiency of the immune system against an infection since high glucose levels cause immune cells to function ineffectively (Rosenberg 1990, Terranova 1991, Vanderpuye & Goldson 2000). By definition, ORN is a non-healing wound with high oxygen requirement and a demand for the basic elements of tissue repair. The fact that there were a high percentage of stage III cases suffering from DM in the present study may explain the reason why DM was a significant predictor for stage III of necrosis.

Tobacco and alcohol abuse is clearly identified as a risk factor for ORN by many studies (Kluth et al. 1988, Schratter-Sahn et al. 1991, Glanzmann & Gratz 1995, Curi & Dib 1997, Thorn et al. 2000, Reuther et al. 2003, Shimizutani et al. 2005, Katsura et al. 2008, Tsai et al. 2013). Oh et al. (2009) showed that patients with ORN who continued to smoke or consume alcohol could not be treated with conservative means and needed a surgical resection. However, no association is found between tobacco and alcohol abuse and severity of ORN (Chopra et al. 2011, Gevorgyan et al. 2013). In the current study 85.0% of cases were active smokers at the time study was conducted which is in accordance with the finding of Gevorgyan et al. (2013). About two thirds of them (n=97) were suffering from stage III necrosis, 28 from stage II and only 5 cases from stage I. On the other side, in the study of Chopra et al. (2011) only 35% of the patients were active smokers.

Active smoking was also identified as significant predictor for stage III of necrosis in the present study. The association between cigarette smoking and wound healing is well known in clinical practice. Toxic constituents of cigarette smoke are responsible for delayed wound healing in smokers. Nicotine reduces nutritional blood flow resulting in ischemia and impaired healing of injured tissues. Carbon monoxide diminishes oxygen transport and metabolism, whereas hydrogen cyanide inhibits enzyme systems necessary for oxygen transport at the cellular level (Silverstein 1992). Moreover, vasoconstriction which occurs owing to smoking may enhance the occurrence of mandibular hypovascularisation after RT (Katsura et al. 2008); thus

nearly all cases in this study were active smokers (n=130). Taking into account all the above the reason for the association found, can be explained.

Normal alcohol consumption is an average of one to two drinks per day for men and one drink per day for women. A drink is one 12 oz. beer, 4 oz. of wine, 1.5 oz. of 80-proof spirits, or 1 oz. of 100-proof spirits (American Heart Association). In this study, excessive alcohol consumption was a significant predictor for stage III of necrosis. Ninety-two percent of cases were drinking above normal alcohol consumption and most of them were stage II and stage III cases (n=115). Only two cases were suffering from stage I necrosis. This percentage is higher than the one reported from Gevorgyan et al. (2013) and Chopra et al. (2011) which were 64.3% and 76% respectively. Chronic exposure to alcohol impairs wound healing and increases the incidence of infection (Guo & DiPietro 2010). It can also cause small vessel vasculitis and excessive consumption is associated with increased incidence of DM which affects the wound healing (Howard et al. 2004). Furthermore, increased alcohol consumption together with smoking may potentiate the effects of other negative factors for ORN such as poor oral hygiene (Katsura et al. 2008).

12.5 Tumor-related characteristics

In this study 72.6% of the cases were suffering from floor of mouth cancer, followed by tongue and pharynx cancer. This finding is in accordance with the literature (Curi & Dib 1997, Store & Boysen 2000, Thorn et al. 2000, Notani et al. 2003, Reuther et al. 2003, Sulaiman et al. 2003, Lee et al. 2009, Oh et al. 2009, Chopra et al. 2011, Monnier et al. 2011, Gevorgyan et al. 2013). Although 60.1% of the cases in the present study were diagnosed with advanced tumor size (T3 and T4) 79.1% were suffering from stage III and stage IV tumor. Stage IV tumors formed a majority of the total (53.6%) which is in accordance with the literature (Reuther et al. 2003, Oh et al. 2004, Lee et al. 2009, Chopra et al. 2011, Monnier et al. 2011, Gevorgyan et al. 2013, Niewald et al. 2013, Tsai et al. 2013). Taking the T classification into account, all but two of the patients whose disease was classified as T4 had stage II or III ORN, which is also in agreement with the literature (Lee et al. 2009, Chopra et al. 2011, Monnier et al. 2011, Gevorgyan et al. 2013).

Tumor size (T), overall stage and proximity to bone have been correlated in the literature with ORN occurrence. The risk of developing ORN is greater in patients with advanced size of tumor and stage of tumor (Bedwinek et al. 1976, Kluth et al. 1988, Reuther et al. 2003, Oh et al. 2009, Tsai et al. 2013) as well as tumor invasion to adjacent bone (Murray et al. 1980c, Morrish et al. 1981, Epstein et al. 1987b). On the other hand, tumor size and stage are not associated with the severity of ORN (Chopra et al. 2011). It is known that the bigger and the more invasive a tumor is, the more extensive surgical treatment and stronger chemotherapy and RT are needed. This results to greater damage to the tissues, reducing the vascularity and vitality of the adjacent tissues and their ability to heal. Moreover, it is proposed that when the tumor invades the adjacent bone, ORN occurrence increases rapidly (Turner et al. 1996, Curi & Dib 1997). The presented data and the superiority of T3, T4 and stage IV patients, can justify the statistically significant association between severity of ORN, tumor size and stage of tumor found in the present study, although both of them were not included in the significant predictors for stage III of necrosis according to the results of logistic regression analysis.

Oral cavity tumors, especially tumors of the tongue, floor of mouth, alveolar ridge or retromolar region contribute to higher risk for developing ORN after irradiation (Watson & Scarborough 1938, Curi & Dib 1997, Evensen et al. 2002, Notani et al. 2003, Reuther et al. 2003, van den Broek et al. 2006), since mandibular bone is directly involved in radiation fields and almost always an aggressive and radical surgical approach for tumor resection is needed (Curi & Dib 1997). On the other hand, tumors of sinonasal or nasopharyngeal areas (Tong et al. 1999, Cheng et al. 2006, Homma et al. 2009), pharyngeal or laryngeal cancers (Ferguson & Stevens 2007), present a lower risk for developing ORN. When the primary tumor is adjacent to or is overlying bone, the risk of ORN is increased (Rohrer et al. 1979, Murray et al. 1980b, Tobias & Thomas 1996). In the current study 10.5% of the cases were suffering from tumors whose initial location was adjacent to bone. Thus, in 59.5% of the cases the mandible was included in initial tumor's location. Nevertheless, no correlation was found between severity of ORN and localization of tumor, regarding jaws and oropharynx, as well as soft and hard tissues. This finding is in accordance with the literature (Chopra et al. 2011, Gevorgyan et al. 2013) and is probably

attributed to the fact that a lot of cases were not adjacent to bone or were suffering from sinonasal or nasopharyngeal tumors in the present study.

12.6 Treatment-related characteristics

All patients in the study received EBRT and none received brachytherapy. For 15 cases the data regarding the RT were missing. In 10 cases an adjuvant RT was necessary and in 3 cases a second adjuvant RT was performed. A significant association between the severity of ORN and the radiation setting was not found in this study which is in accordance with the literature (Chopra et al. 2011). Although studies have shown an association between ORN occurrence and primary surgical treatment followed by adjuvant RT (Curi & Dib 1997), there is no reference in the literature regarding RT setting and severity of ORN.

The mean RT dose was 63.4 Gy, relative close to 60 Gy, which has been regarded as the level beyond which ORN risk is significantly increased (Schwartz & Kagan 2002, Teng & Futran 2005). The dose levels were ranging from 49 to 77 Gy but the majority of patients received more than 60 Gy (n=76). Sixty-four cases who received radiation over 60 Gy were stage II and III cases, a number which is quite close to the number of cases that received less than 60 Gy and were also stage II and III cases (n=52). Interestingly none of the patients was treated with new radiation techniques such as 3D-CRT or IMRT.

Total radiation dose is thoroughly studied by authors regarding occurrence of ORN. Some of them propose and most of them agree that the higher the radiation dose the higher the risk of ORN (Beumer et al. 1972, Murray et al. 1980a, Murray et al. 1980b, Morrish et al. 1981, Beumer et al. 1983a, Beumer et al. 1984, Withers et al. 1995, Reuther et al. 2003, Chang et al. 2007, Lee et al. 2009, Gomez et al. 2011). A correlation between incidence of bone necrosis and volume of irradiated mandible has been also reported since years (Beumer et al. 1984). Many authors report lower incidence of ORN with use of hyperfractionation and accelerated fractionation with dose reduction, which is an expected finding due to total dose reduction (Parsons et al. 1988, Pigott et al. 1993, Mak et al. 1995, Dische et al. 1997, Gwozdz et al. 1997, Fu et al. 2000, Mendenhall et al. 2000, Ang et al. 2001, Fallai et al. 2006, Skladowski et al. 2006, Cummings et al. 2007, Suwinski et al. 2008, Nabil & samman 2012). Other

authors mention that an increase in radiation dose alone can not lead to increase in the incidence of ORN but its occurence is related to the synergic effect of radiation, fractionation and volume of irradiated tissue (Lozza et al. 1997, Jereczek-Fossa & Orecchia 2002, Reuther et al. 2003, Studer et al. 2006, Ben-David et al. 2007, Nabil & Samman 2011).

In the present study there was no correlation between radiation dose and severity of ORN. This finding is in accordance with the findings of Store & Boysen (2000) and Chopra et al. (2011), but is opposed to findings of Gevorgyan et al. (2013). Reasons for this contrast are many. First of all, all cases in the current study were treated with dose ranging from 49 to 77 Gy and it is proposed that mandible shows a tolerance to irradiation doses ranging from 60 to 72 Gy (Emami et al. 1991). Moreover, all cases in this study received EBRT with electrons or photons and standard field sizes. Most of the patients received a conventional fractionation, which means 2 Gy/fraction, one fraction every day and five fractions every week. None of the cases was treated with modern techniques of 3D-CRT or IMRT with restriction of irradiated field size and reduction of total dose resulting in lower risk of ORN (Studer et al. 2004, Ben-David et al. 2007). In contrast, in the study of Gevorgyan et al. (2013) most of the cases were radiated with IMRT and only 4 cases were treated with conventional RT. These cases were all stage III cases. It can also be argued that another reason to explain the non-existence of correlation between severity of ORN and total dose in the present study is the fact that the number of cases which received less than 60 Gy was almost half the size of sample (44.9%).

CRT is used in patients with evidence of a distant metastasis or in those who are not suitable for surgery (Bernier et al. 2005). Some authors report higher incidence of ORN when CRT is used (Hao et al. 1999, Jeremic et al. 2000, Denis et al. 2003, Cooper et al. 2004, Budach et al. 2005, Semrau et al. 2006, Stenson et al. 2010). However, in previous studies CRT was not statistically significant associated with severity of ORN (Chopra et al. 2011, Gevorgyan 2013). In the present study, a great majority of cases were treated with concomitant chemotherapy (80.4%). Ninety-six of them were diagnosed with stage III ORN. In contrast from 23 patients which were suffering from stage I necrosis, only 1 was treated with concomitant chemotherapy. A correlation was also found between concomitant chemotherapy and severity of ORN,

although it was not included in the significant predictors for stage III of necrosis according to the results of logistic regression analysis. There are several reasons for this correlation. Firstly, there was a great superiority of patients that were treated with chemotherapy and were diagnosed with stage III necrosis (n=96) opposed to stage I patients (n=1). Furthermore, most chemotherapeutic drugs are designed to inhibit cellular metabolism, rapid cell division, angiogenesis and many pathways that are critical for appropriate wound healing. Chemotherapeutic drugs delay cell migration into the wound, decrease early wound matrix formation, lower collagen production, impair proliferation of fibroblasts, and inhibit contraction of wounds. In addition, these agents weaken the immune functions of patients, prevent the inflammatory phase of healing and increase the risk of wound infection. Chemotherapy induces neutropenia, anemia, and thrombocytopenia, leaving wounds vulnerable to infection and causing less oxygen delivery to the wound (Guo & DiPietro 2010). Summarizing all the above, it can be concluded that concomitant chemotherapy is likely to weaken local immune response, delay the wound healing and favor infections all of which are associated with the severity of ORN.

Time interval between RT and onset of ORN varies in different studies. Most authors mention that the majority of cases occur within 3 years after RT (Gowgiel 1960, Marx & Johnson 1987, Clayman 1997, Thorn et al. 2000, Notani et al. 2003, Chang et al. 2007). In the present study the majority of ORN cases (n=95) were diagnosed within 6 years after RT. Out of these, 55 were diagnosed within 3 years after RT, most of them being stage III cases in the course of disease. The cases that were diagnosed later than 3 years are also distributed into three stages with a trend of stage III ORN being discovered later. This finding is in accordance with the literature (Notani et al. 2003, Chopra et al. 2011, Gevorgyan et al. 2013). An interesting point is that a great majority of cases (33.1%) were diagnosed 6 years after RT with 26 cases among them being diagnosed even 9 years after RT.

There was no statistically significant association between time after RT until the occurrence of ORN and the severity of the disease in this study, which is in accordance with the literature (Gevorgyan 2013). Nevertheless, it can be argued that the later ORN developed, the more it progressed (advanced stage). The explanation is the reduction in biologic activity which develops with time after RT (Bedwinek et al.

1976, Larson et al. 1983, Marx 1983a & 1983b, Epstein et al. 1987a). This means that ORN which develops early may still have more biologic activity to heal sponataneously and lesions might be localized. On the other hand, late-onset may have less biologic activity and lesion might become serious.

12.7 Oral health condition before radiotherapy and factors that contributed to the onset of osteoradionecrosis

It is well known that a good oral and dental health condition is an important requirement before starting RT. For this reason, all cancer centers, oral and maxillofacial clinics and radiology centers should refer their patients to dental control before RT starts. The same strict requirements are applied in the Department of Oral and Maxillofacial Surgery in Munich (LMU). Nevertheless, in the present study 56.9% of the cases were not subjected to dental examination and treatment before RT. Out of these only one was diagnosed with stage I ORN, whereas 71 (46.4% of cases) were suffering from stage III necrosis. This result can be interpreted as bad oral condition before RT by most of the cases (56.9%) with the majority of them suffering from stage III necrosis. The finding is in accordance with the literature (Murray et al. 1980b, Morrish et al. 1981, Kluth et al. 1988, Jereczek-Fossa & Orecchia 2002, Oh et al. 2009, Chopra et al. 2011, Monnier et al. 2011).

Many authors have proved that risk of developing ORN is increased in patients with poor oral health (Carl et al. 1972, Regezi et al. 1976, Murray et al. 1980b, Murray et al. 1980c, Beumer et al. 1984, Kluth et al. 1988, Bachmann et al. 1996, Katsura et al. 2008). In the study by Katsura et al. (2008) oral health conditions predisposing to ORN were: periodontal pocket depth >5mm, dental plaque score >40% alveolar bone loss >60% and a grade 3 radiographic periodontal status. Although occurrence of ORN is dependent not only on the extent of radiation damage to bone but also on patient's dental health (Nabil & Samman 2012), oral health has not been yet associated with severity of ORN (Chopra et al. 2011). Although dental examination and treatment before RT was not included in the significant predictors for stage III of necrosis according to the results of logistic regression analysis, there was a significant correlation between this and the severity of ORN. There are two fundamental explanations for this finding. First of all, there was a great superiority of patients

suffering from stage III necrosis who did not have good oral health before RT opposed to patients suffering from stage I necrosis. Moreover, more traumatic dental events after RT are to be expected in patients with bad oral hygiene before RT increasing the possibilities of ORN.

In the present study 59.5% of the cases occurred due to a specific cause whereas 40.5% of the cases occurred spontaneously. Interestingly, the majority of spontaneously occurring cases were stage III cases (50 out of 62) whereas in the cases of specific cause a more normal distribution is seen among the three stages, although most of them were stage III cases (49 out of 91). Dental treatment/Local pathological condition was identified as significant predictor for stage III of necrosis in this study. This finding is opposed to findings from other similar studies (Chopra et al. 2011, Gevorgyan et al. 2013). The reason is that the sample size in the present study is much bigger than in other studies with a great majority of cases occurring spontaneously. Thus, there is no focus in other studies to spontaneously occurring ORN cases but only to ORN cases occurring due to dental extraction before or after RT.

As mentioned above, in the present study causes of ORN included many variables such as extraction of a tooth, implantation, denture irritation or even a local pathological condition such as marginal or apical periodontitis. A significant correlation between the severity of ORN and these variables was found, although they were not included in the significant predictors for stage III of necrosis according to the results of logistic regression analysis. Extraction of a tooth either alone or in combination with other dental treatment constituded the main cause (91%) in the occurrence of ORN cases due to dental treatment (56 cases). Teeth extractions play a crucial role in the pathogenesis of ORN (Hansen et al. 2006a) and they are proposed as the most common cause of trauma-induced ORN of the jaws in 60-89% of the cases (Murray et al. 1980a, Marx & Johnson 1987). The reason is that after dental extraction a wound requires protein syntheses which are obtained by cellular activity and vascular events (Maxymiw et al. 1991). However, ionizing radiation promotes irreversible cellular and vascular damage resulting in hypoxic, hypocellular and hypovascular tissue. This fact can drastically affect the reparation process (Beumer et al. 1976, Beumer et al. 1983a, Beumer et al. 1983b, Beumer et al. 1984, Koga et al. 2008a) and result to ORN.

Regarding ORN cases related to extractions performed before RT, most studies show low incidence (Bedwinek et al. 1976, Epstein et al. 1987b, Sulaiman et al. 2003, Oh et al. 2004, Koga 2008b). In several studies postirradiation dental extractions are associated with high rates of ORN (Beumer et al. 1972, Morrish et al. 1981, Beumer et al. 1984, Marx & Johnson 1987, Thorn et al. 2000). Most recent data show a downward trend of ORN risk after extractions (Nabil & Samman 2011). Implantation is also associated with ORN occurrence (Granström et al. 1993, Taylor and Worthington 1993, Franzen et al. 1995, Arcuri et al. 1997). In the present study 5 cases of ORN occurred due to implantation. Most dental surgeries (n=40) that led to ORN were performed after RT opposed to these performed before RT (n=10). There was no statistical significant association between severity of necrosis and time of occurrence of dental surgey, a finding which is in accordance with the literature (Chopra et al. 2011). A possible reason for this finding is the small number of ORN cases due to dental surgery compared to spontaneously occurring ORN cases. The association between the variables could possibly be detected with a higher number of ORN cases owing to extractions.

Concerning ORN cases due to local pathological condition (n=35) the majority of them were attributed to marginal periodontitis (82.9%) followed by denture irritation (8.6%). Many authors refer marginal periodontitis (Thiel 1989, Niewald et al. 1996, Curi & Dib 1997, Jereczek-Fossa & Orecchia 2002, Katsura et al. 2008, Oh et al. 2009) as well as denture irritation (Curi & Dib 1997, Thorn et al. 2000, Oh et al. 2009) as risk factors for occurrence of ORN. The reason is that these patients are in greater danger for trauma after RT than patients without local pathological conditions (Carl et al. 1972, Regezi et al. 1976, Murray et al. 1980b, Murray et al. 1980c, Beumer et al. 1984, Kluth et al. 1988, Bachmann et al. 1996, Katsura et al. 2008).

Taking into account the entire above, special attention must be paid to pretreatment planning of dental therapy and post-treatment controls. Particular care must be taken with extraction techniques, dental hygiene, adequate healing time for teeth extracted before and after RT and protection of tooth with special fluoride devices (Reuther et al. 2003). Every patient who will be treated with RT should be subjected to pretreatment dental control so that periodontal disease and other causes of ORN will be eliminated and unsalvageable teeth will be extracted. The dentist is also obliged to

provide the patient with explanations for the importance of dental management and a "close follow-up" schedule. All these measures can reduce the likelihood of ORN and its severity.

12.8 Treatment of osteoradionecrosis

Regarding the treatment of ORN various different methods have been reported depending on several factors such as presentation of necrotic lesion, response to conservative nonsurgical therapy, general health of the patient, prognosis for successful management of the cancer, wishes of the patient, dose of irradiation and time interval after RT (Epstein et al. 1987a, Kawahara et al. 1987, Notani et al. 2003). They can be categorized in two groups: conservative (improvement of oral hygiene, antibiotics, analgesics, HBO) and surgical. Some investigators agree that initial treatment of ORN should be conservative, since failure of this course can always be followed with a more radical approach (Niebel & Neeman 1957, MacComb 1962, Hahn & Gorgill 1966), while others believe that a radical approach should be instituted at initial diagnosis (MacDougall et al. 1963, Marchetta et al. 1967).

In the present study the surgical treatment, outmatches the conservative treatment independent of stage of necrosis. Overall, 7.8% of the cases were treated in a conservative manner, 69.9% were treated surgically and 22.2% with combination of them. It should be noted that in stage I where the necrosis is not extended, 60.9% of the patients were treated surgically, 17.4% conservatively and 21.7% with both methods. This finding is opposed to the majority of recent studies, in which authors advocate a treatment approach according to the stage of necrosis (Jacobson et al. 2010, Chopra et al. 2011, Gevorgyan et al. 2013), with surgical treatment used only in advanced stages of necrosis. The reason for this is that in the Department of Oral and Maxillofacial Surgery in Munich (LMU) the treatment policy includes a more radical approach than conservative treatment due to better results observed in these cases.

Chapter 13

Conclusion

In conclusion, osteonecrosis remains a severe problem in RT of the jaws. Previous studies on the topic have focused on risk factors associated with the cause and incidence of ORN; the present study aimed to focus on factors that are predictive of the severity of mandibular ORN. The majority of cases was diagnosed as stage III necrosis and was male. The mandible was affected in all cases; no case was diagnosed in the maxilla. There was a predominance of the disease in the posterior region. All cases were treated with radiotherapy and 80.4% of them with concomitant chemotherapy. The affected patients mainly had poor oral hygiene before the onset of RT and approximately two thirds of the cases occured either after dental treatment or in oral regions with a local pathological condition. The main symptom was bone exposure followed by wound healing disorder, swelling and pain. The majority of the cases were treated surgically, independent of the stage of necrosis. DM, active smoking, alcohol and dental treatment/local pathological condition were identified as significant predictors for stage III necrosis. Based on these findings, prospective studies should be conducted, in order to understand the risk factors, the severity and the pathophysiology of ORN better and to improve the treatment strategies for this complication.

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Munich, 2014

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