Dental status, dental treatment procedures and radiotherapy as risk factors for infected osteoradionecrosis (IORN) in patients with oral cancer – a comparison of two 10 years’ observation periods

Marcus Niewald1*, Kristina Mang2, Oliver Barbie3, Jochen Fleckenstein1, Henrik Holtmann4,5, Wolfgang J Spitzer4 and Christian Rübe1

Abstract

Objectives: Dental status, dental treatment procedures and radiotherapy dosage as potential risk factors for an infected osteoradionecrosis (IORN) in patients with oral cancers: Retrospective evaluation of 204 patients treated in two observation periods of approximately ten years each.

Patients and methods: In group A, 90 patients were treated in the years 1993-2003, in group B 114 patients in the years 1983-1992 (data in brackets). All patients had histopathologically proven squamous cell cancers, mainly UICC stages III and IV. 70% (85%, n.s.) had undergone surgery before radiotherapy. All patients were referred to the oral and maxillofacial surgeon for dental rehabilitation before further treatment.

Radiotherapy was performed using a 3D-conformal technique with 4-6MV photons of a linear accelerator (Co-60 device up to 1987). The majority of patients were treated using conventional fractionation with total doses of 60-70 Gy in daily fractions of 2 Gy. Additionally, in group A, hyperfractionation was used applying a total dose of 72 Gy in fractions of 1.2 Gy twice daily (time interval > 6 hours). In group B, a similar schedule was used up to a total dose of 82.8 Gy (time interval 4-6 hours). 14 (0) patients had radiochemotherapy simultaneously. After therapy, the patients were seen regularly by the radiooncologist and – if necessary – by the oral and maxillofacial surgeon. The duration of follow-up was 3.64 years (5 years, p = 0.004).

Results: Before radiotherapy, the dental health status was very poor. On average, 21.5 (21.2, n.s.) teeth were missing. Further 2.04 teeth (2.33, n.s.) were carious, 1.4 (0.3, p = 0.002) destroyed.

Extractions were necessary in 3.6 teeth (5.8, p = 0.008), conserving treatment in 0.4 (0.1, p = 0.008) teeth. After dental treatment, 6.30 (4.8, n.s.) teeth remained.

IORN was diagnosed after conventionally fractionated radiotherapy in 15% (11%, n.s.), after hyperfractionation in 0% (34%, p = 0.01).

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Conclusion: Within more than 20 years there was no improvement in dental status of oral cancer patients. Extensive dental treatment procedures remained necessary. There was an impressive reduction of the IORN frequency in patients treated in a hyperfractionated manner probably resulting from a dose reduction and an extension of the interfraction time.

Keywords: Oral cancer; Radiotherapy; Infected osteoradionecrosis; Dental status

Background
Infected osteoradionecrosis (IORN) is still one of the major problems after radiotherapy for neoplasms in the oral cavity. The chewing and swallowing functions of the patients are impaired, long-lasting conservative and surgical interventions may become necessary. In the last decades, there was an ample discussion about potential risk factors for the development of IORN. Besides the kind of surgical procedures, dosage and fractionation of radiotherapy and the simultaneous application of chemotherapy, the patients’ dental status before treatment and the extent of dental treatment procedures were regarded significant.

Thus, more than 20 years ago, the departments of Radiotherapy and of Oral and Maxillofacial Surgery of the Saarland University Medical School together started a dental examination and rehabilitation program with the aim to prevent IORN as far as possible. All patients referred for radiotherapy for cancer in the oral cavity were examined by the oral and maxillofacial surgeon, the exact dental findings were recorded and – if necessary, specific rehabilitation procedures were performed. Radiotherapy was started only after approval by the Oral and maxillofacial surgeon (OMF surgeon). After therapy, the patients were seen regularly by the radiooncologist, diagnosis and treatment of IORN were performed by the oral and maxillofacial surgeon.

After completion of two theses (Barbie 1997; Mang 2011), published in (Niewald et al. 1996; Niewald et al. 2013) each analyzing a ten years’ period of radiotherapy for oral cancer one after the other, we now had the unique possibility to reanalyze and to compare the data obtained in this very long observation period in terms of dental findings, dental rehabilitation procedures and the frequency of IORN.

Methods
Two groups of patients who had undergone radiotherapy for neoplasms of the oral cavity have been reanalyzed retrospectively:

Group A consists of 90 consecutive patients having been treated in the years 1993-2003.
Group B consists of 114 consecutive patients having been treated in the years 1983-1992 (data in brackets).

All patients suffered from squamous cell carcinoma of the oral cavity mainly in stages III and IV according to the Union Internationale contre le Cancer-(UICC)-definition, one patient had a local recurrence but had not been irradiated before. Patients with treated local or regional recurrences, distant metastases or with insufficient data were excluded. In group B, it seemed impossible to actualize the follow-up data, so that the data from the former analysis were taken. For this reason, no comparison of oncological results was attempted. In order to improve comparability, the inclusion criteria mentioned above were applied to both groups retrospectively which lead to the exclusion of several patients and a complete re-analysis of the data.

70% of the patients in group A (85%, n.s.) had undergone surgery for the primary tumor and the regional lymph node regions. After surgery or after biopsy all patients were referred to the oral and maxillofacial surgeon for assessment of the dental status including a meticulous clinical and x-ray examination. The dental treatment procedures were performed as early as possible with a minimal time interval of 7-10 days from the last procedure to the beginning of radiotherapy. All dental extractions were performed according to a written protocol under “special care” (primary tissue closure, perioperative antibiotics for 7-10 days beginning one day before surgery). In the nineties all patients were advised not to wear their dental prostheses up to 6-12 months after radiotherapy (today until complete healing of mucositis) (Curi and Dib 1997; Reuther et al. 2003). Radiotherapy was started after complete healing of the gingival wounds and thus approval by the OMF surgeon.

After production of a face mask for fixation, the computerized tomography for radiotherapy planning was performed, and the two-dimensional (up to 2000) or three-dimensional dose distribution was computed after target volume delineation. Radiotherapy was applied using 4-6MV photons (electrons for level V lymph node region) of a linear accelerator; a 60-Cobalt machine was in use additionally until 1987. In the majority of patients (n = 73 in group A, n = 74 in group B), conventionally fractionated radiotherapy was applied with total doses of 60-70 Gy (details see Table 1) in daily single fractions of 2 Gy. Furthermore, different hyperfractionated schedules...
| Item                                | Group A | Group B | Remarks |
|-------------------------------------|---------|---------|---------|
| Mean age (years)                    | 57.1    | 54.6    | n.s.    |
| Mean Karnofsky performance Index    | 7.8     | 7.5     | n.s.    |
| Follow-up (years)                   | 4.1     | 5.0     | p = 0.004 |
| T-stage                             |         |         |         |
| T1                                  | 14 (16%)| 20 (18%)| n.s.    |
| T2                                  | 33 (37%)| 49 (43%)|         |
| T3                                  | 8 (9%)  | 19 (16%)|         |
| T4                                  | 35 (38%)| 26 (23%)|         |
| N-stage                             |         |         |         |
| N0                                  | 20 (22%)| 46 (40%)| n.s.    |
| N1                                  | 23 (26%)| 24 (21%)|         |
| N2                                  | 47 (52%)| 30 (26%)|         |
| N3                                  | 0       | 14 (13%)|         |
| UICC stage                          |         |         |         |
| I                                   | 6 (7%)  | 10 (9%) | n.s.    |
| II                                  | 7 (8%)  | 22 (19%)|         |
| III                                 | 19 (21%)| 26 (23%)|         |
| IV                                  | 58 (64%)| 56 (49%)|         |
| Pre-treatment                       |         |         |         |
| None                                | 24 (27%)| 17 (15%)| p < 0.001 |
| Surgery                             | 66 (73%)| 97 (85%)|         |
| Total dose (Gy)                     |         |         |         |
| Conventional fractionation          | N = 75  | N = 73  | p < 0.001 |
| 30Gy (1)                            | 2Gy (1) |
| 36Gy (1)                            | 8Gy (1) |
| 50Gy (7)                            | 36Gy (1) |
| 58Gy (2)                            | 44Gy (1) |
| 60Gy (32)                           | 56Gy (1) |
| 64Gy (9)                            | 60Gy (31) |
| 70Gy (23)                           | 62Gy (1) |
| 66Gy (1)                            | 70Gy (31) |
| 72Gy (2)                            | 66Gy (1) |
| 76Gy (1)                            | 70Gy (2) |
| 80Gy (1)                            | 76Gy (1) |
| 87Gy (1)                            | 80Gy (1) |
| Hyperfractionation                  | N = 15  | N = 41  |         |
| 55.8Gy (1)                          | 13.2Gy (1) |
| 70.8Gy (1)                          | 81.6Gy (2) |
| 72.0Gy (11)                         | 82.8Gy (35) |
| 72.8Gy (1)                          | 85.2Gy (1) |
| 76.8Gy (1)                          | 85.5Gy (1) |
| 87.8Gy (1)                          | 87.8Gy (1) |
| Daily fraction                      |         |         |         |
| Conventional fractionation          | 2.0 Gy (74) | 2.0Gy (73) | p = 0.0012 |
| 3.0 Gy (1)                          |         |         |         |
| Hyperfractionation                  | 1.2 Gy (14) | 1.2 Gy (41) |         |
| 1.4 Gy (1)                          |         |         |         |
| Simultaneous chemotherapy           | 14      | 0       | p < 0.001 |
were performed in both groups: in group A (n = 46) a total
dose of 72 Gy was applied in single doses of 1.2 Gy twice
daily (interfraction interval > =6 hours) to patients with
formerly untreated tumors, in group B (n = 41) a total
dose of 82.8 Gy in single doses of 1.2 Gy twice daily (inter-
fraction interval 4-6 hours) was applied to patients with
untreated and with resected tumors. Two patients in
group A have been treated in a different manner (one with
1.4 Gy twice daily, another with a single dose of 3.0 Gy
once daily).

14(0) patients received chemotherapy consisting of cis-
platinum and 5-FU simultaneously due to their un-
favourable tumour and nodal stage. No patients with
chemotherapy were excluded from the evalution. During
therapy, the patients received dental care by the local
dental colleagues. Fluoridation was used according to
dental advice. Splints were not normally used because of
unfavourable experience of patients with aggravating ra-
diation mucositis by applying fluoride jelly to the gingiva
using these splints.

After radiotherapy, the patients were examined for
locoregional result and possible side effects in the De-
partment of Radiotherapy and Radiooncology. Dental
follow-up was performed by their local dentists. Conse-
quently, detailed data about this phase are not available.
Patients with a suspicion of IORN were referred to the
Dept. of Oral and Maxillofacial Surgery for further diag-
nosis and treatment.

The mean duration of follow-up was 3.64 years (5 years,
p = 0.004).

Infected osteoradionecrosis was minimally diagnosed
when necrosis of the gingiva on top of the eroded bone
became visible as infected mucosal ulcers with eroded
mandibular bone underneath according to grade 2 or
higher of the classification published by Schwartz et al.
(Schwartz and Kagan 2002). Patients with manifest IORN
were treated by the oral and maxillofacial surgeon in
cooperation with the local dentist.

The patients’ data were collected from the records in
the Departments of Radiotherapy and Radiooncology
and Oral and Maxillofacial Surgery. All (panoramic x-ray)
examinations available have been reviewed, thus we are
quite sure that a potential local recurrence has not been
misdiagnosed as an IORN. Furthermore, standardized
questionnaires were mailed to the patients’ general
medical practitioners and general dentists as well as the
local authorities five times within the observation period
in order to get additional data about freedom of local or
regional recurrence, survival or the onset of IORN.

All data were entered into a medical databank (Medlog™,
Parox, Muenster, Germany). Frequency distributions,
means and standard deviations were computed. The
groups were compared using the t-test (means) and the
Kruskal-Wallace test (distributions). Overall survival
and occurrence of IORN over time were computed
using the Kaplan-Meier estimate, the comparison of the

Table 2 Dental findings before radiotherapy

| Tooth (mean values, n=)               | Group A | Group B | Comparison: | Data available from n patients |
|---------------------------------------|---------|---------|-------------|-------------------------------|
| Absent                                | 22.0    | 21.2    | n.s.        | 204                           |
| Present                               | 10.1    | 10.8    | n.s.        | 204                           |
| Carious                               | 2.0     | 2.3     | n.s.        | 198                           |
| Deeply carious destroyed              | 1.4     | 0.3     | p = 0.002   | 200                           |
| Loose                                 | 1.6     | 2.2     | n.s.        | 197                           |
| Root remainders                       | 0.3     | 0.4     | n.s.        | 202                           |
| Devital                               | 0.5     | 1.0     | p = 0.023   | 200                           |
| Roots – filled completely             | 0.2     | 0.1     | n.s.        | 198                           |
| Roots – filled incompletely           | 0.3     | 0.1     | p = 0.006   | 199                           |
| Apical periodontitis                  | 0.3     | 0.2     | n.s.        | 200                           |
| Dentogenic cysts                      | 0.2     | 0.1     | n.s.        | 199                           |
| Retained teeth                        | 0.2     | 0.1     | n.s.        | 198                           |
| Superficial marginal periodontitis (patients) |       |         |             |                               |
| - Localized                           | 7 (8%)  | 33 (29%)| p = 0.002   | 199                           |
| - General                             | 10 (11%)| 16 (14%)|             |                               |
| Profound marginal periodontitis (patients) |       |         |             |                               |
| - Localized                           | 12 (14%)| 25 (22%)| p = 0.002   | 201                           |
| - General                             | 35 (40%)| 14 (12%)|             |                               |

Superficial marginal periodontitis: chronic periodontitis with less to moderate attachment loss.
Profound marginal periodontitis: chronic periodontitis with severe attachment loss.
groups was performed using the Mantel-Haenszel test. Prognostic parameters for IORN were analyzed univariately by comparison of means and distributions in a group containing the patients with IORN compared to another group with the patients who never experienced IORN using the t-test, u-test and chi-square test in the appropriate variables. Multivariate search for independent prognostic factors was performed by logistic regression.

Detailed biographical and oncological data have been summarized in Table 1.

All patients had given their written informed consent before dental examination and treatment as well as radiotherapy. The approval by the local ethics committee was dispensable due to the retrospective nature of this evaluation. This research is in compliance with the Declaration of Helsinki in its actual version.

Results

General remarks

In group A, up to July 2013, 58 patients were dead with a mean follow-up of 2.4 [0-8.8] years. The patients known to be alive were seen irregularly, the most recent information resulted from questionnaires, nearly all patients were lost to follow-up after on average 7.4 [0-15] years.

In group B, 77/114 patients were dead with a mean follow-up of 3.4 [0-11.7] years. The patients known alive were lost to follow-up after on average 8.5 [4.3-13.3] years.

Dental findings before radiotherapy

The patients’ dental status was generally poor. On average 10.1 (10.8) teeth were found present at the time of initial dental examination. For most of the criteria there was no statistically significant difference between the groups. However, we found significantly more destroyed teeth (1.4 vs. 0.3 teeth, \(p = 0.002\)) in the more recent patient collective. Furthermore there were more roots filled incompletely (0.3 vs. 0.1 teeth, \(p = 0.006\)). However, avital teeth were found less frequently in group A (0.5 vs. 1.0 teeth, \(p = 0.023\)). Chronic periodontitis with less to moderate attachment loss was found less frequently (\(p = 0.01\)) whereas chronic periodontitis with severe attachment

![Figure 1 Development of IORN over time (Kaplan-Meier estimate).](image-url)
We can summarize that dental status in these special patients has hardly changed over the decades. Data concerning dental biofilm or the use of dental prostheses had not been collected in group B, thus a comparison could not be performed.

Dental rehabilitation procedures
In the majority of criteria, the extent of dental rehabilitation procedures was identical in both groups. Tooth extractions were found more frequently in group B (3.7 vs. 5.8, p = 0.008) whereas conserving treatment was performed more frequently in Group A (0.6 vs. 0.1, p = 0.008). Detailed data are summarized in Table 3.

Frequency and risk factors of infected osteoradionecrosis (IORN)
IORN was found in the corpus region of the mandible in 11/90 patients (12%) of group A and 22/114 patients (19%) of group B (n.s.). The one-year prevalence was 5%, the two- and three-year prevalence 15%. A subgroup analysis dividing the collectives into two groups each with the patients having been treated with conventional fractionation or with hyperfractionation yielded the following results:

After conventional fractionation IORN was found in group A in 11/74 patients (15%), in group B in 8/73 patients (11%, differences n.s.). After hyperfractionation, IORN was not diagnosed in group A whereas it was observed in 14/41 patients (34%) in group B (p = 0.01).

The Kaplan-Meier estimate showed that IORN normally occurred in the first two years in group A (first five years in group B) after radiotherapy (differences n.s.), after that time the risk remained stable (Figure 1). The subgroup analysis mentioned above resulted in identical curves for patients irradiated conventionally and highly different (but not statistically significant) curves after hyperfractionation.

The search for prognostically significant factors for the occurrence of IORN was performed using the whole patient collective consisting of 204 patients. The number

Table 4 Prognostic factors for the occurrence of IORN (n = 204)

| Teeth | Univariate analysis | p-value | Remarks |
|-------|---------------------|---------|---------|
| Dental status before starting radiotherapy | | | |
| Absent | 0.110 | | |
| Present | 0.107 | | |
| Carious | 0.026 | Significant | |
| Deeply carious destroyed | 0.202 | | |
| Loose | 0.104 | | |
| Root remainders | 0.595 | | |
| Devital | 0.287 | | |
| Roots – filled completely | 0.949 | | |
| Roots – filled incompletely | 0.789 | | |
| Apical periodontitis | 0.888 | | |
| Cysts | 0.392 | | |
| Retained | 0.1620 | | |
| Conservative treatment possible | 0.430 | | |
| No conservative treatment possible | 0.179 | | |
| Filled | 0.751 | | |
| Not sufficiently filled teeth | 0.549 | | |
| Teeth with not sufficient crowns | 0.968 | | |
| Item | | | |
| Chronic periodontitis with less to moderate attachment loss | 0.418 | | |
| Localization | | | |
| General | | | |
| Chronic periodontitis with severe attachment loss | 0.210 | | |
| Localization | | | |
| General | | | |
| Dental treatment before radiotherapy | | | |
| Endodontic treatment | 0.379 | | |
| Removal of root remainders | 0.636 | | |
| Tooth extraction | 0.291 | | |
| Conserving treatment | 0.603 | | |
| Cystectomy | 0.936 | | |
| Healthy teeth remaining after dental rehabilitation | 0.158 | | |
| Demographic and oncological data | | | |
| Age | 0.106 | | |
| Karnofsky performance status | 0.625 | | |
| T-stage | 0.222 | | |
| N-stage | 0.040 | Significant | |
| Total dose | 0.005 | Significant | |
| BED2 | 0.040 | Significant | |
| Daily fraction | 0.036 | Significant | |

All remaining factors as mentioned in Tables 1 and 2 have been tested univariately and found insignificant, thus they were not tested multivariately.
of carious teeth, the N-stage, the total dose, the size of the daily fractions and the BED2 (Biologically effective dose 2 Gy) were found prognostically significant in univariate analysis. These factors were entered into the multivariate analysis where solely the number of carious teeth was found significant (details are depicted in Table 4). The multivariate analysis showed the number of carious teeth a nearly significant prognostic factor, furthermore, the fractionation was found to be trendwise significant. All further factors mentioned in Tables 1 and 2 tested univariately were found insignificant. Further details are depicted in Table 4.

We did not try to compare the oncological data like local and regional tumor outcome or survival because it seemed impossible to achieve reliable data for group B nearly 20 years after treatment. Thus, we could not correlate the frequency of IORN to a local recurrence.

Discussion
Dental health status and dental rehabilitation procedures
From our data we can summarize that – despite all effort in dental prophylaxis – the dental status of patients with oral neoplasms did not improve* over decades nor did the extent of dental rehabilitation procedures necessary before the start of radiotherapy.

The comparison of our data to those of the Forth German Trial of Oral Health (Kern et al. 2006) resulted in marked differences: In this study adults (33-44 years of age) on average 14.5 teeth were found carious, in older people (> = 45 years of age) 22.1 teeth. These teeth were rehabilitated completely in 95.6% and in 94.8%, respectively. A mean of 2.77 teeth in adults and of 14.2 teeth in older people were missing. 72% of the adults and 60.6% of the seniors were found to perform sufficient mouth hygiene. All these values were improved compared to the results of a former trial in 1997. On the other hand, the frequency of periodontitis was rising (moderate in 52.9% and intense in 39.8% of the population). Compared to those data our findings in patients with oral neoplasms were much more unfavourable and did not improve over time.

Further equally detailed analyses were rare. Jham et al. (Jham et al. 2008) reported in 2008 a collective of 207 patients with head and neck cancer with similar dental findings to our investigation detecting periodontal disease in 41%, retained roots in 21%, carious teeth in 12%, and unerupted teeth in 5.8% of their patients, resulting in an IORN rate of 5.5%. Schuurhuis et al. summarized 2011 the data of 185 patients and found oral infectious foci in 75%, a periodontal pocket depth of more than 6 mm in 23%, severe caries in 4%, impacted teeth in 4%, and residual root tips in 3%. Tooth extractions had to be performed in 30% of the patients, a mean of 7.7 teeth had to be removed. Periodontal treatment was performed in 6%. IORN was diagnosed in 11% (Schuurhuis et al. 2011). Further literature data on this topic have been summarized in Table 5. In general, tumor patients frequently showed a noncompliance in routine dental care and daily oral hygiene. Tumor diagnosis did not change the patients’ habits: Lockhart and Clark stated in 1994 that 97% of their patients needed dental care before radiotherapy, but only 81% underwent the indicated treatment.

| Author group                  | Dental status                                      | Rehabilitation procedures | Remarks                                                                 |
|-------------------------------|----------------------------------------------------|---------------------------|------------------------------------------------------------------------|
| Frydrych and Slack-Smith 2011 (n = 82) | No information                                    | No information            | Average (median) date of last dental visit: 66.76 months (18 months) before radiotherapy |
| Guggenheimer and Hoffman 1994 (n = 947) | Edentulous: 59%                                   | No information            |                                                                       |
|                               | Partially edentulous: 9%                           |                           |                                                                       |
|                               | Poor dentition with no replacement: 14%            |                           |                                                                       |
|                               | Intact dentition: 18%                              |                           |                                                                       |
| Maier et al. 1993 (n = 100)    | Tumour vs. control patients: Tartar > 3 mm: 40.91 vs. 21.98% | No information            | Tumour vs. control patients                                             |
|                               | Decayed teeth >50% : 27.2 vs. 3.9%                 |                           | Never tooth brushing 44.9 vs. 23.5%                                    |
|                               |                                                     |                           | Dental visit more than once a year: 6% vs. 43.5%                        |
| Lockhart and Clark 1994 (n = 131) | Alveolar bone loss: 66%                            | Needing dental care: 97%  | Noncompliant with routine dental care: 76%                             |
|                               | Clinical caries: 71%                               | Did not seek the indicated | Noncompliant with routine oral hygiene: 65%                            |
|                               | Failing restorations: 91%                          | treatment: 81%            |                                                                       |
| Jham et al. 2008 (n = 207)     | Periodontal disease: 41%                           | No information            |                                                                       |
Frequency of IORN
The frequency of IORN was almost equal in both groups. However, the influence of fractionation was interesting. The rates of IORN were identical after conventional fractionation over the decades. However, while in group B an unacceptably high amount of IORN was diagnosed after hyperfractionation, we did not see any IORN in group A. One reason may be the reduction of the total dose from 82.8 Gy to 72 Gy, another one the extension of the interfraction interval from 4-6 to generally >6 hours, this relevance of interfractional time intervals for cell recovery was not yet known during radiotherapy of group B patients (Fowler, J., personal communication, approx. 1988).

In the literature, the incidence of IORN varied widely (0-74%) as depicted in Table 6 whereas the majority of data are in a range of 5-10%. However, the comparison of these values to each other and to our results is very difficult because of a different definition of staging of IORN, different tumor localizations, therapy schedules, radiation techniques and dosages results fit well within the range of data taken from the literature (Kim et al. 1974; Niewald et al. 1996). One of the data sets in the literature most comparable to our dataset has been published by Lee et al. (Lee et al. 2008) who experienced comparable IORN frequencies in a collective of patients having been operated on mainly.

Risk factors for the occurrence of IORN
Numerous prognostic factors for the development of IORN have been tested and published. A selection of these is summarized in Table 7. The localization of the primary tumor in the oral cavity with its microbial colonization and the abundant involvement of the mandibular bone with its unique blood supply probably promotes IORN. Unfavorable dental status, periodontal disease and soreness of the gingiva by pressure triggered by dental prostheses are important as well as dental extractions before and especially after radiotherapy.

Radiation dose should not exceed 60 – 66 Gy to the mandibular bone whenever possible, the target volume extending to the bone should be limited. Some authors regard hyperfractionation as a risk factor for IORN. In our ancient publication on this topic (Niewald et al. 1996) we experienced a very high frequency of IORN after hyperfractionated radiotherapy which may have been caused by too high total doses on the one hand and a too short interfraction interval (time interval between the two daily fractions) on the other hand. Both factors have been taken into account since 1992, consequently the results were improved markedly.

Intensity modulated radiotherapy (IMRT) has been found advantageous compared to conventional 3D-planned radiotherapy. Additional factors may be chemotherapy, higher body mass index and the use of steroids.

An important paper has been published by Tsai et al. in 2013 (Tsai et al. 2012). They reviewed the records of patients with small oropharyngeal cancers having undergone radiotherapy or radiochemotherapy. The overall prevalence of IORN was 7.5%, higher doses, use of nicotine and alcohol, dental status as well as more advanced

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### Table 6 Incidence of IORN of the upper and lower jaw in the literature

| Author group          | Incidence | Remarks                                      |
|-----------------------|-----------|----------------------------------------------|
| Ben-David et al. 2007 | 0         | Multiple tumour localizations                |
| (n = 176)             |           | Primary treatment (no surgery)               |
|                       |           | IMRT                                         |
|                       |           | 108/176 radiochemotherapy                    |
| Berger and Bensadoun  | 1-5%      | Literature survey                            |
| 2010                  |           |                                              |
| Crombie et al. 2012   | 36%       | 53/54 radiochemotherapy                      |
| (n = 54)              |           |                                              |
| Gomez et al. 2011     | 1.2%      | Multiple tumour localizations                |
| (n = 168)             |           | IMRT                                         |
| Gomez et al. 2009     | 5%        | IMRT                                         |
| (n = 35)              |           |                                              |
| Jereczek-Fossa and Orecchia 2002 | 0.4-56% | Literature survey                            |
| Jham et al. 2008      | 5.5%      | Head and neck cancer                         |
| (n = 207)             |           |                                              |
| Katsura et al. 2008   | 15%       |                                              |
| (n = 39)              |           |                                              |
| Lee et al. 2008       | 6.6%      | Oral cavity and oropharynx                   |
| (n = 189)             |           |                                              |
| Monnier et al. 2011   | 40%       | Oral cavity and oropharynx                   |
| (n = 73)              |           |                                              |
| Oh et al. 2004        | 4.9%      |                                              |
| (n = 81)              |           |                                              |
| Reuther et al. 2003   | 8.2%      | Oral cavity and oropharynx                   |
| (n = 830)             |           |                                              |
| Stenson et al. 2010   | 18.4%     | Surgery, adjuvant radiochemotherapy          |
| (n = 27)              |           |                                              |
| Storey et al. 2001    | 6%        | Malignant submandibular tumours              |
| (n = 83)              |           |                                              |
| Studer et al. 2011    | Grade 2   | Oral cavity and oropharynx                   |
| (n = 304)             | EORTC: 1.6%| Conventional dental care vs. risk-adapted dental care|
| Thiel 1989            | 4.35%     | Literature survey                            |
| Thorn et al. 2000     | 74%/3 years| Multiple tumour localizations                |
| (n = 80)              |           |                                              |
| Tsai et al. 2012      | 7.5%      | Oropharyngeal cancer, median time to IORN 8 months|
| (n = 402)             |           |                                              |
| Turner et al. 1996    | 5.9%      |                                              |
| (n = 333)             |           |                                              |
| Author group                      | Risk factor(s)                                                                 | Remarks                                                                 |
|----------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Ahmed et al. 2009                | Intensity modulated radiotherapy (IMRT) advantageous compared to conventional radiotherapy |                                                                         |
| Berger and Bensadoun 2010        | Total dose >66 Gy                                                             | Literature survey                                                       |
| Bhide et al. 2012                | Total dose > 60 Gy                                                            | Literature survey                                                       |
|                                 | Volume of mandible within the treatment field. Trauma related ORN after lower doses |                                                                         |
| Chopra et al. 2011               | White ethnicity                                                               |                                                                         |
|                                 | Secondary infection                                                          |                                                                         |
|                                 | Advanced age                                                                 |                                                                         |
|                                 | Stage IV                                                                     |                                                                         |
|                                 | Total dose                                                                   |                                                                         |
|                                 | Post-RT dental extractions                                                   |                                                                         |
|                                 | Lack of pre-RT dental extractions                                           |                                                                         |
| Curi and Dib 1997, 2007          | Oral cancer                                                                  |                                                                         |
|                                 | Invasion of bone                                                             |                                                                         |
|                                 | Tumour surgery                                                               |                                                                         |
|                                 | Total radiation dose                                                          |                                                                         |
|                                 | Dose rate/day                                                                |                                                                         |
|                                 | Mode of radiation delivery                                                   |                                                                         |
|                                 | Dental status                                                                |                                                                         |
|                                 | Time from radiation therapy until the onset of ORN                           |                                                                         |
| Goldwasser et al. 2007           | Higher body mass index                                                        | Multivariate analysis                                                   |
|                                 | Use of steroids                                                              |                                                                         |
|                                 | Radiation dose >66 Gy                                                        |                                                                         |
| Jereczek-Fossa and Orecchia 2002 | Total dose                                                                   | Literature survey, only part of the factions mentioned in the paper cited here |
|                                 | Brachytherapy dose                                                            |                                                                         |
|                                 | Dose per fraction                                                            |                                                                         |
|                                 | Interval between fractions                                                   |                                                                         |
|                                 | Volume of the horizontal ramus of the mandible irradiated with a high dose   |                                                                         |
|                                 | Dental status                                                                |                                                                         |
|                                 | Bad oral hygiene                                                             |                                                                         |
|                                 | Dental extractions after radiotherapy                                         |                                                                         |
| Katsura et al. 2008              | Oral health status after radiotherapy                                         |                                                                         |
|                                 | Periodontal pocket depth                                                     |                                                                         |
|                                 | Dental plaque                                                                |                                                                         |
|                                 | Alveolar bone loss level                                                     |                                                                         |
|                                 | Radiographic periodontal status                                              |                                                                         |
| Lee et al. 2009                  | Univariate: Mandibular surgery                                               | Multivariate analysis:                                                 |
|                                 | Co-60                                                                         | Mandibular surgery                                                      |
|                                 | BED >106.2 Gy                                                                | BED >106.2 Gy                                                          |
| Lozza et al. 1997                | Dose rate                                                                    | Brachytherapy exclusively                                               |
|                                 | Reference volume                                                             |                                                                         |
tumors were found significant risk factors for the development of IORN. In contrast to this paper our patients’ primary situation seems more unfavorable: we only examined patients with oral cancer where the whole mandible was within the 100%-isodose, thus we applied even higher doses to a large amount of bone. Furthermore, older techniques have been used; unfortunately, no information about fractionation has been given. Consequently, a higher prevalence of IORN here seems to be explainable.

Unfortunately, we did not succeed in identifying clearly significant independent prognostic factors for the development of IORN. In our patient collective, hyperfractionation seemed to have a protective effect whereas this could not be examined further due to the small number of events. In our dataset the number of carious teeth was found to be the only independent prognostic factor after multivariate analysis. Univariate, total dose and BED2 were significant which could be expected. In majority of patients, the total doses lie in a narrow range of 60-82 Gy which may have been a reason for the result, additionally the fact that few IORN cases have been observed.

The authors are well aware of the limitations of this retrospective evaluation. In this nearly homogenous collective of patients with oral cavity cancer having
The patients’ dental status before radiotherapy was very poor compared to an otherwise healthy population. Apparently we did not succeed in improving these findings over the decades despite all effort in terms of dental prophylaxis. Consequently, extensive dental rehabilitation procedures had to be performed which did not change over time as well.

Examining patients irradiated with conventional fractionation, the incidence of IORN was found constant in a range of 10-15% over time. As stated earlier, the influence of the interfraction interval and of very high doses became known after the patients in group B had been irradiated, we thus diagnosed an unacceptably high frequency of IORN which became virtually zero after reduction of the total dose and extension of the interfraction interval. The multivariate search for prognostic factors only resulted in the assumption that dental status and fractionation could influence the occurrence of IORN.

Conclusions

The patients’ dental status before radiotherapy was very poor compared to an otherwise healthy population. Apparently we did not succeed in improving these findings over the decades despite all effort in terms of dental prophylaxis. Consequently, extensive dental rehabilitation procedures had to be performed which did not change over time as well.

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Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

MK supervised the theses written by KM and OB. and wrote the manuscript. KM collected and evaluated the data in collective A. OB. collected and evaluated the data in collective B. J.F. was mostly responsible for planning and delivering of radiotherapy, furthermore he corrected and approved the manuscript. H.H. corrected and approved the manuscript from the viewpoint of an oral and maxillofacial surgeon. W.J.S. supervised dental diagnosis and treatment and revised the manuscript. C.R. supervised radiotherapy and revised the manuscript. All authors read and approved the final manuscript.

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