REVIEW

OPEN

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

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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, $P=0.81$, $I^2=0\%$]. 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, $P=0.10$, $I^2=56\%$).

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,

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KEY POINTS

- Dental implant placement during ablative surgery is an effective treatment option in head and neck cancer patients.
- Radiotherapy does not significantly affect dental implant survival or functionality in HNC patients.
- A practical guideline needs to be considered to allow more uniformity with regard to oral rehabilitation protocols in HNC patients and thus comparison of treatment outcomes.

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 (HBO_2), 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▪▪,21]. 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 suppuration (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

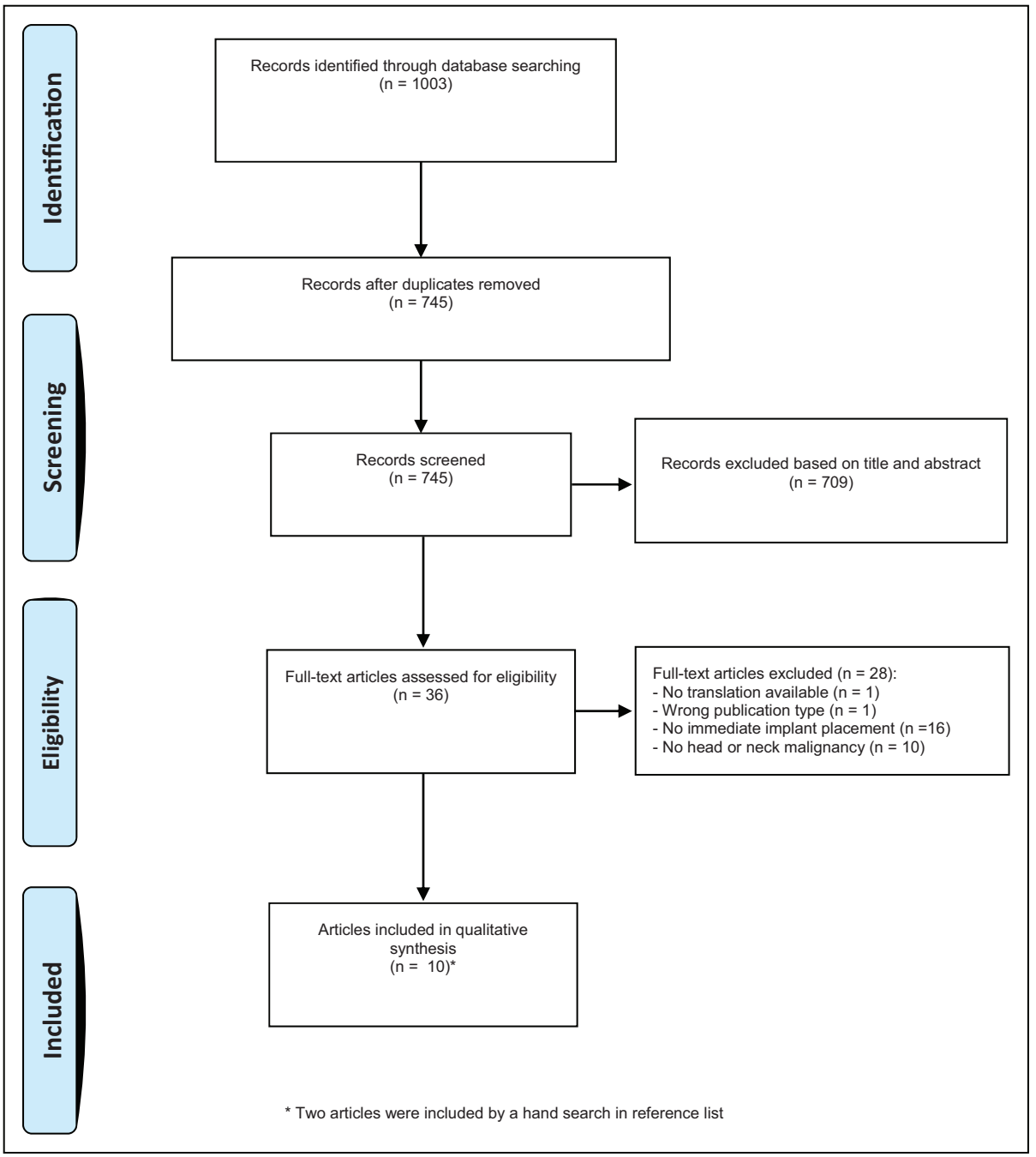


FIGURE 1. Flowchart of article selection process.

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

Table 1. Characteristics of the 10 included studies in the literature review

Ref.	Study type	Groups	No. of patients	Sex (M/F)	Age range (years)	Radiotherapy (None, pre, post)	Radiation dose (Gray)	Implant system	Implant type	Timing of implant placement (immediate, postponed or both)	Osseointegration period for abutment connection in months	Follow-up range (months)
Ettl *et al.* [22]	Prospective	RTX vs. non-RTX	52	38/14	48–82	None and post	40–72	Astra Tech	Osseospeed (ASTRA TECH Implant System, Molndal, Sweden)	Immediate	4–6	12 max.
Korfage *et al.* [19]	Prospective	RTX vs. non-RTX	50	35/15	41–81	None and post	> 40	NobelBiocare (Brånemark)	3.75 mm Brånemark screw implants with a machined surface (Nobel BioCare, Gothenburg, Sweden)	Immediate	3 or 9	60 max.
Korfage *et al.* [30]	Prospective	RTX vs. non-RTX	164	98/66	39–88	Post	Unknown	NobelBiocare (Brånemark)	3.75 mm Brånemark implants (Nobel BioCare, Gothenburg, Sweden), with a machined surface or a Ti-Unite surface	Immediate	3 or 9	174 (median 45.6)
Mizbah *et al.* [21]	Retrospective	DAS vs. P	510	294/216	Unknown	Post	> 60	NobelBiocare (Brånemark)	Brånemark Mk II/III two-phase implants or Frialit two-phase implants	Both	3 or 9	60 max.
Schepers *et al.* [31]	Retrospective	RTX vs. non-RTX	48	29/19	64.8 mean	None and post	> 60	NobelBiocare (Brånemark)	Brånemark Mk II/III two-phase implants	Immediate	Minimal 3	89 max.
Schoen *et al.* [32]	Prospective	RTX	5	3/2	48–69	Post	> 60	NobelBiocare (Brånemark)	Brånemark implants (Nobel BioCare, Gothenburg, Sweden)	Immediate	Minimal 3	13–40
Schoen *et al.* [33]	Prospective	RTX vs. non-RTX	50	35/15	41–81	None and post	> 30	NobelBiocare (Brånemark)	Brånemark implants (Nobel BioCare, Gothenburg, Sweden)	Immediate	3 or 9	24 max.
Wetzels *et al.* [34]	Prospective	DAS vs. P	56	33/23	69.6 mean	None and post	56–66	NobelBiocare (Brånemark)	Brånemark Mk III two-phase implants; Nobel BioCare, Gothenburg, Sweden.	Both	3 or 9	60 max.
Wetzels *et al.* [35]	Retrospective	DAS vs. P	193	104/89	67.3 mean	None and post	< 70	NobelBiocare (Brånemark) or Straumann or Astra Tech	Brånemark Mk III two-phase implants (Nobelbiocare, Gothenburg, Sweden), Straumann (Basel, Switzerland) or Osseospeed (ASTRA TECH Implant System, Molndal, Sweden)	Both	3 or 9	60 max.
Woods *et al.* [20▪▪]	Retrospective	DAS vs. P	20	13/7	17–91	None and post	–	Straumann or Neoss	ITI/Straumann (Basel, Switzerland) or Neoss implant (Neoss, Harrogate, UK)	Both	–	2–140

DAS, during ablative surgery; Gy, Gray; n-RTX, nonradiotherapy; P, postponed; RTX, radiotherapy.

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%)
			T4	6 (21%)		
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.

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.

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,

Table 3. Placement during ablative surgery vs. postponed placement of dental implants: implant survival 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 patients receiving implants immediately/ delayed	No. of implants immediate/ delayed placement	Implant tissue (no. of implants)	Implant location (no. of implants)	Implant survival (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	Mandible	284 (90.4%)	30 (24/6)	205/249 (82.3%) in DAS-group 59/65 (90.8) in P-group	82/99 (82.8%) in DAS-group 27/29 (93.1%) in P-group	7.4 months (mean) in DAS-group 27.4 months (mean) in P-group	Yes
Wetzels *et al.* [34]	34/22	Unknown	18/9	40/19	NB (34 patients) Plate reconstruction (7 patients) Obturator (9 patients) FF or DCIA (6 patients)	Maxilla and mandible	Unknown	Unknown	27/40 (67.5%) after 5 years in DAS group	13 in DAS-group after 5 years 9 conventional dentures in P-group after 5 years	325 days in DAS-group 396 days in P-group	Yes
Wetzels *et al.* [35]	Unknown	Unknown	79/18	225/43	NB (135 patients) Plate reconstruction (22 patients) Obturator (15 patients) FF or DCIA (21 patients)	Maxilla (44) and mandible (224)	248 (92.5%)	20 (17/3)	173/225 (76.9%) in DAS-group after 5 years 37/43 (86.0%) in P-group after 5 years	61/62 (98.4%) in DAS- group after 5 years 16/16 (100%) in P-group after 5 years	291 days in DAS-group 389 days in P-group	Yes
Woods *et al.* [20▪▪]	10/10	51/51	Unknown	39/63	NB (92) + FF (10)	Maxilla and mandible	95 (93.1%)	7 (1/6)	24/39 (61.5%) in DAS-group 56/63 (88.9%) in P-group	Unknown	321 days in DAS-group 726 days in P-group	Yes

DAS, placement during ablative surgery; DCIA, deep circumflex iliac artery flap; DM, dorsal maxilla; FFF, free fibular flap; GB, grafted bone; HBO_2, 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 immediate/ delayed placement	Implant tissue (no. of implants)	Implant location (no. of implants)	Implant survival (survival rate)	Total implants lost (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
Etl *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	Yes
Schepers *et al.* [31]	21/27	61/78	139/0	NB	Mandible	137 (98.6%)	2 (2/0)	46/61 in RTX group 59/78 in non-RTX group	36 (15/21)	Unknown	Unknown
Schoen *et al.* [32]	4/0	16/0	16/0	NB	Mandible	16 (100.0%)	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 64 in non-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.

inability to retrieve the implant(s), removal of the superstructure due to local irritation of the surrounding soft tissues and the impossibility of fabricating a prosthesis due to anatomical limitations.

DISCUSSION

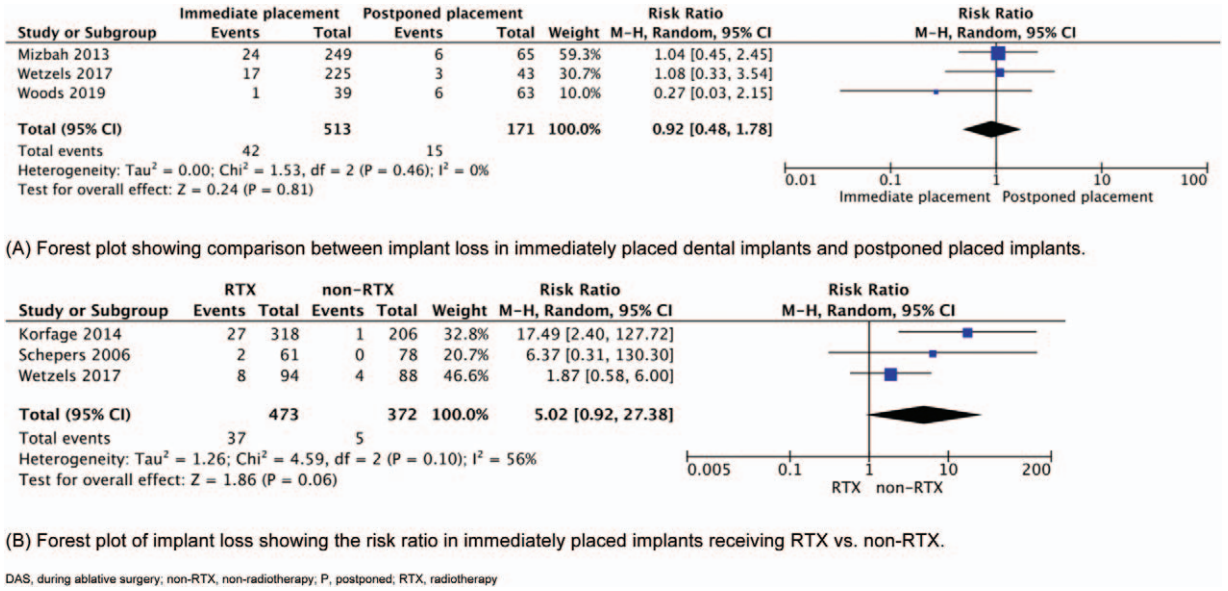
The aim of this systematic review was to identify and appraise the treatment outcome of immediately placed dental implants in the edentulous mandible during panendoscopy or ablative surgery in dental focus-free HNC patients prior to radiotherapy.

In this systematic review, the follow-up varies from 12 to 174 months. The dental implant survival rate varies between 92.8 and 100% and the implant functionality between 67.5 and 90.8%. The wide variety in percentages regarding implant and overdenture functionality depends on tumour location, tumour stage, patients' survival and the duration of follow-up. Another explanation of this variety in percentages regarding functionality is the lack of uniform definitions. Although strict inclusion and exclusion criteria were used, further heterogeneity was found in terms of the implant site (maxilla or mandible) and the implant bed (native or grafted bone).

In the literature, there is lack of consensus regarding the timing of dental implant placement in HNC patients, especially in relation to radiotherapy. The timing is an important topic regarding the success or failure of dental implants in terms of osseointegration. Nooh *et al.* [36] suggest that preoperative RTX increases the risk of ORN and subsequently lead to a lower implant survival rate. In contrast, some authors report a reduced risk of late complications, such as ORN, in immediately placed dental implants during tumour surgery and thus prior to irradiation [37,38]. Schepers *et al.* [31] reported that RTX did not affect the osseointegration of implants placed prior to RTX.

Disadvantages of immediate placement during ablative surgery are the risk of inappropriate implant positioning due to the altered anatomical situation. However, since the era of computer-assisted surgery and computer-guided implants, correct positioning of the dental implants during ablative surgery has been improved [39]. Clear advantages of dental implant placement prior to RTX are the following: osseointegration takes place before RTX; no second surgical intervention is needed; no implant surgery in the radiated area and the total oral rehabilitation time can be reduced [40–43]. Regarding the timing of implant placement, Mizbah *et al.* [21], Wetzels *et al.* [34] and Woods *et al.* [20▪▪] compared immediately placed dental implants with postponed placed implants receiving RTX. These studies concluded that implant failure and loading were comparable

Table 5. Forest plots displaying the results of the meta-analysis regarding implant loss



DAS, during ablative surgery; non-RTX, nonradiotherapy; P, postponed; RTX, 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 HbO_2-therapy is still a controversial topic. Due to its fibroblastic activity and the capability to create a matrix to encourage neovascularization, HbO_2 therapy could be useful in treating and preventing ORN [54]. In this systematic review, the use of HbO_2 therapy is described in five studies [20▪▪,21,30,34,35]. However, the effect of the HbO_2-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.

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Conflicts of interest

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

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- ▪▪ of outstanding interest

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