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Implant placement in oral squamous cells carcinoma patients treated with chemoradiotherapy: "Sapienza Head and Neck Unit" clinical recommendations

E. BRAUNER[1], D. MUSIO[2], S. MEZI[2], A. CIOLFI[1], F. MAGHELLA[2], A. CASSONI[2], F. DE ANGELIS[1], G. GUARINO[1], U. ROMEO[1], G. TENORE[1], G. PIESCO[2], F. DE FELICE[2], V. TOMBOLINI[2], V. VALENTINI[1], A. POLIMENI[1], S. DI CARLO[1]

[1]Department of Oral and Maxillofacial Sciences, Sapienza Università di Roma, Rome, Italy
[2]Department of Radiological Oncological and Pathological Sciences, Sapienza Università di Roma, Rome, Italy

Abstract. – OBJECTIVE: To date, the treatment of patients affected by head and neck squamous cell carcinoma (HNSCC) is highly challenging for clinicians. Possible therapies are surgical resection of the tumor mass, radiotherapy, chemotherapy or, more often, a combined treatment that inevitably affects both normal and tumor cells. Consequently, patients' anatomy and functions become reduced or altered. Nowadays the functional restoration is significantly improved thanks to the innovation in prosthetic rehabilitation and in radiotherapy. The current IMRT (Intensity Modulated Radiation Therapy) allows planning adequate treatments evaluating different tissues' involvement and radiation dosage. It is possible to define the most suitable sites for implant insertion, using data provided by dose-volume histogram (DVH). This study aims to illustrate the idea of obtaining a unique CT image by blending radiation-planning CT and Cone Beam CT.

PATIENTS AND METHODS: Five patients among 54 candidates were selected for this study. Selection criteria were: good general health (PS0-1), age between 18 and 72 years, absence of metastatic disease or local recurrence, disease-free interval of at least 18 months. Radiation planning CT scan and maxillo-facial CT Cone Beam of every patient were overlapped and merged. Only one CT for every evaluated patient was obtained in order to plan the most suitable areas for implant placement.

RESULTS: The placement of 10 implants in 5 patients was programmed using the explained method. Patients (all male) were aged between 48 and 72 years old, with a median age of 64.4 years. In every case of this study, a modification of the initial program of implant placement was necessary. The new imaging method we are proposing was able to provide information about radiation isodoses received in the planned osseointegrated implants' positions.

CONCLUSIONS: This new method allows operators to correct their own therapy plans and choices, customizing the treatment plan on the actual condition of the patient. Moreover, it makes all the rehabilitation process safer and can reduce the risk of failure, side effects and inconveniences for the patients.

Key Words:
Chemoradiotherapy, Implant placement, Oral cancer, New imaging method.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is sixth among the most frequent kinds of cancers, and still today treatment can provide only a 50-57% survival rate over 5 years[1-3]. Possible treatments are surgical resection of the tumor mass, radiotherapy, chemotherapy or, more often, a combined therapy. As a consequence of all these treatments, patients' anatomy and physiological functions may become reduced or altered[1]. First of all, ablative surgery produces serious alterations of oral and neck's anatomical structures. This therapeutic choice causes functional disabilities and aesthetic problems. Moreover, changes in oral anatomy can often compromise or totally prevent dental rehabilitation using conventional

Corresponding Author: Alessandro Ciolfi, MD; e-mail: alessandro5ciolfi@gmail.com

prosthesis devices[1,4]. More serious alterations involving soft and hard tissues are due to radiation or chemoradiotherapy (CRT). These changes consist in acute and chronic treatment effects, which are both determined by total dosage and size of treatment volume[2]. The most common acute effects are mucositis (up to 80%), taste and smell loss, hyposalivation, secondary infections and bone marrow suppression. Acute side effects usually occur within 1 or 2 weeks after the beginning of the treatment and last for 2-4 weeks after its end[1,2]. Chronic effects are persistent hyposalivation and xerostomia, changes in bacterial flora, soft tissues fibrosis, lockjaw, delayed healing, reduced angiogenesis[1]. All these events cause increase in the onset of radiation caries, periodontal diseases, and osteoradionecrosis (ORN)[1,2]. Late effects are usually seen within both soft and hard tissues, where decreased oxygen tension causes impairment of tissue recovery[1]. The goal in radiotherapy is to sufficiently separate the dose-response curve of local tumor control and normal tissue complications. Advances in radiologic imaging and computer technology have significantly enhanced the ability to achieve this goal through the development of three-dimensional (3-D) image-based conformal CRT and intensity-modulated radiotherapy (IMRT). The implementation of these technologies permits better shaping of the high-dose volume of the radiation treatment so as to better conform to the tumor volume while minimizing the radiation dose delivered to surrounding normal tissue. IMRT is becoming a mature technology and it is widely applied to head and neck cancer. Many treatment-planning comparison studies have demonstrated the evident dosimetric advantages of IMRT and have shown the reduction of treatment toxicities. 3DCRT and IMRT use simulation CT and Magnetic Resonance Imaging (MRI) and Positron emission tomography (PET) scan can be fused with simulation CT to help delineate the gross tumor and sparing the normal tissues. The capability of obtaining CT images of irradiated fields is another important advantage of 3DCRT IMRT compared to traditional RT. Nevertheless, ORN is the most feared effect of CRT[5-7], especially because it can be triggered by surgical procedures, such as tooth extraction or implant placement. Traumas or surgery in the irradiated area usually lead to a reduction of the vascular portion, a reduction of cells and determines hypoxia. These changes lead to the destruction of osteoblasts and impaired bone modeling and remodeling which causes ORN. However, osseointegrated implants enhance oral rehabilitation in irradiated patients, and the procedure was judged feasible in several clinical reports[8]. Many issues are still being debated, such as the maximum radiation dose associated with acceptable risk for implant placement, the time that should intervene after radiation treatment prior to implant placement and whether implants should be placed prior to or after radiation therapy. Moreover, implant placement could reduce micro-traumas caused by prosthodontics mobility thus minimizing the risk of osteonecrosis. Therefore, implant positioning in implant placement should be approached using consolidated and valid techniques, such as computer-guided techniques that are the best choice adopted even in non-irradiated patients. The use of minimally invasive techniques that avoid exposure of the mandibular bone, helping its healing around the implants (flapless technique) is generally considered the preferred option. Above all, in irradiated patients the implants positioning must be performed taking into account the radiation dose received, which could be different in the different maxillas areas, in order to reduce the osteonecrosis in the treated bone and to avoid implant failure.

The aim of this study was to evaluate the possibility to exploit a new method in implant planning placement by using a unique CT image obtained by blending radiation-planning CT scan, which provides the amount of dose received in each individual point of the jaws, and a CT dentascan, in order to create a melded image that allows us to plan the most suitable areas for implant placement for each irradiated patient. With this new method, the safety of implant placement procedure would be increased since only not-irradiated or low-irradiated areas would be interested by the surgery. In this way, the risk of developing ORN due to implant placement would be considerably reduced.

To our knowledge this is the first proposal for this computer-guided technique for implant placement that basing itself on the maxilla radiotherapy dose that was received, allows us to plan the best and safest position for implants insertion in patients treated with RCT in head-neck region.

Patients and Methods

Between January 2015 and December 2016, we evaluate in a prospective study 54 patients with a diagnosis of HNSCC who had received radiotherapy as part of their oncologic treatment,

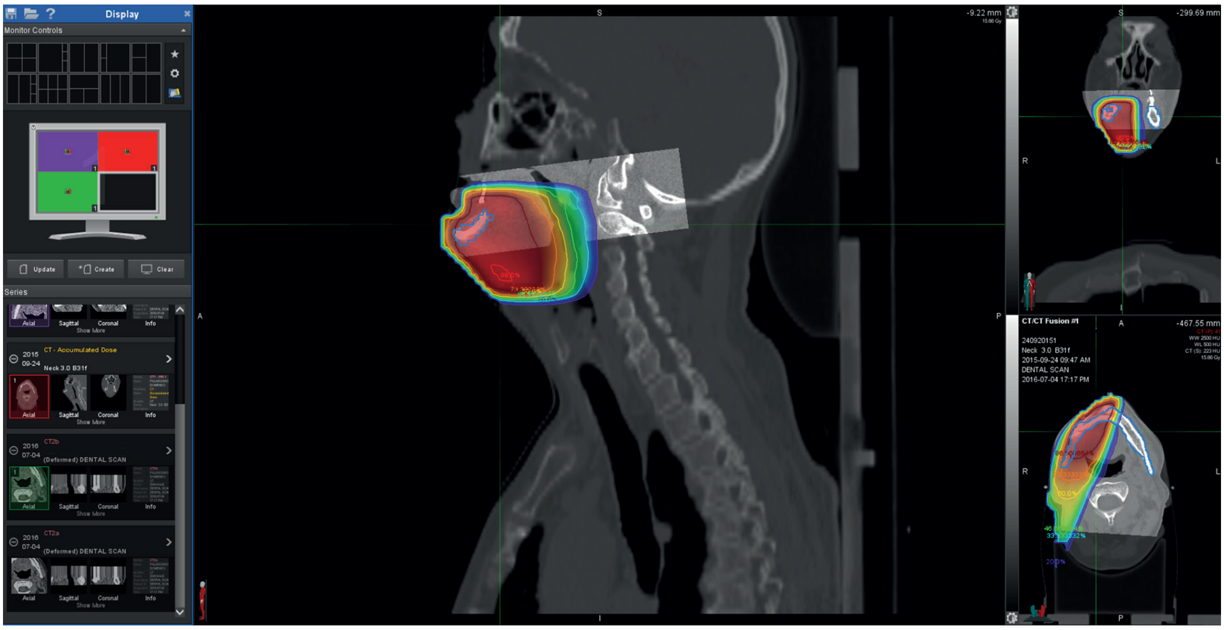

Figure 1. Unique CT scan obtained by fusion of radiation planning CT scan and CT Cone Beam.

for an oral prosthetic rehabilitation. Removable devices were provided to every patient. A total removable prosthesis or partial removable devices with metallic hook were made, accurately adapted on the patients' oral conditions. Among these, 12 patients, after an accurate clinic and radiographic evaluation, including qualitative and quantitative hard and soft tissues analysis, oral hygiene and patient's compliance, turned out to be potential candidates for implant-supported rehabilitation. Selection criteria were: good general health (PS0-1), age between 18 and 72 years, absence of metastatic disease or local recurrence, disease-free interval of at least 18 months. Seven patients did not provide informed consent to the procedure, preferring the conventional removable prosthesis device able to fully meet the functional and aesthetic needs of the patient. The remaining 5 patients were candidate to implant supported fixed prosthesis. A CT Cone Beam, conducted with the template in the correct position, was realized for all five patients. On the basis of the CTs, the most suitable implant placement program was created in every case. Head and neck radiation planning CT scan with intravenous contrast had been acquired for each patient, one week prior to CRT. Patients were treated supine and were immobilized in a thermoplastic shell, fixed to the couch in five places. Images were acquired with 3 mm slice thickness and were obtained from base of skull to the top of the aortic arch. In all cases, image registration had been performed using MIM maestro ver. 6.4 (MIM Software Inc., Cleveland, OH, USA) on dedicated workstation. Planning CT was transferred from institutional PACS database to MIM workstation; Pinnacle software (Philips Healthcare, Amsterdam, The Netherlands) planned treatment doses were also transferred to MIM workstation. A dose-accumulation co-registration was performed using planning CT and treatment doses structures. Afterward a new rigid co-registration was performed adding Dental scan images. DVH for the jaw OAR was calculated. Radiation planning CT scan provided the radiotherapy treatment plan, the total radiation dose and the single isodoses received for every bone site (Figures 1-2). Radiation planning CT scan and CT Cone Beam of every patient were overlapped and merged. Only one CT for every evaluated patient was obtained.

Results

The placement of 10 implants in 5 patients was programmed using the explained method. Patients (all male) were aged between 48 and 72 years old, with a median age of 64.4 years. The new imaging method that we propose was

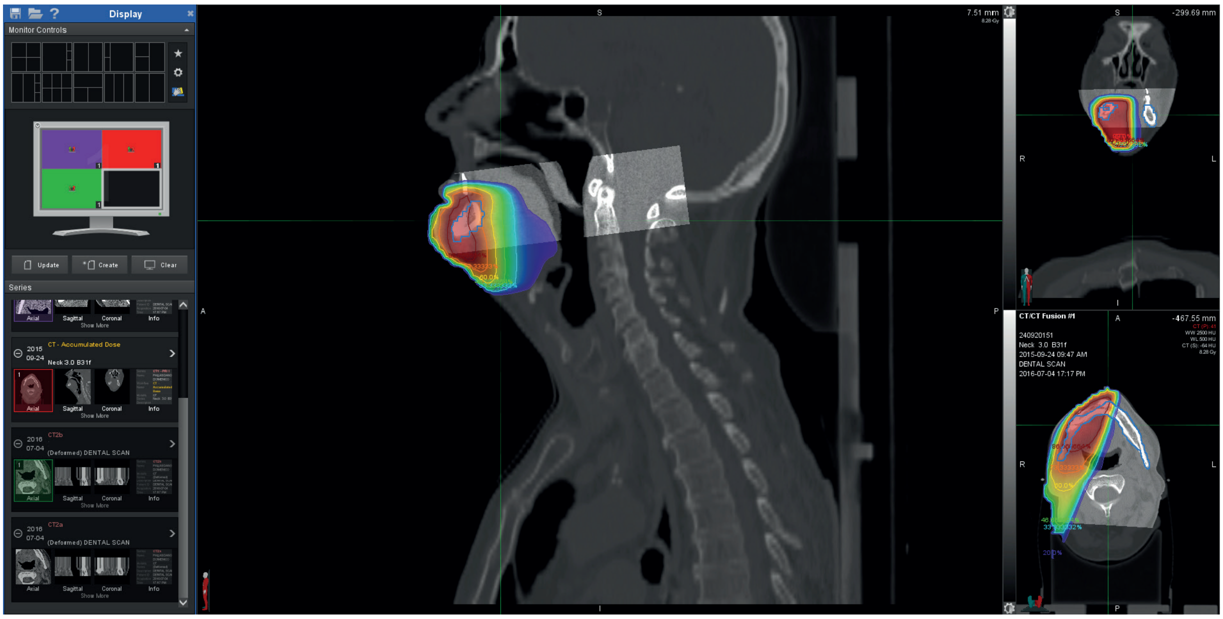

Figure 2. Unique CT scan obtained by fusion of radiation planning CT scan and CT Cone Beam.

able to provide information about radiation isodoses received in the planned osseointegrated implants positions. In every case of this study, a modification of the implant placement program was necessary. In 4 patients the implant positioning program and the whole prosthesis program were modified on the basis of the relative received isodose of RT for every implant site. Following this method was always possible to evaluate the safe site for the implant placement, avoiding the most irradiated areas (Table I).

Patient 1

A 53 years old man previously affected by mildly differentiated oropharyngeal, stage IV squamous cells carcinoma, treated with definitive CRT (total dose to high risk volume 67.5 Gy in 30 fractions), came to our attention. Poor oral hygiene and absence of 3 teeth (4.5, 4.6, 4.7) were noticed. Firstly, he was rehabilitated with removable partial prosthesis, from which a radiological template was obtained. A CT dentascan was requested. Analyzing the CT images, the implant placement of 3 fixtures was planned and 4.5, 4.6, 4.7 were the chosen sites.

Table I. Implant placement program and single sites' isodoses for patient 1.

Tooth	Patient 1 Implant site	Isodose (Gy)
4.5	4.5 (CT slice n. 51)	38.4
4.6	4.6 (CT slice n. 42)	41.2
4.7	4.7 (CT slice n. 33)	65.2

The CT dentascan images were melded with the radiation planning CT scans and an accurate evaluation of isodose for every implant site was made. One of the planned sites was included in areas treated with isodose of 65.2 Gy. This could have caused an increase of implant failure and the development of side effects in the 4.7 site. A new implant placement program was made, avoiding the most irradiated site (Table I).

Patient 2

A 66 years old man previously affected by well-differentiated oral cavity, stage III, squamous cells carcinoma treated with surgery and adjuvant CRT (dose to high risk volume 66 Gy in 33 fractions), came to our attention. Complete mandibular edentulia was noticed.

Firstly, he was rehabilitated with removable total prosthesis, from which a radiological template was obtained. A CT dentascan was requested. Analyzing the CT images, the implant placement of 5 fixtures was programmed. 3.6, 3.3, 3.1, 4.3 and 4.6 were the chosen sites.

The CT Dentascan images were melded with the radiation planning CT scans and an accurate evaluation of isodose for every implant site was made. Two of the planned sites were included in areas

Table II. Implant placement program and single sites' isodoses for patient 2.

Tooth	Patient 2 Implant site	Isodose (Gy)
3.6	3.6 (CT slice n. 99)	58.3
3.3	3.3 (CT slice n. 82)	32.4
3.1	3.1 (CT slice n. 61-66)	19
4.3	4.3 (CT slice n. 48)	31.1
4.6	4.6 (CT slice n. 31)	58.3

treated with isodoses of 58.3 Gy. A new implant placement program was made, changing the sites involved in the most irradiated sites and taking advantage of the area that absorbed a lower isodose. The new implant placement program includes sites 3.5 and 4.5 instead of 3.6 and 4.6 (Table II).

Patient 3

A 70 years old man previously affected by mildly differentiated oral cavity, stage III, squamous cells carcinoma, treated with surgery and adjuvant CRT (dose to high risk volume 66 Gy in 33 fractions), came to our attention. Complete mandibular edentulia was noticed.

Firstly, he was rehabilitated with removable total prosthesis, from which a radiological template was obtained. A CT dentascan was requested. Analyzing the CT images, the implant placement of 6 fixtures was programmed. 3.6, 3.4, 3.2, 4.2, 4.4 and 4.6 were the chosen sites.

The CT dentascan images were melded with the radiation planning CT scans and an accurate evaluation of isodose for every implant site was made. Four of the planned sites were included in areas treated with isodoses between 65.5 Gy and 60.8 Gy. This could compromise surgical and prosthetic treatment's outcome. A new implant placement program was made, reducing the number of implants from 6 to 2, avoiding the most irradiated sites and taking advantage of the area that absorbed a lower isodose. The realization of an overdenture

Table III. Implant placement program and single sites' isodoses for patient 3.

Tooth	Patient 2 Implant site	Isodose (Gy)
3.6	3.6 (CT slice n. 102)	65.5
3.4	3.4 (CT slice n. 89)	60.8
3.2	3.2 (CT slice n. 71)	35.1
4.2	4.2 (CT slice n. 66)	35.1
4.4	4.4 (CT slice n. 56)	61.1
4.6	4.6 (CT slice n. 42)	65.5

Table IV. Implant placement program and single sites' isodoses for patient 4.

Tooth	Patient 4 Implant site	Isodose (Gy)
3.5	3.5 (CT slice n. 88)	69.07
3.2	3.2 (CT slice n. 78)	60.46
4.2	4.2 (CT slice n. 61)	60.46
4.5	4.5 (CT slice n. 40)	51.16

anchored on two implants was the most recommended solution. The new implant placement program includes sites 3.2 and 4.2 (Table III).

Patient 4

A 69 years old man previously affected by mildly differentiated oral cavity, stage III, squamous cells carcinoma, treated with surgery and adjuvant CRT (dose to high risk volume 66 Gy in 33 fractions), came to our attention. Complete mandibular edentulia was noticed.

Firstly, he was rehabilitated with removable total prosthesis, from which a radiological template was obtained. A CT dentascan was requested. Analyzing the CT images, the implant placement of 4 fixtures was programmed. 3.5, 3.2, 4.2 and 4.5 were the chosen sites.

The CT dentascan images were melded with the radiation planning CT scans and an accurate evaluation of isodose for every implant site was made. All of the planned sites were included in areas treated with isodoses between 69.07 Gy and 51.16 Gy. This could heavily compromise surgical and prosthetic treatment's outcome. The isodose absorbed by every implant site was significantly high; an implant-supported rehabilitation was not recommended. The patient was rehabilitated with a permanent removable prosthesis (Table IV).

Patient 5

A 64 years old man previously affected by mildly differentiated oropharyngeal, stage IV squamous cells carcinoma, treated with definitive CRT (dose to high risk volume 67.5 Gy in 30 fraction), came to our attention. Poor oral hygiene and absence of a single tooth were noticed. Firstly, he was rehabilitated with fixed temporary prosthesis; a radiological template for a subsequent implant placement was not considered necessary. A CT dentascan was requested. Analyzing the CT images, the implant placement of 1 fixture was programmed. 3.1 was the chosen site. The CT dentascan images were melded with the radiation

Table V. Implant placement program and single sites' isodoses for patient 5.

Tooth	Patient 5 Implant site	Isodose
3.1	3.1 (CT slice n. 73)	14.21

planning CT scans, in which the lost tooth was still present. An accurate evaluation of isodose for implant site was made. The planned site was included in area treated with isodose of 14.21 Gy. The isodose was low and there was no risk of implant failure or development of ORN (Table V).

Discussion

The incidence of ORN of the mandible varies from 5% to 15%, and the incidence of ORN of the maxilla is much lower. ORN is closely related to the implants failure rate. Implants failure is more often found in patients who smoke or have poor oral hygiene with dental infections, or have undergone radiation therapy[1,3,9]. The condition of the periodontium affects the success and survival rate of the implants. After the patients received irradiation, the cells and the vascular portion of the periodontal membrane decrease and the periodontal space widens. The radiation-related changes in the cementum and the periodontal ligament may induce infection and increase the risk of hyposalivation, plaque accumulation, and the shift of oral microflora. The effects of radiotherapy on the periodontium increase risk of periodontal attachment loss as well as an increased risk of ORN development. Another important factor that affects the survival implants rate can be found in the change in salivary glands. Radiotherapy could lead to a chronic salivary gland dysfunction, which brings a reduced salivary flow and changes in the saliva composition. The affected patients suffered from xerostomia, oral mucositis, difficulty in speaking, increase in oral pathologies, difficulty in chewing and swallowing food, and malnutrition due to a loss of the salivary flow. Overall, these changes would destroy the environment of the oral cavity and ultimately, decrease the survival rate of the implants. Radiotherapy and even more CRT cause different levels of damage to oral health. In addition to the changes in the hard and soft tissues in the oral cavity mentioned above, the damage of the oral mucosa, radiation caries, periodontal disease, dysfunction of muscles and joints, and imbalance of the nutritional status would all increase the risk of implant failure. Urken et al[10] regard radiotherapy as a contraindication to implant placement because of the low success rate when implants have been placed into previously irradiated bone (>64 %). Mancha de la Plata et al[8] studied 225 implants placed in 30 patients who had received radiotherapy and reported that irradiated patients had a marginally significantly higher implant loss than non irradiated patients. The authors report a difference in implants survival of 92.6% *vs.* 96.5% in patients with or without irradiation. Implant losses in patients with irradiation occurred mainly because of peri-implant infection or asymptomatic peri-implant bone loss and consecutive integration loss. Thus, prevention and treatment considerations for irradiated patients are essential to improve the implant survival rate. The capability of obtaining CT images of irradiated fields allows us to program adequate implant treatments that are programmed by evaluating different tissues' involvement and radiation dosage. Using data provided by dose-volume histogram (DVH), it is possible to define the most suitable sites for implant insertion. Placing implants in less irradiated fields minimizes the impact of radiation dosage on treated areas. Moreover, choosing implant sites on the basis of the absorbed radiation dose can lead both to an increased implant survival into irradiated bone tissues and an ORN occurrence reduction[3,9,11]. According to standard fractionation therapy, 2-Gy fractions are usually given in the radiotherapy treatment planning of HNSCC; daily fractions can be given every day, five days a week, for a total dose of 66-70 Gy to macroscopical diseaseor surgical bed. Intensity modulation offers the ability to simultaneously treat two or more volumes concurrently with different daily dose per volume (SIB). When Radiation therapy is delivered with intensity modulate-simultaneous integrated boost (IMRT-SIB) technique it's possible to utilize for example a dose of 67.5 Gy (2.25 Gy/fraction) to macroscopic disease, 60 Gy (2 Gy/fraction) to high-risk regions and 54 Gy (1.8 Gy/fraction) to sites of potential disease. Great attention must therefore be given to respect for the quality of life; the dental rehabilitation occupies a very important role in its enhancement. Not only must we obtain improvement of the masticatory function, but also consider the aesthetic aspect of the treatment. It is necessary to assess and plan the implant surgery according to radiation timing and radiation dosage[1,12,13]. With respect

Table VI. Original implant placement program and new implant placement program for every patient of the study.

Patient	First program & implant sites	New program & implant sites
1	3 (4.5, 4.6, 4.7)	2 (4.5, 4.6)
2	5 (3.6, 3.3, 3.1, 4.3, 4.6)	5 (3.5, 3.3, 3.1, 4.3, 4.5)
3	6 (3.6, 3.4, 3.2, 4.2, 4.4, 4.6)	2 (3.2, 4.2)
4	4 (3.5, 3.2, 4.2, 4.5)	0
5	1 (3.1)	1

to the timing, implant therapy is highly contraindicated during irradiation treatment as the risk for ORN increases with trauma during this period. High-risk dental work should be completed before beginning radiation treatment so to avoid bone necrosis. If pre-radiation implant placement is preferred, it is recommended to be performed at least 14 days before RT starts. If implant therapy is going to be performed after radiation, treatment is suggested between 6 and 18 months after the therapy is completed[1,2]. According to latest articles, 24 months should not be exceeded. During this time, normal healing processes can still occur and the late effects of radiation have not fully developed. With regard to dosing, there is little risk from implant failure when dosage is less than 50 Gy: standard precautions are suggested and treatment can be continued with caution. When doses are approximately 50 to 65 Gy, there is low risk for implant loss. This risk increases with increasing doses, and when doses are very high (75-120 Gy), implant failure is likely as is the risk for ORN. No treatment is advisable when total doses exceed 120 Gy[1,2,11,14,15].

Conclusions

The radiation oncologist must cooperate with the dentist by providing him all the information on the dose distribution. This can be done by displaying the distribution of isodose on simulation TC images[16,17]. Since ORN is the most feared consequence of implant placement in irradiated fields, oncology radiotherapists and dentists can work together to identify, at the end of the radiation treatment, the appropriate patient and the appropriate areas of the jaws to receive implants, avoiding the most irradiated fields. A modification of the implant program based on the radiotherapy information was always possible by obtaining a single CT image for every patient, containing complete data about isodoses in the treated areas. In this way, it was possible to program the most suitable therapy plan for every patient, minimizing the risk of radiotherapy's side effects. This new method allows operators to correct their own therapy plans and choices, customizing the treatment plan on the actual condition of the patient. Moreover, it makes all the rehabilitation process safer and can reduce the risk of failure, side effects and inconveniences for the patients (Table VI).

In short, this study explains a new method, for the first time reported in the literature, to program implant placement and it has proven to be safe, fast and easy to obtain, to apply and to consult. This procedure could easily become a new routine measure in rehabilitation plan of patients who undergo radiation therapy of head and neck areas. This work, now in preliminary phase of realization, needs further evaluation based on a larger sized sample, in order to verify the effectiveness of guided tailored positioning of the implants in oral cancer treatment-related disability rehabilitation.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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