Aus der Klinik für Mund-, Kiefer- und Gesichtschirurgie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Long-term survival analysis of dental implants & implant-supported prostheses in patients after squamous cell carcinoma in head and neck region

zur Erlangung des akademischen Grades
Doctor medicinae dentariae (Dr. med. dent.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

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Datum der Promotion: 04.06.2021

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Chapter 1: Introduction

1.1 Abstract in English

Purpose: The prosthetic rehabilitation of head and neck cancer patients following ablative surgery and possible radiochemotherapy can be extremely challenging for the surgeons and prosthetists. A conventional prosthetic solution is often not feasible due to the alteration of anatomical conditions following surgical rehabilitation. In such cases, implant-retained prostheses are often the only option for the successful rehabilitation of patients in the long-term. In this study, the long-term clinical success of dental implants and implant-supported prostheses in patients following surgical resection are evaluated and analyzed. Additionally, potential influencing factors were evaluated.

Material and Methods: In this study, 60 patients (20 women, 40 men) with the mean age of 62.75 years (41-88 years) were included. Prior to implant placement, 35 patients also received radiotherapy and cisplatin-based chemotherapy postoperatively. Overall, 330 implants were inserted in these patients. The mean observation period was 86 months (4-272 months). The patients were examined every 6 months at the first 3 years and then every 12 months according to a standard protocol and complications were documented. In the clinical examinations, the implant success was regularly assessed according to the criteria of Buser. Kaplan-Meier Curve was used for the evaluation of implant survival and the Log Rank test for overall differences according to gender, radiotherapy, localization (maxilla/mandible) and vestibuloplasty.

Results: Of the 330 implants examined, 122 were placed in the maxilla and 208 in the mandible. Overall, 212 implants were placed in 35 irradiated patients. A total of 27 implants were lost during the observation period. The cumulative survival rate was 99.7% after 3 years, 92.7% after 7 years and 88.3% after 10 years. Gender and radiotherapy did not have a significant influence of the survival of dental implants in oral cancer patients. However, age, localization of the implants (maxilla/mandible) and a vestibuloplasty according to Heberer and Nelson as soft tissue management showed a significant difference.

Discussion: This study reveals a high and steady cumulative survival rate of dental implants after 10 years following ablative surgery in non-irradiated and irradiated head

and neck cancer patients. The requirements for long-term success are: optimal soft tissue management, recall system and excluding irradiated patients with a smoking habit from the study.

1.2 Abstract in German

Zielstellung: Die prothetische Rehabilitation von Patienten mit Tumoren im Kopf-Halsbereich nach erfolgter chirurgischer Behandlung und etwaiger Radiochemotherapie stellt eine große Herausforderung für die Chirurgen und Prothetiker dar. Eine konventionelle prothetische Lösung ist oftmals aufgrund der therapiebedingten Veränderungen der anatomischen Verhältnisse durch Defektrekonstruktionen nicht durchführbar. Die Verankerung des Zahnersatzes mit dentalen Implantaten stellt in solchen Fällen meist die einzige Möglichkeit dar, die Patienten langfristig suffizient zu rehabilitieren. In der vorliegenden Studie wird der klinischer Langzeiterfolg dentaler Implantate und implantat-prothetischer Versorgungen von Patienten nach Tumorresektionen untersucht und ausgewertet. Zusätzlich sollen mögliche Einflussfaktoren evaluiert werden.

Material und Methoden: In die vorliegende Studie wurden 60 Patienten (20 Frauen, 40 Männer) mit einem Durchschnittsalter von 62.75 Jahren (41 - 88 Jahre) involviert. Prä implantationem wurden 35 Patienten zusätzlich bestrahlt und erhielten eine cisplatinbasierte Chemotherapie. Insgesamt wurden bei diesen Patienten 330 Implantate inseriert. Der Nachuntersuchungszeitraum betrug durchschnittlich 86 Monate (4 – 272 Monate). Die Patienten wurden anhand eines Standardprotokolls klinisch alle 6 Monate in den ersten 3 Jahren und dann alle 12 Monaten nachuntersucht und die Komplikationen wurden dokumentiert. Bei den klinischen Untersuchungen wurde der Implantaterfolg entsprechend den Erfolgskriterien nach Buser bewertet. Die Kaplan-Meier-Kurve wurde für die Auswertung der Überlebensrate dentaler Implantate und Log Rank Test für den Gesamtvergleich nach Geschlecht, Radiotherapie, Lokalisation (Oberkiefer/Unterkiefer) und Vestibulumplastik benutzt.

Ergebnisse: Insgesamt wurden 330 Implantate untersucht, 122 Implantate wurden in den Oberkiefer und 208 Implantate in den Unterkiefer eingesetzt. 212 Implantate wurden bei 35 bestrahlten Patienten inseriert. 27 Implantate gingen innerhalb des Nachuntersuchungszeitraumes zu Verlust. Die kumulative Überlebensrate lag nach 3 Jahren bei 99.7%, nach 7 Jahren bei 92.7% und nach 10 Jahren bei 88.3%. Das Geschlecht und die Radiotherapie hatten keinen Einfluss auf den Langzeiterfolg der Implantate bei Tumorpatienten. Jedoch hatten das Alter, die Lokalisation

(Oberkiefer/Unterkiefer) und eine Vestibulumplastik nach Heberer und Nelson als Weichgewebsmanagement einen Einfluss auf den Langzeiterfolg gezeigt.

Diskussion: Die Studie zeigt guten klinischen Langzeiterfolg dentaler Implantate nach 10 Jahren bei bestrahlten Patienten und nicht bestrahlten Patienten nach Tumortherapie im Kopf-Hals-Bereich. Die Voraussetzung für den Langzeiterfolg ist optimales Weichgewebsmanagement, ein engmaschigem Recallsystem und das Ausschlusskriterium Nikotinabusus bei bestrahlten Patienten.

Chapter 2: Literature Review

2.1 Incidence, prevalence and etiology of oral cancers

According to a study at the Robert Koch Institute, in Germany, in 2012, oral cavity and pharynx tumors were found to be the 7th leading tumor type in men (3.7%) and the 15th leading tumor type in women (1.6%), with more than 10,000 new cases observed every year. Approximately 90% of the oral cavity cancers in Germany are squamous cell carcinomas.[1]

The most common site for squamous cell carcinoma in the oral cavity is the lateral and anterior two-thirds of the tongue, accounting for approximately 40% to 50% of all cases. The floor of the mouth is the second most common site and the occurrence rate of oral cancer on the buccal mucosa, gingiva and hard palate is lower.[2]

The risk of developing oral cancer is associated with the progression of age. Consequently, it is observed that the majority of oral cancer cases occur in individuals over 50 years of age. The occurrence of oral cancer is more frequent in men than women. In Germany, when genders are compared, lifetime risk of developing oral cancer is higher in men (1.7%) than in women (0.7%).[1]

In most countries, 50–60% of patients diagnosed with cancers of the tongue, oral cavity, and oropharynx survive for five years.[1,3] Poor prognosis for oral cancer is mostly accounted for by late-stage presentation of the disease.[3]

Smoking, alcohol consumption, demographic variables, a lack of irregular oral hygiene, occupational exposure and defective dental prosthesis comprise the main risk factors associated with oral cancer.[4,5] Smoking has been found to be related to more than 50 pathological alterations and is considered a public health issue. Cigarettes contain approximately 5000 chemicals that are converted into reactive metabolites capable of interacting with DNA by the action of oxidative enzymes, which result in oral tissues being negatively affected by smoking and subsequent damage.[6]

The damage to the oral mucosa is further magnified by continuous exposure to the heat resulting from tobacco combustion. People who do not use tobacco or consume alcohol may still possess factors that influence disease; however, it is generally accepted in the

literature that smoking has a multiplying effect for increasing the risk of the development of oral cancer by nearly ten times.[6]

Alcohol consumption is associated with the increased risk of oral cancer, especially when consumed alongside tobacco. According to the hypothesis, due to the previous action of ethanol on cells, the buccal epithelium is more permeable to the action of other carcinogens, such as tobacco products.[6] Furthermore; different types of alcoholic beverages contain different amounts of alcohol. For comparability, one drink is equivalent to 14 grams, 18 ml, or 0.49 ounces of alcohol, which generally corresponds to 330 ml of beer, 150 ml of wine, and 36 ml of hard liquor.[7] The increased risk of oral cancer is also associated with the amount of alcohol consumed. According to the International Alliance for Responsible Drinking (IARD), low-risk alcohol consumption in Germany is up to 24 g/day for men and up to 12 g/day for women, risky consumption is above 20–60 g/day for men and above 12–40 g/day for women, dangerous consumption is above 60–120 g/day for men and 40–80 g/day for women, and high consumption is above 120 g/day for men and above 80 g/day for women (updated in April 2016 on an ongoing basis as government entities publish and revise their guidelines).[8] In the review by Goldstein et al., a strong dose-response relationship on the intensity of alcohol use was reported.[7]

The possible correlation between HPV and its role in the etiology of oral cancer was first evaluated in the 1980s. HPV is a group of host-specific DNA viruses with remarkable epithelial cell specificity (keratinocytes). The occurrence of HPV infection from oral-genital sexual contact in young adults is another significant issue that needs to be addressed. Even though various research has shown that the frequency of oral infection is less than the frequency of anogenital infection, studies indicate that HPV, which infects the genital area, can also infect the oral cavity.[3]

2.2 Treatment of squamous cell carcinoma

2.2.1 Ablative surgery

The treatment of oral cavity cancer must be determined according to TNM classification by an interdisciplinary tumor board with expertise in oromaxillofacial surgery, ENT, radiology, pathology and oncology. TNM classification is the internationally accepted standard for cancer staging; T describes the primary tumor site, N the regional lymph

node involvement and M the presence of distant metastatic spread. TNM classification of carcinomas of the oral cavity is as follows[2]:

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor 2 cm or less in the greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in the greatest dimension
T3	Tumor more than 4 cm in the greatest dimension
T4a (lip)	Tumor invades through cortical bone, inferior alveolar nerve, floor of the mouth, or skin (chin or nose)
T4a (oral cavity)	Tumor invades through cortical bone, into deep/extrinsic muscle of the tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face
T4b (lip and oral cavity)	Tumor invades the masticator space, pterygoid plates, or skull base, or encases the internal carotid artery
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in the greatest dimension
N2	Metastasis as specified in N2a, 2b, 2c below
N2a	Metastasis in a single ipsilateral lymph node; more than 3 cm but not more than 6 cm in the greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes; no more than 6 cm in the greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes; no more than 6 cm in the greatest dimension
N3	Metastasis in a lymph node more than 6 cm in the greatest dimension
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table 1: TNM classification Note: Midline nodes are considered ipsilateral nodes

The use of the TNM system alone can generate a large number of different sub-

categories. To simplify the description, the categories can therefore be grouped together as an anatomical stage classification and given a Roman numeral stage (Stage I, II, III, and IV).[2]

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0, N1	M0
Stage IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Table 2: Anatomical stage classification

Ablative surgery with a safe surgical margin is the aim of the therapy for T1 and T2 head and neck cancers. It includes the resection of soft tissue, the resection of bony structures, or a combination of both.[2] The choice of treatment depends on the individual picture of the patient and the localization of the tumor; i.e. if there are surgically difficult to access structures. The literature describes in such cases the administration of radiotherapy or chemotherapy.[2,9]

After the surgical therapy of T1 and T2 head and neck cancers, and especially after histological analysis, primary reconstruction with local flaps (platysma, tongue etc.) or with distant flaps (radialis forearm flap) is performed. In the case of extensive defects of the soft tissue and bony structures, reconstruction with vascularized transplants (fibula, Ilium, scapula) can be considered.[9]

In the treatment of T3 and T4 head and neck cancer, surgical therapy should also be considered. Surgical therapy can be discussed individually, depending on the size and localization of the tumor. The reconstruction of the resulting defects of the soft tissue and bony structures can be performed with vascularized transplants (fibula, ilium). It can either be performed primarily with ablative surgery in the same session following the histological analysis, or secondarily.[2,9] Radiochemotherapy is often recommended in the literature,

depending on the indication. The possible treatment of inoperable head and neck tumors is radiochemotherapy solely without ablative surgery.[2]

When deciding on the choice of treatment, the patient's general health, disease site, functional and cosmetic outcomes, and quality of life during and following treatment must be taken into account.[9,10]

2.2.2 Neck dissection

Squamous cell carcinoma has the ability to spread locally into bone and soft tissue, like muscle, and spread distantly to the cervical lymph nodes, lung and liver.[11]

Dividing the cervical lymph nodes by levels, the submental and submandibular lymph node groups can be found in level I. Levels II, III and IV are composed of the superior, middle and inferior jugular groups, respectively, whereas level V determines the posterior triangle nodes, and level VI includes the anterior compartment group.[11]

According to the Committee for Head and Neck Surgery and Oncology of the American Academy of Otolaryngology–Head and Neck Surgery, the classification of the neck dissection procedures are: radical neck dissection, modified radical neck dissection, extended neck dissection and selective neck dissection.[11] Radical neck dissection is considered to be the standard basic procedure for cervical lymphadenectomy. All other procedures represent one or more alterations of this procedure. When the alteration involves the preservation of one or more non-lymphatic structures routinely removed in radical neck dissection, the procedure is termed a modified radical neck dissection; when the alteration involves the preservation of one or more lymph node groups/levels routinely removed in radical neck dissection, the procedure is termed selective neck dissection; and when the alteration involves the removal of additional lymph node groups or non-lymphatic structures relative to the radical neck dissection, the procedure is termed extended neck dissection.[10]

2.2.3 Oral sequelae of head and neck ablative surgery

The problems in saliva control, swallowing function, speech articulation and intelligibility, nutrition and mastication are among the oral sequelae of oral ablative surgery.[12,13]

Temporarily or permanently impaired swallowing function and impaired speech articulation can occur after maxillectomy and mandibulectomy. Particularly after

maxillectomy, swallowing can be challenging due to food and liquids coming out through the nose. Hypernasality with unintelligible speech can also occur.[12]

For edentulous patients, mastication can be difficult due to the loss of surfaces for dental structures after surgical resection. Other disabilities, which can occur after ablative surgery (especially in tongue-mandible defects), are deviation of the mandible during functional movements, malocclusion and poor control of salivary secretions.[13]

2.3 Surgical Rehabilitation

Due to advanced reconstruction techniques, tumors must be removed with a safe surgical margin without needing to be concerned with preserving tissue for reconstruction.[9]

If soft tissues are lost, local or distant flaps, or vascularized free tissue transfer can be performed depending on the size of the defect. If the bone continuity is lost, a vascularized free fibula flap or iliac crest free flap can be used for reconstruction.[14]

A vascularized free fibula flap or iliac crest free flap has a supporting blood supply, which provides the transplant with a better chance of survival. At the new defect area, vascular pedicle is re-anastomosed to the blood supply and drainage. Especially in irradiated patients, vascularized bone transfer is the optimal type of reconstruction when the added complexity of radiation therapy in malignancy is taken into consideration.[14] Up to 30 cm of the fibula can be used in the reconstruction of bony defects after tumor surgery.[15] However, the short bone height of the fibula (~13 mm) is a challenge for oral rehabilitation due to the vertical inadequacy of bone, which is required for lengthy implants.[16] Furthermore, the vascularized bone flaps sometimes show a volumetric mismatch between transplanted bone and the size of the remaining mandible.[17] Vascularized bone flaps are time consuming, associated with donor-site morbidity, place a heavy burden on hospital resources and are technically demanding. These can therefore be considered among the disadvantages of vascularized bone flaps.[17,18]

2.4 Radiotherapy and chemotherapy to the head and neck region

In the management of head and neck cancer, the role of radiotherapy is significant. Radiotherapy is required as a primary treatment, complementary to surgery, in combination with chemotherapy, or as a palliative treatment. The radiation dose depends on the tumor localization and size, and the type of malignancy, as well as whether the

radiotherapy will be implemented alone or in combination with chemotherapy. As a curative intent, radiation doses varying between 50 and 70 Gy are administered to the majority of patients with head and neck cancer.[19] The postoperative radiation dose is 60–66 Gy, whereas radiation dose of 70 Gy during concurrent chemotherapy may be used with adequate results.[20] The dose is generally administered over a five–seven week period, once a day, for five days a week, with 2 Gy per fraction.[19]

Furthermore, radiotherapy can be implemented through a machine outside the body (external-beam radiation therapy) or from radioactive material placed within the body, close to cancer cells (internal radiation therapy, more commonly called brachytherapy). One of the most common types of external-beam radiation therapy is 3-dimensional conformal radiation therapy (3D-CRT).

Actual newer methods of external-beam radiation therapy such as intensity modulated radiotherapy (IMRT) can avoid the collateral damage to the salivary glands as they are able to deliver high doses of radiation directly to cancer cells in a highly targeted manner and preserve more of the surrounding healthy tissue.[21] Image-guided radiation therapy (IGRT) and tomotherapy are other methods of external-beam radiation therapy.

In the literature, there are only a few studies about the influence of radiation on the crestal bone after prosthetic rehabilitation with dental implants. In the study of Landes and Kovács[22], crestal bone loss was significantly higher in irradiated patients after 2 years. Ernst et al.[23] showed that the mean amount of crestal bone loss in irradiated patients was twice as high as those in non-irradiated patients after 3 years. According to the study by Ernst et al.[23], there was a period of increased bone loss during the first 12 months followed by a period of stagnation with almost stable levels of crestal bone. Although limited in number, there are some studies in the literature which have shown the long-term success of dental implants.[24] What has not been studied in depth until now is how much radiation the bone will receive, where the implants are located, and how much the radiation dose affects the peri-implant state. Therefore in the past, implants in irradiated patients were strongly discouraged. Nowadays, with IMRT, the irradiation is more focused and with the compliance of certain protocols, it can be shown that the implants are functioning.

Chemotherapy can be used as an initial neo-adjuvant or induction chemotherapy prior to surgery with or without radiation therapy with the aim of organ preservation, as a

concurrent radiochemotherapy with the expectation of reducing the risk of distant recurrence and improving local control in locally advanced tumors, as an adjuvant chemotherapy combined with radiation therapy in cases with a high risk of recurrence of tumor, and as a palliative chemotherapy, with or without radiation therapy, in patients with an inoperable tumor with the aim of slowing the growth of the cancer for as long as possible and to relieve any symptoms that the cancer is causing.[25]

The use of chemotherapy concurrent to radiotherapy, compared with the use of radiotherapy alone, improves survival rates of the patients in locally advanced squamous cell head and neck cancer.[26]

The chemotherapy drugs used most often for cancers of the oral cavity and oropharynx are Cisplatin, Carboplatin, 5-fluorouracil (5-FU), Paclitaxel (Taxol®) and Docetaxel (Taxotere®). These chemo drugs can be used alone or combined with other drugs (cisplatin alone, cisplatin or carboplatin associated with 5-FU or other poly-chemotherapy including either platin or 5-FU). Through combining the drugs, tumor shrinkage will be more effective, but it is likely to cause more side effects. For oral cancer, chemotherapy is combined concurrently with radiotherapy and single agent cisplatin appears to be one of the standard treatments in combination with radiotherapy.[27]

2.4.1 Oral sequelae of head and neck radiochemotherapy

The side effects of radiotherapy are associated with the volume and area being irradiated (oral cavity, maxilla, mandible and salivary glands), the age and clinical condition of the patient, the total dose of radiotherapy, fractioning and the associated treatments.

Acute reactions can be observed during the treatment period or in the weeks following the treatment in tissues with rapid turnover rates. However, these reactions are mostly reversible. On the other hand, late complications may occur months or years following radiotherapy in tissues with slower turnover rates and are generally irreversible. These late complications can lead to permanent debilitation of the patient along with the diminishing quality of life. Loss of mucosal pliability, paleness and thinning of the epithelium, submucosal induration, potentially chronic ulceration and necrosis with exposure of the underlying bone and/or soft tissue are just some of the late effects of radiotherapy on mucosal linings.[28]

Different types of chemotherapy drugs have severe acute side effects in many tissues (bone marrow and oral mucosa), which vary according to the patient population, the malignancy being treated and the status of the patients' oral/dental health. These side effects in the oral cavity may be categorized as mucositis, pain and a tendency to infection.[29]

2.4.1.1 Mucositis

The incidence, severity and duration of oral mucositis increase due to the association between radiotherapy and chemotherapy. This increase takes place particularly when different drug combinations and hyper-fractionation schedules are used.[30]

The formation of pseudomembranes and ulceration, which are more serious symptoms of mucositis, may be seen around the third week of radiotherapy. Patients with compromised oral mucous membranes, secondary to alcoholism and/or excessive smoking, are seen to display the most serious mucosal changes.[30]

There are limited prevention methods of mucositis, composed of oral care programs to decrease the severity of mucositis, relief of pain and discomfort, and/or strategies to remove micro-organisms that are believed to be involved in the development of radiation mucositis.[31]

Most oral care programs aim to[31]:

- Remove mucosal irritating factors
- Cleanse the oral mucosa
- Maintain the moisture of the lips and oral cavity
- Relieve mucosal pain and inflammation
- Prevent or treat infection

Numerous anesthetics, analgesics and mucosal-coating agents have been recommended for the relief of pain and discomfort due to mucositis.[32]

2.4.1.2 Candidiasis

Candidiasis is the most common infection in the oral cavity that occurs during or shortly after radiotherapy. The symptoms of candidiasis vary from no symptoms to burning

sensitivity and pain, a sensation of coating in the mouth, odynophagia, dysgeusia (often described as a metallic taste), and the smell of a yeast infection.[32]

Pseudomembranous and erythematous candidiasis, and angular cheilitis are the clinical symptoms of candidiasis. Hyperplastic and invasive candidiasis are less common. In milder forms of candidiasis, topical oral treatments are recommended. Systemic treatments should be used in cases when local treatment fails.[32]

2.4.1.3 Taste loss

One of the early responses to being exposed to radiation is an alteration in taste, which begins early and progresses rapidly during the second week of treatment.[29]

All taste qualities are affected by radiation to the oral cavity. Initially, sweet perception may decrease, resulting in symptoms of increased bitter and salt taste, followed by a general abnormal taste and a reduction in taste perception. The effect of radiation on the taste buds, as well as the decreased salivary flow rate, leads to a loss of taste.[32]

The recovery of taste following radiation varies. In some cases, an improvement is observed within 2–6 months after treatment, but in others, the changes may continue *ad infinitum*. Zinc sulfate supplementation has been therapeutically tested with inconsistent outcomes in clinical studies.[32]

2.4.1.4 Hyposalivation

Changes in the quantity and composition of saliva that occur shortly after radiotherapy show the acute response of the gland tissue to radiotherapy. Saliva production decreases to almost 50% after a week of radiotherapy.[29]

A reduction in salivary flow has numerous effects. It decreases the capability of saliva to control the oral pH, re-mineralization and antimicrobial effects.[32] Thickened saliva may cause difficulties in speech, swallowing, and taste loss.[29]

The exclusion of both major and minor salivary glands from irradiation fields, especially the parotid and submandibular glands, will enable the avoidance of significant quantity and composition changes of saliva.[32]

Drinking sufficient water daily and moisturizing mucosal surfaces with commercial dry-mouth products, as well as respective topical agents can be used individually for the

treatment of hyposalivation. In addition, for patients with severe hyposalivation, systemic agents can be used. Pilocarpine is the most extensively studied as a choice of treatment.[33]

2.4.1.5 Radiation caries

Radiation caries is a highly destructive form of dental caries, which is characterized by a rapid onset and progression. Radiation caries are also associated with a higher rate of recurrence and a greater risk of failure of the dental treatment requiring additional dental procedures. The decrease in the amount of saliva and its qualitative alterations is the main factor for the development of radiation caries. Furthermore, a shift to a more cariogenic oral flora, difficulty in oral hygiene and a possible shift to a diet high in carbohydrates can increase the risk.[32]

Proper oral hygiene, dental follow-up visits every 6 months, daily self-application of topical fluoride, limitation of cariogenic foods, re-mineralizing mouth rinse solutions and artificial saliva preparations have been recommended as preventive measures for head and neck cancer patients before, during and after radiotherapy.[32]

2.4.1.6 Periodontal disease

Periodontitis is a chronic microbial/inflammatory disease, which is characterized by the loss of tooth-supporting tissue, inclusive of the tooth-supporting alveolar bone. Ammajan et al.[34] noted a consistent rapid loss of tooth-supporting tissue when comparing patients pre- and post-radiotherapy. The effect of radiation on periodontal health is dose-dependent and pre-existing periodontitis, which is very common in adults, is likely to worsen with cancer treatment.[32]

The risk of periodontal infection is increased due to the changes mentioned above and also due to radiation-induced hyposalivation, accompanied by increased plaque accumulation and alterations in the oral microflora with a shift to periodontal disease-associated flora.[32]

Mechanical oral hygiene procedures, composed of calculus removal, root planning, soft tissue curettage, tooth surface polishing and daily plaque removal, can be used as a pre-treatment intervention. Removal of the local etiologic factors can help to reverse or control inflammation of the periodontium.[32]

2.4.1.7 Trismus

Radiation causes inflammatory changes to mastication muscles, which can cause a limitation of the jaw opening. Trismus develops three to six months after radiation, and is one of the late side effects of radiotherapy. A significant association between the dose of radiotherapy and trismus was observed. With an increased dose of radiation, the frequency of trismus also increases.[29] The incidence of trismus is decreasing with intensity-modulated radiotherapy (IMRT).[32]

Trismus negatively affects oral hygiene, dental treatment, and use of dental prosthesis, speech, nutritional intake and comfort of the patient. Oral appliances, physical therapy and appropriate medications can be used for the management of trismus.[32]

2.4.1.8 Osteoradionecrosis

One of the late complications of radiotherapy is osteoradionecrosis (ORN). It is classically defined as[35]:

“Exposed bone through an opening in the overlying skin or mucosa, persisting as a non-healing wound for 3 months or more”.

The pathophysiology of osteoradionecrosis is associated more with the basic tissue damage effect than to subsequent trauma or infection. According to Marx, the sequence of this tissue damage is[36]:

1) Radiation
2) Formation of hypoxic-hypovascular-hypocellular tissue (three H principle)
3) Tissue breakdown with collagen lysis and cellular death exceeding synthesis and cellular replication
4) Chronic non-healing wounds

Prophylactic oral care for patients prior to, during and after the completion of radiation therapy is necessary for the prevention of ORN.[35] Prior to radiotherapy, aggressive pre-irradiation extraction at least 21 days before the initiation of radiotherapy should be practiced.[35,37] Post-radiotherapy, if a tooth extraction is necessary, it can be performed 4 months after radiotherapy. To control compliance with instructions for proper oral hygiene, patients should receive routine weekly check-ups during radiotherapy. Medical and surgical interventions are the two options for the management of ORN. Conservative

treatment is composed of oral care and local debridement, whereas surgical management is composed of resection of the necrotic bone with reconstruction.[38]

2.5 Implant-prosthetic rehabilitation

Prosthetic rehabilitation is an essential aspect of the oral cancer treatment, which aims to restore esthetics and oral function, and contributes to the patient`s psychological well-being.[39]

After surgical rehabilitation, for edentulous or partially dentate patients, removable partial dentures and complete dentures can be the choices for prosthetic rehabilitation. In these patients, all basic principles of partial and complete denture construction must be considered, applied and occasionally modified to the unusual anatomic and functional situation. The classification of dentures is based on the amount of arch coverage being partial or complete, or their anchorage being fixed or removable.

The success in obtaining the proper stability and retention of a conventional denture is directly related to the extent of the tumor resection. Oral cancer patients are often not able to wear conventional dentures because of the lack of retention, the presence of scar tissue and complicated soft tissue conditions, functional disabilities and paresthesia as a result of tumor resection. Moreover, when the denture is not stable, it may cause pain when biting and chewing food, which prevents patients from wearing dentures.[40]

Particularly following postoperative radiotherapy, the intolerance of denture-bearing mucosa (including in both native and reconstructed tissues) can be observed against mechanical loading, which can limit prosthetic rehabilitation with partial or complete conventional dentures.[41] The vulnerability of the atrophic oral mucosa may increase due to the absence of the protective layer of saliva, which is another effect of radiotherapy.[40]

Due to distortion of the oral anatomy and the adverse effects of radiotherapy, the use of conventional prostheses is rather limited in oral cancer patients. The fitting of dental prostheses in irradiated patients is also critical. Unfavorable prosthetic pressure can result in pressure sores and dehiscence followed by septic osteoradionecrosis.[5] Implant-supported or -retained prostheses are often the only choice of prosthetic rehabilitation for these patients.[42]

2.5.1 Osseointegrated implants and implant-supported dentures

2.5.1.1 Dental implants

In 1969, Brånemark advocated that titanium could be integrated with bone. He developed and tested a system using pure titanium screws, which was first used in patients in 1965 to replace missing teeth.[43,44] These were the first dental implants. With this implant came the concept of "osseointegration" which flourished rapidly in the 1980s, and brought about a defining moment in the clinical field of implants.

2.5.1.2 Osseointegration

Osseointegration is defined by Brånemark as:

"A direct structural and functional connection between ordered, living bone, and the surface of a load carrying implant".[44]

The biologic sequence of osseointegration around dental implants is composed of three phases:

1) *The osteophyllic phase*: Takes place during the first month following the placement of dental implants. It marks the migration of endosteal osteoblasts and marrow stems to the implant surface and differentiation into functioning osteoblasts.
2) *The osteoconductive phase*: Occurs during the 3 months after the osteophyllic phase. Represents bone conduction along the metal surface.
3) *The osteoadaptive phase:* The final phase occurs after 4 months. In this phase, dental implants can be loaded and masticatory stresses can be transferred directly to the anchoring bone.[44]

This study was published in the literature in 1998. Unfortunately, current studies do not exist. The timespans are currently much shorter and under discussion.

2.5.1.3 Implant supported dentures and distribution of implants

The number of implants and prosthetic design are directly related to each other. While the number of implants determines the type and design of the prosthesis, the number of implants is in turn determined by the prosthetic design. Furthermore, there is a correlation between the size, curvature and shape of the ridges and the distribution of implants.

Anatomy of the patients, such as inferior alveolar canal or maxillary sinus, may limit the insertion of an appropriate number or length of implants.

For a fixed implant-supported prosthesis, the insertion of four or more implants in the mandible and six or more implants in the maxilla is required, whereas for a removable prosthesis, four implants in the maxilla and two implants in the mandible are necessary.

Studies have shown that abutment connections can be successfully performed after 3 months in the maxilla and 2 months in the mandible following implant insertion in non-irradiated or irradiated oral cancer patients.[23,45]

2.5.1.4 Dental implants and implant supported dentures in oral cancer patients

In the past, implant rehabilitations were an absolute contraindication in irradiated patients.[46,47] In 1988, the first clinical report to define the possible osseointegration process in irradiated bone was published by Jacobsson et al.[48] The success rate was 86%, with 5 failures in 35 implants in 9 patients after 44 months. In 1991, Parel and Tjellström reported a 61% success rate for implants in irradiated bone.[49] According to Sammartino et al.[46], the osseointegration process may be compromised in oral cancer patients due to reduced remodeling and healing potential following radiotherapy.

Various studies published at the beginning of the 21st century show that dental implants in irradiated oral cancer patients can osseointegrate and be functionally stable over long periods.[47,50,51] In the study by Yerit et al.[50], after a 3-year follow-up, the survival rate of dental implants in the irradiated mandible was 90%. Similar results were reported by Cuesta-Gil et al.[47] In his study, the osseointegration success rate of dental implants in irradiated patients was 92.9% after a 9 year follow-up. The use of dental implants in irradiated oral cancer patients has increased over the past years and an exposure of 50–65 Gy is not considered a limit for implant treatment.[46,51] According to Granström[52], if the term “cumulative radiation effect” is applied, which is calculated as (Total time of treatment/Number of treatments)$^{\mathbf{-0.11}}$ x Dose per treatment x (Number of treatments)$^{\mathbf{0.65}}$, a more reliable estimation of irradiation dose can be obtained since the Gy dose does not account for the number of fractions given. According to this study, relatively few implants will fail below a cumulative radiation effect of 18 to 20 (corresponding to 48–65 Gy given as standard fractionation radiotherapy), and all implants will fail at doses above the cumulative radiation effect of 40 (120 Gy standard fractionation).[52]

In the literature, there is no standard appliance for oral cancer patients regarding prosthetic rehabilitation. Topography and the size of the defect specify the individuality of prosthetic restorations.[53]

In young patients or partially edentulous patients with a minor defect in soft and hard tissue, fixed implant-supported restorations can be the primary choice of prosthetic rehabilitation.[42]

In cases in which the soft and hard tissue defects in oral cancer patients need to be compensated, implant-retained prostheses are recommended.[39,42,53] The rigid bar-retained over-dentures, which required little maintenance, or implant-supported fixed prostheses minimize technical complications and relieve the vulnerable underlying soft tissue to avoid denture-related lesions in oral cancer patients.[39]

The overall survival rate of dental implants in oral cancer patients after long-term follow-up (for example after 10 years) is still under debate due to the lack of studies in the literature with a long-term follow-up. There are only a few studies, which have reported long-term results in extensive patient series. According to the study by Nelson et al.[42], long-term implant prosthetic rehabilitation is possible in oral cancer patients despite radiotherapy and tissue deficiencies. However, further prospective studies with long-term follow-up are required to show that oral cancer patients can be treated with fixed implant-supported restorations or implant-retained prostheses for longer durations.

2.5.2 Success criteria

The success criteria are applied in the assessment of the long-term efficacy of dental implants. In the literature, there are 3 different success criteria according to Buser et al., Naert et al. and Albrektsson et al.[54,55,56]

In this study, due to the simplicity of the documentation, the success criteria according to Buser et al. were applied.

According to Buser et al.[54], the success criteria of osseointegrated implants include:

- The absence of persistent subjective complaints, such as pain, foreign body sensation and/or dysthesia
- The absence of peri-implant infection with suppuration
- The absence of mobility

- The absence of a continuous radiolucency around the implant

According to Albrektsson et al.[56], the success of an osseointegrated implant depends on:

- The absence of mobility
- The absence of any evidence of peri-implant radiolucency
- Vertical bone loss less than 0.2 mm (following the implant`s first year of service)
- The absence of persistent and/or irreversible signs and symptoms such as pain, infections, neuropathies, paresthesia, or violation of the mandibular canal
- A success rate of 85% at the end of a five-year observation period and 80% at the end of a ten-year period (minimum criterion for success)

The success criteria according to Naert et al.[55] include implant mobility, peri-implant radiolucency, pain and infection around the implant. The results of the survival rates of dental implants can vary according to the success criteria, which are used for the assessment of the study. Therefore, standardized criteria for the success of implants would simplify the comparison of different studies.

2.6 The aim of the study

The use of dental implants and fixed implant-supported restorations or -retained prostheses in oral cancer patients have increased over the past years due to advances in surgical rehabilitation and adjuvant radiochemotherapy. The purpose of this study was to evaluate the long-term clinical success of dental implants and implant-supported prostheses in oral cancer patients following surgical resection. Additionally, potential influencing factors of dental implants should be evaluated.

Chapter 3: Materials and Methods

3.1 Study design

The study was a retrospective long-term evaluation of implant survival and potential influence factors in patients with tumor therapy in the head-neck region.

3.1.1 Inclusion criteria

Inclusion criteria of this study comprised:

- Oral cancer patients with squamous cell head neck carcinoma,
- Oral cancer patients with radiotherapy and chemotherapy,
- Oral cancer patients who are attending follow-up controls at the Department of Oral Maxillofacial Surgery, Campus Virchow-Clinic, Charité University Hospital.

3.1.2 Exclusion criteria

Nicotine users receiving radiochemotherapy were not included in this study. Patients with considerable weakened general health conditions like poor nutritional condition, immunocompromised patients (e.g., HIV infection, autoimmune diseases, cortisone treatment), and patients with uncontrolled diabetes were excluded from the study.

3.1.3 Patient selection

In total, 60 patients (20 women and 40 men) who had been diagnosed with a squamous cell carcinoma in the oral cavity treated with ablative surgery alone or in combination with radiochemotherapy were included in the study. The mean age was 62.75 years (41–88 years). Among the 60 patients, 35 (212 implants) received radiochemotherapy before the implant placement. Over a six-week period, a dose of 50–72 Gy was administered to the 35 patients in fractions of 2 Gy for 5 days per week. Concomitant to radiation, the patients were administered platinum-based chemotherapy (30mg/m^2 body surface area). All implants were placed after a minimum of 6 months following the completion of radiation therapy in all irradiated patients.

3.2 Data Collection

The surgical resection of the tumor, the treatment of patients with dental implants, and the prosthodontic treatment with implant-supported prostheses were performed at the Department of Oral Maxillofacial Surgery, Virchow-Clinic, Charité University Hospital.

3.2.1 Implants

A total of 330 implants (122 maxilla/208 mandible) of 3 systems were placed according to the manufacturer's protocol: Brånemark MKII (Nobel Biocare AB, Sweden); Straumann Tissue Level (Straumann AG, Switzerland); Camlog Root-Line (Camlog Biotechnologies AG, Switzerland).

The implants were allowed to osseointegrate for 3 months in the mandible and 6 months in the maxilla in all participants, regardless of whether they were irradiated or not. From 2004, the healing time of the implant was reduced to 3 months in the maxilla and 2 months in the mandible.

Non-irradiated patients were treated peri-operatively with a single shot antibiosis i.v. (Clindamycin 600 mg; MIP Pharma GmbH, Germany). In order to minimize the risk of osteoradionecrosis in irradiated patients, the patients were given 300 mg Clindamycin p.o. (MIP Pharma GmbH, Germany) preoperatively and postoperatively (3 days preoperatively, and 3 days postoperatively).

3.2.2 Pre-prosthetic and prosthetic treatment

Vestibuloplasty according to Heberer and Nelson[57] was performed in 32 patients in the maxilla and mandible to reach optimal soft tissue conditions. An impression of all implants, with system-specific seated transfer copings by use of alginate (Kanidenta, Herford, Germany), was taken at implant placement. The dental technician fabricated an individually manufactured implant-retained splint. After two months, vestibuloplasty was performed under general anesthesia. After preparation of the mucosal flap, it was reflected to the lingual and buccal sites, avoiding sensitive structures like the mental nerve to prevent damage. The suture of the flap to the periosteum was performed in the predetermined position, which ensured adequate mobilization of the tongue and adequately deepened vestibulum.

Following disinfection (Braunol; B. Braun Melsungen AG, Melsungen, Germany) of the shaved upper thigh, a 0.4 mm split-thickness skin graft was harvested with an electric dermatome. The external upper thigh was chosen as the donor site at all times. From here, a sufficient amount of skin for the oral defect size was obtained. The conventional bandage consisted of paraffin gauze (Lomatuell H; Lohmann&Rauscher, Rengsdorf, Germany) impregnated with Braunovidon ointment (B. Braun Melsungen AG).

Through the use of No.5 resorbable sutures (Monocryl; Ethicon, Somerville, NJ), the graft was secured and perforated with a scalpel, thus preventing hematoma. Pressure was applied during fastening of the splint screws on the implants. To avoid inconvenient pressure on the graft, the surgical splint was relined with Peripac (Dentsply, Konstanz, Germany). The patients underwent a soft diet for 6 days post-operatively and received analgesics (Ibuprofen, 400mg) for 2 to 3 days. Daily examinations were conducted on all patients while they were hospitalized for 4 days. After a week, in order to renew the relining material, the implant-retained splint was removed for the first time. Fourteen days after the operation, the removal and reinsertion of the splint was initiated until the definitive placement of the implant retained restoration.

In cases without vestibuloplasty, the second stage implant surgery was performed after an osseointegration period (3 months in the mandible and 6 months in the maxilla, after 2004 after 3 months in the maxilla, 2 months in mandible). The exposure of the implant body was performed with minimal soft tissue trauma under local anesthesia.

Two weeks after the second stage implant surgery, an impression was conducted using an open tray technique with polyether impression material (Impregum; 3M ESPE, Seefeld, Germany) for the prosthetic treatment. 60 oral cancer patients were treated with 86 implants retained removeable or fixed prostheses. Out of the total of 86 prostheses; 58 were removable over-dentures retained by an individually fabricated bar, 15 were screw-retained fixed bridges, 3 were Telescopic prostheses and 10 of them were removable over-dentures retained by a locator. Acrylic resin artificial teeth (Creapearl; Amann Girbach GmbH, Pforzheim, Germany and SR Vivodent or Orthotyp PE; Ivoclar Vivadent, Schaan, Lichtenstein) were used in all of the removable prostheses.

The implants of the patients were clinically assessed and evaluated every 6 months during the first 3 years. Subsequently, the timeframe between the examinations was extended to 12 months. The clinical examination comprised a standardized protocol. The

implant success was regularly assessed according to the criteria of Buser et al.[54] These included: implant mobility and radiolucency around the implant, the absence of subjective complaints like pain, and peri-implant infections. X-ray examination was performed post operatively at 1 year, 3 years, 5 years, and 7 years.

3.3 Statistical analysis

Descriptive data were analyzed using SPSS 13 (SPSS Inc., USA). The survival of implants was evaluated through the use of the Kaplan-Meier curve. Overall differences according to gender, radiotherapy, localization (maxilla/mandible) and vestibuloplasty were assessed using the Log Rank test. Log Rank test is the most popular method of comparing the survival of groups, which takes the whole follow-up period into account. With this test, it can be detected whether the two groups differ significantly concerning the survival times. It does not allow the effect of the other independent variables to be tested. The results were considered statistically significant at $P<0.05$. Cox-Regression was used to evaluate the influence of age on the survival of the implants and Cox-Regression multivariate analysis was used to assess the influence of age and localization of the implants (maxilla/mandible).

Chapter 4: Results

In this study, 330 dental implants in 60 patients were observed for an average observation period of 86 months (4–272 months). Three patients with 20 implants died during the observation period and 27 of the 330 dental implants were lost. All of the 27 failed implants were lost after the first 3 months following implant placement and were considered to be late implant failures. The cumulative survival rate of implants in oral cancer patients was 99.7% at 3 years, 92.7% at 7 years and 88.3% at 10 years. With a follow-up period of up to 20 years, the cumulative survival rate remained constant after 11 years with 83% (Figure 1, Table 3).

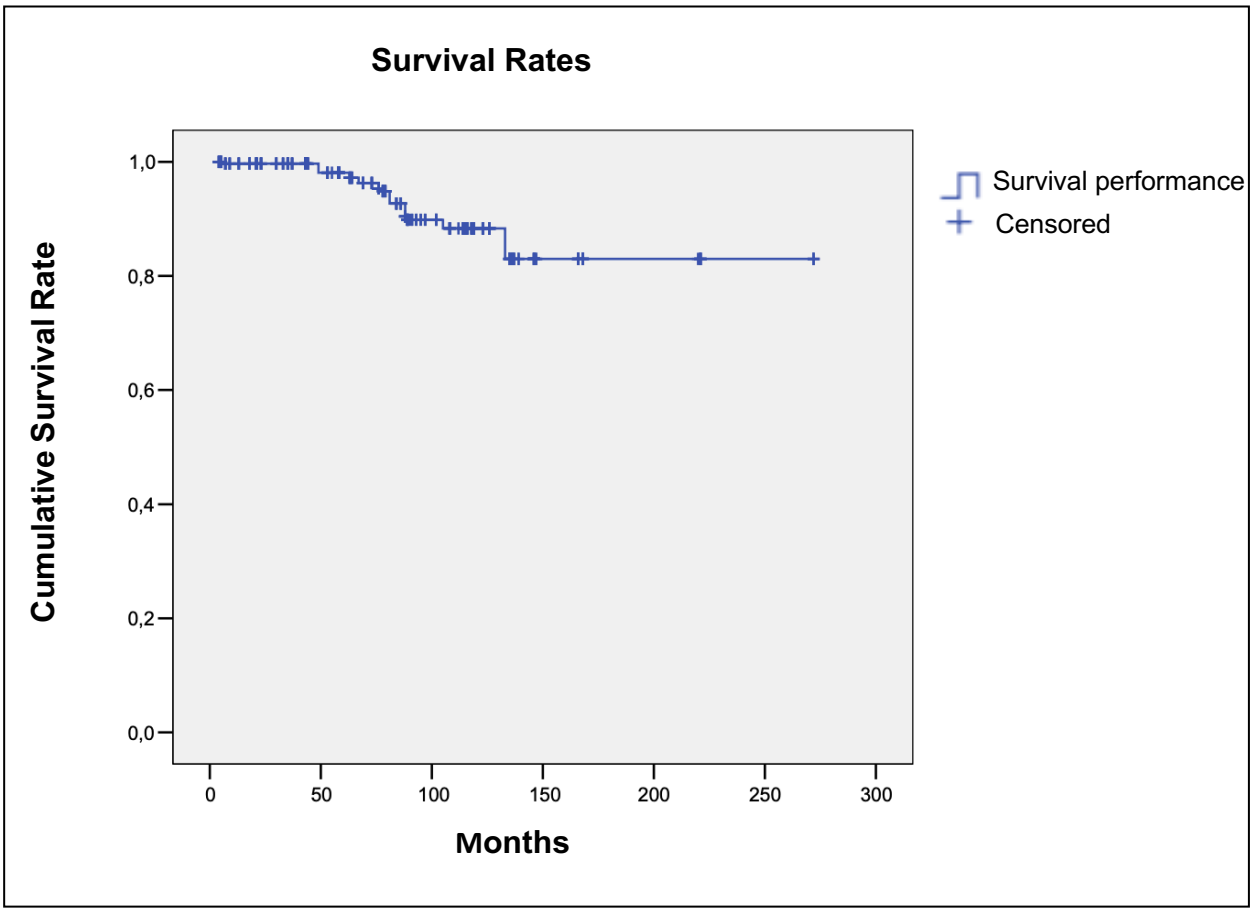

Figure 1: Kaplan-Meier survival analysis for an observation period of 20 years for implants placed in oral cancer patients

	Time	Status	Cumulative Amount of Survivals in an Instant of Time		Number of Occurrences	Number of Remaining Cases
			Estimator	Standard Error		
10	7.000	Loss	.997	.003	1	320
82	49.000	Loss	.	.	2	248
83	49.000	Loss	.	.	3	247
84	49.000	Loss	.	.	4	246
85	49.000	Loss	.981	.009	5	245
108	63.000	Loss	.	.	6	222
109	63.000	Loss	.972	.010	7	221
119	67.000	Loss	.	.	8	211
120	67.000	Loss	.963	.012	9	210
129	76.000	Loss	.	.	10	201
130	76.000	Loss	.953	.014	11	200
139	78.000	Loss	.948	.015	12	191
155	81.000	Loss	.	.	13	175
156	81.000	Loss	.	.	14	174
157	81.000	Loss	.	.	15	173
158	81.000	Loss	.927	.018	16	172
167	88.000	Loss	.	.	17	163
168	88.000	Loss	.	.	18	162
169	88.000	Loss	.	.	19	161
170	88.000	Loss	.904	.021	20	160
175	89.000	Loss	.898	.021	21	155
213	105.000	Loss	.	.	22	117
214	105.000	Loss	.883	.024	23	116
265	133.000	Loss	.	.	24	65
266	133.000	Loss	.	.	25	64
267	133.000	Loss	.	.	26	63
268	133.000	Loss	.830	.034	27	62

Table 3: Lifetime analysis of evaluated dental implants in oral cancer patients

Three different implant systems were used: 269 Camlog Root-Line implants (Camlog Biotechnologies AG, Switzerland), 58 Straumann Tissue Level implants (Straumann AG, Switzerland) and 3 Brånemark MKII implants (Nobel Biocare AB, Sweden).

Of the 330 implants, 100 implants were inserted in women, and 230 implants were inserted in men. During the observation period, 4 dental implants in women and 23 dental implants in men were lost. Kaplan Meier analysis of the implant survival rate was 100% for women and 99.6% for men at 3 years, 91.7% for women and 92.9% for men at 7 years and 91.7% for women and 87.3% for men at 10 years (Table 4). With a follow-up period of up to 20 years, the cumulative survival rate remained constant after 7 years with 91.7% for women and after 11 years with 81% for men. There were no significant differences between the genders (Figure 2) (*P*=0.235).

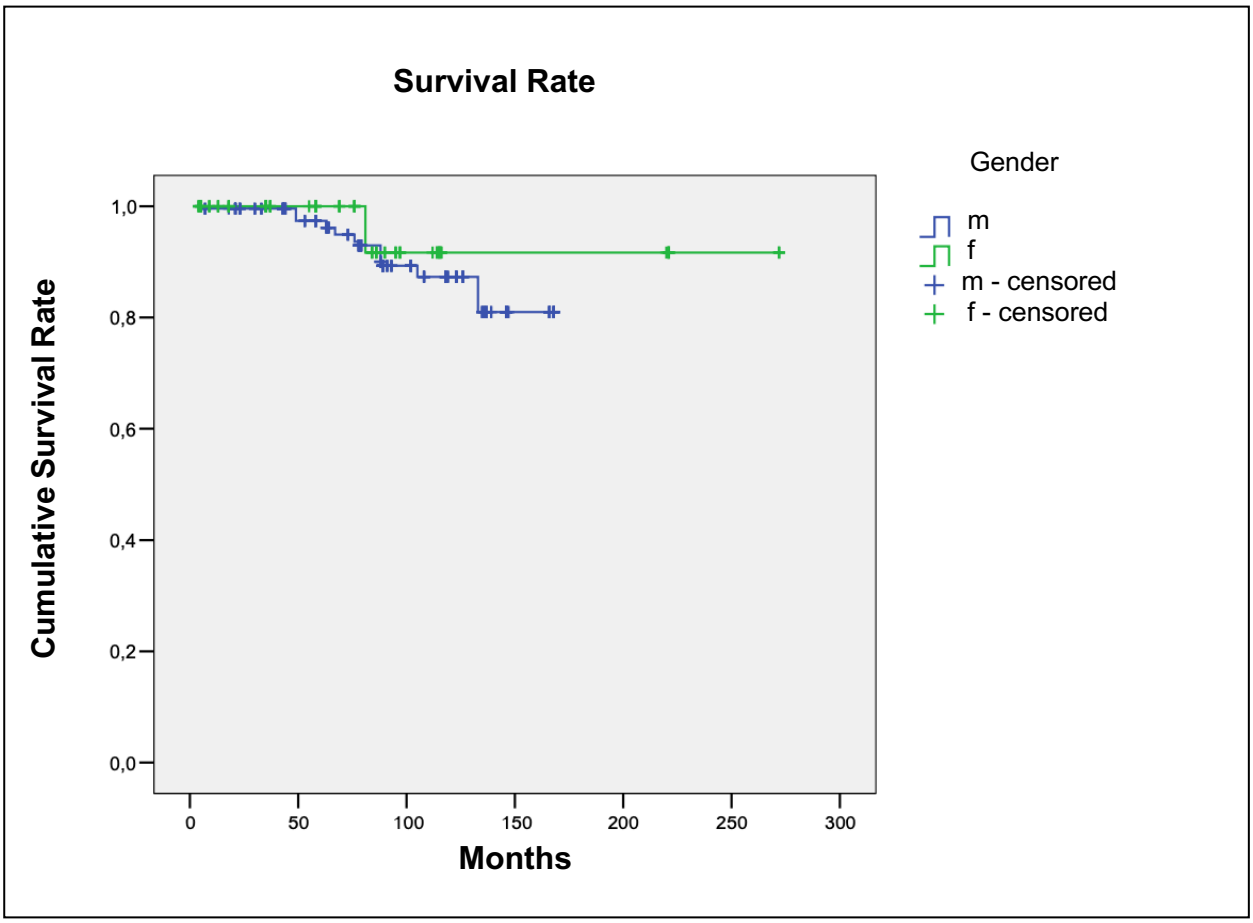

Figure 2: Kaplan-Meier survival analysis for the observation period of 20 years for implants according to the gender of oral cancer patients

Gender		Time	Status	Cumulative Amount of Survivals in an Instant of Time		Number of Occurrences	Number of Remaining Cases
				Estimator	Standard Error		
Female	53	81.000	Loss	.	.	1	47
	54	81.000	Loss	.	.	2	46
	55	81.000	Loss	.	.	3	45
	56	81.000	Loss	.917	.040	4	44
Male	2	7.000	Loss	.996	.004	1	228
	51	49.000	Loss	.	.	2	179
	52	49.000	Loss	.	.	3	178
	53	49.000	Loss	.	.	4	177
	54	49.000	Loss	.974	.012	5	176
	68	63.000	Loss	.	.	6	162
	69	63.000	Loss	.962	.014	7	161
	79	67.000	Loss	.	.	8	151
	80	67.000	Loss	.949	.017	9	150
	85	76.000	Loss	.	.	10	145
	86	76.000	Loss	.936	.019	11	144
	87	78.000	Loss	.929	.020	12	143
	103	88.000	Loss	.	.	13	127
	104	88.000	Loss	.	.	14	126
	105	88.000	Loss	.	.	15	125
	106	88.000	Loss	.900	.024	16	124
	111	89.000	Loss	.893	.025	17	119
	140	105.000	Loss	.	.	18	90
	141	105.000	Loss	.873	.028	19	89
	176	133.000	Loss	.	.	20	54
	177	133.000	Loss	.	.	21	53
	178	133.000	Loss	.	.	22	52
	179	133.000	Loss	.810	.040	23	51

Table 4: Lifetime analysis of evaluated dental implants according to the gender of oral cancer patients

In this study, 122 implants were placed in the maxilla and 208 implants were placed in the mandible. Among these, 5 dental implants in the maxilla and 22 dental implants in the mandible were lost. After 3 years, the implant survival rate was 99.2% for the maxilla and 100% for the mandible. The cumulative survival rate was 96.6% for the maxilla and 90.2% for the mandible at 7 years and 92.9% for the maxilla and 85.5% for the mandible at 10 years. With an observation period of up to 20 years it remained constant after 11 years with 92.9% for the maxilla and 75.4% for the mandible (Table 5). Over the entire observation period, the localization had an impact on the implant survival (Figure 3) (P<0.016). The risk of the implant loss in the mandible is higher than in the maxilla.

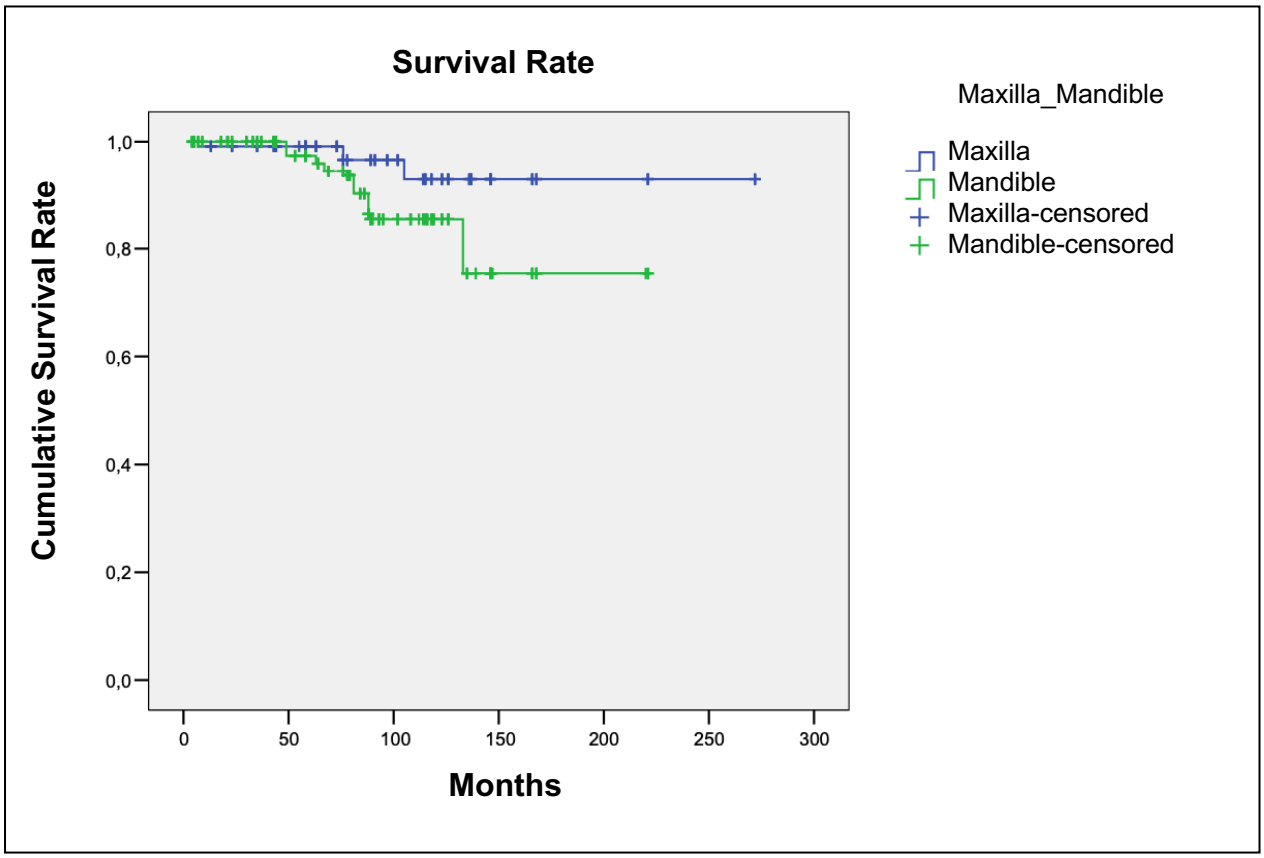

Figure 3: Kaplan-Meier survival analysis for an observation period of 20 years for implants placed in the maxilla and mandible in oral cancer patients

Maxilla_ Mandible		Time	Status	Cumulative Amount of Survivals in an Instant of Time		Number of Occurrences	Number of Remaining Cases
				Estimator	Standard Error		
Maxilla	1	7.000	Loss	.992	.008	1	121
	40	76.000	Loss	.	.	2	77
	41	76.000	Loss	.966	.019	3	76
	66	105.000	Loss	.	.	4	51
	67	105.000	Loss	.929	.032	5	50
Mandible	62	49.000	Loss	.	.	1	151
	63	49.000	Loss	.	.	2	150
	64	49.000	Loss	.	.	3	149
	65	49.000	Loss	.974	.013	4	148
	78	63.000	Loss	.	.	5	135
	79	63.000	Loss	.959	.016	6	134
	84	67.000	Loss	.	.	7	129
	85	67.000	Loss	.945	.019	8	128
	94	78.000	Loss	.937	.020	9	119
	106	81.000	Loss	.	.	10	107
	107	81.000	Loss	.	.	11	106
	108	81.000	Loss	.	.	12	105
	109	81.000	Loss	.902	.026	13	104
	118	88.000	Loss	.	.	14	95
	119	88.000	Loss	.	.	15	94
	120	88.000	Loss	.	.	16	93
	121	88.000	Loss	.864	.031	17	92
	126	89.000	Loss	.855	.032	18	87
	180	133.000	Loss	.	.	19	33
	181	133.000	Loss	.	.	20	32
	182	133.000	Loss	.	.	21	31
	183	133.000	Loss	.754	.055	22	30

Table 5: Lifetime analysis of evaluated dental implants according to localization (maxilla/ mandible) in oral cancer patient

The elderly patients are more likely not to lose the implants (P=0.006 Exp(B)=0.935 with 95%CI[0,89;0,98]) (Table 6). The multivariate analyses of the age and localization of the implants (maxilla/mandible) showed that age remains as a risk factor and the risk of loss of an implant in the mandible is 2.9 times higher Exp(B)=2.9 with 95%CI[1,12;7,84] than in the maxilla (Table 7).

	B	SE	Wald	df	Significance	Exp(B)	95,0% Confidence Range for Exp (B)	
							Upper	Lower
Age	-,070	,026	7,464	1	,006	,932	,887	,980

Table 6: Cox-Regression analyses for the influence of age of the survival of the implants

	B	SE	Wald	df	Significance	Exp(B)	95,0% Confidence Range for Exp (B)	
							Upper	Lower
Age	-,067	,025	7,052	1	,008	,935	,890	,983
Maxilla/ Mandible	1,085	,497	4,771	1	,029	2,958	1,118	7,829

Table 7: Cox-Regression multivariate analyses of the age and localization of the implants (maxilla/mandible)

After oral cancer resection, 35 participants with 212 implants received additional radiochemotherapy. In these patients, 19 implants were lost. In 25 non-irradiated patients, 118 implants were placed and 8 of these were lost. The cumulative implant survival rate in patients who received radiochemotherapy was 99.5% at 3 years, 91.8% at 7 years and 88.9% at 10 years. In comparison to irradiated patients, the cumulative implant survival rate in non-irradiated patients was 100% at 3 years, 94.9% at 7 years and 87.5% at 10 years. With a follow-up period of up to 20 years, the cumulative survival rate remained constant after 11 years with 87.5% in non-irradiated patients and 82.3% in irradiated patients (Table 8). The difference in implant survival rate between irradiated jaws and non-irradiated jaws was not significant (*P*=0.948) (Figure 4).

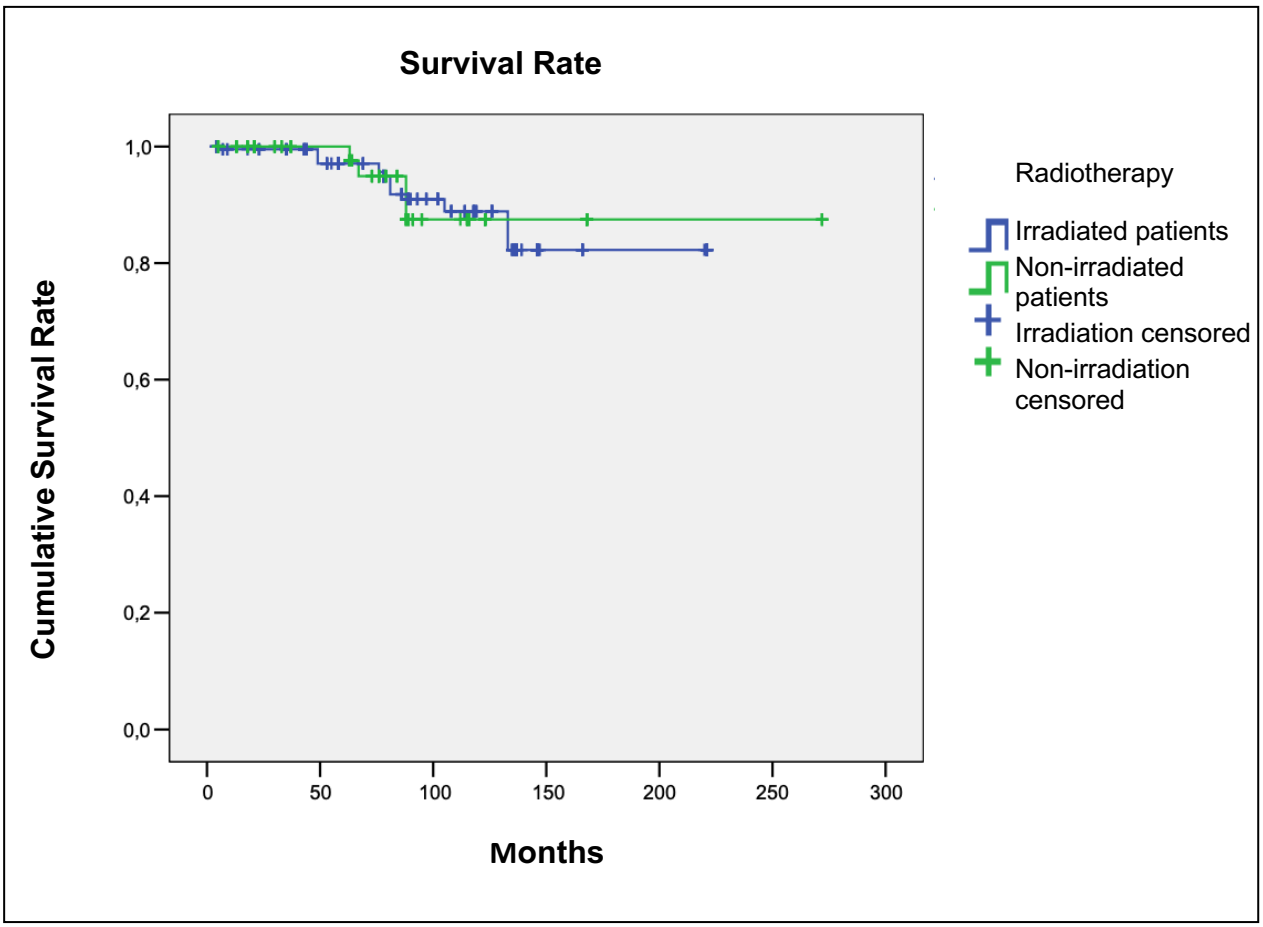

Figure 4: Kaplan-Meier survival analysis for observation period of 20 years for implants placed in irradiated oral cancer patients

Radiotherapy		Time	Status	Cumulative Amount of Survivals in an Instant of Time		Number of Occurrences	Number of Remaining Cases
				Estimator	Standard Error		
Irradiated	5	7.000	Loss	.995	.005	1	207
	48	49.000	Loss	.	.	2	164
	49	49.000	Loss	.	.	3	163
	50	49.000	Loss	.	.	4	162
	51	49.000	Loss	.971	.013	5	161
	78	76.000	Loss	.	.	6	134
	79	76.000	Loss	.957	.016	7	133
	80	78.000	Loss	.949	.018	8	132
	92	81.000	Loss	.	.	9	120
	93	81.000	Loss	.	.	10	119
	94	81.000	Loss	.	.	11	118
	95	81.000	Loss	.918	.023	12	117
	100	89.000	Loss	.910	.024	13	112
	127	105.000	Loss	.	.	14	85
	128	105.000	Loss	.889	.028	15	84
	159	133.000	Loss	.	.	16	53
	160	133.000	Loss	.	.	17	52
	161	133.000	Loss	.	.	18	51
	162	133.000	Loss	.823	.041	19	50
Non-irradiated	35	63.000	Loss	.	.	1	83
	36	63.000	Loss	.976	.017	2	82
	46	67.000	Loss	.	.	3	72
	47	67.000	Loss	.949	.025	4	71
	68	88.000	Loss	.	.	5	50
	69	88.000	Loss	.	.	6	49
	70	88.000	Loss	.	.	7	48
	71	88.000	Loss	.875	.042	8	47

Table 8: Lifetime analysis of evaluated dental implants according to additional radiochemotherapy in oral cancer patients

Vestibuloplasty according to Heberer and Nelson[57] was performed in 32 patients with 141 implants in the maxilla and mandible to reach optimal soft tissue conditions. Out of these 141 implants, 4 were lost. During this period, 107 implants were inserted into the patients without vestibuloplasty. Out of these, 19 were lost. The cumulative survival rate of implants with vestibuloplasty was 100% at 3 years and 95.5% at 7 years. With a follow-up period of up to 10 years, the cumulative survival rate remained constant after 7 years with 92.9%. The cumulative survival rate of implants without vestibuloplasty was 99.1% at 3 years and 79.6% at 7 years and it remained constant after 8 years with 66%, with a follow-up period up to 10 years (Table 9). The implant survival rate between the patients with or without vestibuloplasty was significantly different (P=0.001) (Figure 5).

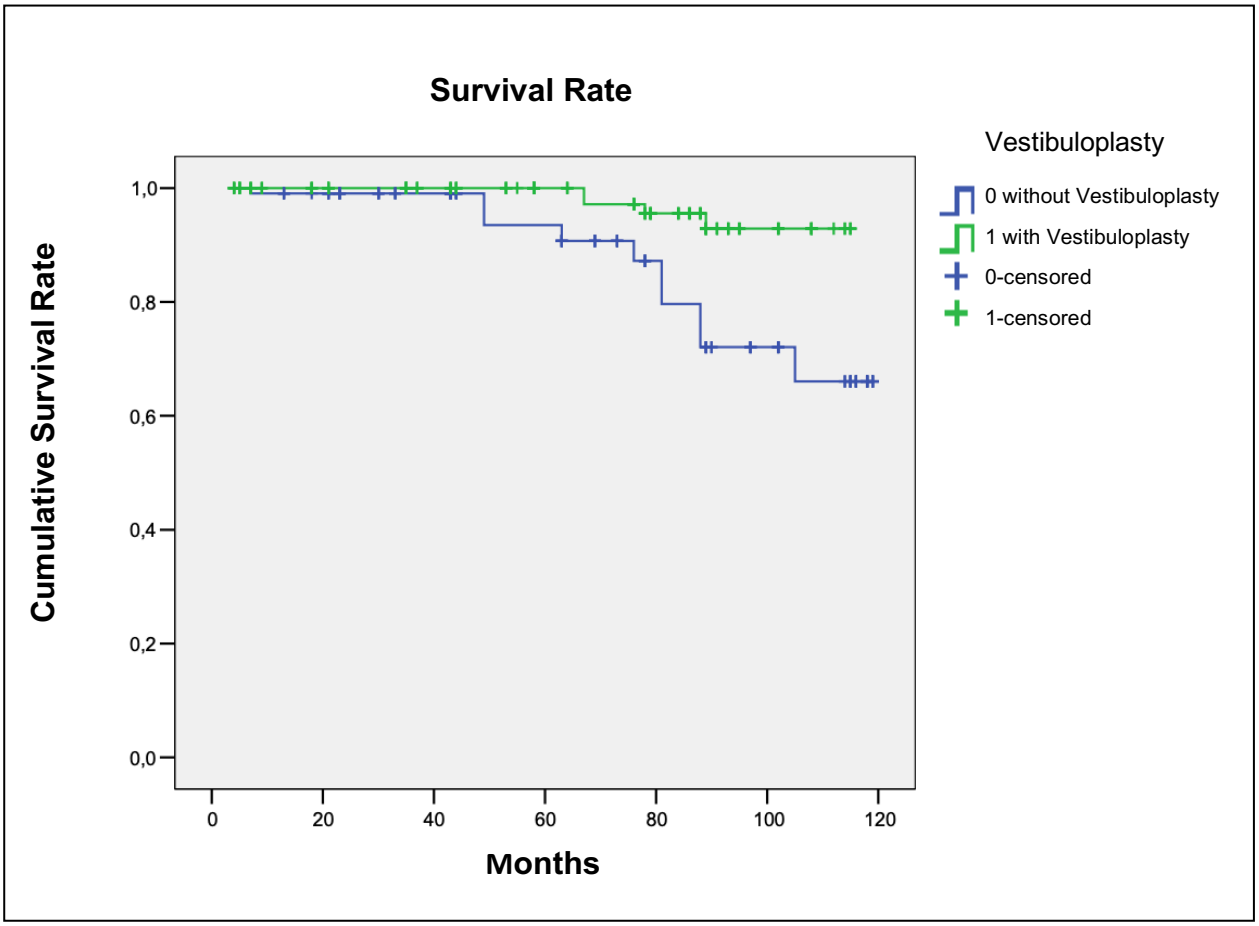

Figure 5: Kaplan-Meier survival analysis for observation period of 10 years for implants according with or without vestibuloplasty

Vestibuloplasty	Time	Status	Cumulative Amount of Survivals in an Instant of Time		Number of Occurrences	Number of Remaining Cases
			Estimator	Standard Error		
0 1	7.000	Loss	.991	.009	1	106
37	49.000	Loss	.	.	2	70
38	49.000	Loss	.	.	3	69
39	49.000	Loss	.	.	4	68
40	49.000	Loss	.935	.028	5	67
41	63.000	Loss	.	.	6	66
42	63.000	Loss	.907	.034	7	65
56	76.000	Loss	.	.	8	51
57	76.000	Loss	.872	.041	9	50
62	81.000	Loss	.	.	10	45
63	81.000	Loss	.	.	11	44
64	81.000	Loss	.	.	12	43
65	81.000	Loss	.796	.052	13	42
66	88.000	Loss	.	.	14	41
67	88.000	Loss	.	.	15	40
68	88.000	Loss	.	.	16	39
69	88.000	Loss	.720	.059	17	38
84	105.000	Loss	.	.	18	23
85	105.000	Loss	.660	.068	19	22
1 72	67.000	Loss	.	.	1	69
73	67.000	Loss	.971	.020	2	68
82	78.000	Loss	.955	.025	3	59
106	89.000	Loss	.929	.036	4	35

Table 9: Lifetime analysis of evaluated dental implants according to vestibuloplasty in oral cancer patients

Chapter 5: Discussion and Conclusion

The present study is concerned with the evaluation of the long-term survival rate of dental implants in the risk group of oral cancer patients. Several influencing parameters are examined to discuss the prospective treatment concepts. In the present study, the mean follow-up period was 86 months. Studies in the literature have information value if they have a long-term follow-up period over 5 years.

There are a few comparable studies in the literature, which evaluated dental implant treatment concerning long-term success and potential influencing factors.

In the study of Nelson et al.[42] in which 435 implants were inserted in 93 patients, the overall implant survival in oral cancer patients following ablative surgery was 92% after 3.5 years, 84% after 8.5 years and 69% after 13 years. The implants were observed for an average of 10.3 years according to the criteria of Buser et al.[54], which includes a lack of persistent complaints like pain and a lack of repeated peri-implant infection, fistula or abscess. In the study by Nelson et al.[42], limited implant survival was not a consequence of the failure of osseointegration; on the contrary, the mortality rate of patients was high and 65% of the unsuccessful implants were lost due to patient death. In this study the mortality rate of patients was not as high and the lost implants due to the patient death were not evaluated as unsuccessful implants. Additionally, the exclusion of irradiated smokers from the patient group and the strict protocol for postoperative management could be an explanation for the difference between the survival rates of dental implants in oral cancer patients.

In the study by Linsen et al.[53], a total of 262 implants in 66 patients were inserted in the mandible (213 implants) and in the maxilla (49 implants) in both non-irradiated (135 implants) and irradiated (127 implants) patients. Four patients with 16 implants (maxilla/mandible) died during the observation period. The success criteria were based on the absence of pain, mobility and recurrent peri-implant infection and radiolucency. The average observation period after implant insertion was 47.9 months. In the study of Linsen et al.[53], the cumulative survival rates of the 262 implants were 96.6%, 96.6% and 86.9% for the 1, 5, and 10-year observation period, respectively. These results showed similarity to the results found in the present study.

Furthermore, according to the study by Linsen et al.[53], implant loss is to be expected due to the lack of primary osseointegration (early failures). In the present study, early failures did not occur and all implant losses were due to late failures. According to the present study, the inability to establish osseointegration (early failure) during the healing phase of the implants does not cause a lower implant survival rate for oral cancer patients. The reduced implant survival rate seems to be caused by a failure in maintaining the established osseointegration. The causes for this failure cannot be determined from this study.

In a similar study by Barrowman et al.[58], a total of 115 dental implants were placed in 30 irradiated and non-irradiated patients, with 48 of these dental implants inserted in irradiated tissues. 5 implant failures occurred in irradiated free flaps. The retention rate of dental implants in irradiated bone was 89.5% after 2 years. Comparing the present study to that of Barrowman et al.[58], the survival rate of dental implants in irradiated bone in the present study was higher, with a level of 99.5% at 3 years and 91.8% at 7 years. Soft tissue management may have positively influenced the higher rates of implant survival. According to Barrowman et al.[58], bulky soft tissue flaps may preclude the provision of implants. In the present study, in 32 patients with inadequate keratinized gingiva, a vestibuloplasty according to Heberer and Nelson[57] was performed to achieve optimal soft tissue conditions. Optimal soft tissue conditions are: the presence of thin and immobile soft tissue to enable maintenance of the implants, and the soft tissues being soft and pliable, tolerating natural movements as much as possible. Vestibuloplasty according to Heberer and Nelson[57] has been performed on patients within the present study first in 2004 to eliminate the soft tissue inflammation due to lacking attached mucosa, which could result in peri-implantitis with marginal bone loss and might be a cause of implant failure. The study which was published by Heberer and Nelson[57] in 2009 (based on 17 patients with 68 implants with improper mucosal situations, with a follow up period of 19.2 months), showed that the well-known shrinkage phenomenon of vestibuloplasties with or without grafts can be minimized using an implant-retained splint, which allows adequate equal pressure for revasculatization of the graft necessary for the success of the vestibuloplasty procedure. During the observation period within the study of Heberer and Nelson[57] no implants were lost and peri-implantitis was not observed in any of the patients. These results encouraged the treatment of oral cancer patients with large bone defects and bulky soft tissue conditions with implants and implant supported prostheses.

Since the last 10 years in the Department of CMF Surgery, Charité, with the use of free flaps to reconstruct the large bone defects, the vestibuloplasty procedure has also become a regular part of treatment planning to achieve long-term success by implants and implants supported overdentures. Accordingly, the observation period for vestibuloplasty in the present study was recorded for up to 10 years, to prevent any potential bias on the statistical results. The cumulative survival rate of implants with vestibuloplasty was 100% at 3 years and 95.5% at 7 years. With a follow-up period of up to 10 years, the cumulative survival rate remained constant after 7 years with 92.9%. According to this study, vestibuloplasty showed an influence on the implant survival.

In the study of Doll et al.[24], 157 patients with 830 implants were included and the mean observation period was 121 months. The cumulative survival rate was 94.9% at 3 years and 92.5% at 7 years. With an observation period up to 20 years, the cumulative survival rate remained constant after 11 years with 90.8%. These results showed similarity to the results found in the present study. According to the study of Doll et al.[24], localization (maxilla/mandible) of implants did not show any influence on the survival of the implants. On the contrary, the present study showed that localization (maxilla/mandible) of implants had an impact on the implant survival. The risk of loss of an implant in the mandible was 2.9 times higher Exp(B)=2.9 with 95%CI[1,12;7,84] than in the maxilla. One potential explanation for the variation in the results between these two studies is the localization of the tumor. In the present study, 52 oral cancer patients had the tumor in the mandible, whereas 8 patients had the tumor in the maxilla. Accordingly, the treatment-related surgical resections and corresponding reconstructions and/or radiation therapies were mainly in the mandible, which explains the higher loss of dental implants in the mandible. In the study of Doll et al.[24], no precise distributions of the locations with regard to maxilla and mandible were reported.

The review by Javed et al.[51] noted that it could be assumed that the location of implants may contribute to the survival rate and functional stability of dental implants. From the review of the literature, it seems that the success of implants was higher in the mandible compared to the maxilla. The results in this present study are in agreement with the review by Javed et al.[51]. It should be noted that in all of the included studies in the review of Javed et al.[51], with the exception of 2, dental implants were inserted exclusively in the mandible. In this study, 122 implants were placed in the maxilla and 208 implants were

placed in the mandible. After 7 years, the implant survival rate was 96.6% for the maxilla and 90.2% for the mandible.

However, in the current study, it was observed that the implant survival rate between the patients with or without vestibuloplasty was significantly different. Especially if the oral cancer patients who received radiochemotherapy and vestibuloplasty are compared with the patients who received radiochemotherapy but no vestibuloplasty, the loss of the implants was observed to be higher in the group where no vestibuloplasty was performed. According to these results, vestibuloplasty seems to have a positive effect on the long-term survival of the implants, especially in irradiated oral cancer patients. Therefore, further studies will be beneficial in evaluating the correlation between vestibuloplasty according to Heberer & Nelson[57] and radiochemotherapy, and the influence of this correlation on the survival rate of the implants in oral cancer patients.

On the one hand, the postoperative management includes the performance of vestibuloplasty, as outlined by Heberer & Nelson[57], to achieve optimal peri-implant tissue conditions, and on the other hand, regular recall of patients. Studies have shown that healthy peri-implant soft tissue is decisive in the long-term success of dental implants.[58] The positive results regarding the long-term data confirm this procedure. Unfortunately, there are no comparable studies in the literature to date. Various influencing factors on implant survival are analyzed below.

Within the present study, the influence of gender on the implant survival was evaluated, but no comparison was found. Other studies (with follow-up durations ranging from 6 months to 10 years) have not shown any effect of gender on the survival of implants in oral cancer patients who underwent ablative surgery.[50,51]

The influence of radiochemotherapy was examined in the present study and the difference in implant survival rate between irradiated jaws and non-irradiated jaws was not significant (P=0.948). Furthermore, according to the study of Doll et al.[24], patients who had received additional radiochemotherapy had a 1.9-fold higher risk of losing an implant compared to patients who had been treated exclusively by ablative surgery. In the present study the difference in implant survival rate between irradiated jaws and non-irradiated jaws was not found to be significant. Nevertheless the loss of dental implants in irradiated oral cancer patients was slightly more than twice the number of the implant loss in non-irradiated patients. The literature contained only a few comparable studies with equivalent

follow-up periods. In the study by Yerit et al.[50], the survival rate of dental implants in the non-irradiated mandible was 99% after a 3 year follow-up, whereas the survival rate in the irradiated mandible was 90%. After an observation period of 8 years, it was determined that there is a difference in the implant survival rate for the mandible between irradiated patients (72%, 154 implants) and non-irradiated patients (95%, 84 implants). The study evaluated a total of 316 implants with a follow-up period up to a maximum of 13 years; all patients in this study underwent the same radiotherapy with a total dose of 50 Gy. The following success criteria were observed: no complaints from the patient, mobility, peri-implant tissue inflammation and no peri-implant bone loss-exceeding one-third of implant length. Another comparable study was published by Sammartino et al.[46], with similar implant numbers (130 implants) in the irradiated mandible and with a follow-up period of at least 36 months. In this study, the survival rate of implants (98.4% survival rate after 3 years follow-up) was higher compared to the study by Yerit et al.[50] The higher rates in the study by Sammartino et al.[46] may be explained by the exclusion of those patients who are smokers and have systemic diseases (uncontrolled diabetes mellitus). In the present study, the overall implant survival rate in irradiated oral cancer patients was 99.5% after 3 years and 91.8% at 7 years. This was also higher compared to the study by Yerit et al.[50] This may be explained by the postoperative management, which contains the performance of a vestibuloplasty according to Heberer & Nelson[57] to achieve optimal peri-implant tissue conditions and regular recall of the patients. Furthermore, smokers were also excluded from the present study, and the survival rate of the implants at the 3 year follow-up was found to be similar to that of the study by Sammartino et al.[46] However, in the present study after the 10-year follow-up period, the survival rate in irradiated patients was 82.3%, which was slightly lower in comparison to the results for the 3-year follow-up period. The reason for the increased failure rates of implants in irradiated bone with the longer time span may be caused by the late effects of radiation, which is the formation of hypoxic-hypovascular-hypocellular tissue (Marx three H principles). As the mortality rate of patients who received additional radiochemotherapy showed an insignificant difference from that of the patients who did not receive radiochemotherapy, this higher loss ratio might be explained by either an effect of soft tissue infection or by a late failure caused by the inability to maintain the established osseointegration.

In the study by Hessling et al.[59], composed of 272 implants in irradiated and non-

irradiated patients with a mean follow-up period of 30.9 months (ranging from 3 to 82), a high survival rate of 96.3% was observed. Compared to the survival rate of 99.5% at 3 years in the present study, the slight difference in survival rates can be explained by the difference in the radiation doses delivered to the patients. In the present study, radiation therapy was delivered up to a total dose of 50–72 Gy to 35 patients. On the other hand, in the study by Hessling et al.[59], approximately half of the 49 patients included were delivered a total dose of 40 Gy during the radiation therapy. However, it is observed that the risk of ORN increases if the patient has had a radiotherapy dose greater than 50–55Gy.[60] Furthermore, according to various authors, a total dose over 65 Gy is associated with reduced resistance against general infections and trauma.[53] Even though higher doses of radiation were implemented for the oral cancer patients in the present study, the survival rates were comparable with the results of the study by Hessling et al.[59] This can be explained by the postoperative (post-implantation) management performed in the present study, which consisted of the performance of vestibuloplasty as described by Heberer & Nelson[57] and regular recall of the patients. There are no studies in the literature to date which have shown clinical success depending on the irradiation dose in certain localizations of dental implants.

Various studies recommend the insertion of implants following ablative surgery during the same surgical session as when additional radiotherapy is indicated.[61,62] These studies confirm that implant placement prior to additional radiotherapy will allow for a better osseointegration rate, since biological changes in the bone and soft tissue due to irradiation will not occur during osseointegration.[61,62] However, other studies show that the timing of implant insertion before or after irradiation was not a significant influencing factor for the survival rates of dental implants in oral cancer patients.[62,63] The suggestions concerning when the implant should be inserted after the completion of radiotherapy vary from 6 weeks to 2 years.[53] In the literature, some protocols have been recommended in which implant insertion should range from 6–12 months and an osseointegration time of 5–6 months should be given before the second stage surgery and the loading of the implants can be performed.[44,62] Visch et al.[64] analyzed the survival of 446 implants inserted after radiation, over a period of up to 14 years, in 130 patients, to determine the effects of the time interval between radiotherapy and implant therapy. Overall, 175 implants were inserted in the 12 months after the completion of radiotherapy and 217 implants were inserted after the first 12 months following irradiation. The implant survival

rate in the first group was 76% with 29 implant failures, and that in the second group was 81% with 35 implant failures. Insertion time of the implants after the first 6 months following the completion of radiotherapy was not significantly different from implant survival. However, the review by Ihde et al.[63], which summarized and compared 8 clinical studies on dental implants in irradiated bone, did not show any significant difference in the survival rates of implants when several insertion times of dental implants before or after irradiation were compared.

The treatment concept which was routinely performed in the present study includes waiting at least 6 months for the implant insertion following radiotherapy and waiting for the healing of the implants: 3 months for the maxilla and 2 months for the mandible. In the literature, other studies prefer these periods as well.[65] The high cumulative survival rate in the present study justifies this parameter. Another factor for the better survival success is that the irradiated patients are treated with dental implants only if the patients had not smoked for at least 6 months.

A clinical study by Lambert et al.[66], including 2,887 implants in non-tumor patients and a 3-year follow-up period of implant survival, assessed the implant failure rates in current smokers and non-smokers (which included smokers who quit). The total failure rate was 8.9% for smokers and 6.0% for the non-smoker-quitter group, with an approximately 3.0% difference between two groups. According to this study, the implants in smokers were approximately 1.5 times more likely to fail than the implants in non-smokers or quitters. Moreover, in the study by Bain and Moy[67], it was determined that the failure rate of 2,194 Brånemark implants in 540 patients was 11.28% in smokers; this was significantly higher than in non-smokers, with a rate of 4.76% ($P<0.001$). Smoking seems to be a significant influencing factor for the survival of the implants. These studies showed the negative effect of smoking on the ability of the bone or other periodontal tissues to adapt over time after the insertion of implants.[66,67] Unfortunately, to date there has been no study on the influence of smoking on irradiated patients. The results in these studies confirm the exclusion criteria of the present study, as no study reported the insertion of implants in oral cancer patients with adjuvant radiochemotherapy that still smoked. Furthermore, the the present study showed that the higher survival rate of dental implants in irradiated oral cancer patients after a 10-year follow-up can be achieved with the support of this exclusion criterion.

In the study by Linsen et al.[53], the survival rate of implant-supported prosthetic appliances was 90% over a follow-up of more than 6 years. According to this study, dental implants provide a more effective oral rehabilitation due to the retention, support and stability being better. Moreover, implant-supported prostheses provide an appropriate oral space for mastication and speech, as well as enabling support for soft tissue.[68] Linsen et al.[53] pointed out that there is a lack of standards of prosthetic appliances in the literature regarding prosthetic rehabilitation, which probably stems from individual prosthetic restorations due to alterations of the anatomy and size of the defect. A favorable superstructure was not found in the study by Linsen et al.[53]. However according to the study of Ernst et al.[23], crestal bone changes were slightly more extensive in locator-retained implants than after rehabilitation with bar-retained prostheses or fixed bridges. In the study of Ernst et al.[23], irradiated patients received bar-retained prostheses or fixed bridges according to individual anatomic and patient-centered parameters.

The difficulty in accessing the implants due to the inappropriate soft tissue conditions and/or a lack of patient motivation results in insufficient oral hygiene, which causes conditions such as inflamed soft tissue, peri-implant mucositis and peri-implantitis. Therefore, achieving the hygiene standards and increasing the motivation of these patients is very important for dental care**.** Numerous studies[42,57,59] state that the regular recall of oral cancer patients was essential for the long-term success of implants.

The present study is based on a strict protocol in which dental implants were not inserted in irradiated oral cancer patients that still smoke. Additionally, ensuring peri-implant soft tissue was considered a high priority. As mentioned above, a modified vestibuloplasty, as described by Heberer and Nelson[57], was performed to attain appropriate peri-implant soft tissue conditions in patients with adequate keratinized gingiva. Regular recall of tumor patients with dental implants was seen as an essential procedure for the long-term success of implants. The high survival rates observed in the present study for dental implants in irradiated and non-irradiated oral cancer patients after ablative surgery may be explained by the regularly performed treatment concept, which is based on the protocol mentioned above.

Conclusion

The present study shows a high cumulative survival rate of 88.3% after 10 years, with an observation period of up to 20 years. The gender and radiation have no significant influence of the survival of dental implants in oral cancer patients. However, the age and the localization of the implants (maxilla/mandible) showed a significant difference. The survival rate of dental implants in oral cancer patients was lower in the mandible in comparison to the maxilla. The risk of the implant loss in the mandible is 2.9 times higher Exp(B)=2.9 with 95%CI[1,12;7,84] than in the maxilla. Furthermore, the implant survival rate between the patients with or without vestibuloplasty was significantly different (P=0.001), where the survival rate was higher with vestibuloplasty according to Heberer and Nelson[57]. Additionally, to achieve higher implant survival rates, regular recall and soft tissue management was found to be very important.

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„Ich, Ilsu Erisir Berberoglu, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: “Langzeitüberlebensanalyse von Zahnimplantaten & implantat-prothetischer Versorgungen bei Patienten nach Plattenepithelkarzinom im Kopf- und Halsbereich”, “Long-term survival analysis of dental implants & implant-supported prostheses in patients after squamous cell carcinoma in head and neck region” selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
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Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen

einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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Acknowledgement

First of all, I would like to express my deepest gratitude to my supervisor Prof. Dr. Susanne Nahles from the Oral and Maxillofacial Surgery Department of the Charité - Universitätsmedizin Berlin for her endless patience, understanding and support through the whole process. It was a great pleasure and privilege to work with her. She was always there for me and took the time to help whenever I needed guidance. Without her valuable input, this study would not have been successfully completed.

I would also like to acknowledge and give my special regards to my colleague Dr.med.dent. Claudia Sachse from the Oral and Maxillofacial Surgery Department of the Charité - Universitätsmedizin Berlin for her collegial support. Without it, I would not have been able to complete this thesis.

Finally, I would like to extend my heartfelt gratitude to all my family for the support they have provided throughout the years. I am forever thankful to my mom, for believing in me, for her encouragement and unconditional love. I am forever indebted to her for supporting me in completing my studies. To my one and only Kerem, for his Zen-like serenity, helpful guidance, endless support and always being there for me. Thanks to all my family for keeping me going and reinforcing my faith in myself at times I felt discouraged. This would not have been possible without you.

In memory of my father, with eternal love…