Immediate dental implant placement and restoration in the edentulous mandible in head and neck cancer patients: a systematic review and meta-analysis

Matthijs in ’t Veld, Engelbert A.J.M. Schulten, and Frank K.J. Leusink

Purpose of review
Oral rehabilitation with dental implants in head and neck cancer (HNC) patients is challenging. After tooth removal prior to radiotherapy, immediate placement of dental implants during panendoscopy or surgery is thought to reduce the oral rehabilitation time improving patients’ quality of life.

Recent findings
There is lack of consensus on the timing of dental implant placement and loading protocols. The aim of this study was to perform a systematic review of the literature regarding the performance and survival rate of immediately inserted dental implants placed prior to radiotherapy. Of 1003 articles, 10 were finally included comparing immediate vs. delayed placement of implants and comparing the effect of radiotherapy on immediately placed implants. Meta-analysis demonstrated a slightly higher survival of immediately placed implants compared with postponed placed implants [risk ratio: 0.92, 95% confidence interval (95% CI): 0.48–1.78, P = 0.81, I² = 0%]. The other meta-analysis comparing radiotherapy vs. nonradiotherapy showed a clearly better survival of immediately placed implants not having received radiotherapy [risk ratio: 5.02, 95% CI: 0.92–27.38, P = 0.10, I² = 56%].

Summary
Guidelines are recommended for immediate dental implant placement in the edentulous mandible in HNC patients prior to radiotherapy to allow homogeneity regarding the treatment protocols and thus comparison of treatment outcomes.

Keywords
dental implants, head and neck cancer, immediate implant placement, mandible, radiotherapy

INTRODUCTION
Head and neck cancer (HNC) is an increasing global health problem. The worldwide annual incidence is more than 550 000 new cases with around 300 000 associated deaths, which accounts for 4.6% of the total cancer mortality [1,2,3,4]. HNC comprises malignancies in the upper respiratory and digestive tract (e.g. oral cavity, pharynx and larynx) and the majority of these malignancies are squamous cell carcinomas (SCCs). The most important risk factor that contributes to the increasing incidence of HNC is the excessive use of tobacco and alcohol. Furthermore, recent studies suggest that mainly in oropharyngeal cases, the human papilloma virus (HPV) would contribute to the increase of new HNC cases [5,6].

Treatment of HNC may include ablative surgery with or without postoperative radiotherapy (RTX) or chemoradiation (CRT), primary RTX or CTR alone. RTX in HNC patients is often accompanied by side effects, such as hyposalivation, neuropathy, atrophy and ischemia [7]. Furthermore, due to exposure of the mandible to ionizing radiation,
there is an increased risk of the development of osteoradionecrosis (ORN) [7]. To minimize the risk of ORN, dental screening and tooth removal should be performed on indication prior to RTX, especially in patients with periapical lesions arising from nonvital teeth and an impaired periodontal condition [8,9]. In this context, the placement of dental implants in the irradiated mandible for oral rehabilitation is more challenging with an increased risk for the development of ORN [10,11].

Oral rehabilitation protocols for edentulous and irradiated HNC patients usually consist of dental implant placement, perioperative hyperbaric oxygen therapy (HBO2), and, only after a period of 6–12 months, further rehabilitation with overdentures [12–15]. In the meantime and during the course of radiotherapy, there is often no possibility for wearing or fabricating new dentures, leading to difficulty in speech and mastication and consequently reduced quality of life.

Regarding oral rehabilitation, dental implants can be placed either prior to radiotherapy, immediately after dental extractions during panendoscopy or ablative surgery, or after completion of the radiotherapy in a later stage. In the literature, there are two different study protocols describing the oral rehabilitation with dental implants in HNC patients. One group describes the influence of immediate dental implant placement compared with delayed placement on the survival rate or implant success, and the other group describing the influence of radiotherapy in immediately placed dental implants. Over the last years, different studies suggest that dental implants placed during ablative surgery show a high survival rate and will lead to an earlier restoration of oral function, thus improving the quality of life [16–19,20]. Likewise, dental implants placed immediately during full dental clearance prior to curative radiotherapy show similar results [20,22]. Furthermore, apart from dental implant placement, the implant success and functionality are of great importance. Criteria for implant success have been proposed by Albrektsson et al. [23] and are based on successful osseointegration and implant survival. Since then, new parameters have been added by other authors to assess dental implant success. These include continuous prosthesis stability, radiographic bone loss and absence of peri-implant infection [24,25]. The use of different criteria in the dental literature has subsequently led to a lack of homogeneity regarding dental implant success [26]. In addition, there is a difference between ‘placed dental implants’ and ‘functional dental implants’. In the literature, there is no uniformity with regard to the definition of dental implant functionality.

In this study, we aimed to perform a systematic review to identify and appraise the treatment outcome of immediate placement and loading of dental implants in the edentulous mandible and the functioning of overdentures in HNC patients.

**Materials and Methods**

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines regarding the literature search. To identify all relevant studies, PubMed, EMBASE and the Cochrane Library databases were used. MeSH terms were used in PubMed and EMTree terms in EMBASE. The PICO elements relating to this review were as follows:

**Patients:** adult patients with HNC who are or become edentulous prior to RTX; **Intervention:** immediate dental implant placement during panendoscopy or ablative surgery; **Control:** not applicable; **Outcome:** dental implant survival, dental implant functionality and overdenture functionality.

The search strategy combined terms representing ‘head and neck cancer’, ‘edentulous mouth’ and ‘prosthodontics’. Furthermore, free text terms were used in all databases. The full search strategy for all databases is summarized in Appendix 1, http://links.lww.com/COOH/A41.

**Inclusion Criteria**

The reviewed studies had to fulfil the following criteria before inclusion in this study: published in English; published before 3 October 2019; patients with HNC who were referred for panendoscopy or ablative surgery; patients with HNC who were edentulous or have become edentulous during panendoscopy or ablative surgery; intraoperatively placed dental implants; and dental implants should be placed in native mandibular bone.
Exclusion criteria
Articles were excluded from the present systematic review for the following reasons: animal or cadaveric studies, and not original research articles (e.g. case reports, editorials, letters to editor, oral papers and posters, conference abstracts).

Before a final decision regarding inclusion was made, two authors (MV and FL) independently reviewed all relevant articles for eligibility. Disagreements were resolved by discussion. Duplicate studies were excluded and Endnote X9 (Thomson Reuters, New York, New York, USA) was used to organize references.

Definition of survival rate, implant success and implant functionality
The study performed by Ettl et al. [22] defined dental implant success according to the Albrektsson criteria (modified by Buser et al. [27] and Weibrich et al. [28]) as follows: ‘An implant was considered successful when it met all the following criteria: loaded in situ implant; absence of persistent pain; no lesion of the nerve; absence of peri-implant infection with suppurative (probing depth of more than 4 mm was considered comparable to infection); absence of mobility; absence of continuous peri-implant radiolucency; and absence of peri-implant bone resorption of more than 1.5 mm in the first year of function and of more than 0.2 mm during the subsequent years measured by radiographic investigation’ [22,23,27,28].

A dental implant was defined as functional when an overdenture could be placed on the placed dental implant.

Meta-analysis
The meta-analysis was based on the Mantel–Haenszel method. Dichotomous outcome measures of the lost implants were presented as risk ratios for the number of implants receiving RTX vs. n-RTX and for the number of implants placed immediately vs. delayed. The meta-analysis was performed using Review Manager Software Version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The risk ratio is displayed with a 95% confidence interval (95% CI) and $I^2$ describes the amount of heterogeneity among the included studies. $I^2$ values of 25, 50 and 75% were assigned as low, moderate and high levels of heterogeneity, respectively [29].

RESULTS
The initial literature search yielded a total of 1003 articles. The flowchart regarding the literature search and article selection process is shown in Fig. 1. After removing the duplicated references, 745 records were included for further analysis. These included 621 records in PubMed, 117 in EMBASE and seven in The Cochrane Library. On the basis of title and abstract, 709 articles were excluded and the full text of 36 articles was obtained for further consideration. Two more references were found by a hand search during analysis of the full text of these 36 studies. Ten articles met the inclusion criteria regarding evaluation of immediate dental implant placement in HNC patients including implant survival [19,20*,22,30–35]. The characteristics of the 10 included studies are summarized in Table 1.

Tumour location and staging
The tumour characteristics, such as location and TNM classification, are summarized in Table 2. Only two studies calculated the tumour stage using the TNM classification [21,30]. In the study by Mizbah et al. [21] patients had the following tumour stages: stage I (23 patients, 23%), stage II (35 patients, 36%), stage III (12 patients, 12%) and stage IV (29 patients, 29%). Korfage et al. [30] included 35 patients (22%) with stage I, 40 patients (24%) with stage II, 40 patients (24%) with stage III and 49 patients (30%) with stage IV. The numbers represent the patients who received the dental implants during ablative surgery.

Lost to follow up
The main reason for missing data was patients’ dead due to tumour and nontumor-related causes [19,22,31–35]. Other reasons in the included studies regarding ‘lost to follow-up’ comprises patients not attending their recall, withdrawal of consent and not willing because of psychological reasons.

Immediate vs. delayed dental implant placement: implant survival rate and implant functionality
Of the 10 included studies, four studies aimed to compare the survival rate and implant functionality of immediately placed dental implants during ablative surgery and postponed placed implants after ablative surgery (see Table 3). The survival rate of dental implants placed during ablative surgery was more than 90.4% and the implant functionality varied between 61.5 and 90.8%.

In the study by Mizbah et al. [21], the survival rate of immediately placed dental implants was 90.4% (225 of the 249 implants) and 82.3% (205 of the 249) of the dental implants were functional.
and used for the implant-supported overdenture after a 5-year follow-up. Wetzels et al. [34] found an implant functionality of 67.5% with a maximum follow-up of five years (27 out of the 40 implants). In another study by Wetzels et al. [35], 17 of the 225 immediately placed implants were lost (implant survival of 90.4%) and 76.9% (173 of 225 implants) of the implants in the immediately placed implant group were loaded, also with a maximum follow-up period of 60 months.

In the study by Woods et al. [20**, the implant survival of immediately placed dental implants was 97.4% (38 of the 39 implants) and 61.5% of the implants immediately placed were functional (24 of the 39 implants) after a mean observation period of 23.0 months.

Three of the 10 studies were included in the meta-analysis. A total of 513 dental implants were placed during ablative surgery and 171 were placed after the surgical procedure, respectively. The forest
| Ref. | Study type | Groups | Time of implant placement (group) | Follow-up range (months) | Timing of implant osseointegration | Radiation dose (Grays) | Implant system | Implant type | Ref. |
|------|------------|--------|---------------------------------|---------------------------|-----------------------------------|-----------------------|----------------|-------------|------|
| Ettl et al. [22] | Prospective RTX vs. n-RTX | 52/36 14 | None and post | Immediate | Osteo整合ASRA TECH implant system | Immediate | 37 Fyrom 2B12 | Femoral component and stem | Ettl et al. [22] |
| Korfage et al. [19] | Prospective RTX vs. n-RTX | 50/35 15 | None and post | Immediate | NobelBiocare (Branemark) | Immediate | 3.75 mm Branemark screw implants with a machined surface | Korfage et al. [19] |
| Korfage et al. [30] | Prospective RTX vs. n-RTX | 164/98 66 | | Immediate | NobelBiocare (Branemark) | Immediate | 3.75 mm Branemark implants (Nobel BioCare, Gothenburg, Sweden), with a machined surface or a TiUnite surface | Korfage et al. [30] |
| Mizbah et al. [21] | Retrospective DAS vs. P | 510/294 216 | | Immediate | NobelBiocare (Branemark) | Immediate | 3 or 9 | Mizbah et al. [21] |
| Schepers et al. [31] | Retrospective RTX vs. n-RTX | 48/29 19 | None and post | Immediate | NobelBiocare (Branemark) | Immediate | 3 or 9 | Schepers et al. [31] |
| Schoen et al. [32] | Prospective RTX | 5/3 2 | Post | Immediate | NobelBiocare (Branemark) | Immediate | 3 or 9 | Schoen et al. [32] |
| Wetzels et al. [34] | Prospective DAS vs. P | 56/33 22 | None and post | Immediate | NobelBiocare (Branemark) | Immediate | 3 or 9 | Wetzels et al. [34] |
| Wetzels et al. [35] | Retrospective DAS vs. P | 193/104 89 | | Immediate | NobelBiocare (Branemark) or Straumann or Astra | Immediate | 3 or 9 | Wetzels et al. [35] |
| Woods et al. [20] | Retrospective DAS vs. P | 20/13 7 9 | None and post | Immediate | ITI/Straumann (Basel, Switzerland) | Immediate | Both | Woods et al. [20] |

DAS, during ablative surgery; Gy, Gray; n-RTX, non-radiotherapy; P, postponed; RTX, radiotherapy.
plot in Table 5A summarizes a slightly higher survival rate for the immediately placed dental implants. However, there was no significant difference between the two groups (risk ratio: 0.92, 95% CI: 0.48–1.78, $P = 0.81$, $I^2 = 0%$).

**Radiotherapy vs. nonradiotherapy in immediately placed dental implants: implant survival rate, implant success and implant functionality**

The remaining seven articles included in this review described the influence of RTX on immediately placed dental implants (see Table 4). Ettl et al. [22] was the only study describing the implant success based on the Albrektsson criteria and reported an implant success rate after a one-year follow-up period of 86.7% (143 of 165 implants) [23]. Korfage et al. [19] described an implant functionality of 39.0% (76 of the 195 implants) in patients with a functional overdenture after 5 years. Another study by Korfage et al. [30] described a survival rate of 94.7% (496 of 524 implants) after a median follow-up of 3.8 years. Schepers et al. [31] reported an implant functionality of 75.5% (105 of the 139 implants) with a mean follow-up of 29.6 months.

### Table 2. Tumour characteristics of the 10 included studies in the literature review

| Ref.          | Primary tumour                | No. of patients | Tumour (T) | No. of patients (%) | Lymph nodes (N) | No. of patients (%) |
|---------------|-------------------------------|-----------------|------------|---------------------|----------------|--------------------|
| Ettl et al. [22] | Anterior FOM, tongue or mandible | 12 (43%)        | T1         | 7 (25%)             | N0             | 18 (62%)           |
|               | Lateral FOM, BOT, DM, OP      | 15 (52%)        | T2         | 11 (39%)            | N1             | 2 (7%)             |
|               | Larynx, hypopharynx           | 2 (7%)          | T3         | 4 (14%)             | N2             | 9 (31%)            |
| Korfage et al. [19] | FOM, tongue                   | 29 (58%)        | T1         | 6 (12%)             | N0             | 28 (56%)           |
|               | BOT, OP                       | 6 (12%)         | T2         | 21 (42%)            | N1             | 11 (22%)           |
|               | Mandibular gingiva            | 12 (24%)        | T3         | 10 (20%)            | N2             | 11 (22%)           |
|               | Tonsil                        | 3 (6%)          | T4         | 13 (26%)            |                |                    |
| Korfage et al. [30] | –                            | –               | –          | –                   | –              | –                  |
| Mizbah et al. [21] | –                             | –               | –          | –                   | –              | –                  |
| Schepers et al. [31] | FOM or tongue                | 13 (62%)        | –          | –                   | –              | –                  |
|               | Buccal mucosa                 | 1 (5%)          |            |                     |                |                    |
|               | Retromolar trigone            | 6 (28%)         |            |                     |                |                    |
|               | Lower alveolar ridge          | 1 (5%)          |            |                     |                |                    |
| Schoen et al. [32] | FOM                           | 1 (20%)         | T1         | 0 (0%)              | N0             | 1 (20%)            |
|               | BOT                           | 2 (40%)         | T2         | 0 (0%)              | N1             | 3 (60%)            |
|               | OP                            | 2 (40%)         | T3         | 4 (80%)             | N2             | 1 (20%)            |
|               |                               | T4              | 1 (20%)    |                     |                |                    |
| Schoen et al. [33] | FOM, tongue                   | 29 (58%)        | T1         | 6 (12%)             | N0             | 28 (56%)           |
|               | BOT, OP                       | 6 (12%)         | T2         | 21 (42%)            | N1             | 11 (22%)           |
|               | Mandibular gingiva            | 12 (24%)        | T3         | 10 (20%)            | N2             | 11 (22%)           |
|               | Tonsil                        | 3 (6%)          | T4         | 13 (26%)            |                |                    |
| Wetzels et al. [34] | FOM or tongue                | 10 (42%)        | T1         | 2 (8%)              |                |                    |
|               | Mandible                      | 11 (46%)        | T2         | 12 (50%)            |                |                    |
|               | Maxilla                       | 2 (12%)         | T3         | 1 (4%)              |                |                    |
|               |                               | T4              | 8 (38%)    |                     |                |                    |
| Wetzels et al. [35] | Tongue or FOM                | 56 (57%)        | T1         | 20 (21%)            | N0             | 60 (61%)           |
|               | Lower alveolar process        | 24 (25%)        | T2         | 43 (44%)            | N1             | 11 (11%)           |
|               | Maxilla                       | 6 (6%)          | T3         | 14 (14%)            | N2             | 27 (28%)           |
|               | Lip                           | 4 (4%)          | T4         | 21 (21%)            |                |                    |
|               | Cheek                         | 8 (8%)          |            |                     |                |                    |
| Woods et al. [20**] | –                            | –               | –          | –                   | –              | –                  |

BOT, base of tongue; DCIA, deep circumflex iliac artery flap; DM, dorsal maxilla; FFF, free fibular flap; FOM, floor of mouth; OP, oropharynx; OSCC, oral squamous cell carcinoma.
The study by Schoen et al. [32] showed an implant survival rate of 100% (16 of the 16 implants) with a mean follow-up of 25.2 months. Another study by Schoen et al. [33] reported a functionality of 61.3% (76 of the 124 implants) in the RTX-group. Three of these seven articles were included in the meta-analysis. To include the study by Wetzels et al. [35] in the meta-analysis, we received the following data, via personal communication, to distinguish between implants placed in the maxilla or grafted bone and the mandible: 182 implants were immediately placed in the native mandible, 94 of the 182 implants received RTX and 88 did not receive RTX. Eight of the 94 implants receiving RTX were lost and no implants were lost in the non-RTX group [35].

A total of 473 immediately placed dental implants received RTX and 37 dental implants were lost in this group. In the non-RTX group, five of the 372 dental implants were lost. There was no significant difference between the RTX and non-RTX group, with the forest plot (Table 5B) favouring the non-RTX immediately placed dental implants (risk ratio: 5.02, 95% CI: 0.92–27.38, \( P = 0.06, I^2 = 56\)).

**Reasons of dental implant failure**

Schoen et al. [32] inserted 20 implants and four of the implants (20.0%) were lost in one patient who died due to tumour recurrence. In the study by Ettl et al. [22], eight of the 165 dental implants (4.8%) placed in the maxilla and mandible were lost. The main reason for implant failure was progressive peri-implant bone loss. Four implants were lost due to lack of osseointegration (2.4%) and four more could not be incorporated into the superstructure (2.4%). Three of the four implants in the latter group were placed in a fibular transplant.

Korfage et al. [19] inserted 195 implants in the interforaminal region of the mandible. In this study, 14 of the 195 dental implants failed (7.2%). Thirteen out of the 14 implants (92.9%) were installed in irradiated bone. Eight of the 14 implants (57.1%) were lost after prosthetic loading; all eight implants were placed in patients who had received radiotherapy.

In another study by Korfage et al. [30], the authors evaluated the implant survival with a maximum follow-up of 14 years. Five hundred and twenty-four endosseous dental implants were placed. Excluding the implants loss as result of resection of a recurrent tumour, a total of 28 of the 524 placed implants failed (5.3%) during follow-up. Twenty-seven of these 28 lost implants (96.4%) were inserted in irradiated bone. Five patients developed ORN and 10 dental implants were removed.

In the study by Mizbah et al. [21], 24 of the 249 immediately placed implants were lost (9.6%), all due to a failing osseointegration. No statistical differences were seen between the postponed placed implants and the immediately placed implants regarding implant failure and postoperative radiation.

Schepers et al. [31] placed 139 dental implants during ablative surgery. Two implants failed (1.4%), both in the irradiated group, due to lack of osseointegration. Fifteen of the 61 dental implants in the irradiated group were not functional (24.6%).

Schoen et al. [33] lost four of the 200 (2.0%) inserted implants. Two of these (1.0%) failed in non-irradiated patients during the healing period prior to abutment connection. One irradiated patient lost two implants (1.0%) after abutment connection, but prior to the placement of the overdenture. No ORN was observed in the included patients.

Three of the 40 dental implants (7.5%) were lost in the study by Wetzels et al. [34]. Implant failure presented in two separate patients, one patient received radiotherapy and lost one implant due to peri-implantitis. The other patient did not receive radiotherapy and lost two implants, because of tumour recurrence.

Another study by Wetzels et al. [35] inserted 225 dental implants during surgery. Seventeen of the 207 implants (8.2%) were lost in 10 separate patients for different reasons, five implants were located in the maxilla and 12 in the mandible. Five implants (2.4%) were eliminated during surgery because of local tumour recurrence. Seven implants (4.1%) in four different patients were lost while being removed during segmental resection of the mandible due to ORN. Four other patients lost five implants (2.9%) due to peri-implantitis or failing osseointegration.

Woods et al. [20**] placed 39 dental implants immediately; one implant (2.6%) failed in this group. There was no significant difference regarding implant failure in native bone compared to a free flap. Also, no significance was found regarding implant loss between non-RTX and postoperative RTX patients.

**Overdentures**

Overdentures were fabricated and placed in the majority of the 10 included studies. The numbers of functional overdentures are summarized in Tables 3 and 4.

The main reasons described in these studies for dysfunctional overdentures and not placing an overdenture were implant failure, tumour recurrence,
| Ref.             | No. of irradiated/ nonirradiated patients | No. of irradiated/ nonirradiated implants | No. of patients receiving implants immediately/ delayed placement | No. of implants (no. of implants) | Implant tissue location (no. of implants) | Implant survival rate | Total implants lost (DAS/P) | No. of functional implants (%) | No. of functional overdentures (%) | Average time between operation and placement of overdenture | HBO2-therapy |
|-----------------|------------------------------------------|------------------------------------------|---------------------------------------------------------------|-----------------------------------|-------------------------------------------|----------------------|-----------------------------|-------------------------------|----------------------------------|---------------------------------|--------------|
| Mizbah et al. [21] | 64/64                                    | 151/163                                  | 99/29                                                        | 249/65                            | NB Mx and Mx                                      | 284 (90.4%)       | 30 (24/6)                      | 205/249 (82.3%) in DAS Group | 82/99 (82.8%) in P Group          | 7.4 months (mean) in DAS Group | Yes          |
| Wetzels et al. [34]   | 34/22                                    | Unknown                                  | 18/9                                                         | 40/19                             | NB (34 patients) Maxilla and mandible           | Unknown             | 27/40 (67.5%) after 5 years in DAS Group | 13 in DAS Group after 5 years | 27.4 months (mean) in P Group | 325 days in DAS Group | Yes          |
| Wetzels et al. [35]   | Unknown                                  | Unknown                                  | 79/18                                                        | 225/43                            | NB (135 patients) Maxilla (44) and mandible    | 248 (92.5%)       | 20 (17/3)                      | 173/225 (76.9%) in DAS Group | 61/62 (98.4%) in P Group after 5 years | 291 days in DAS Group | Yes          |
| Woods et al. [20**]  | 10/10                                    | 51/51                                    | Unknown                                                      | 39/63                             | NB (22 + FF) Maxilla and mandible               | 95 (93.1%)        | 7 (1/6)                        | 24/39 (61.5%) in DAS Group | 72.6 days in P Group | 321 days in DAS Group | Yes          |

DAS, placement during ablative surgery; DCIA, deep circumflex iliac artery flap; DM, dorsal maxilla; FFF, free fibular flap; GB, grafted bone; HBO2, hyperbaric oxygen therapy; MB, mandible; MX, maxilla; NB, native bone; P, postponed placement.
**Table 4. Radiotherapy vs. nonradiotherapy: dental implant survival and functionality and complications, based on the 10 included studies in the literature review**

| Ref. | No. of irradiated/nonirradiated patients | No. of irradiated/nonirradiated implants | No. of implants immediately/delayed placement | Implant tissue (no. of implants) | Implant location (no. of implants) | Implant survival (survival rate) | Total no. implants last (RTX/non-RTX) | No. of functional implants immediately placed | No. of functional overdentures (RTX/non-RTX) | Average time between operation and placement of overdenture | HBO2-therapy |
|------|----------------------------------------|----------------------------------------|---------------------------------------------|----------------------------------|-----------------------------------|----------------------------------|--------------------------------------|-----------------------------------------------|-----------------------------------------------|---------------------------------------------|----------------|
| Ettl et al. [22] | 20/9 | 110/52 | 0/165 | NB (147) FF or DCIA (18) | Maxilla (57) + mandible (108) | 157 (95.2%) | 8 (unknown) | 143/165 | 29 (unknown) | Unknown | Unknown |
| Korfage et al. [19] | 31/19 | 133/62 | 195/0 | NB | Mandible | 181 (92.8%) | 14 (13/1) | 76 implants after 5 years | 20 after 5 years (9/11) | Unknown | Unknown |
| Korfage et al. [30] | 100/64 | 318/206 | 524/0 | NB | Mandible | 496 (94.6%) | 28 (27/1) | Unknown | 138 (81/57) | 11.3 months in RTX-group | 6.2 months in n-RTX-group |
| Schepers et al. [31] | 21/27 | 61/78 | 139/0 | NB | Mandible | 137 (98.6%) | 2 (2/0) | 46/61 in RTX group | 36 (15/21) | Unknown | Unknown |
| Schoen et al. [32] | 4/0 | 16/0 | 16/0 | NB | Mandible | 16 (100%) | 0 (0/0) | 16/16 in RTX group | 4 (4/0) | Unknown | Unknown |
| Schoen et al. [33] | 31/19 | 124/76 | 200/0 | NB | Mandible | 196 (98.0%) | 4 (2/2) | 76 in RTX group with functional overdenture | 35 (19/16) | Unknown | Unknown |
| Wetzels et al. [35] | 39/39 | 94/88 | 182/0 | NB | Mandible | 174 (95.5%) | 12 (8/4) | Unknown | Unknown | Unknown | Yes |

DAS, placement during ablative surgery; DCIA, deep circumflex iliac artery flap; DM, dorsal maxilla; FFF, free fibular flap; GB, grafted bone; HBO2, hyperbaric oxygen therapy; MB, mandible; MX, maxilla; NB, native bone; n-RTX, not receiving radiotherapy; RTX, receiving radiotherapy.

**DISCUSSION**

The aim of this systematic review was to identify and appraise the treatment outcome of immediately placed dental implants in the context of cancer patients with head and neck cancer. The focus-free HNC patients prior to radiotherapy. The treatment outcome of immediately placed dental implants in the context of cancer patients with head and neck cancer. The focus-free HNC patients prior to radiotherapy. The treatment outcome of immediately placed dental implants in the context of cancer patients with head and neck cancer. The focus-free HNC patients prior to radiotherapy.
between the two groups. Furthermore, patients in whom the dental implants had been immediately placed, received their overdenture in an earlier stage [20**].

Abutment connection and implant loading in nonirradiated HNC patients usually take place at three months after RTX. In patients who received RTX, abutment connection is delayed up to 6 months post-RTX. On the basis of the literature, this extra time results in an improved healing ability of the bone, which will lead to a better osseointegration and reduces the risk of implant failure. However, the timing of abutment connection and the value of this additional 6-month healing period is still under debate [15,41,44–46]. No literature is available regarding one-stage dental implants in HNC patients receiving RTX. The use of one-stage implants avoids a second surgical procedure to connect the abutment, which leads to a reduction of total oral rehabilitation time.

Implant survival is affected by the anatomical site in which the implants are placed. Studies reported that implants placed in the mandible had a better outcome in terms of implant survival compared with those placed in the maxilla [40,47]. Apart from the anatomical site, implant positioning plays an important role. Dental implants placed in the posterior mandible are more prone to fail than implants in the anterior (symphyseal) region [11].

Studies also described that implant failure was statistically higher in grafted bone [fibula free flap (FFF), deep circumflex iliac artery (DCIA) flap, scapular free flap and radial forearm free flap] than in native bone [47–49]. In this review, studies were included describing dental implants placed in maxilla, mandible and grafted bone [20**,34,35]. It remains unclear whether the site of the inserted dental implants and the use of grafted bone affected the implant survival or functionality.

Radiation guidelines are variable since they depend on tumour type, location and stage. As the implementation of intensity-modulated radiation therapy (IMRT), the therapeutic dose commonly consists between 50 and 70 Gy [50]. There are no doubts regarding radiotherapy-induced side effects. However, it is not clear at which threshold the ionizing radiation affects dental implants. In this systematic review, the radiation dose ranges from 30 to 72 Gy, according to the therapeutic dose described earlier. Several studies reported a lower implant survival rate when the radiation dose exceeded 70 Gy compared with studies in which the dose remained below 50 Gy [19,36,51–53].

The effectiveness of HbO2-therapy is still a controversial topic. Due to its fibroblastic activity and the capability to create a matrix to encourage neo-vascularization, HbO2 therapy could be useful in treating and preventing ORN [54]. In this systematic review, the use of HbO2 therapy is described in five studies [20**,21,30,34,35]. However, the effect of the HbO2-therapy on implant survival in these studies remains unclear.

The limitations of the included studies are the lack of uniformity regarding the definitions of
implant survival, implant success and implant functionality. This also applies to the definition of overdenture functionality. In the 10 included studies, it is not clear whether ‘fabricated’ or ‘made’ overdentures were indeed functional. In other words, did patients indeed wear their overdentures. Regarding implant success, most studies described ‘failure’ if the dental implant was removed, but it was not clearly defined when the implants were functional. Only one study, performed by Ettl et al. [22] used the Albrektsson criteria to define implant success [23]. Furthermore, in this review, there is a wide variety in percentages regarding survival and functionality.

Apart from the heterogeneity regarding the definitions, the variety in survival and functionality rates could be explained by the diversity of included patients in terms of tumour stage and the wide range in the patients’ follow-up. As stated earlier, in some studies, dental implants were placed both in the maxilla and mandible and were not only placed in native bone, but also in FFF and DCIA [20*,22,34,35]. The results regarding implant survival rate and functionality could be influenced by the type of bone. For example, if dental implants were only placed in native bone, the survival rates and functionality could even be higher. On the basis of the suspected tumour location, patients undergo either panendoscopy as diagnostic procedure or ablative surgery as part of the curative treatment. Both procedures can be combined with (adjuvant) RTX, which carries the risk of the development of ORN. Patients receiving panendoscopy followed by RTX undergo the similar risks as patients receiving ablative surgery regarding dental status. However, in the literature, there are no studies available describing placement of dental implants during panendoscopy prior to RTX.

As there is a lack of comparable and uniform data, a lack of homogeneity regarding definitions in terms of implant success and overdenture functionality and the lack of literature regarding immediate dental implant placement during panendoscopy prior to radiotherapy, more research has to be performed and the development of a standardized protocol and a uniform postoperative evaluation methodology is advocated.

**CONCLUSION**

This systematic review demonstrates a high survival rate of dental implants placed during ablative surgery in HNC patients. Furthermore, patients with immediately placed dental implants did receive their overdentures earlier compared to patients with postponed placed implants. However, there is a lack of uniformity regarding the use of definitions in term of implant success and functionality. Because of a lack of homogeneity regarding implant sites (maxilla vs. mandible) and type of bone (native vs. grafted), a guideline needs to be considered to create uniformity with regard to immediate mandibular dental implant placement during surgical procedures (i.e. panendoscopy or ablative surgery) to allow further comparison between reported studies.

**Acknowledgements**

None.

**Financial support and sponsorship**

None.

**Conflicts of interest**

None of the authors have a conflict of interest regarding the techniques and materials described.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as: ■ of special interest ● of outstanding interest

1. Siegel RL, Miller KD, ‘Jemal A. Cancer statistics. CA Cancer J Clin 2019; 69:7–34.
2. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68:394–424. This article describes the global burden of cancer worldwide using the GLOBOCAN 2018 estimates of cancer incidence and mortality.
3. Gatta G, Botta L, Sancchez MJ, et al. Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: the EUROCARE-5 population-based study. Eur J Cancer 2015; 51:2130–2143.
4. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011; 61:69–90.
5. D’Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 2007; 356:1944–1956.
6. Maur S, D’Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. Lancet Oncol 2010; 11:781–789.
7. Stroussi HY, Epstein JB, Bensadoun RJ, et al. Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis. Cancer Med 2017; 6:2918–2931.
8. Schuurhuis JM, Stolkan MA, Rosendahl JL, et al. Efficacy of routine preradiation dental screening and dental follow-up in head and neck oncology patients on intermediate and late radiation effects. A retrospective evaluation. Radiat Oncol 2011; 101:403–409.
9. Schuurhuis JM, Stolkan MA, Witjes MJH, et al. Patients with advanced periodontal disease before intensity-modulated radiation therapy are prone to develop bone healing problems: a 2-year prospective follow-up study. Support Care Cancer 2018; 26:1133–1142.

In this prospective cohort study, the authors evaluated the effect of preradiation dental screening and elimination of dental foci in head and neck cancer patients receiving radiotherapy. This study shows the importance of dental screening and eliminating of dental foci prior to radiotherapy to reduce the risk of osteoradionecrosis, especially in patients with periodontal diseases.

10. Scibba JJ, Goldenberg D. Oral complications of radiotherapy. Lancet Oncol 2006; 7:175–183.
11. Pompa G, Saccuccio M, Di Carlo G, et al. Survival of dental implants in patients with oral cancer treated by surgery and radiotherapy: a retrospective study. BMC oral health 2015; 15:5.
12. Njeb J, Hertzman S, Svensson B, Johansson CB. Osseointegration of implants in irradiated bone with and without hyperbaric oxygen treatment: an experimental study in rat. Tibiae. Int J Oral Maxillofac Implants 2013; 28:739–746.
Immediate dental implant placement and restoration Veld et al.

13. Granstrom G. Placement of dental implants in irradiated bone: the case for using hyperbaric oxygen. J Oral Maxillofac Surg 2006; 64:812–818.

14. Larsen PE. Placement of dental implants in the irradiated mandible: a protocol involving adjunctive hyperbaric oxygen. J Oral Maxillofac Surg 1997; 55:967–971.

15. Granstrom G. Radiotherapy, osseointegration and hyperbaric oxygen therapy. Periodontol 2000 2003; 33:145–162.

16. Korfage A, Dijkstra PU, Rooodenburg JL, et al. Dental implants in irradiated patients: which factors influence implant survival? Clin Oral Investig 2015; 19:1689–1690.

17. Korfage A, Raghoebber GM, Rooodenburg JL, et al. Mandibular implants placed during ablative tumour surgery: which patients can benefit? Int J Oral Maxillofac Surg 2013; 42:1037–1039.

18. Korfage A, Schoen PJ, Raghoebber GM, et al. Five-year follow-up of oral function and quality of life in patients with oral cancer with implant-retained mandibular overdentures. Head Neck 2011; 33:831–839.

19. Korfage A, Schoen PJ, Raghoebber GM, et al. Benefits of dental implants installed during ablative tumour surgery in oral cancer patients: a prospective 5-year clinical trial. Clin Oral Implants Res 2010; 21:971–979.

20. Woods B, Schenker M, Chandu A. A comparison of immediate and delayed dental implant placement in head and neck surgery patients. J Oral Maxillofac Surg 2019; 77:1156–1164.

This study compared immediate and delayed dental implant placement in head and neck cancer patients. The authors described a high implant survival rate in the immediately placed group. This observation could be of interest in reducing the total oral rehabilitation time in head and neck cancer patients.

21. Mihal K, Dings JP, Kaanders JH, et al. Interfacial mandible implant placement in oral cancer patients: during ablative surgery or delayed? A 5-year retrospective study. Int J Oral Maxillofac Surg 2015; 44:651–655.

22. Enl T, Weindorl J, Gosau M, et al. Impact of radiotherapy on implant-based prosthetic rehabilitation in patients with head and neck cancer: a prospective observational study on implant survival and quality of life-preliminary results. J Craniomaxillofac Surg 2016; 44:1453–1462.

23. Albrektsson T, Zarb G, Worthington P, Eriksson AR. implants in irradiated oral cancer patients. A systematic review of the literature. Int J Oral Maxillofac Implants 2013; 28:1233–1242.

24. Collella G, Carnavale R, Penenterno M, Gandolfo S. Oral implants in irradiated patients: a systematic review. Int J Oral Maxillofac Implants 2007; 22:616–622.

25. Barbori AJ, Butterworth CJ, Rogers SN. Systematic review of primary osseointegrated dental implants in head and neck oncology. Br J Oral Maxillofac Surg 2011; 49:29–38.

26. Fletcher-Stark ML, Rubagodski AJ. The use of computer-aided manufacturing during the treatment of the edentulous mandible in an oral radiation therapy patient: clinical report. J Prosthet Dent 2011; 105:154–157.

27. Schoen PJ, Reintsema H, Raghoebber GM, et al. The use of implant retained mandibular prostheses in the oral rehabilitation of head and neck cancer patients. A review and rationale for treatment planning. Oral Oncol 2004; 40:862–871.

28. Sclaroff A, Haughey B, Gay WD, Paniello R. Immediate mandibular reconstruction and placement of dental implants. At the time of ablative surgery. Oral Surg Oral Med Oral Pathol 1994; 78:711–717.

29. Urken ML, Buchbinder D, Weinberg H, et al. Functional evaluation following microvascular oenoadontal reconstruction of the oral cancer patient: a comparative study of reconstructed and nonreconstructed patients. Laryngoscope 1991; 101:935–950.

30. Kwakman JM, Freihofer HP, van Waas MA. Osseointegrated oral implants in head and neck cancer patients. Laryngoscope 1997; 107:619–622.

31. Sammartino G, Marenzi G, Ceci I, et al. Implant therapy in irradiated patients. J Craniol Surg 2011; 22:443–445.

32. Marx RE, Morales MJ. The use of implants in the reconstruction of oral cancer patients, Dent Clin N Am 1998; 42:177–202.

33. Dhollam KP, Gaurav SV. Dental implants in irradiated jaws: a literature review. J Cancer Res 2012; 8 Suppl:1:585–593.

34. Shugaa-Addin B, Al-Shami HH, Al-Maweri S, Taraki B. The effect of radiotherapy on survival of dental implants in head and neck cancer patients. J Clin Exp Dent 2016; 8:e194–e200.

35. Laverty DP, Addison O, Wubie BA, et al. Outcomes of implant-based oral rehabilitation in head and neck oncology patients: a retrospective evaluation of a large, single regional service cohort. Int J Implant Dent 2019; 5:8.

36. Flores-Rui R, Castellanos-Cosano L, Sierra-Figallo MA, et al. Implant survival in patients with oral cancer: a 5-year follow-up. J Clin Exp Dent 2018; 10:e603–e609.

37. Van Gestel D, Van Den Weyngaert D, Schrijvers D, et al. Intensity-modulated radiotherapy in patients with head and neck cancer: a European single-centre experience. Br J Radiol 2011; 84:367–374.

38. Schoen PJ, Raghoebber GM, Bonna J, et al. Rehabilitation of oral function in head and neck cancer patients after radiotherapy with implant-retained dentures: effects of hyperbaric oxygen therapy. Oral Oncol 2007; 43:379–388.

39. Buddula A, Assad DA, Salinas TJ, et al. Survival of dental implants in irradiated head and neck cancer patients: a retrospective analysis. Clin Implant Dent Relat Res 2012; 14:716–722.

40. Visch LL, van Waas MA, Schmitz PT, Levendag PC. A clinical evaluation of implants in irradiated oral cancer patients. J Dent Res 2002; 81:856–859.

41. Marx RE, Ames JR. The use of hyperbaric oxygen therapy in bony reconstruc- tion of the irradiated and tissue-deficient patient. J Oral Maxillofac Surg 1982; 40:412–420.