Peri-implantitis, implant loss and osteoradionecrosis in oral cancer patients

Published: 20-10-2011
Last updated: 27-04-2024

Primary Objective: What are the consequences of irradiation for the human jaw bone and oral mucosa on a macroscopic, microscopic and molecular level?Can possible prognostic factors be identified for the occurrence of peri-implantitis, dental implant...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Therapeutic and nontherapeutic effects (excl toxicity)
Study type	Observational invasive

Summary

ID

NL-OMON39152

Source
ToetsingOnline

Brief title
ORN in oral cancer patients

Condition

- Therapeutic and nontherapeutic effects (excl toxicity)
- Head and neck therapeutic procedures

Synonym
non-healing dead bone due to irradiation, osteoradionecrosis, radiation osteomyelitis

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: dental implants, irradiation, osteoradionecrosis, peri-implantitis

Outcome measures

Primary outcome

- Differences in histomorphometric parameters between healthy and irradiated human jaw bone and jaw bone involved in an osteoradionecrosis lesion.

- Gene expression profiles of irradiated oral mucosa and oral mucosa associated with an osteoradionecrosis lesion compared to healthy oral mucosa.

- Differences in cell surface characteristics (microplication and microvilli) of irradiated and non irradiated oral mucosa and oral mucosa associated with an osteoradionecrosis lesion.

Secondary outcome

- Abnormalities in histomorphometric parameters in jaw bone of smokers in the control group and non-irradiated patients treated for a malignancy of the oral cavity compared to non-smoking controls.

- Genexpressieprofiles in oral mucosa of smokers in the control group as opposed to non-smokers and gene expression profiles of non-irradiated patients treated for a malignancy of the oral cavity compared to non smoking controls.

- Cell surface characteristics (microplications and microvilli) in the oral mucosa of smokers in the control group and in non-irradiated patienst treated

for a malignancy of the oral cavity compared to non-smokers.

These parameters are important to filter the contributing effect of smoking and

malignancy to oral tissue alterations in irradiated oral cancer patients.

Study description

Background summary

Each year, on average, 520 new cases of cancer of the oral cavity are diagnosed in the Netherlands. This represents 0,9% of all newly diagnosed cases of cancer. The treatment for oral cancer consists, depending on localisation and staging, of surgery and/or radiotherapy(1). Oncologic resections in oral cancer patients are often complex and mutilating. Reconstruction with osteomyocutaneous flaps are commonly performed in these patients. This is a major surgical procedure that has extensive consequences for oral functions such as swallowing, chewing and speech. Many patients need oral rehabilitation after the treatment for oral cancer, which consists of logopedia and dental prosthetics.

Oral rehabilitation with dental implants of patients treated for oral cancer is a meaningful postoperative procedure to increase quality of life(2). Dental implant surgery is often indicated in these patients to create a sound fitting prosthesis in the altered anatomy of the reconstructed oral cavity. Though radiotherapy plays an important role in the treatment of head and neck malignancies, side effects occur that have a major impact on the final results of oral rehabilitation. Irradiation of the oral cavity is known to give acute and chronic adverse local effects such as mucositis, xerostomia, hypogeusia, trismus, radiation caries, candidiasis and osteoradionecrosis(3).

Osteoradionecrosis (ORN) is a severe complication and is characterized by a non-healing area of exposed bone of at least three months duration(4). ORN is associated with pain, drainage and fisteling of the mucosa or skin and usually has a high morbidity. In advanced stages, ORN typically requires surgical resection and reconstruction. Its incidence in de mandible is between 2-22% of irradiated oral cancer patients. Factors that are thought to affect the development of ORN include site and size of tumour, dose of irradiation, type of resection, trauma (dental extractions), infection, immune deficiencies and malnutrition(5). Placement of dental implants increases the risk of ORN. Placing dental implants in irradiated tissue therefore is a clinical challenge. Implant loss is observed in up to 24% of these patients(6).

Little is known about the etiology of ORN. During the past 80 years a number of theories have been proposed, with consequent implications for its treatment. In 1983, Marx proposed the hypoxic-hypocellular-hypovascular theory: after irradiation hypoxic-hypocellular-hypovascular tissue is formed, and breakdown of this tissue driven by persistent hypoxia can cause a chronic non-healing wound(7). This theory formed the basis of the use of hyperbaric oxygen therapy for the treatment of ORN. Conflicting opinions about its efficacy exists, which is reflected in the literature(8).

In 2004 another hypothesis was proposed: that of the fibro-atrophic process. In this model, three successive clinical and histopathological phases can be distinguished: a pre-fibrotic aspecific inflammatory phase, a constitutive fibrotic cellular phase, and a matrix densification and remodelling phase, possibly ending in terminal tissular necrosis(9). In the fibrotic process different cytokines and growth factors are thought to play a role, such as TNF-*, PDGF, FGFb, IL1,4 and 5, TGF*-1 and CTGF. TGF-*1 has been associated with different fibrotic processes such as atherosclerosis, kidney, liver and lung fibrosis and is thought to play a key role in post-radiation fibrosis. The exact cascade of events and role of different cytokines and growth factors in this process has not yet been clarified.

In order to avoid or decrease irradiation-induced complications, it is of vital importance to get more insight in the histological and molecular background of the effects of irradiation on oral soft and hard tissues. Previous studies have focused on the effects of irradiation on bone tissue. Radiogenic bone damage(10-17) and osseo-integration of implants in irradiated bone(18-22) has been studied in various animal models. In irradiated rat mandible models, diminished bone volume and mineral apposition rate were observed al well as diminished numbers of osteoclasts and osteoblasts, hypovascularity, presence of fibrosis and inflammation and unusually high presence of osteoclasts in extraction sockets10,11.With regards to osseointegration of implants in animal models, a dose dependent relationship between radiotherapy and osseointegration is observed: the osseointegration diminishes with increasing dose of irradiation(18-22).

This relationship has also been described in a retrospective analysis of dental implant survival after radiotherapy in humans(23). Although the data with regard to irradiated bone are not conclusive, it has clearly been shown that after irradiation, there is a higher chance of failure of dental implants(6,23-24). However evidence for a dose-dependent relationship of irradiation dosage and implant failure in humans is conflicting. One systematic review on dental implant osseointegration after radiotherapy suggests that increased implant loss occurs in patients that received a radiation dose that exceeds 50 Gray(24), whereas another describes no dose-dependent relationship with regards to osseointegration(6). A possible contributing factor to these

conflicting reports is that radiotherapy went through a rapid development over the past decades with respect to dosimetry and strategies to keep normal anatomical structures outside the irradiation field(25-27). It has been suggested that these more sophisticated methods of irradiation contribute to lower incidence of ORN(27). However, improved dosimetry in radiotherapy regimes has not been identified as an independent factor for reducing the risk of ORN or implant loss in clinical setting with long-term follow-up.

In the current literature, no studies focusing primarily on histological and histomorphometric changes in irradiated human jaw bone could be found. One study has performed a histological and histomorphometrical evaluation of bone tissue adjacent to post-mortem retrieved dental implants from irradiated head and neck cancer patients(28). This study focused on osseointegration by measuring bone-implant contact. In the retrieved dental implants, lowered metabolic activity of bone tissue and diminished bone-implant contact was observed. This finding suggests that irradiation has effect on bone metabolism in human jaw bone that can possibly be objectified by performing histological and histomorphometrical analysis of irradiated human jaw bone as proposed in this research protocol.

One of the key processes of ORN is thought to be the altered expression of inflammation mediators and growth factors. In order to assess altered expression of genes in tissue a micro-array analysis can be performed(29). A micro-array analysis detects levels of different strands of mRNA in a tissue sample. When a gene is expressed, mRNA is transcribed from DNA and serves as a template for protein synthesis. Because an mRNA transcript is an exact copy of a corresponding DNA coding region, genomic analysis at the mRNA level can be used as a measure of gene expression. Previous studies using microarray analysis in oral cancer patients have mainly focused on gene expression of tumor cells(30-33). Few studies focusing on the effect of irradiation on the tissues surrounding the tumor could been found in the literature. In one study, a microarray analysis of dermal keratinocytes in radiation induced skin wounds demonstrated altered expression of keratins, growth factors and matrix metalloproteinases(34). Another study demonstrated altered gene expression in peripheral blood cells following adjuvant chemoradiation therapy for head and neck cancer(35). Late changes in cutaneous gene expression after radiotherapy for head and neck cancer were demonstrated in microarray analysis of irradiated, non-ulcerating skin specimen harvested at secondary corrective surgical procedure(36). However, expression profiles of oral tissues involved in osteoradionecrosis have not yet been studied.

In the field of rheumatology, the microarray technique has been used to identify expression patterns of inflammatory mediators in rheumatoid arthritis patients, that could to some extent be correlated with clinical parameters such as disease activity and biomarkers in peripheral blood(37,38). This finding suggest that certain phenotypes of immune response can predispose for pathologic inflammatory conditions such as auto-immune diseases. According to

the fibro-atrophic theory, ORN, like rheumatoid arthritis is considered a pathologic inflammatory response. It is possible that a specific *fingerprint* of inflammation response, as found in rheumatoid arthritis patients, can play a part in the etiology of ORN. Therefore, it will be interesting to perform a gene expression microarray analysis of irradiated human mucosa versus human mucosa involved in ORN.

The effects of irradiation on mucosal cells can be observed in scanning electron microscopy. Scanning electron microscopy (SEM) studies have shown that the outer surface of epithelial cells of the oral mucosa is covered by numerous microplicae (microvilli/ microprojections)39. Several functions have been attributed to this characteristic structure. It is thought to maximize the uptake of oxygen and nutrients and facilitate the movement of metabolic products across the outer cell membrane. Microplicae functions are thought to be closely related to glycocalyx and extracellular matrix (ECM) sturcture.37 Although the exact function of microplicae remains unclear, it is widely accepted that this structure is essential to maintain intact tissue physiology40. Scanning electron microscopy of irradiated buccal human mucosa swaps have shown loss of microplication and microvilli of the mucosal cells41,42, however, cells retrieved from buccal smears are subject to bias due to contamination and lack of tissue structure. It would be a great value to investigate the effects of irradiation on the mucosal tissue in humans by performing scanning electron microscopy on mucosal tissue specimen surfaces as opposed to buccal swaps, hereby creating an image that also contains the intercellular junctions, maintaining normal tissue architecture and diminishing contamination with mucus and bacteria.

Hyaluronan (HA) is a multifunctional glycosaminoglycan that forms the structural basis of the extracellular matrix (ECM). Hyaluronan synthases (HASs) are plasma membrane enzymes that simultaneously elongate, bind, and extrude the growing hyaluronan chain directly into extracellular space. Hyaluronan (HA) is thought to promote cancer cell growth and migration43. HA has been shown to be a prognostic marker in oral squamous cell carcinoma, and a diminished intensity of HA staining is associated with poor survival44. HASs play a role in wound healing and in some oral diseases45. The role of hyaluronan (HA) in irradiated oral tissues has not yet been researched. Altered expression of hyaluronan could have structural effects on the extracellular matrix, that we assume does not only play a role in invasive cancer growth, but also in the altered wound healing in irradiated mucosa.

Our hypothesis is that peri-implantitis, implant failure and ORN in irradiated oral cancer patient is caused by abnormalities in both hard and soft oral tissues, possibly with similar molecular mechanisms. This study aims to investigate the process of irradiation-induced changes in both jaw bone and oral mucosa. By investigating gene expression of inflammatory markers, histological properties and cell surface and extracellular matrix changes of the irradiated versus non-irradiated oral tissues we aim to find clues to

predict future peri-implantitis, implant loss and ORN.

In the Department of Oral and Maxillofacial Surgery (OMFS) of the VU University medical center in Amsterdam there is a longstanding and large experience with the reconstruction and oral rehabilitation with dental implants in oral cancer patients. During many years there has been a collaboration in the field of bone research between the department of oral and maxillofacial surgery and the department of endocrinology. There are strong bonds with the Finnish experts in the field irradiated oral tissues, especially at electron microscopy level.

Literature

1. Vereniging integrale kankercentra (VIKC). Landelijke richtlijn mondholte- en oropharynxcarcinoom, versie 1.4 (2004). VIKC: Utrecht. [online] http://www.oncoline.nl. (visited: 6-12-2010)
2. Hollister MC, Weintraub JA. The association of oral status with systemic health, quality of life, and economic productivity. J Dent Educ 1993;57:901-12.
3. Bonan PRF, Kaminagakura E, Pires FR, Vargas, PA, de Almeida OP. Histomorphometry and immunohistochemical features of grade I (WHO) oral mucositis. Oral Dis 2007;13:170-6.
4. Chrcanovic BR, Reher P, Sousa AA, Harris M. Osteoradionecrosis of the jaws * a current overview * part 1. Oral Maxillofac Surg 2010;14:3-16.
5. Lyons A, Ghazali N. Osteoradionecrosis of the jaws: current understanding of it's pathophysiology and treatment. J Oral Maxillofac Surg 2008;46:653-60.
6. Javed F, Al-Hezaimi K, Al-Rasheed A, Almas K, Romanos GE. Implant survival rate after oral cancer therapy: a review. Oral Oncol 2010:46;854-859.
7. Marx R. Osteoradionecrosis: a new concept of it*s pathophysiology. J Oral Maxillofac Surg 1983;41:283-8.
8. Spiegelberg L, Djasim UM, van Neck HW, Wolvius EB, van der Wal KG. Hyperbaric oxygen therapy in the management of radiation induced injury in the head and neck region: a review of the literature. J Oral Maxillofac Surg 2010;68:1732-9.
9. Delainan S, Lefaix JL. The radiation induced fibroatrophic process: therapeutic perspective via the anti-oxidant pathway. Radiother Oncol 2004:73;119-31.
10. Cohen M, Nishimura I, Tamplen M, Hokugo A, Beumer J, Steinberg ML, Suh JD et al. Animal model of radiogenic bone damage to study mandibular osteoradionecrosis. AM J Otolaryngol 2010 (epub ahead of print)
11. Fenner M, Park J, Schulz N, Amann K, Grabenbuer GG, Fahrig A, Karg J et al. Validation of histologic changes induced by external radiation in mandibular bone. An experimental animal model. J Cran Maxillofac Surg 2009;38:47-53.
12. Niehoff P, Springer IN, Yahya A, Lange A, Marget M, Roldán JC Köppe K et al. HDR brachytherapy irradiation of the jaw * as a new experimental model of radiogenic bone damage. J Cran Maxillofac Surg 2008;36:203-9
13. Zhang WB, Zheng LW, Chua D, Cheung LK. Bone regeneration after radiotherapy in an animal model.
14. Jacobsson M, Albrektsson T, Turesson I. Dynamics of irradiation injury to

bone tissue. Acta Radiol Oncol 1985;24:343-50.
15. Yachouh J, Breton P, Roux JP, Goudot P. Osteogenic capacity of vascularised periosteum: an experimental study on mandibular irradiated bone in rabbits. J Plast Reconst Aes 2010 (epub ahead of print)
16. Lerouxel E, Moureau A, Bouler JM, Guimelli B, Daculsi G, Weiss P, Malard O. Effects of high doses of ionising radiation on bone in rats: a new model for evaluation of bone engineering. Br J Oral Maxillofac Surg 2009;47:602-7.
17. Verdonck HWD, Meijer GJ, Nieman FH, Stoll C. Riediger D, de Baat C. Quantitative computed tomography bone mineral density measurements in irradiated and non-irradiated minipig alveolar bone: an experimental study. Clin Oral Impl Res 2008:19;464-8.
18. Asikainen P, Klemetti E, Kotilainen R, Vuillemin T, Sutter F, Voipio HM, Kullaa A.
Osseointegration of dental implants in bone irradiated with 40, 50 or 60 Gy doses
Clin Oral Impl Res 1998; 9 : 20-25.
19. Asikainen P, Kotilainen R, Vuillemin T, Sutter F, Viopio HM, Kullaa A. Osseointegration of dental implants in radiated mandibles: An experimental study with beagle dogs. J of Oral Implantology 1991; 17: 48-54.
20. Matsui Y, Ohno K, Michi K, Tachikawa T. Histomorphometric examination of healing around hydroxylapatite implants in 60Co-irradiated bone. J Oral Maxillofac Surg 1994;52:167-72.
21. Ohrnell LO, Branemark R, Nyman J, Nilsson P, Thomsen P. Effects of irradiation on the biomechanics of osseointegration. Scan J Plast Reconstr Hand Surg 1997:31;281-93.
22. Johnsson AA, Sawaii T, Jacobsson M, Granström G. A histomorphometric and biochemical study of the effect of delayed titanium implant placement in irradiated rabbit bone. Clin Implant Dent Res 2000;2:42-9.
23. Granström G. Osseointegration in irradiated cancer patients: an analysis with respect to implant failures. J Oral Maxillofac Surg 2005;63:579-85.
24. Ihde S, Kopp S, Gundlach K, Konstantinovic VS. Effects of radiation therapy on craniofacial and dental implants: a review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;107:56-65.
25. Struder G, Gratz KW, Glanzmann C. Osteoradionecrosis of the mandibula in patients treated with different fractionations. Strahlenther Onkol 2004;180:233-40.
26. Puri DR, Chou W, Lee N. Intensity-modulated radiation therapy in head and neck cancers: dosimetric advantages and update of clinical results. Am J Clin Oncol 2005;28:415-27. Ben-David MA, Diamante M, Radawski JD, Vineberg KA, Stroup C, Murdoch-Kinch CA, Zwetchenbaum SR et al. Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of both dental care and improved dose distributions. In J Rad Oncol Biol Phys 2007;68:396-402.
28. Bolind P, Johansson CB, Johansson J, Granström G, Albrektsson T. Retrieved implants from irradiated sites in humans: a histologic/histomorphometric investigation of oral and craniofacial implants. Clin Implant Dent Res 2006;8:142-50.

29. Kuo WP, Whipple ME, Sonis ST, Ohno-Machado L, Jenssen TK. Gene expression profiling by DNA microarrays and its application to dental research. Oral oncology 2002;38:650-6.
30. Radhakrishnan R, Solomon M, Satyamoorthy K, Martin LE, Lingen MW. Tissue microarray - a high throughput analysis in head and neck cancer. J Oral Pathol Med 2008;37:166-76.
31. Coutinho-Camillo CM, Laurenço SV, Nishimoto IN, Kowalski LP, Soares FA. Caspase expression in oral squamous cell carcinoma. Head Neck J Sci Spec 2010 12 nov (epub ahead of print)
32. Tomoika H, Morita K, Hasegawa S, Omuro K. Gene expression analysis by cDNA microarray in oral squamous cell carcinoma. J Oral Pathol Med 2006;35:206-11.
33. Chen CH, Chioen CY, Huang CC, Hwang CF, Chuang HC, Fang FM, Huang HY et al. Expression of FLJ10540 is correlated with aggressiveness of oral cavity squamous cell carcinoma by stimulating cell migration and invasion through increased FOXM1 and MMP-2 activity. Oncogene 2009;28:2723-37.
34. Goessler UR, Bugert P, Kassner S. Stern-Straeter J, Bran G, Sadick H, Hörmann K, Riedel F. In vitro analysis of radiation-induced dermal wounds. Otolaryng head neck 2010;142:845-50.
35. Sonis S, Haddad R, Posner M, Watkins B, Fey E, Morgan TV, Mookanamparambil et al. Gene expression changes in peripheral blood cells provide insight into the biological mechanisms associated with regimen/related toxicities in patients being treated for head and neck cancers. Oral Oncology 2007;43:289-300.
36. Mueller CK, Thorwarth M, Schultze-Mosgau S. Late changes in cutaneous gene expression patterns after adjuvant treatment of oral squamous cell carcinoma (OSCC) by radiation therapy. Oral surg oral med oral pathol oral radiol endod 2010;109:694-9.
37. van der Pouw Kraan TCTM, van Gaalen FA, Kasperkovitz PV, Verbeet NL, Smeets TJM, Kraan MC, Fero M et al. Rheumoatoid arthritis is a heterogeneous disease. Evidence for differences in the activation of the STAT-1 pathway between rheumatoid tissues. Arhtritis Rheum 2003;48:2132-45.
38. van Baarsen LGM, Wijbrandts CA, Trimmer TCG, van der Pouw Kraan TCTM, Tak PP, verweij CL. Synovial tissue heterogeneity in rheumatoid arthritis in relation to disease activity and biomarkers in peripheral blood. Arthritis Rheum 2010;62:1602-7.
39. Kullaa-Mikkonen A. Scanning electron microscopic study of surface of human oral mucosa. Scand J Dent Res 1986;94:50-6.
40. Koufakis DI, Karabatsas CH, Sakkas LI, Alvanou A, Manthos AK, Chatzoulis DZ. Conjunctival surface changes in patients with Sjögren*s syndrome: a transmission electron microscopy study. Invest Ophthalmol Vis Sci 2006;47:541-4.
41. Johnson ME, Murphy PL. Changes in the tear film and ocular surface from dry eye syndrome. Prog Retin Eye Res 2004;23:449-74.
42. Robertson AG, Wilson P, Wilson DJ, Carr KE, Hunter I. Microplication patterns on human buccal epithelia following radiotherapy: a scanning electron microscopic analysis. J Submicrosc Cytol 1987;19: 515-21.
43. Soames JV, Macleod RI. Effects of radiotherapy on oral epithelium. Quantitative cytology using light and scanning electron microscopy. Anal Quant Cytol Histol 1995;17:389-96.

44. Tammi RH, Kultti A, Kosma VM, Pirinen R, Auvinen P, Tammi MI. Hyaluronan in human tumors: pathobiological and prognostic messages from cell-associated and stromal hyaluronan. Semin Cancer Biol 2008;18:288-95.
45. Kosunen A, Ropponen K, Kellokoski J, Pukkila M, Virtaniemi J, Valtonen H, Kumpulainen E, Johansson R, Tammi R, Tammi M, Nuutinen J, Kosma VM. Reduced expression of hyaluronan is a strong indicator of poor survival in oral squamous cell carcinoma. J Oral Oncol 2004;40:257-63.

Study objective

Primary Objective:
What are the consequences of irradiation for the human jaw bone and oral mucosa on a macroscopic, microscopic and molecular level?
Can possible prognostic factors be identified for the occurrence of peri-implantitis, dental implant loss and/or ORN in irradiated patients with oral cancer?
Is it possible to enhance the treatment decisions and prognoses of patients with dental implants in reconstructive surgery?

Secondary Objective(s):
1. By performing histomorphometric analysis and micro-CT scanning of the irradiated bone samples retrieving data on:
- Histological features of irradiated, osteoradionecrotic and 'control' bone * Histology
- Number and size of blood vessels * Histology
- Number of osteoblasts per tissue area (N.Ob/T.Ar, cells/mm2), osteoclasts per surface area (N.Oc/T.Ar, cells/mm2), osteocytes (N.Ot/Md.Ar. Cells/0,01 mm2) and empty lacunae per mineralized surface area (N.Lac/Md.Ar. Cells/0,01 mm2) * Histomorphometry
- Number of osteocytes that show signs of apoptosis (N.Apopt/Md.Ar. Cells/0,01 mm2) * Immunohistochemical staining of cleaved PARP
- Trabecular width (Tb.Wi., um) * Histomorphometry
- Trabecular thickness (Tb.Th. , um) * Micro CT
- Osteoid width (O.Wi., um) * Histomorphometry
- Osteoid thickness (O.Th, um) * Micro CT
- Absolute osteoid volume (OV/TV, %) * Micro CT
- Relative osteoid volume (OV/BV, %) * Micro CT
- Resorption surface - Histology
- Labeled surface (mineral apposition rate) (tertracycline labeling) * Fluorescence Microscopy
- Surface area of bone, fibrosis, necrosis and marrow * Histology
- Presence of inflammatory cells/macrophages - Histology
- Calculating bone volume (BV), tissue volume (TV) and vital bone volume (BV/TV, %) * Micro-CT
- Anisotropy (direction of trabecles) (Tr.Pf) * Micro CT
- Differences in types of irradiated bone (after surgery, depending on reconstruction, the jaw bone can consist of original mandibular/maxillar, or

transplanted autograft (fibula, crista) bone) * Histology

2. By performing micro array analysis on irradiated mucosa, retrieving data on
- Gene-expression of proteins (focusing on cytokines and growth factors) in post-cancer non-irradiated, post cancer irradiated and osteoradionecrotic tissue compared to healthy smoking an non-smoking controls
- Determine what proteins are differently expressed in clinically evident osteoradionecrosis
- Determine whether different expression profiles exist between irradiated patients
- In case these different expression profiles are found, correlate these with clinical data, investigating whether certain expression profiles in irradiated tissue predispose for developing peri-implantitis, ORN and dental implant loss
- Significantly differently expressed inflammatory proteins, growth factors and cytokines can be investigated on tissue level with immunohistochemistry analysis to assess presence and localisation in the tissue.

3*. By performing scanning electron microscopy and different non-invasive microspectrosopy on healthy, post-cancer, post-cancer irradiated and post-cancer irradiated radionecrotic mucosa and bone tissue specimens, obtaining information about:
- Cell surface changes in oral cancer mucosa, irradiated mucosa and osteonecrotic mucosa compared to healthy controls
- Changes in microplication/microvilli and their interaction with hyaluronan biosynthesis

* This part of the research will be performed at the SIB-labs Laboratory of the University of Eastern Finland, Kuopio, Finland.

Study design

Prospective observational study

Study burden and risks

Venapuncture for blood sampling is an invasive procedure which may cause slight discomfort for the patient.
Tetracycline labeling of bone has a potential risk for adverse reactions that are known for tetracycline use and are described in the 'farmacotherapeutisch kompas'.

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1118
Amsterdam 1081 HZ
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1118
Amsterdam 1081 HZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients treated for cancer of the oral cavity receiving oral rehabilitation with dental implant surgery. (cases)
Patients treated for oral cancer with irradiation and dental implants, complicated by osteoradionecrosis.
Healthy subjects receiving implant surgery for missing dental elements. (controls)

Exclusion criteria

Age <18
Legal incapacity
Patients with impaired bone metabolism (e.g. haemodialysis, hyperparathyroidism,

osteomalacia) (registration, no inclusion).
Patients having used systemic immunosuppressive medication up to three months prior to the dental implant surgery (registration, no inclusion).
Patients allergic to tetracycline will be excluded for the tetracycline labelling of bone analysis exclusively.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-08-2012
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	20-10-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-01-2013

Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL34966.029.11