

Dental loss after radiotherapy for head and neck cancer

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Key points

Identifies specific risk factors for tooth loss in a cohort of post-radiotherapy patients.

Aims to improve recognition and awareness of the condition which has an increasing incidence in post-radiotherapy patients.

This study is innovative in the degree of radiotherapy dose-mapping for individual teeth.

Reflects the need for specialised dental aftercare in these post-radiotherapy patients, at a level not currently provided.

Abstract

Introduction In radiotherapy (RT) for head and neck cancer (HNC), dental morbidity is significant and it may result in loss of the dentition following treatment.

Aims The aim of this clinical study is to identify the incidence of tooth loss over time and correlate this to the RT dose and various risk factors in patients with HNC treated with radical RT.

Design A retrospective observational study.

Materials and methods The records of 1,118 patients with HNC treated with radical or adjuvant RT from January 2010 to December 2019 were analysed. After applying strict inclusion criteria, 78 patients with 1,566 individual tooth data were selected. RT dose mapping was performed for each tooth.

Results A total of 253 teeth (16.2%) were extracted. The following risk factors were significant: gender ($p = 0.0001$), xerostomia ($p < 0.0001$), RT dose ($p < 0.0001$) and smoking ($p < 0.0001$). Non-significant factors were age, RT delivery technique and the addition of cisplatin.

Conclusion Detailed RT dose mapping was used to identify RT dose as a risk factor for dental loss. Careful pre-RT dental treatment and minimisation of RT dose to teeth and salivary glands is required to prevent or reduce the loss of dentition.

Introduction

More than 600,000 patients are diagnosed with head and neck cancer (HNC) each year worldwide. The survival rates have improved significantly in recent decades and therefore the number of HNC survivors is growing.¹ This increasing number of survivors raises additional challenges, including a higher prevalence of dental complications.

Radiation-related oral toxicity can be acute or late. Acute oral side effects begin

during radiotherapy (RT) and last for several weeks following completion of the treatment. These are oral mucositis, taste disorder and xerostomia. Late oral effects begin several weeks, months, or even years after RT and include trismus, taste disorder, xerostomia, radiation-induced dental caries leading to tooth loss, and osteoradionecrosis.^{2,3,4,5,6}

During the last decade, few studies have attempted to identify various risk factors causing dental loss. These risk factors are: patient-related risk factors – age, gender, primary site of the tumour, oral hygiene, frequency of intake of dietary carbohydrates and treatment-related risk factors – total dose of RT and the presence or absence of xerostomia.^{7,8,9,10}

The aim of this single-centre, retrospective, observational clinical study was to identify the incidence of tooth loss over time and correlate this to RT dose and various risk factors in patients with HNC treated with radical RT.

Material and methods

Patient population

Strict inclusion criteria were applied for the purpose of this study. They included:

- Pre-RT dental assessment by a consultant/specialist restorative dentist in a regional dental hospital
- RT prescribed dose to the tumour target ≥ 55 Gy
- Regular review by a dental hygienist during RT
- Regular follow-up by a dental hygienist and dental team post-RT
- Date and exact tooth location of extracted teeth
- RT dose mapping available for all teeth
- The absence of any local disease recurrence.

The records of 1,118 patients with HNC treated with radical or adjuvant RT from January 2010 to December 2019 were analysed.

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All patients with less than three months' follow-up ($n = 183$), edentulous patients before diagnosis ($n = 116$), patients who required completed dental clearance as a part of pre-RT preparation ($n = 90$), patients with local recurrence ($n = 181$) and patients with incomplete records ($n = 470$) were excluded from the study.

This resulted in 78 patients with 1,566 teeth in whom all the details of post-treatment interventions were available. Dose mapping was performed and exact dose of RT in each of the 1,566 teeth was obtained. All these patients have been under the care of a dental hygienist with regular dental checks during and after the RT. All patients have been provided with toothpaste with high fluoride content. All patients have been followed post-RT by the head and neck surgical team; all extractions have been performed at the regional dental hospital where records of dental interventions with images were available.

Radiotherapy treatment

All patients received either definitive primary RT or adjuvant RT post-operatively, either with or without the addition of concomitant chemotherapy. The patients underwent a planning computed tomography [CT] scan using 3–5 mm thick slices. Twenty-six patients (33.3%) were treated using 3D conformal radiotherapy (3D CRT) and 52 patients (66.7%) were treated with intensity-modulated radiotherapy (IMRT). A total dose of 55–65 Gy was administered in 20–30 daily fractions.

Xerostomia

The degree of xerostomia was assessed according to the RTOG/EORTC late radiation morbidity scoring schema.¹¹

Dental evaluation and treatment

Prior to the start of RT, all patients received a comprehensive dental evaluation by our specialist restorative dentistry clinicians according to national guidelines.^{12,13,14}

Out of a total of 78 patients included in the final analysis, 40 patients required dental extractions before RT. Median number of extracted teeth was three (range: 1–14). Table 1 summarises the details of pre-RT dental extractions.

During the course of RT, dental care was provided by a dedicated dental hygienist to reinforce oral hygiene measures and perform non-surgical periodontal therapy, and addition of fluoride varnish if caries was evident. Three

Table 1 The details on pre-radiotherapy dental extractions

Number of extracted teeth before RT	Number of patients	% of patients
1	4	10.0
2	7	17.5
3	11	27.5
4	5	12.5
5	4	10.0
6	3	7.5
7	2	5.0
8	2	5.0
12	1	2.5
14	1	2.5
Total	40	100%

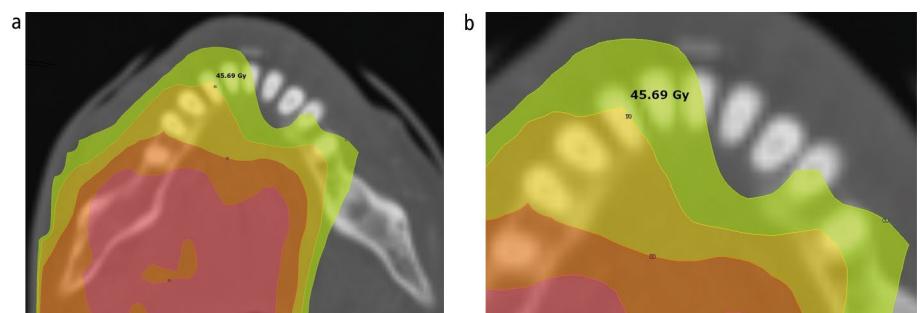


Fig. 1 Example of dose mapping: sectional cut of mandibular plan showing the exact dose to the right lower incisor (colours represent areas with the same percentage of total dose – for example, green area represents 60% of prescribed radiotherapy dose)

to six months post-treatment, all patients had at least one follow-up review under the care of the restorative dental team and had subsequent follow-up, if required.

Post-treatment follow-up

After completion of treatment, all patients had follow-up every three months for the first two years, then every six months for the next three years either by the head and neck or maxillofacial surgical teams. During follow-up, appropriate radiological investigations were carried out, as clinically indicated.

Dosimetric information

Dose mapping has been performed and the exact dose of RT to each of the 1,566 teeth was obtained. RT treatment plans were reconstructed and dose distribution analysed. Knowing the precise location of each tooth, exact RT dose mapping was performed to explore the relationship of RT dose distribution

with the extraction site. Datasets from previously irradiated patients were exported from their respective planning systems (Oncontra Masterplan, Accuray Tomotherapy or Raystation) and imported into Raystation V7.0 along with relevant diagnostic CT. The treatment plans have been reconstructed and exact dose in the centre of each tooth has been established by a radiation oncologist (JK) and a dentist (JPK). Figure 1 demonstrates an example of RT dose mapping.

Socioeconomic status

The data on socioeconomic status of patients were obtained using the Consumer Data Research Centre (CDRC) UK website.¹⁵

Statistics

Statistical analysis was performed using MedCalc (Medical Calculations Software Ltd. Ostend, Belgium) version 18.10.2. A p value <0.05 was considered statistically significant.

Results

Seventy-eight patients were included in the study. The median age of the whole group was 62.0 years (range: 35–82). The median follow-up was 58 months (range: 7–116). In total, 15 patients had died (19.2%). Out of these, four died of metastatic disease (26.7%) and the remaining 11 patients (73.3%) died disease-free. Sixty-three patients (80.8%) are alive. The detailed demographics of the patient cohort are summarised in Table 2.

Out of a total of 1,566 teeth, 253 (16.2%) were extracted; 105 were extracted from the maxilla (41.5%) and 148 (58.5%) from the mandible. The average number of teeth extracted per patient was 3.2 (median 1.5, range 1–21). Out of the 1,313 teeth preserved, 628 (47.8%) were in the maxilla and 685 (52.2%) were in the mandible. The median interval between completion of RT and extraction was 25.0 months (range: 1–101 months). Out of the 253 teeth extracted, 173 were extracted because of extensive caries while 67 were extracted because of periodontal disease. Two teeth were extracted because of location above osteoradionecrosis, one tooth was extracted because of prosthetic work (denture) and one tooth was causing trauma to adjacent buccal mucosa. In eight teeth, the reason for extraction has not been recorded. The information on the location of all extracted teeth by quadrant and RT dose related to each extracted tooth is summarised in Table 3. Our analysis showed that there was a decrease in the number of teeth surviving over time in absolute terms (Fig. 2). A steep decrease in tooth survival within the first four years after RT, with then subsequent slower decrease, was demonstrated. Figure 3 shows the decrease in teeth survival in relative terms, as percentage post-RT.

Risk factors

Age (≤ 60 years versus >60) was not a risk factor ($p = 0.058$). Female patients were prone to having more extractions when compared to their male counterparts ($p = 0.0001$, Fig. 4). Smoking status was a risk factor, tooth extraction being more common in smokers ($p < 0.0001$). The RT delivery method (that is, 3D CRT versus IMRT) was not a risk factor ($p = 0.270$), nor was the addition of systemic cisplatin therapy to RT ($p = 0.230$). However, addition of cetuximab systemic therapy, as compared to cisplatin, was a risk factor ($p < 0.0001$), although there were only five

Table 2 Demographics, treatment and risk factors of the cohort

Total number of teeth: 1,566		Patients	Teeth extracted	Teeth preserved	P value
N		78	253	1,313	–
Gender	Female	24 (30.8%)	102 (40.3%)	368 (28.0%)	0.0001
	Male	54 (69.2%)	151 (59.7%)	945 (72.0%)	
Age (years)	≤ 60	37 (47.4%)	144 (56.9%)	662 (50.4%)	0.058
	>60	41 (52.6%)	109 (43.1%)	651 (49.6%)	
Method of RT	3-DRT	26 (33.3%)	98 (38.7%)	461 (35.1%)	0.270
	IMRT	52 (66.7%)	155 (61.3%)	852 (64.9%)	
Systemic treatment	No	27 (34.6%)	73 (28.9%)	429 (32.7%)	0.230
	Yes	51 (65.4%)	180 (71.1%)	883 (67.3%)	
Systemic treatment	No	27 (34.6%)	73 (28.9%)	429 (32.7%)	<0.0001
	Cisplatin	46 (59.0%)	135 (53.4%)	852 (64.9%)	
	Cetuximab	5 (6.4%)	45 (17.8%)	31 (2.4%)	
Xerostomia (grade)	0	33 (42.3%)	84 (33.2%)	624 (47.5%)	0.0001
	I	25 (32.1%)	93 (36.8%)	391 (29.8%)	
	II	18 (23.1%)	74 (29.2%)	271 (20.6%)	
	III	2 (2.6%)	2 (0.8%)	27 (2.1%)	
Xerostomia	No	33 (42.3%)	84 (22.3%)	624 (47.5%)	<0.0001
	Yes	45 (57.7%)	169 (66.8%)	389 (52.5%)	
Dose of RT (Gy)	<40		91 (36.0%)	900 (68.5%)	<0.0001
	40–60		111 (43.9%)	316 (24.1%)	
	>60		51 (20.2%)	97 (7.4%)	
Dose of RT (Gy)	Mean		44.2	33.9	<0.0001
	Median (range)		45.7 (1–66)	31.9 (1–67)	
Smoking	Non-smoker	24 (30.8%)	60 (23.7%)	485 (36.9%)	<0.0001
	Smoker	22 (28.2%)	112 (44.3%)	291 (22.2%)	
	Ex-smoker*	26 (33.3%)	67 (26.5%)	431 (32.8%)	
	Unknown	6 (7.7%)	14 (5.5%)	106 (8.1%)	

Key:
* = no smoking for >6 months.

patients who received cetuximab. Both the presence of xerostomia ($p < 0.0001$) (Fig. 5) and its severity (grade I versus II versus III; $p = 0.0001$) were independent risk factors. RT dose to the extracted tooth (<40 Gy versus 40–60 Gy versus >60 Gy) was also a risk factor ($p < 0.0001$), with the higher doses of RT (>60 Gy) more likely to result in dental extractions and lower doses of RT (<40 Gy) less likely to result in tooth loss (Fig. 6). These data are summarised in Table 2.

We also studied the impact of socioeconomic status on number of teeth extracted using the CDRC map (Index of Multiple Deprivation 2019).¹⁵ In total, 12 (15.4%) patients were identified with low socioeconomic status (lowest decile) as compared to the remaining 66 patients (84.6%) from non-deprived areas. There was no difference in the two groups (median number of teeth extracted per patient

from areas of deprivation was 1.5 with range: 1–21 versus median of 1.5; range 1–19 in patients from non-deprived areas; $p = 0.988$).

Discussion

The risk of dental loss is life-long and therefore maintenance of adequate oral hygiene, presence of salivary flow and managing frequency of dietary carbohydrate in this patient population is of paramount importance over time.⁸ RT has an indirect and a direct destructive effect on dental tissue. The most widely accepted aetiology of post-radiation dentition breakdown is the indirect effect of radiation-induced xerostomia.^{4,16} However, in areas of high radiation dose, a direct effect is thought to occur.⁹

The impact of xerostomia on tooth loss was as expected. RT-induced salivary gland damage significantly contributes to the development

of dental caries due to deterioration in quality and quantity of saliva. As a result of the combination effect of decreased salivary flow and its poorer composition, it causes a change in the concentration of the chemical

constituents in saliva. This leads to a rise in proteins within saliva while the bicarbonate concentration decreases. The consequences of this process are a decrease in salivary pH and buffering capacity. This reduction in salivary

pH (7.0 to 5.0) leads to a more cariogenic environment, resulting in tooth enamel demineralisation and dentin fragility.^{16,17} The protective role of saliva is thus reduced. The consequence of this process is a permanent change in oral flora, which ultimately becomes more cariogenic with a greater likelihood of the development of cariogenic-associated species; for example, *Streptococcus mutans* and *Lactobacillus*.⁸

Radiation-induced xerostomia with dietary carbohydrates in dental plaque may result in tooth loss. It is also thought that RT causes decreased circulation through the pulp, leading to fibrosis and degeneration of the odontoblast processes. The involved teeth become discoloured and demineralised, with erosions in the cervical region, which allows them to fracture more easily. Tooth damage seems to occur at RT doses greater than 60 Gy.⁹ In doses between 30–60 Gy, there appears to be a 2–3 times increase in tooth damage that is likely to be related to salivary gland impact.⁷ Our analysis showed that there was significant difference in development of tooth loss between the group of patients treated with RT doses <40 Gy, 41–60 Gy and >60 Gy and it confirms the hypothesis that the destructive effect on tooth structure is dose-dependent, as described by other studies.^{16,17} Our study describes the dynamics of dental loss in time, which according to the best of the authors' knowledge has not been described before. For all patients, the tooth survival curve is steep in the first four years after treatment (Figures 2 and 3). A detailed analysis of impact of RT dose revealed that for those teeth which received the lowest dose of RT (<40 Gy), the curve becomes almost flat after two years post-treatment. For the teeth which received an intermediate RT dose (40–60 Gy), tooth loss was continuous during the first four years which was followed by a plateau. However, for the teeth exposed to a high RT dose (>60 Gy), there was continuous tooth loss during the first four years, more marked than in the teeth exposed to intermediate RT dose, and that loss continued beyond four years (Fig. 6).

In this study, a significant impact of gender on tooth loss was surprising; women were more prone to have tooth loss compared to men. A review of the literature has not revealed any record of higher incidence of dental decay in women. At the present level of knowledge, it is not possible to explain why women are more prone to tooth loss and this finding requires further research.

Table 3 Sites of extractions with total dose (Gy)

Dose of RT per quadrant															
Dose of RT of teeth of the upper right quadrant															
18	49.1	55.7	62.2	62.3	63.6										
17	45.4	45.7	48.5	51	54.7	62.1	62.6	63.5							
16	23.4	25.1	33.5	36.1	40.9	44.4	45.8	46.9	57.3	60.4					
15	1.14	27.5	28.4	40.1	42.6	51	57	62.2							
14	14.7	23	24.5	36.9	36.9	47.2	56.8	61.3							
13	34.2	36.6	44.2	48.4											
12	5.8	25.6	31.7	35.6											
11	30.7	30.7	31.9	49.6											
Dose of RT of teeth of the upper left quadrant															
21	32.4	39.9	44.5												
22	1.57	9.4	18.9	22.2	28	28.7	35.2	37.6	43.7						
23	19.9	23.9	26.6	26.9	35.1	37	44.2	53.5							
24	10.7	15.3	19.6	25.4	29.1	29.4	34.6	38.4	41.8	46.7	60.3				
25	38.1	38.4	39.3	47.2	62										
26	5.7	32.2	45.1	50.2	51	58.1	59.3	63	65						
27	26.3	30	38.6	47.5	55.7	61	64.7	64.8							
28	59.3	59.4													
Dose of RT of teeth of the lower right quadrant															
48	49.3	62.8	63.5	64.4											
47	22.7	38.2	52.7	60.7	61.2	62.4	63.7								
46	61	64													
45	30.1	41.8	51.7	57.9	58	62.8	63.7	66.2							
44	27.4	37.8	38.9	44	53.1	53.8	56.8	60.8							
43	24	27.4	36.2	45.1	47.2	49.5	49.6	53.2	60.1						
42	22.6	25.3	26.3	35.3	42.8	43.3	43.4	47.8	48.2	48.3	48.4	51.5	60.9		
41	23.3	24.2	24.4	28.3	40	44.7	47.3	47.8	48.7	48.8	50.5	53.5	60.4		
Dose of RT of teeth of the lower left quadrant															
31	23.3	24.2	24.6	32.1	35.9	41	42.4	42.9	47.8	48	49.2	49.5	50.4	50.6	58.8
32	24.4	25	34.5	35.5	38.2	42.8	46	46.8	48.4	59.3	61.6				
33	7.9	24.9	39.3	42.9	45.4	45.7	48.4	49.1	58.7	61.9	62.9				
34	8	30	30.2	36.5	43.3	45.7	52	58.2	59.4	59.8	64.3				
35	41.4	43	47.2	50.7	52.2	54.8	60.3								
36	41	42.4	48.7	58.7	61.4	62.8	65.3								
37	27.4	29.7	33.6	38.9	42.8	44.2	45.7	58.2	60.5	61.7	62.5	62.9	63.4	64.2	
38	49.6	50	61.4	61.9	62	64	65								

Concerning the addition of cisplatin to RT, theoretically, an increase in the probability of tooth loss was expected, although again there is no literature demonstrating this in adults. The only available literature comes from paediatric oncology, where the impact of (chemo) radiotherapy on odontoblasts resulting in dental development abnormalities including dental hypoplasia, root stunting and enamel defects is described.^{18,19,20} However, in this cohort of patients, their dental development would be complete by the age of 35, which was the youngest study participant. The explanation of the absence of additional toxicity in adults with HNC could be the fact that the dose of cisplatin is relatively low (to act as a radiosensitiser and enhance the effect of RT) and is given for a relatively short time period (concomitantly with RT, only). It is known that cisplatin increases acute toxicity, but its impact on late toxicity is limited.

In our study, the impact of concomitant use of cetuximab on tooth loss was significant, but it is important to note that there were only five patients who received cetuximab and this finding could be by chance. The possible explanation of this effect might be due to the fact that cetuximab binds to the epidermal growth factor receptor on both normal and tumour cells, and stomatitis is a recognised side effect of this agent.²¹

The importance of dental hygiene is well known and it is our standard practice that during and after the treatment, all patients remain under the care of a dental hygienist. During treatment, the regional oncology dental hygienists attend the RT clinics on a weekly basis to provide advice on dental hygiene to patients. Procedural appointments for non-surgical periodontal therapy and supportive periodontal therapy are scheduled three to six months following completion of RT. Thus, the oral hygiene was regularly reinforced.

Strengths and weaknesses of study

The main innovative strength of our study is the mapping of exact RT dose in all 1,566 teeth which has not been published before. Our study, as all retrospective studies, carries a potential for selection bias. Logistically, conducting a prospective study in this field of research would be extremely difficult. Another weakness was lack of information on pre-treatment dental history of patients. After applying strict inclusion criteria, 470 patients were excluded due to incomplete records which might have led to introduction of selection

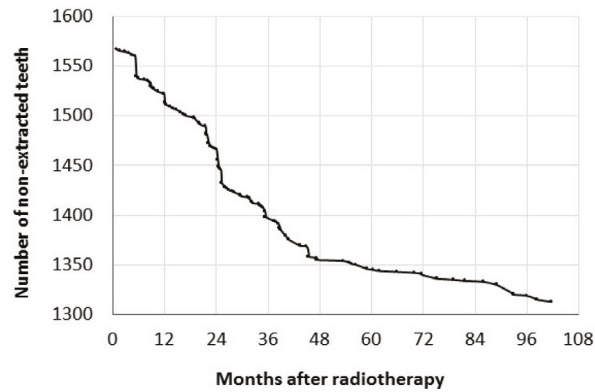


Fig. 2 Teeth survival in absolute numbers over time

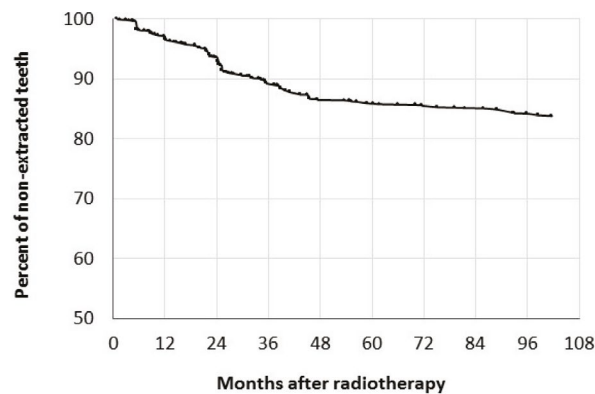


Fig. 3 Teeth survival as a percentage over time post-radiotherapy

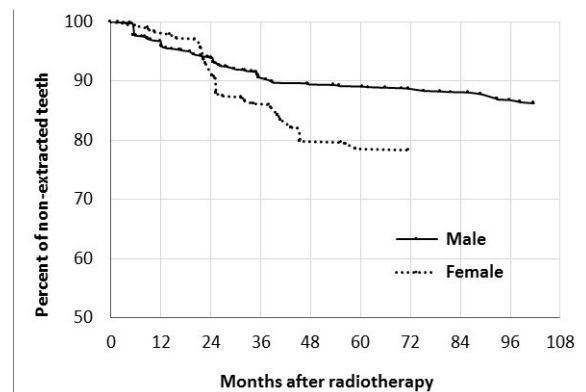


Fig. 4 The number of teeth surviving as a percentage for men and women over time

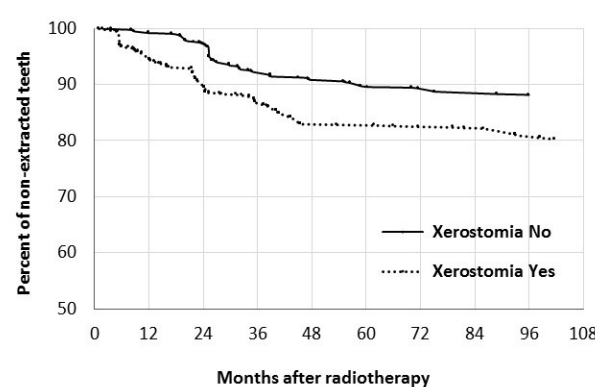


Fig. 5 The number of teeth surviving as a percentage in patients with xerostomia

bias; however, we believe that inclusion of 78 patients with detailed information on more than 1,500 teeth (time, location of extraction and RT dose mapping) is a useful contribution to the literature. Also, the impact of other comorbidities and medications that could have contributed to tooth loss were not studied in our analysis, though all patients were with World Health Organisation performance status 0–2 and none of the patients were treated with bisphosphonates during the course of chemoradiotherapy treatment.

Conclusion

Tooth loss is a recognised complication of RT in HNC treatment. It is associated with smoking status, the presence and severity of xerostomia and RT dose. Smoking cessation advice and provision of regular dental care should be considered to reduce the incidence of tooth loss. Every effort should be made to minimise the dose of RT to the teeth and to the salivary glands to try to minimise the risk of xerostomia and thus reducing the risk of tooth loss.

Ethics declaration

The authors do not declare any conflict of interest. This retrospective study was registered with the local hospital clinical effectiveness register as a service review project (project number 9698). The data used in this study were obtained from the previous clinical practice and the patient's identification and personal information was protected anonymously. The Chair of Newcastle and North Tyneside 1 Research Ethics Committee confirmed ethical approval was not required. The authors followed the local institutional ethical protocols.

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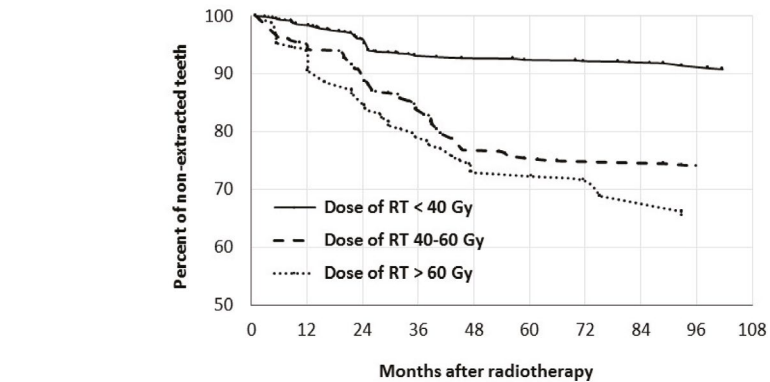


Fig. 6 The number of teeth surviving as a percentage in patients with three differing radiotherapy dose levels

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