UiT The Arctic University of Norway

Department of Clinical Dentistry

Faculty of Health Sciences

Dental implant treatment in irradiated oral cancer patients. Clinical routines in Norway and a review of the literature.

Ida Johansen Hestnes and Amalie Storaa Jensen

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Abstract

Aims: The study seeks to find out if there is a difference in prognosis of primary and secondary dental implantation, i.e. before or after radiotherapy respectively, in cancer patients. We carried out a literature search, as well as investigating if there were different practices at the various hospitals in Norway who perform such treatment.

Materials and Methods: We contacted the four hospitals in Norway which perform implant placement in head and neck cancer patients. We asked each department if they performed primary or secondary implantation, and their use of hyperbaric oxygen therapy (HBOT). In addition, we performed a review of the literature published between Jan 2000 and May 2022. We used the search engine PubMed and included 13 articles. Furthermore, the study assesses other factors that may affect the prognosis of both primary and secondary implantation, such as implant location, HBOT and osteoradionecrosis (ORN).

Results: There are different clinical routines at the various hospitals in Norway. In the reviewed literature the overall survival rate of dental implants varies from 67%-97% for implants placed both prior to and after radiotherapy.

Conclusion: There are different practices at the various hospitals in Norway who perform implant placement in patients with head-neck cancer. The literature does not point to any evidence-based recommendations about one type of treatment over the other. There are currently too few studies on primary implantation compared to secondary implantation, to be able to conclude whether one gives a better prognosis than the other. However, the small number of studies that included implant placement prior to radiation therapy, had results that are comparable to implantation in irradiated bone. This indicates that more studies should be done on the prognosis of preimplantation.

Keywords: “Radiation therapy, oral cancer, dental implant, time”

1 Introduction

Cancer is a term for a group of diseases that can affect any part of the body. Cancer is defined as a rapid growth of abnormal cells, which can invade and spread (1). Statistics show that one out of every third person will get at least one cancer diagnosis before turning 75 years old (2). There is a gradual increase of head-neck cancer cases (3). With a larger population of oral cancer, there is a need for oral rehabilitation, to address their needs. It is reasonable to believe that there will be a gradual increase in patients diagnosed with head and neck cancer in the future, with an elderly population and an increase in dental awareness.

Cancer that either arise from mucous membranes or glands from the upper respiratory tract, such as the larynx, pharynx, salivary glands, lips, oral cavity, nose, or the sinuses have the collectively term head-neck cancer (4). According to WHO many cancers can be cured if detected early and treated effectively (1). The combination of surgery and radiation therapy is the most common form of treatment. In some cases, chemotherapy is also used during the course of treatment, for head and neck cancers, most often in combination with radiotherapy, i.e. Chemoradiotherapy (5).

Radiation therapy is frequently used because it is not always possible to carry out surgical treatment without extensive loss of function. In other cases, radiation therapy is used secondary to surgery. Radiation therapy alone, or combined with other treatment options, has significantly increased the survival rate for many malignancies of the head and neck cancer region (6). External radiation is the most common type of radiation therapy. Due to new technology the external radiation leads to less damage to normal tissue than previous (3).

Radiation therapy may however result in unpleasant reactions that appear during or after treatment (7). This can be explained by the ionizing radiation that causes direct cell damage to normal tissues, in addition to tumor cells, in the radiation field. The side effects caused by radiation therapy can be categorized into two groups: *Early* or *acute*, and *late*, depending on the time of their occurrence. The early or acute side effects are noted in the course of treatment or immediately after. Furthermore, side effects that occur months or years after the end of the radiation therapy are defined as late (8). Based on the tumor location, different anatomical structures may be affected such as the skin, oral mucosa, maxilla, mandibula and salivary glands in cases with head and neck cancer (6, 7).

Most patients will, as mentioned above, experience side effects both during and after cancer treatment. Mucositis, progressive periodontal attachment loss, radiation caries, xerostomia and osteoradionecrosis (ORN) are some of the complication's radiation therapy may cause. The side effects of cancer treatment can have a significant impact on the patient's quality of life. It is therefore important that the oral rehabilitation is done properly (7, 9). Major concerns may involve the ability to speak, masticate and swallow. It is therefore necessary that these functions are restored to an acceptable level (10).

A serious side-effect to radiation therapy is ORN. Due to reduced blood supply, simple trauma such as tooth extractions may cause necrosis and subsequent severe infections in irradiated bone. ORN is difficult to treat and can be a challenge for several years and even for life. Given the incidence of oral cancer and the use of radiation therapy is increasing, it is expected that population risk for ORN will increase further (11). Hyperbaric oxygen treatment (HBOT) combined with surgical debridement is still treatment of choice for ORN, i.e. a very expensive and demanding modality. To prevent future ORN, it is not unusual to extract teeth at risk *before* planned radiation therapy. Teeth that will receive >50-60 Gray (Gy) will typically be subjects to such prophylactic extractions (11, 12).

The major functional impairments caused by surgical treatment or prophylactic extractions, is one of the reasons for the need of dental implants. The use of dental implants is now the rule rather than the exception in oral rehabilitation (12). Oral cancer surgery often results in altered anatomy and can cause deformities. Therefore, oral implants are used for reconstructing these deformities as well as replacing teeth (11, 12).

There are a number of adjunctive treatments available for patients who have received radiotherapy, one of them is hyperbaric oxygen therapy. The treatment was first tried out in the U.S in the early 20th century, it was mainly used to treat deep-sea divers with decompression sickness in the Navy (13). HBOT is a form of treatment where the patient breathes in 100% pure oxygen in a pressurized chamber. The treatment options vary in different parts of Europe (14). Indications for the treatment are mainly delayed injuries after radiation therapy in head-neck cancer patients, it is also indicated in carbon-monoxide poisoning and diabetic foot ulcers. The purpose of HBOT is to increase blood and oxygen supply, thereby influencing wound healing and stimulating new formation of capillaries, bone formation and it may favor implant osseointegration (14, 15). It can be used as adjuvant

treatment for established ORN, but also as a tool to prevent ORN in irradiated patients who is in need of surgery (11, 16).

Implant treatment has become a relevant treatment option because it is comparable to traditional prosthetics in terms of function and duration (17). With an increased population and life expectancy, it is likely that the incidence of oral cancer will grow. The research of implant-based rehabilitation is therefore both informative and necessary.

There are a number of benefits of dental implant systems. It can preserve surrounding bone and gums, improve health related quality of life, restore the ability to chew, speak and swallow etc. However, there are risks associated with dental implants. Implant failure is one of many complications. Implant failure can arise due to delayed healing, local infections, systemic infections, or poor oral hygiene (18). Implant surgery in irradiated jaws may also induce ORN (11).

Osseointegration is critical for the stability and prognosis of the implant. Osseointegration is defined as a structural and functional connection between living bone and the implant. The growth of bone around the implant is therefore necessary for long-term implant success. Osseointegration is a complex process. Factors affecting osseointegration include loading conditions, surgical technique, undisturbed healing phase and biocompatibility of the implant material (19). As well as the factors mentioned above, there are also patient-related aspects such as smoking habits, osteoporosis, toxic drugs, systemic diseases as well as a number of factors which can be related to cancer treatment (20).

Patients treated for cancer in the head-neck area are commonly treated with a combination of surgery and radiotherapy as previously mentioned. Both procedures have a major effect on the healthy tissues in the oral cavity (21). In connection to this dental implants can either be placed primary or secondary to the radiotherapy. A primary implantation is when the dental implant is placed prior to exposure to radiotherapy, as opposed to secondary implantation, when the dental implant is placed after exposure.

2 Material and Methods

This study can be divided into two parts. The first part is the investigation of whether there are different clinical routines at the various hospitals that carry out dental implantation in patients with head and neck cancer in Norway. The second part is a review of the literature on primary and secondary dental implantation.

We wanted to investigate whether there are different guidelines in implant placement in Norway. We therefore contacted the four hospitals in Norway who perform head and neck cancer surgery, and the leaders of the units responsible for eventual implant placement in relation to cancer therapy: Paula Hanna Therese Frid (The University Hospital in North of Norway (UNN), Tromsø), Nils Petter Fossland (St.Olavs Hospital, Trondheim), Johanna E. Rykke Berstad (Oslo University Hospital, Rikshospitalet (OUH), Oslo) and Sigbjørn Løes (Haukeland University Hospital (HUH), Bergen). Moreover, we asked each department head if they performed primary or secondary implantations, as well as their use of HBOT.

In addition to investigating the protocols at various hospitals in Norway, we also performed a review of literature on the prognosis of primary vs secondary implantation. We used the search engine PubMed (22). We performed literature searches to find relevant articles. We started with the keywords “dental implant”, “cancer” and “radiation therapy”. We included articles between Jan. 2000- May 2022 and got 328 results. We chose to adjust the search between this specific time period in order to minimize the number of studies, and to obtain updated information on the topic.

We used the following MESH-terms: “oral cancer”, “mouth neoplasms”, “electromagnetic radiation” and “radiotherapy”. The MESH-terms did not give relevant results and were therefore not included in our final search string.

We chose to use “Radiation therapy AND oral cancer AND dental implant AND time” as our final search string. We tried using the keyword “timing”; however, this gave a significantly smaller pool of articles. Therefore, our final search string included the disputed word “time”.

In total our search string gave 64 results. We adjusted the search of the literature published between Jan 2000- May 2022 and got 52 results. Both authors read through all the 52 abstracts individually. If one of the author found the abstract relevant, it was included in the review process. In cases were both authors did not find the abstract relevant, it was excluded.

In total 21 articles were included, of which the remaining 31 articles were excluded, due to the fact that they were not relevant to our research questions.

Of the remaining articles both authors read the full texts individually, and an article was only included in the review if both parts were in agreement. Rereading and discussion took place if there were any disagreement during this process. Of the 21 included articles, 8 were excluded during the full text evaluation due to the fact they did meet our inclusion criteria. For the purpose of this study, we included systematic reviews, prospective reviews, retrospective reviews and meta-analysis which presented data on survival rate on dental implants in patients receiving radiotherapy for head and neck cancer.

2.1 Inclusion and exclusion criteria

- Research articles published in English, based on systematic reviews, meta-analysis, retrospective studies and prospective studies related to oral rehabilitation with dental implants in relation to cancer therapy, were included.
- Studies containing information regarding radiation therapy, radiation dosage, number of implants placed, anatomical site of implant placement, timing of implant placement, cases of ORN and the use of HBOT, were included.
- There were no requirements of a follow-up period nor size of participants.
- Lack of information on published data, animal studies and data published before Jan. 2000 or after May 2022 led to exclusion.

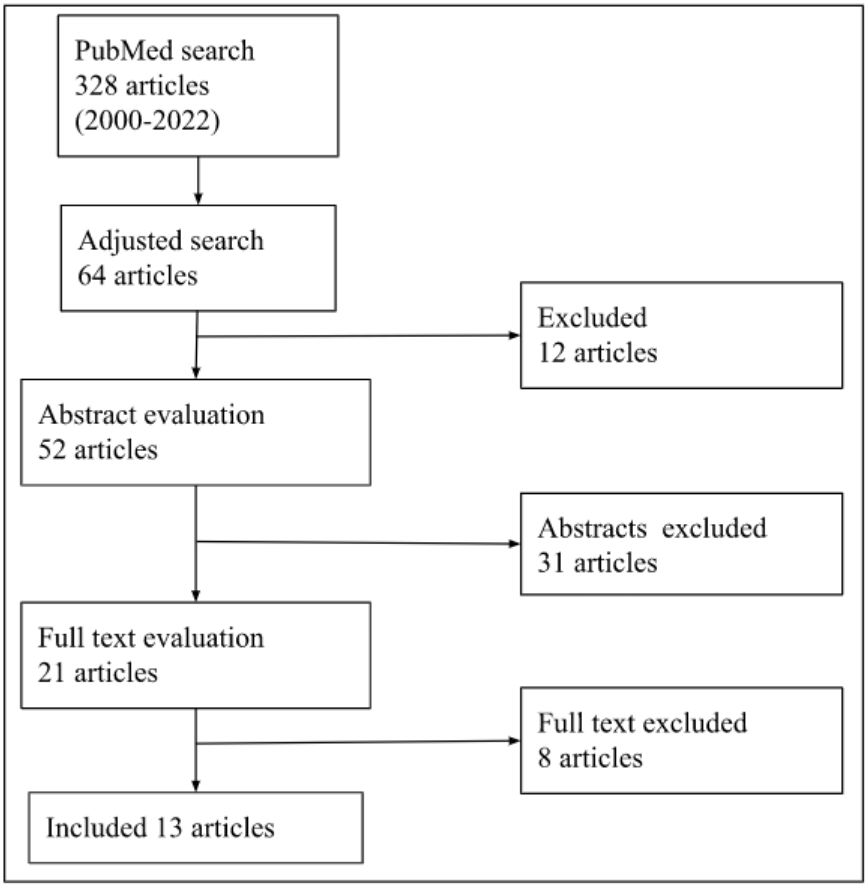

Fig.1 Flow chart illustrating the selection process of articles for the review.

3 Results

A subject we wanted further information about was whether there were different guidelines in implant placement in Norway. A summary of these results is shown in Table 2.
At Haukeland University Hospital in Bergen, all patients who are to be treated with radiation are admitted to the maxillofacial surgery department. If possible, remediation and insertion of dental implants is carried out as part of the main surgery before radiotherapy. Surgical procedures, including dental implant treatment, in irradiated areas with high risk for ORN is considered an indication for HBOT. The typical protocol is 20 daily treatment sessions preoperative where the patient breathes 100% oxygen at a pressure of 14 ATM for 90 minutes. After surgery, 10 additional sessions are performed. HUH has national function for this treatment, so patients from all hospitals will eventually get HBOT in Bergen if needed.

Similar to Haukeland University hospital, UNN tries to install dental implants before the start of radiation, i.e. in the same session as the tumor surgery for patients. This therefore applies if dental implants are installed in an area exposed to full dose radiation 60-70 Gy. Furthermore, areas that have received radiation below 50 Gy, or areas which are not in the radiation field are uncomplicated**.** The oral surgeons study the radiation fields together with the radiation therapists at UNN. Tooth extractions that are necessary in a full dose irradiated area are planned in combination with HBOT in Bergen.

At Oslo University Hospital, individual assessments are made regarding the need for immediate rehabilitation. OUH pointed out that this is a heterogeneous group of patients in need of rehabilitation and the risk of ORN is related to various risk factors, such as patient-related, tumor-related and treatment-related risk factors.

Moreover St.Olavs Hospital inserts implants within 6 months after radiotherapy. They rarely plan to insert an implant in an irradiated area shortly after completing radiotherapy. Moreover, HBOT is not a part of their routine. The clinicians extract numerous teeth; however they do not have a protocol to evaluate implant therapy within a certain period of time. The majority of patients get followed up by their general dentist, who plan the rehabilitation together with the patients.

Table 2. Results of the practices performed at the various hospitals in Norway

	Haukeland University Hospital	University hospital in North of Norway	Oslo University hospital	St.Olavs Hospital
Perform primary implantation	Yes	Yes	Yes, if needed	No
Perform secondary implantation	Yes, if needed	Yes, if needed	Yes, if needed	Yes
Uses HBOT	Yes	Yes	Yes, if needed	No

The table shows that there are performed different practices at the various hospitals.

HBOT, Hyperbaric oxygen treatment

In the 13 included studies in our review a total of 4180 patients were identified with a number of 17303 implants placed before or after radiotherapy. Primary implantation was investigated in three studies (338 patients, 989 implants), while secondary implantation was presented in six studies (2165 patients, 9442 implants). In the remaining four studies both primary and secondary implantation was evaluated (1677 patients, 6872 implants). The different results are presented in Table 3, 4 & 5.

As mentioned above three studies reported data on primary implantation alone (Table 3). Wetzels et al. (23) found an overall survival rate of 90,7% in their total follow-up period (207 patients, 548 implants). However, these results included 93 patients who did not receive postoperative radiotherapy. Despite this there were no significant results comparing survival rate between irradiated/non-irradiated patients in this study. In addition, no significant differences comparing implant placement in maxilla/mandible were found. Most of the patients who underwent radiotherapy after implant placement were irradiated with a dosage of ≥50 Gy. Out of the 114 irradiated patients a total of 16 developed ORN (14%). HBOT was however not used as an adjunctive treatment. More advanced reconstruction of the mandible significantly increased the risk of ORN ($P = 0.042$).

Korfage et al. (24) showed similar results with a 5-year follow-up on 50 patients who in total installed 195 implants. Out of the 50 patients in this study, 31 patients received radiotherapy after implantation, 123/195 implants were placed in the irradiated group, and 13 implants were lost during the follow-up period, which led to a significant implant survival rate of 89,4%. There were no numbers that could indicate results on survival based on location in this study. There were no cases of ORN, and HBOT was not used as an adjunctive treatment.

Furthermore, Korfage et al. (25) has comparable results, with an overall survival rate of 90,3% in patients who later received radiotherapy. All the implants in this prospective study were placed in the mandible, and therefore no results comparing locations would be considered. Three patients were given HBOT, and five patients developed ORN (5%) during this study (25).

Secondary implantation was investigated alone in six studies (Table 4). The highest survival rate was found in a study by Curi et al. (26), (92,9%) ($P < 0.001$). The survival rate was higher in the maxilla (92,4%) than in the mandible (90,9%), however the differences in location was nonsignificant ($P = 0.808$). None of the patients developed ORN during implant surgery, nor during follow-up. The use of HBOT had no significant effect on implant survival. The lowest survival rate of implants placed in irradiated patients was found in a retrospective study by Rana et al. (27) (67%).

Schiegnitz et al. (28) did a meta-analysis on the survival rate of implants placed after radiotherapy, with a total of 1814 patients receiving a total of 8177 implants. 1989/8177 implants were a part of control groups with installation in the non-irradiated jaw. They found the survival rate for irradiated native bone to range from 72-100%, while irradiated grafted bone varied from 54-89%, with a statistically higher implant survival in the irradiated native bone. Due to missing data, no investigation of the influence concerning location (maxilla/mandible) could be made. HBOT was not used, and there were no data on the development of ORN.

Yerit et al. (15) carried out a prospective study with a follow-up on 71 patients who had 316 implants installed in the mandible alone. 154 implants were placed in an irradiated jaw with a total dosage of 50 Gy. The survival rate of irradiated bone was 72%, grafted bone (54%), whereas the survival rate in the non-irradiated jaw was 95% ($P < 0.0019$). However, there were no statistically significant differences in the survival rate between irradiated residual bone and grafted bone, compared to the results by Schiegnitz et al. (28). Two patients suffered from ORN (2,8%) (15). HBOT was not used during the study.

Furthermore, a prospective study by Sammartino et al. (29) found the success rate to be higher for irradiated patients (88,3%), with a statistically significant difference comparing the location of the implantation. The mandibula had an overall survival rate of 98,4%, with a considerably lower survival rate in the maxilla (57,1%) ($P < 0.05$). The survival rate of

implants was higher in patients receiving a radiation dosage ≤50 Gy, than patients treated with dosages >50 Gy ($P < 0.05$). There was not performed HBOT in this study, nor any comments concerning the development of ORN.

A study done by Rana et al. (27) found a significantly higher implant survival in the mandible (71%), compared to the maxilla (65%) ($P < 0.005$). The study presented the lowest results of the articles investigated for implants survival in patients treated with radiotherapy prior to installation, with an overall survival rate of 67%. Patients receiving a radiation dosage <50 Gy showed a higher 5-year survival rate of implants ($P < 0.05$). There was no mentioning of patients developing ORN, nor the use of HBOT.

Likewise, a study done by Visch et al. (21) found the location to have a significant influence on survival, 50% in the maxilla and 85% in the mandible ($P = 0.001$). Implants in sites that received radiotherapy with a dosage of <50 Gy showed a survival rate of 84%, compared to a dosage of ≥50 Gy (71%) ($P = 0.05$). The overall survival rate was 78%. HBOT was not applied, and no cases of ORN were mentioned.

Four of the included studies showed results on both primary and secondary implantation (Table 5). The overall survival rate varied from 76,7% to 97%. A systematic review by Nooh, N (12) found there to be a higher survival rate when placing an implant prior to radiation therapy (92,2%), than after (88,9%). However, there were a greater number of patients in the group who were irradiated before implant insertion, than those who received radiation after, and no statistical comparisons in the primary implantation group could be performed in the study. On the other hand, there were found statistically significant results on the location of implants in the group of patients who were irradiated prior to implant placement. The survival rate of implants inserted in the mandible was 93,3% and had a significantly higher survival compared to implants in the maxilla (78,9%). HBOT was also reported in the systematic review for patients who had implants placed prior to radiotherapy (preimplantation). The survival rate of dental implants was 93,8% in patients receiving HBOT, compared to 90,6% in patients who did not have this adjunctive treatment. These results were however nonsignificant. The occurrence of ORN was not reported.

Moreover, a systematic review and meta-analysis was performed by Toneatti et al. (30). The overall survival rate for irradiated patients was 91,9%, but no comparison on primary/secondary implantation could be made. However, they found the average interval

between primary implantation and radiotherapy to be 6 weeks, whereas for secondary implantation the average waiting period for implant placement was 30,7 months. A retrospective study by Patel et al. (31) also mentioned the time interval and found that placement during primary resection reduced the time from diagnosis to placement significantly ($P = 0.016$). Toneatti et al. (30) also investigated the occurrence of ORN, which was developed in 11 cases (2,6%). They found that the risk for ORN was unrelated to the radiation dose surpassing 60 Gy, however these results were nonsignificant, and factors influencing ORN could not be determined. 64 of the irradiated patients underwent HBOT, but no significant impact was found.

Patel et al. (31) found the overall survival rate of dental implants to be 97%, regardless of the timing of radiotherapy. Nine implants failed primary, and eight implants secondary, however there were no comment on the total number of implants placed before/after treatment in the study, therefore no individual survival rate was given. The comparison of location maxilla/mandible was nonsignificant. There was no mentioning of the use of HBOT, nor any incidence of ORN.

Granstöm, G. (20) performed a retrospective study on osseointegration in irradiation patients with the lowest overall survival rate of 76,7%. Regarding the location, the survival rate was significantly higher in the oral maxilla (87,5%), than in the mandible (66%). There were no results comparing the use of primary vs secondary implantation. They found the use of HBOT to increase implant survival significantly. 340 implants were installed under the use HBOT. Five patients developed ORN (4,7%), four of these were treated with a combination of radiation therapy pre- and postoperative, and therefore received high radiation doses. This is however the only article in our study who found HBOT to have a significant effect on the survival rate.

TABLE 3. Studies describing implant survival for implants placed prior to radiotherapy, and associating factors

	Study	No. of patients	No. of OI placed	Overall survival rate (%)	HBOT (yes/no)	No. of OI and survival rate (%) Maxilla/Mandible	No. of patients developing ORN
1.	Wetzels et al. (23)	207	548	(90,7%)	No	N/A[a]	16
2.	Korfage et al. (24)	31	123	(89,4%)	No	N/A[a]	0
3.	Korfage et al. (25)	100	318	(90,3%)	yes	- / 524 (90,3%)[b]	5

Overall survival rate was between 89,4%-90,7%.

No, number of; OI, oral implants; HBOT, hyperbaric oxygen therapy; ORN, osteoradionecrosis; N/A, not available

[a] Comparing implant survival based on location could not be done due to inadequate data

[b] The study investigated implant survival in the mandible alone

TABLE 4. Studies describing implant survival for implants placed after radiotherapy, and associating factors

	Study	No. of patients	No. of OI	Overall survival rate (%)	HBOT (yes/no)	No. of OI and survival rate (%) Maxilla/Mandible	No. of patients developing ORN
1.	Curi et al. (26)	35	169	(92,9%)	yes	79 (92,4%) / 90 (90,9%)	0
2.	Schiegnitz et al. (28)	1814	8177	(72-100%)	no	N/A[a]	N/A[c]
3.	Yerit et al. (15)	71	316	(72%)	no	- / 316 (72%)[b]	2
4.	Sammartino et al. (29)	69	172	(88,3%)	no	42 (57,1%) / 130 (98,4%)	N/A[c]
5.	Rana et al. (27)	46	162	(67%)	no	70 (65%) / 92 (71%)	N/A[c]
6.	Visch et al. (21)	130	446	(78%)	no	108 (59%) / 338 (85%)	N/A[c]

Overall survival rate was between 67%-92,9%

No, number of; OI, oral implants; HBOT, hyperbaric oxygen therapy; ORN, osteoradionecrosis; N/A, not available

[a] Comparing implant survival based on location could not be done due to inadequate data

[b] The study investigated implant survival in the mandible alone

[c] The development of ORN was not investigated

TABLE 5. Studies describing implant survival for implants placed before and after radiotherapy, and associating factors

	Study	No. of patients	No. of OI	No. of OI & Survival rate (%) preimplantation	No. of OI & Survival rate (%) postimplantation	Overall survival rate (%)	HBOT (yes/no)	No. of OI and survival rate (%) Maxilla/Mandible	Cases of patients developing ORN
1.	Nooh, N. (12)	1030	4095	320 (92,2%)	3775 (88,9%)	(90,55%)	yes	516 (78,9%) / 2344 (93,3%)	N/A[f]
2.	Toneatti et al. (30)	425	1770	N/A[a]	N/A[b]	(91,9%)	yes	N/A[d]	11
3.	Patel et al. (31)	115	376	N/A[a]	N/A[b]	(97%)	N/A[c]	N/A[d]	N/A[f]
4.	Granström, G. (20)	107	631	N/A[a]	N/A[b]	(76,7%)	yes	N/A (87,5%) / N/A (66%)[e]	5

Overall survival rate was between 76,7%-97%

No, number of; OI, oral implants; HBOT, hyperbaric oxygen therapy; ORN, osteoradionecrosis; N/A, not available

[a] There were no survival rate for preimplantation alone

[b] There were no survival rate for postimplantation alone

[c] The use of HBOT was not mentioned

[d] Comparing implant survival based on location could not be done due to inadequate data

[e] Number of implants placed in the maxilla and mandible were not available

[f] The development of ORN was not investigated

4 Discussion

With an increase in the use of dental implants in the treatment of oral cancer patients going through radiotherapy, and inconsistent results in the literature, we wanted to investigate further on this subject (12). There are no clear guidelines in the literature, nor in the Norwegian hospitals, regarding the timing of radiotherapy in relation to implant placement. As previously mentioned, we contacted the four different regional hospitals who perform implant placement in relation to cancer therapy. In addition, we conducted a review of the available literature on the prognosis and outcome of dental implants placed both prior to and after radiation.

The selection of the literature has not been carried out strictly systematically. We have chosen to conduct a review of the literature that was available based on our research questions and keywords. We chose not to write a meta-analysis as the criteria would probably be too different for it to be possible to compare the different studies. Based on our search string, we did not find any randomized control studies that showed a direct comparison between implant insertion before and after radiotherapy. When reviewing our study, we realize that it is difficult to draw a conclusion, and that we found little or no difference between primary and secondary implantation. It would therefore have been insightful to have carried out an RCT study**.**

4.1 Practices performed at the various hospitals in Norway

In conclusion it can be argued that there is a difference in the routines at the institutions. In summary Haukeland University Hospital aims to sanitize the oral cavity and implant insertions in the same session as tumor resection. Similar to HUH, the University hospital in Tromsø strives to either insert implants primary or in the same sessions as tumor resection. The University of Oslo pointed out that this particular group is a heterogeneous group, and they therefore evaluate every patient individually, with regards to the need for rehabilitation and risk factors. In contrast to all of the above St.Olavs Hospital inserts implants secondary to radiotherapy.

4.2 Primary implantation compared to secondary implantation

Radiotherapy has been considered a relative contraindication for dental implants in cancer patients (20). One of the concerns are altered anatomy, secondly impaired wound healing, failed osseointegration and finally ORN (30). However, during the last decades, there has been immense development in dentistry along with dental rehabilitation. This includes biocompatible materials, surgical techniques as well as new surgical concepts (20). During our review, various articles present results of dental implantation in both irradiated and non-irradiated groups.

As Table 3 shows, there were limited studies investigating dental implant placement prior to radiotherapy, but for those mentioned the survival rate was quite high, varying from 89,4% to 90,7% (23-25). Major benefits may come from preimplantation. With a primary insertion, the rehabilitation time is greatly reduced. As mentioned in the results Toneatti et al. (30) found the average interval between primary implantation and radiotherapy to be 6 weeks, compared to secondary implantation which had an average waiting period of 30,7 months. Patel et al. (31) found that primary resection significantly reduced the timing of implant placement. This is beneficial, as it allows patients to faster regain oral functionality, as well as being able to finish their rehabilitation earlier compared to secondary implantation (25). Korfage et al. (25) also implied preimplantation to be convenient considering that patients may postpone or decline implant treatment after resection and postoperative radiotherapy, due to additional treatments and lack of motivation.

Regardless, the results showed several disadvantages of using preimplantation. In some cases, a source of error could be tumor recurrence, incorrect implant positioning, alterations in anatomical relationships, delay of oncological treatment, post treatment complications, comorbidity or the patient dying (23, 24). In these cases, it would be beneficial to have carried out post implantation, as one can better predict the prognosis regarding possible complications. At the same time, it would be rather meaningless to insert an implant if it is placed incorrectly, or if the patient dies and has no use for it.

In contrast to preimplantation there were more studies found investigating postimplantation (Table 4). As regards to postimplantation the prognosis varied based on the amount of radiotherapy and the damage to the irradiated area. The survival rate of implants placed after radiotherapy varied from 67%-92,9%. The results on postimplantation had a greater diversity

compared to the results found for preimplantation and is perhaps more credible based on the number of articles examined.

Based on the findings on primary and secondary implantation it can be argued that there are advantages and disadvantages in both treatments. Although the number of studies conducting primary implantation were low, in total the survival rate was quite high. Overall, the results suggest that there is a high survival rate for implants placed in irradiated bone, regardless of the timing of the radiation. For that reason, this study justifies dental implantation in irradiated bone as well as in non-irradiated bone. Despite our results, there is still a need for more evidence-based research to be able to conclude whether one method is preferred over the other.

4.3 The influence of the anatomical site of implantation

In addition to studying the prognosis of primary and secondary implantation, we have also become aware that the survival rate can be influenced by the anatomical site of implant placement. The traditional interpretation is that implants have a better prognosis in the mandible compared to the maxilla. Similar to the statement, our results show that the mandible has the most favorable survival rate. Then again, sources of errors may be small patient groups.

In the majority of the articles we have reviewed, most implants are placed in the mandible. Nooh, N (12) found implant placement in the mandible to have a significantly better prognosis (93,3%) compared to maxilla (78,9%). The mandible has presumably a better prognosis due to a higher amount of dense and compact bone. This seemingly leads to an improved primary stability compared to the maxilla (30). Sammartino et al. (29) also found the mandible to have a higher survival rate (98,4%) compared to maxilla (57,1%). According to Visch et al. (21) the implants survival was mostly influenced by the location of the implant. This study also concluded that the mandible had a significantly better prognosis compared to the maxilla.

In contrast to this, Curi et al., Wetzels et al., and Toneatti et al. (23, 26, 30) found no significant differences in the anatomical implantation sites. On the other hand Granström, G (20) found a high implant failure in the mandible compared to other anatomical sites, and showed greater failures in the mandible with increased time. In total our results indicate that the anatomical location of the implant has an influence on the prognosis. The mandible has an

overall presumably better prognosis compared to the maxilla based on our selection of studies. As to the variation of the results, sources of error may be due to different sizes of the selected patient groups, implants lost during the follow up period and not included in the statistics.

4.4 Osteoradionecrosis

As previously mentioned ORN is a serious complication in relation to dental implant placement regarding patients with head-neck cancer. Although there were few studies documenting the incidence, ORN was present in both primary and secondary dental implantation. The highest number of cases was found in a study on primary implantation by Wetzels et al. (23), where 14% of the irradiated patients developed ORN. This is interesting considering that one of the advantages for primary implantation is the fact that implant surgery can be avoided in areas compromised by radiotherapy (24). Korfage et al. (24) mentioned this as an important factor in reducing late complications such as ORN. They also did a study on primary dental implantation and had no occurrence of ORN.

Only two of the six articles investigating secondary dental implantation mentioned the development of ORN. Curi et al. (26) had no occurrence of ORN, while Yerit et al. (15) only had two cases (2,8%). The other four articles had inadequate data on the subject, and no summary could be made.

The studies comparing primary and secondary implantation also found cases of ORN, varying from 2,6%-4,7% (20, 30). However, there were also inadequate data in this group, with two articles not commenting on the development of ORN. This taken into consideration it would be difficult to conclude whether there are higher risks installing an implant prior to/after radiotherapy is given. However, we know that ORN can occur even if an implant is placed in a later irradiated area, and that primary installation does not necessary reduce the risk of ORN.

4.5 Hyperbaric oxygen treatment

Another essential point of our study is the use of HBOT. In total five of the 13 reviewed studies chose to implement the adjunctive treatment. As previously mentioned, the effect remains controversial. HBOT has been reported to promote capillary neoangiogenesis, bone

formation and improve viability, which may reduce the risk for ORN (11, 26). A selection of our studies did not find a significant influence on HBOT in relation to implant survival, but there can be found a difference in survival rate despite not being statistically significant. For example, Curi et al. (26) showed an increased 5-year survival rate on dental implants when comparing patients who underwent HBOT (94.1%) with patients who did not (88.2%), however this was nonsignificant. Whereas Nooh, N (12) showed no links between HBOT and implant survival.

On the other hand, Granström, G (20) found there to be an increased failure rate of implants installed in previously irradiated bone and argued that they chose to apply the therapy in the study due to increased awareness of sources of errors. This was also the only study that found HBOT to have a significant influence on the survival rate on dental implants placed in irradiated bone. However, Yerit et al. (15) did not have HBOT available at the beginning of their study but concluded that the treatment may favor wound healing and regeneration in irradiated bone. This considered, the effects of HBOT still seems to be controversial. Our study also shows that the various hospitals in Norway have different approaches to the adjunctive treatment. More studies should preferably be performed to be able to draw a conclusion about the presumably beneficial effect.

5 Conclusion

Our master thesis sought to find out if there were different practices at the various hospitals who perform implant placement prior to or after radiotherapy. In conclusion, there are different practices at each of the institutions. Ideally, it would have been beneficial to have national guidelines, but as the literature does not point to any evidence-based recommendations about one type of treatment over the other, there is a need for more research on the topic before there is established a common guideline.

In summary, there is also a difference in prognosis by comparing primary and secondary dental implantation in oral cancer patients. There are currently too few studies on primary implantation as well as primary implantation compared to secondary implantation, to be able to conclude whether one gives a better prognosis than the other. However, the small number of studies that included implant placement prior to radiation therapy, had results that are comparable to implantation in irradiated bone. This indicates that more studies should be done on the prognosis of preimplantation.

6 References

1. World Health Organization. Cancer. [Internet]. [updated 03.02.22; cited 2022 27.02]. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer
2. Kreftregisteret. Kreft i Norge. [Internet]. [updated 21.09.21; cited 2022 03.03]. Available from: https://www.kreftregisteret.no/Temasider/om-kreft/
3. Kreftforeningen. Hode- og halskreft. [Internet]. [updated 05.02.22; cited 2022 03.03]. Available from: https://kreftforeningen.no/om-kreft/kreftformer/hode-og-halskreft/
4. Helsenorge. Hode- og halskreft. [Internet]. [updated 22.02.22; cited 2022 03.03]. methodAvailable from: https://www.helsenorge.no/sykdom/kreft/hode-og-halskreft/.
5. Munn- og halskreftforeningen. Munnhulekreft. [Internet]. [cited 2022 15.03]. Available from: https://www.munnoghalskreft.no/hva-er-munn-og-halskreft/munnhulekreft/.
6. Rosales AC, Esteves SC, Jorge J, Almeida OP, Lopes MA. Dental needs in Brazilian patients subjected to head and neck radiotherapy. Braz Dent J. 2009;20(1):74-7.
7. Tolentino Ede S, Centurion BS, Ferreira LH, Souza AP, Damante JH, Rubira-Bullen IR. Oral adverse effects of head and neck radiotherapy: literature review and suggestion of a clinical oral care guideline for irradiated patients. J Appl Oral Sci. 2011;19(5):448-54.
8. Otmani N. Oral and maxillofacial side effects of radiation therapy on children. J Can Dent Assoc. 2007;73(3):257-61.
9. Kreftforeningen. Senskader etter kreftbehandlingen blant voksne. [Internet]. [updated 17.01.23; cited 2023 23.02]. Available from: https://kreftforeningen.no/om-kreft/senskader-voksne/.
10. Pace-Balzan A, Rogers SN. Dental rehabilitation after surgery for oral cancer. Curr Opin Otolaryngol Head Neck Surg. 2012;20(2):109-13.
11. Shaw RJ, Butterworth CJ, Silcocks P, Tesfaye BT, Bickerstaff M, Jackson R, et al. HOPON (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis): A Randomized Controlled Trial of Hyperbaric Oxygen to Prevent Osteoradionecrosis of the Irradiated Mandible After Dentoalveolar Surgery. Int J Radiat Oncol Biol Phys. 2019;104(3):530-9.
12. Nooh N. Dental implant survival in irradiated oral cancer patients: a systematic review of the literature. Int J Oral Maxillofac Implants. 2013;28(5):1233-42.
13. Johns Hopkins Medicine. Hyperbaric Oxygen Therapy. [Internet]. [cited 2023 03.03]. Available from: https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/hyperbaric-oxygen-therapy.

14. Vigdis Lauvrak KBF, Sari S. Ormstad, Guro Vaagbø, Brynjar Fure. Effekt av hyperbar oksygenbehandling ved senskader etter stråleterapi eller diabetiske fotsår Rapport fra Kunnskapssenteret 2015;Nr.4
15. Yerit KC, Posch M, Seemann M, Hainich S, Dörtbudak O, Turhani D, et al. Implant survival in mandibles of irradiated oral cancer patients. Clin Oral Implants Res. 2006;17(3):337-44.
16. Dieleman FJ, Phan TTT, van den Hoogen FJA, Kaanders J, Merkx MAW. The efficacy of hyperbaric oxygen therapy related to the clinical stage of osteoradionecrosis of the mandible. Int J Oral Maxillofac Surg. 2017;46(4):428-33.
17. Jacobsen N. Pasientrelaterte faktorer ved dentale implantater Nor Tannlegeforen Tid. 2019;129:684-91.
18. FDA. Dental implants: What you should know. [Internet]. [updated 29.10.21; cited 2023 03.02]. Available from: https://www.fda.gov/medical-devices/dental-devices/dental-implants-what-you-should-know.
19. Parithimarkalaignan S, Padmanabhan TV. Osseointegration: an update. J Indian Prosthodont Soc. 2013;13(1):2-6.
20. Granström G. Osseointegration in irradiated cancer patients: an analysis with respect to implant failures. J Oral Maxillofac Surg. 2005;63(5):579-85.
21. Visch LL, van Waas MA, Schmitz PI, Levendag PC. A clinical evaluation of implants in irradiated oral cancer patients. J Dent Res. 2002;81(12):856-9.
22. NIH National Library of Medicine. PubMed [Internet]. Available from: https://pubmed.ncbi.nlm.nih.gov/
23. Wetzels JGH, Meijer GJ, de Haan AFJ, Merkx MAW, Speksnijder CM. Immediate implant placement in edentulous oral cancer patients: a long-term retrospective analysis of 207 patients. Int J Oral Maxillofac Surg. 2021;50(11):1521-8.
24. Korfage A, Schoen PJ, Raghoebar GM, Roodenburg JL, Vissink A, Reintsema H. Benefits of dental implants installed during ablative tumour surgery in oral cancer patients: a prospective 5-year clinical trial. Clin Oral Implants Res. 2010;21(9):971-9.
25. Korfage A, Raghoebar GM, Slater JJ, Roodenburg JL, Witjes MJ, Vissink A, et al. Overdentures on primary mandibular implants in patients with oral cancer: a follow-up study over 14 years. Br J Oral Maxillofac Surg. 2014;52(9):798-805.
26. Curi MM, Condezo AFB, Ribeiro K, Cardoso CL. Long-term success of dental implants in patients with head and neck cancer after radiation therapy. Int J Oral Maxillofac Surg. 2018;47(6):783-8.

27. Rana MC, Solanki S, Pujari SC, Shaw E, Sharma S, Anand A, et al. Assessment of the Survival of Dental Implants in Irradiated Jaws Following Treatment of Oral Cancer: A Retrospective Study. Niger J Surg. 2016;22(2):81-5.
28. Schiegnitz E, Al-Nawas B, Kämmerer PW, Grötz KA. Oral rehabilitation with dental implants in irradiated patients: a meta-analysis on implant survival. Clin Oral Investig. 2014;18(3):687-98.
29. Sammartino G, Marenzi G, Cioffi I, Teté S, Mortellaro C. Implant therapy in irradiated patients. J Craniofac Surg. 2011;22(2):443-5.
30. Toneatti DJ, Graf RR, Burkhard JP, Schaller B. Survival of dental implants and occurrence of osteoradionecrosis in irradiated head and neck cancer patients: a systematic review and meta-analysis. Clin Oral Investig. 2021;25(10):5579-93.
31. Patel J, Antov H, Nixon P. Implant-supported oral rehabilitation in oncology patients: a retrospective cohort study. Br J Oral Maxillofac Surg. 2020;58(8):1003-7.