CHAPTER 3

IPSILATERAL IRRADIATION FOR ORAL AND OROPHARYNGEAL CARCINOMA TREATED WITH PRIMARY SURGERY AND POSTOPERATIVE RADIOTHERAPY

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Abstract

Purpose: The purpose was to evaluate the contralateral nodal control (CLNC) in postoperative patients with oral and oropharyngeal cancer treated with ipsilateral irradiation of the neck and primary site. Late radiation-induced morbidity was also evaluated.

Material and methods: The study included 123 patients with well lateralized squamous cell carcinomas treated with surgery and unilateral postoperative irradiation. Most patients had tumors of the gingiva (41%) or buccal mucosa (21%). The majority of patients underwent surgery of the ipsilateral neck (n=102; 83%). The N-classification was N0 in 73 cases (59%); N1 or N2a in 23 (19%); and N2b in 27 cases (22%).

Results: Contralateral metastases developed in 7 patients (6%). The 5-year actuarial CLNC was 92%. The number of lymph node metastases was the only significant prognostic factor with regard to CLNC. The 5-year CLNC was 99% in N0, 88% in N1 or N2a and 73% in case of N2b (p=0.008). Borderline significance (p=0.06) was found for extranodal spread. Successful salvage could be performed in 71% of patients with contralateral metastases. The prevalence of Grade 2 or higher xerostomia was 2.6% at 5 years.

Conclusion: Selected patients with oral or oropharyngeal carcinoma treated with primary surgery and postoperative ipsilateral radiotherapy have a very high CLNC with a high probability of successful salvage in case of contralateral metastases. However, bilateral irradiation should be applied in case of multiple lymph node metastases in the ipsilateral neck, particularly in the presence of extranodal spread. The incidence of radiation-induced morbidity is considerably lower as observed after bilateral irradiation.

Introduction

Permanent xerostomia is one of the most frequent and distressing adverse effects of radiotherapy for head and neck cancer. Patients with radiation-induced xerostomia frequently complain of oral discomfort and pain, and have difficulties with chewing, swallowing and speech (1). Reduced salivary flow also predisposes patients to oral infections and dental caries (2, 3, 4). As a consequence, xerostomia significantly impairs health-related quality of life in potentially cured patients (5-7).

Radiation-induced salivary damage is dose and volume dependent (8, 9). Therefore, the most logical approach to prevent radiation-induced xerostomia is to avoid unnecessary irradiation of salivary gland tissue. New radiation delivery techniques, such as three-dimensional conformal radiotherapy and intensity-modulated radiotherapy (IMRT) enable sparing of the salivary glands and subsequent prevention of xerostomia (10). Another approach to prevent xerostomia is by avoiding irradiation of the contralateral neck in well selected patients. Some studies showed that xerostomia rates in unilaterally treated patients showed faster recovery as compared to patients treated with bilateral three-dimensional conformal radiotherapy and IMRT techniques and that xerostomia rates among unilaterally treated patients nearly returned to their pre-treatment levels. (11, 12). Henson *et al.* (13) also showed that total parotid flow rates in unilaterally treated patients 2 years after irradiation were similar to pre-treatment rates, suggesting that the spared contralateral salivary glands compensate for loss of function of the irradiated glands.

Several studies have questioned the need to treat the contralateral neck in well-selected and well-lateralized oropharyngeal and oral carcinomas, because the risk of contralateral failure is very low and survival rates are equal to those with bilateral treatment. (14-16). In selected patients with well-lateralized tumors, not crossing the midline, and without clinical evidence of contralateral lymph node metastases, the clinical target volume may be confined to the primary tumor and ipsilateral neck to spare the contralateral salivary glands and subsequently reduce the risk on xerostomia and acute mucosal toxicity (14-16).

It should be emphasized that these studies mainly included patients treated with primary radiotherapy. Considering the low incidence of contralateral metastases in these patients, the need to treat the contralateral

neck in the postoperative setting after surgery of the primary site and ipsilateral neck could be considered even more controversial, as numerous studies showed that ipsilateral pathologic nodal status is a strong prognostic factor for the incidence of occult contralateral neck metastases or recurrences (14, 17, 18). Knowledge of the pathologic instead of the clinical ipsilateral nodal status may therefore enable an even more accurate prediction of the contralateral nodal neck status.

Therefore the purpose of this study was to evaluate the incidence of contralateral neck recurrence and to assess prognostic factors for contralateral neck recurrence among well-selected patients with oral cavity and oropharyngeal carcinomas treated with unilateral irradiation in the postoperative setting. The incidence of late radiation-induced morbidity was also evaluated.

Material and Methods

Patients

The population of this study was composed of 123 patients with squamous cell carcinoma of the oral cavity and oropharynx from five institutions. Patients were treated between July 1991 and December 2003 by curatively intended surgery of the primary site with or without ipsilateral neck dissection, followed by unilateral postoperative irradiation. All patients were selected from a national database consisting of 1,600 patients from the eight Dutch head-and-neck centers. For logistic reasons, patients from institutes that treated fewer than 10 patients with unilateral postoperative irradiation were excluded. Patients with any treatment of the contralateral neck and patients with distant metastases were also excluded from the analysis. Fifty percent of the patients were men. The median age was 63 years (range from 35 - 89 years). Histological diagnosis was confirmed by biopsy of the primary tumor in all cases. Of all patients 114 (93%) had well-lateralized primary tumors, in which the tumor was located more than 1 cm from the midline. In 4 patients (3%) the tumor was within 1 cm from the midline but not extending over the midline, and in 5 cases (4%) the tumor was extending over the midline. A detailed description of the distribution of primary sub-sites and T categories is shown in Table 1.

Table 1: Distribution of primary tumor subsites and T-stage

Primary tumor	T-stage				Total
	T1 (%)	T2 (%)	T3 (%)	T4 (%)	
Oral cavity					
Mobile tongue	12 (46%)	9 (27%)	5 (19%)	0 (0%)	26
Floor of mouth	4 (50%)	2 (25%)	1 (13%)	1 (13%)	8
Alveolar process	4 (8%)	13 (26%)	0 (0%)	33 (66%)	50
Buccal mucosa	5 (25%)	7 (35%)	4 (20%)	4 (20%)	20
Oropharynx					
Base of tongue	0 (0%)	1 (50%)	1 (50%)	0 (0%)	2
Tonsillar fossa	2 (12%)	11 (65%)	2 (12%)	2 (12%)	17

Pre-operative evaluation included complete medical and head-and-neck examination and panendoscopy under general anesthesia. Ultrasound of the neck, with fine-needle aspiration if indicated, was performed in 84 cases (68%). Computed tomography was performed in 24 cases (20%), and magnetic resonance imaging in 14 cases (11%). Of all patients 13 (10%) underwent a combination of these procedures. In 14 cases (11%) imaging of the contralateral neck was not performed. We assigned T and N classification according to the 1997 staging system of the International Union Against Cancer (19). Extranodal spread (ENS) was present in 25 patients, including 11 cases (48%) staged as pN1/N2a and 14 cases (52%) staged as pN2b. The pre-treatment characteristics are listed in Table 2. Patients were subjected to regular follow-up visits for at least 5 years at the departments of head-and-neck surgery and radiation oncology.

Tumor extension

The degree of tumor extension in the base of the tongue (BOT), soft palate, and posterior pharyngeal wall was categorized in a similar manner to that described previously by O'Sullivan *et al.* (14), by use of Computed Tomography, Magnetic Resonance Imaging, panendoscopy reports or by use of information in the clinical records. Lesions involving 1 cm or less of the ipsilateral hemistructure of the soft palate or BOT were classified as having lateral hemistructure involvement. Lesions extending within 1 cm of the midline or extending over the midline were classified as involving the medial hemistructure of the soft palate or BOT. The remaining lesions extending to the intermediate area were classified as involving the middle hemistructure. None of the primary tumors invaded the posterior pharyngeal wall. Because of

the small numbers of tumors involving the intermediate and medial structures of BOT and soft plate, invasion of these structures was only categorized as yes or no (Table 2).

Table 2: Pre-treatment characteristics and univariate analysis regarding contralateral regional control.

Variable	Number (%)		Actuarial contralateral regional control (5 years)	Log Rank
Gender				p=0.765
Male	62	(50%)	91%	
Female	61	(50%)	93%	
Age				p=0.277
0-60 years	46	(37%)	89%	
> 60 years	77	(63%)	94%	
T-classification				p=0.648
T1	27	(22%)	93%	
T2	43	(35%)	89%	
T3	13	(11%)	92%	
T4	40	(33%)	94%	
N-classification				p=0.008
N0	73	(59%)	99%	Trend: p=0.002
N1-N2a	23	(19%)	88%	
N2b	27	(22%)	73%	
Primary site				p=0.672
Oral cavity	104	(85%)	92%	
Mobile tongue	26	(21%)		
Floor of mouth	8	(6%)		
Alveolar process	50	(41%)		
Buccal mucosa	20	(16%)		
Oropharynx	19	(15%)	94%	
Base of tongue	2	(2%)		
Tonsillar fossa	17	(14%)		
Invasion base of tongue				p=0.284
No	109	(89%)	93%	
Yes	14	(11%)	93%	
Invasion soft palate				p=0.958
No	108	(88%)	92%	
Yes	15	(12%)	100%	
Nodes with ENS (excluding N0 necks)				p=0.057
No ENS	25	(50%)	91%	
ENS	25	(50%)	85%	
Preoperative CT, MRI and/or ultrasound of the contralateral neck				p=0.408
None	14	(11%)	93%	
Lateral 1/3 (limited to 1 cm of lateral involvement)	109	(89%)	92%	

Surgery

All patients underwent resection of the primary tumor. The primary tumor was treated by local excision (n=60; [49%]), partial pharyngectomy (n=31; [25%]) or composite resection with or without a marginal or segmental mandibulectomy (n= 66; [50%]). Partial or total glossectomy was performed in 35 cases (28%). Several patients underwent a combination of these procedures.

The majority of patients underwent surgery of the ipsilateral neck (n=102; [83%]). A radical neck dissection was performed in 13 cases (11%) and a modified radical neck dissection in 60 cases (49%). An ipsilateral selective (I-III) neck dissection was performed in 29 patients (24%).

Radiotherapy

Patients were treated with unilateral irradiation to minimize the dose to the contralateral salivary glands and reduce the incidence of radiation-induced xerostomia. Another reason to use this technique was to reduce the amount of irradiated mucosal tissue to prevent acute mucosal toxicity. All patients were immobilized in the supine position by the use of individually designed facial masks for reproducible positioning and received postoperative radiotherapy with curative intent. Radiotherapy was delivered by megavoltage equipment (6- or 4- MV linear accelerator) via isocentric techniques. Postoperative radiotherapy to the primary tumor bed was applied in all cases. The ipsilateral neck was treated with postoperative radiotherapy in 111 cases (90%) whereas in 12 cases (10%) only the primary tumor site was irradiated.

The initial clinical target volume consisted of the area of the resected primary tumor with margins of 1 to 2 cm with or without the nodal areas of the ipsilateral neck. To correct for set up errors, an extra margin of generally 0.5 cm was taken for the planning target volume (PTV). In general, two opposing anterior-posterior and posterior-anterior fields were used for the cranial part of the PTV and an additional single anterior field to cover the ipsilateral low jugular and supraclavicular nodal regions. In some cases an additional low-weighted lateral field for the cranial part was used in order to spare a larger amount of the anterior part of the oral cavity.

The median total dose to the primary tumor bed was 63 Gy (range: 50 - 70 Gy). In the case of a microscopically irradical resection, the primary tumor bed was irradiated up to a median dose of 64 Gy (range: 55 – 70 Gy) in 2 Gy fractions, whereas in the case of wide surgical margins (≥ 5 mm), the median

total dose was 56 Gy (range: 50 – 70 Gy). The lymph node areas that contained pathological lymph nodes with ENS received a median total dose of 66 Gy (range: 60 – 80 Gy). The PTV of nodal areas was electively irradiated up to 46 Gy in 23 fractions of 2 Gy in 48 patients. In 63 patients an elective dose of 50 Gy in 25 fractions was used.

Late morbidity, contralateral regional recurrence, and salvage

Late toxicity was retrospectively assessed every 6 months up to 5 years after treatment according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme (20) for mucous membrane, subcutaneous tissue/muscle, and bone. Only Grade 3 and 4 complications were scored, as described by Withers *et al.* (21) as these are unlikely to escape documentation. In addition, Grade 2 and higher xerostomia was scored according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late morbidity scheme. Since 2000, one of the participating centers included all treated head-and-neck squamous cell carcinoma patients in a prospective follow-up program. In these 37 patients, late toxicity was prospectively assessed on a routine basis.

Ipsilateral and contralateral regional recurrences were analyzed, and subsequent salvage treatments were evaluated as successful or unsuccessful. The contralateral neck was considered successfully salvaged when this site remained with no evidence of disease 24 months after treatment.

Statistics

Contralateral nodal control (CLNC) and overall survival were measured from the day of surgery until the time of first failure or until the most recent follow-up date if no relapse was detected. The minimal follow-up period was 2 years. In the univariate analysis, CLNC and overall survival were estimated with the Kaplan-Meier method. To test the statistical significance of differences between survival rates, the log-rank test was used.

A multivariate analysis using the Cox proportional hazards model was performed to identify determinants that were significantly associated with CLNC.

Late radiation morbidity was analyzed in three different ways: (1) the crude percentage (*i.e.* the number of patients with toxicity / total number at

baseline); (2) the prevalence (*i.e.* the number of patients with toxicity / total number of patients still at risk at a specific time point), and: (3) the cumulative incidence (*i.e.* the actuarial percentage of patients who had toxicity during follow-up on at least one or more time points).

The statistical analysis was performed with SPSS for Windows (Version 11.5; SPSS, Chicago, IL).

Results

Contralateral neck recurrence, salvage treatment, and overall survival

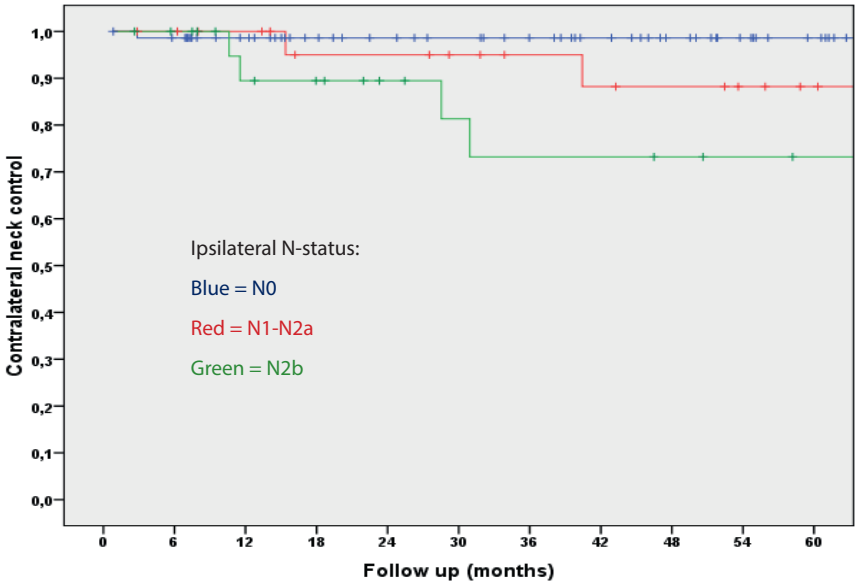
Contralateral metastases developed in 7 patients (6%). In 1 of these patients local recurrence was present as well. Successful salvage could be performed in 5 of these 7 patients (71%). Salvage treatment of the contralateral neck consisted of a (modified) radical neck dissection with or without postoperative radiotherapy or radiotherapy alone. The ultimate CLNC for all patients included after 5 years was 92%.

Overall survival of all patients was 61% after 5 years. The 5-years overall survival among patients in whom contralateral metastases developed was 42%, as compared to 63% among those in whom they did not develop (p=0.87). Ipsilateral regional recurrence occurred in 7 patients. None of these patients survived beyond 5 years.

Prognostic factors on contralateral regional recurrence

On univariate and multivariate analysis, the number of lymph node metastases in the ipsilateral neck was the single significant prognostic factor with regard to CLNC (Table 2). The 5-year CLNC was 99% in N0 cases, 88% in N1 or N2a cases and 73% in N2b cases (p=0.008) (Figure 1). Borderline significance (p=0.081) was found for ENS. The 5-year CLNC was 94% in ENS-negative cases and 86% in ENS-positive cases. In the subset of patients with pN+ necks, the 5-year CLNC was 85% among patients with ENS compared to 91% in patients without ENS (p=0.057) (Table 2). No significant association was found between CLNC and gender, age, primary tumor site, T-classification, BOT extension or extension in the soft palate, and preoperative diagnostic procedures of the contralateral neck.

Figure 1: Contralateral neck control according to ipsilateral N-status.



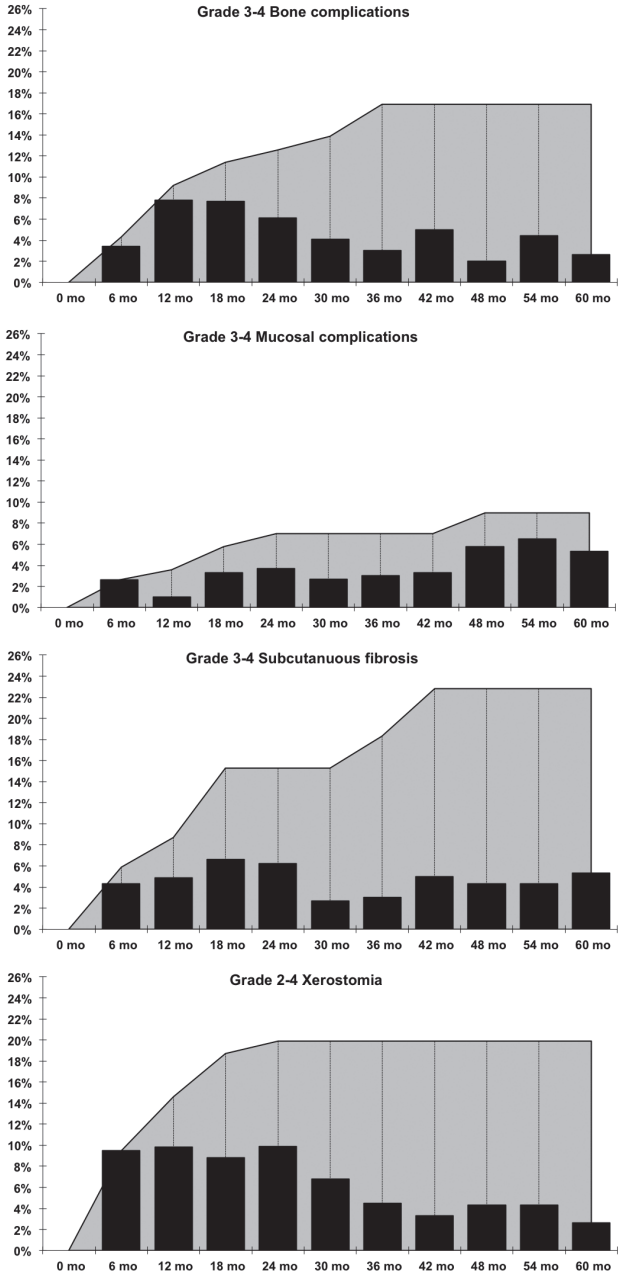
Late morbidity

We did not find any significant difference between retrospectively and prospectively collected data on late radiation-induced morbidity, so these data were evaluated together.

The crude rates for late toxicity were 13.0% for Grade 3 to 4 bone complications, 6.5% for Grade 3 mucosal complications, 10.6% for Grade 3 subcutaneous fibrosis and 17.1% for Grade 2 xerostomia. The only Grade 4 radiation-induced late morbidity was osteoradionecrosis with or without spontaneous fracture, which occurred in 8 patients (6%) during follow-up. Of these 8 patients, 6 (75%) underwent surgery of the mandible (marginal or segmental mandibulectomy) before radiotherapy, 2 of whom underwent reconstruction with a fibula free flap.

The prevalence and cumulative incidence of late radiation-induced morbidity is shown in Figure 2. The cumulative incidence after 5 years was 16.9% for Grade 3 to 4 bone complications, 9.0% for Grade 3 mucosal complications, 22.8% for subcutaneous fibrosis and 19.9% for Grade 2 xerostomia.

Figure 2: Late radiation-induced morbidity according to the RTOG Late Radiation Morbidity Scoring System. The GREY areas indicates the cumulative incidence (similar to the percentage of in which patients that at least at one time point the endpoint occured) while the BLACK columns indicate the prevalence (similar to the percentage of patients in which the endpoint was present on that specific endpoint).



Discussion

In this study we showed that in patients with lateralized oral or oropharyngeal carcinomas, postoperative radiotherapy of the neck can be limited to the ipsilateral side. In these patients, we found a very low risk of contralateral nodal metastases (6%). In case of a contralateral regional failure, the majority of patients could undergo successful salvage. We also showed that the number of positive lymph nodes in the ipsilateral neck was the only significant prognostic factor with regard to CLNC, and borderline significance was found for ENS. In addition, the cumulative incidence and prevalence of long-term radiation-induced morbidity, in particular late xerostomia, was relatively low.

Several others authors have reported on unilateral irradiation in lateralized oral and oropharyngeal tumors with very low incidences of contralateral failure (14-16). O' Sullivan *et al.* (14) found contralateral failures in 3.5% of patients with lateralized carcinoma of the tonsil treated by primary ipsilateral radiation. Kagei *et al.* (15) reported no contralateral recurrences in 32 patients with tonsillar and soft palate carcinomas treated by unilateral irradiation. However, these studies mainly concerned patients primarily treated by irradiation. Until now, limited data were available about the role of postoperative unilateral irradiation in lateralized oral cavity and oropharyngeal cancers. Lin *et al.* (22) investigated 145 patients with buccal cancers mostly treated with unilateral postoperative irradiation. They found contralateral neck failure in only 2%. However, buccal cancers are typically lateralized, so the question remained whether these results could be extrapolated to other oral cavity cancers and oropharyngeal cancers.

Considering the low incidence of contralateral recurrences in primary patients undergoing primary irradiation (14-16), the need to treat the postoperative contralateral neck in similar patients but who are treated with surgery of the primary site and ipsilateral neck could be questioned.

Surgical studies have reported on the incidence of occult contralateral cervical metastases (17, 18). Koo *et al.* (17) found that in case of clinically positive ipsilateral neck nodes, contralateral occult lymph node metastases were present in 36% of patients, as compared to 5% in patients with clinically negative ipsilateral necks. Our study confirmed these results because the number of positive lymph nodes was significantly associated with contralateral regional recurrence. However, in case of ipsilateral metastases,

the contralateral recurrence rate in our study was much lower. This might be explained by differences in patient selection; the series of Koo *et al.* consisted exclusively of oral cavity carcinomas with a higher incidence of midline extension.

Contralateral nodal control was very high in ipsilateral N0 to N2a necks but was significantly reduced in N2b necks; therefore we recommend either elective irradiation of the contralateral neck or close surveillance by ultrasound in case of an ipsilateral N2b neck. Similar results were presented by O' Sullivan *et al.* (14), where no contralateral failures were found in ipsilateral N0 patients. In addition, O'Sullivan *et al.* suggested an increased risk of contralateral recurrence in the case of a positive neck with involvement of the soft palate and BOT. Similar results were found in our study. Invasion in the BOT and soft palate was not significantly associated with CLNC. However, this may be underestimated because the number of patients with involvement of the more medial parts of the BOT and/or soft palate was limited.

In our series 5 of 7 patients (71%) with a contralateral regional recurrence could undergo successful salvage. Similar high salvage rates have been found by Ord *et al.*(23), who reported salvage rates of 68% in patients with previously untreated necks. Several other authors have reported lower salvage rates after regional recurrence (23, 24). However, these studies also included regional recurrences in previously treated necks and regional recurrences salvaged by radiation/chemoradiation alone, which are associated with marginal outcome (23). In our study the prognosis of patients in whom neck recurrences developed in the ipsilateral treated neck was also very poor.

In bilaterally treated patients, reducing the dose to the parotid glands can be achieved by new radiation delivery techniques such as IMRT (25, 26), resulting in improved preservation of salivary output (27) and decreasing xerostomia rates (10). Although studies comparing unilateral irradiation with bilateral parotid-sparing IMRT have not yet been performed, approximately 40% of patients undergoing bilaterally irradiation with IMRT will still have moderate or severe xerostomia (10).

The decision to exclude the contralateral neck from the radiation portals is based on the general policy to electively treat the neck if the risk at nodal metastases exceeds 20% (28). This policy is based on the balance between risk of regional recurrence and expected toxicity from treatment. With the use of IMRT, treatment-related toxicity (*e.g.* xerostomia) can be reduced, and

therefore it might be argued that patients should be treated bilaterally even when the risk of contralateral recurrence is less than 20% (*e.g.* patients with a lateralized oral cavity or oropharyngeal cancer and an ipsilateral N2b neck and no ENS, who were associated with a reduced CLNC in our study).

A major advantage of ipsilateral irradiation is that radiation-induced morbidity is decreased by excluding the contralateral neck from the radiation portals. This is one of the first studies that reported on late radiation-induced morbidity in three different ways, including the crude percentage, the prevalence on each time point and the cumulative incidence. The cumulative risk turned out to be highest as expected in this kind of analysis, because each patient in whom toxicity once developed will be taken into account, even when this specific toxicity was transient. In particular, the probability on Grade 2 or higher xerostomia was lower than reported among patients treated with bilateral irradiation, and after 24 to 36 months, the prevalence of Grade 2 xerostomia decreased to approximately 5%.

Radiation-induced morbidity was scored retrospectively, so we decided to score only the higher grades of late morbidity, because these are unlikely to escape documentation. Nevertheless, it is possible that some events were missed in this analysis, which could result in some underestimation of morbidity. However, the subgroup analysis of the prospectively scored patients showed similar low morbidity rates. In addition, several studies investigating similar techniques show comparable low morbidity rates (14, 15, 22). O'Sullivan *et al.* (14) found low cumulative incidences of Grade 3 or higher late morbidity for mucous membrane (3.4%), subcutaneous tissue/muscle (0.5%) and bone (7%), using primary radiotherapy to the ipsilateral neck.

The present study showed Grade 2 or higher xerostomia in only 10% of the cases, decreasing to less than 5% at 5 years. Kagei *et al.*(15) found a similar prevalence at 24 months with Grade 2 or higher xerostomia in 9% of the cases with oropharyngeal carcinoma treated by unilateral irradiation. In patients with buccal cancers treated with postoperative unilateral irradiation, Lin *et al.* (22) found a somewhat higher crude rate of Grade 2 xerostomia at long term follow-up (27%), Whereas 12% of their patients had no complaints of xerostomia at all.

Overall survival in all patients was 61% after 5 years. Of all patients 40% were diagnosed with an ipsilateral N+ neck and 44% were staged as T3 or T4. In a roughly similar population, Kagei *et al.*(15) found an overall survival rate of

64%. Kagei *et al.* also performed an extensive comparison with large series in the literature treated with bilateral techniques with similar stage distributions. No significant differences in overall survival, cause-specific survival and local control rates were observed.

It should be noted that our series is not representative of the usual distribution of oral cavity and oropharyngeal cancers, because cancer of the alveolar process represent the majority of patients in this series. In the Netherlands, cancer of the gingiva represents approximately 10% of all oral cavity cancers (29), whereas in this study approximately 50% of all oral cavity cancers were located in the gingivae. This difference is likely to be due to selection bias, because usually only lateralized tumors with a low risk of contralateral metastases were selected for unilateral irradiation. During the inclusion period of this study, Computed tomography-based treatment-planning systems were gradually introduced at the participating institutions. Computed tomography-based treatment-planning systems reduce the incidence of geographic miss (30), which is of particular importance in medially extending primary tumours. In addition, three-dimensional treatment-planning systems have the capacity of minimizing hotspots in the mandibular bone, which is of importance in ipsilateral wedge techniques. By obtaining a homogeneous dose distribution, mandibular complications such as osteoradionecrosis and spontaneous fracture might be reduced (31). Because most patients in our study were treated by standard 2-dimensional techniques, the introduction of three-dimensional techniques might improve survival and reduce radiation-induced morbidity even more.

In conclusion, we showed that in selected postoperative patients with well-lateralized oral cavity and oropharyngeal carcinomas and a contralateral cN0 neck, the target volume can be restricted to the ipsilateral neck with very high contralateral regional control. In the case of development of contralateral metastases, most recurrences can be successfully salvaged. The main advantage of such an approach is the reduction of Grade 2 or higher radiation-induced xerostomia, which ultimately decreased to approximately 5%. However, in case of multiple ipsilateral lymph node metastases, particularly in the presence of ENS, patients are at increased risk of occult contralateral metastases and should be treated bilaterally.

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