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Original Article

Postoperative radiotherapy for oral cavity cancer with or without elective neck radiotherapy of the pN0 en bloc dissected neck: oncologic outcomes and late toxicity

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ABSTRACT

Background and purpose: The benefit of elective postoperative radiotherapy (PORT) to the pN0 neck after en bloc primary tumor with neck dissection in patients with oral cavity cancer remains unclear. This nationwide multicenter retrospective observational study investigates the effect of adding or omitting elective neck irradiation to PORT of the primary tumor bed.

Materials and Methods: Treatment data from 12 head and neck cancer centers in the Netherlands was pooled to compare oncologic outcomes and long-term toxicity between 2 groups of patients, i.e. in whom the PORT volume involved the primary tumor bed only (PORT-T, 118 patients) and in whom the pN0 neck was also irradiated, along with the primary tumor bed (PORT-TN, 146 patients).

Results: After a median follow-up of 60 months, 5-year regional control was 96 % in both groups. The 5-year local control was 92 % vs 91 % and the 5-year overall survival was 80 % vs 78 % for the PORT-T and PORT-TN group, respectively (p-value > 0.05 for all). Multivariable analyses showed that elective irradiation of pN0 neck was significantly associated with late grade 2–3 xerostomia (OR 4,93, $p < 0.01$) and dysphagia (OR 5.29, $p < 0.01$).

Conclusion: The omission of elective radiotherapy to the pN0 en bloc dissected neck in patients with oral cavity cancer resulted in comparable regional control rate to those who received elective irradiation of the neck along with the primary tumor bed with a significant reduction of late grade 2–3 radiation-related xerostomia and dysphagia. Therefore, elective irradiation of the pN0 en bloc dissected neck can safely be omitted.

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Introduction

Oral cavity carcinoma (OCC) is the 16th most common cancer worldwide with approximately 390,000 new cases per year[1]. Standard of care for OCC is surgery with or without postoperative radiotherapy (PORT). The indication for PORT is based on histopathological characteristics of the primary resected tumor and/or on the nodal status[2]. However, in case of an indication for PORT to the primary tumor bed while the neck dissection specimen showed no malignancy in the removed lymph nodes (pN0), it is debatable whether or not the en bloc dissected pN0 neck should be irradiated electively[3]. The main argument to include the dissected lymph node regions in the radiation volume is the risk of tumor spill from the primary tumor site into the en bloc dissected node region. Counterarguments are the added side effects associated with neck irradiation and the concern in case of re-irradiation for recurrent, metastatic or new malignancies after previous radiotherapy to the neck.

In the Netherlands, radiotherapy (RT) for head and neck cancer care is well organized on a national level and is centralized in 14 centers. Representatives of all departments participate in regular joint meetings of the Head and Neck Radiation Oncology Society several times a year in order to discuss and share innovations, studies and protocols. To date, due to the lack of evidence and international guidelines regarding elective RT of the pN0 neck, local guidelines to treat or to omit the postoperative pN0 neck differ between institutions. All centers would irradiate the primary tumor site based on the same tumor characteristics, but some keep the en bloc dissected neck (with pN0) outside the radiation volume, while others always include the neck in the elective target volume. To assess the consequence of adding or omitting elective neck irradiation of the pN0 neck in patients with OCC with indications for PORT of the primary tumor bed, we retrospectively pooled the data from 12 head and neck cancer centers with the primary aim to evaluate regional control. Secondary aims were local control, overall survival and long-term toxicity.

Materials and Methods

This multicenter retrospective observational study was conducted in 12 Dutch radiotherapy centers. Patients were eligible if they were treated between January 2010 and December 2019. Only patients who received local surgery for OCC with uni- or bilateral neck dissection in continuity with the primary tumor were eligible. No lymph node metastases had to be present in the dissected neck specimens (pN0). All patients were irradiated postoperatively in accordance to international guidelines based on characteristics of the primary tumor[2]. These characteristics included positive surgical margins (<1 mm), close surgical margins (1–5 mm), perineural growth (PNG), lymphovascular invasion (LVI), non-cohesive tumor border and pT3-4 status. In general, an equivalent dose of 66 Gy in 33 fractions was given to the tumor bed in case of incomplete resection of the primary tumor and 56 Gy in 28 fractions when the tumor was closely resected or in the presence of one or more other risk factors. The elective neck was usually irradiated to an equivalent dose of 46 Gy in 23 fractions, predominantly with a simultaneous integrated boost technique (SIB). PTV margin was initially 5 mm in all centers. Over the last years, 3 mm margin was gradually introduced. Concurrent cisplatin was used in case of a microscopically incomplete resection of the primary tumor. All patients were treated with intensity modulated radiotherapy (IMRT). Volumetric modulated arc therapy (VMAT) was gradually introduced after 2015. Patient informed consent was waived by the Research Ethics Committee, Radboud University Medical Centre due to the retrospective nature of the study. We did not receive any specific funding for the study.

Two groups were defined based on the RT volume: one group of patients where the PORT volume involved primary tumor bed only and the pN0 neck was not irradiated (PORT-T) and the other group in whom the pN0 neck was irradiated, along with the primary tumor bed (PORT-TN). As stated above this was an institution-dependent selection, since some centers historically always include the neck, while others do not.

Study endpoints

The primary endpoint was the incidence of regional failure in the PORT-T and PORT-TN groups. The secondary endpoints were local failure, overall survival and highest grade late toxicity (more than 3 months after end of treatment) as defined by CTCAE v5. Toxicity was only reported if it was prospectively scored or in case it could be clearly extracted retrospectively from the patient records. In case of doubt, toxicity was reported as “missing”.

Statistical analysis

The following details were collected for all patients: age, sex, smoking status, history of prior neck surgery, history of prior head and neck radiotherapy, location of the primary tumor in the oral cavity, pT-stage and pN-stage according to the 7th edition of the American Joint Committee on Cancer (AJCC), number of removed lymph nodes, indication for PORT, whether or not concurrent chemotherapy was given, RT volume, fractionation scheme, highest scored late xerostomia and dysphagia, date of local recurrence, date of regional recurrence, site of regional recurrence, date of distant metastasis and date of death.

Differences at baseline between the two groups were compared using Pearson’s Chi-square test or by *t*-test (age) or Fisher’s Exact Test for Count Data (primary tumor site). Toxicity was compared as dichotomous variable using logistic regression and using a linear-by-linear test that takes the grade into account. Survival curves were calculated with the Kaplan-Meier method and compared using the log-rank test. Median follow-up was calculated from start of radiotherapy using the reverse Kaplan-Meier method. For the local and regional failure free interval estimation, second primary tumors and death were censored, distant metastases were ignored. Cox models were used to find confounders and prognostics factors. All variables that were statistically significant predictors for late toxicity in univariable analysis were included for multivariable analysis. The number of removed lymph nodes (contralateral and ipsilateral separately) was log transformed (using base 2). A sensitivity analysis of overall survival was performed creating confounder-adjusted survival curves using the method of inverse probability of treatment weighting[4]. The propensity score was calculated using a logistic model with sex, age, pT, concurrent chemotherapy, and previous neck surgery. Histograms were used to inspect the overlap in propensity scores between the two treatment groups. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 28 and R, version 4.4.1 with package adjustedCurves version 0.11.1.

Results

According to the departmental protocol for PORT, 4 departments would irradiate only the primary tumor site, 5 departments the primary site in continuity with the operated neck and 3 departments let the decision to the individual physician. Only one department had treated 100 % of the patients according to local protocol, while the other 8 departments had exceptions to their own protocol in respectively 2–38 % of the cases.

In total, 264 patients were included, 118 patients (45 %) in the PORT-T group and 146 patients (55 %) in the PORT-TN group. Most characteristics were relatively well balanced between the two patient groups (Table 1). In the PORT-T group, there were more primary tongue cancers ($p = 0.01$) and less patients received concurrent chemotherapy ($p < 0.01$). The indication for postoperative radiotherapy was in the majority of cases (55.3 %) based on a combination of risk factors, like close resection margin and/or pT3-4 status and/or PNG and/or LVI and/or non-cohesive tumor border. The second biggest groups (25.4 %) was a

Table 1
Baseline characteristics.

	PORT-T (N = 118)	PORT-TN (N = 146)	Total (N = 264)	p-value
Sex				0.18
Male	72 (61.0 %)	77 (52.7 %)	149 (56.4 %)	
Female	46 (39.0 %)	69 (47.3 %)	115 (43.6 %)	
Age, median (range)	62 (33–86)	65 (37–89)	64 (33–89)	0.08
Smoking status				0.89
No	19 (17.4 %)	21 (15.3 %)	40 (16.3 %)	
Former	60 (55.0 %)	79 (57.7 %)	139 (56.5 %)	
Current	30 (27.5 %)	37 (27.0 %)	67 (27.2 %)	
Missing	9	9	18	
Previous neck surgery				0.50
No	114 (96.6 %)	143 (97.9 %)	257 (97.3 %)	
Yes	4 (3.4 %)	3 (2.1 %)	7 (2.7 %)	
Previous neck radiotherapy				0.11
No	114 (96.6 %)	145 (99.3 %)	259 (98.1 %)	
Yes	4 (3.4 %)	1 (0.7 %)	5 (1.9 %)	
Primary tumor site				0.01
Buccal mucosa	2 (1.7 %)	8 (5.5 %)	10 (3.8 %)	
Retromolar triangle	17 (14.4 %)	28 (19.2 %)	45 (17.0 %)	
Alveolar process of mandible	24 (20.3 %)	43 (29.5 %)	67 (25.4 %)	
Tongue	31 (26.3 %)	18 (12.3 %)	49 (18.6 %)	
Floor of mouth	44 (37.3 %)	49 (33.6 %)	93 (35.2 %)	
pT				0.29
1–2	29 (24.6 %)	28 (19.2 %)	57 (21.6 %)	
3–4	89 (75.4 %)	118 (80.8 %)	207 (78.4 %)	
No. of removed lymph nodes				0.59
<10	5 (4.2 %)	9 (6.2 %)	14 (5.3 %)	
10–14	13 (11.0 %)	12 (8.2 %)	25 (9.5 %)	
15–17	11 (9.3 %)	18 (12.3 %)	29 (11.0 %)	
>17	88 (74.6 %)	107 (73.3 %)	195 (73.9 %)	
Unknown	1 (0.8 %)	0 (0.0 %)	1 (0.4 %)	
PORT indication				0.28
<1mm margin (positive)	24 (20.3 %)	43 (29.5 %)	67 (25.4 %)	
1–5 mm margin (close)	11 (9.3 %)	13 (8.9 %)	24 (9.1 %)	
pT3-4	11 (9.3 %)	14 (9.6 %)	25 (9.5 %)	
Perineural growth	0 (0.0 %)	2 (1.4 %)	2 (0.8 %)	
Combination of risk factors (close margin and/or pT3-4 and/or PNG and/or LVI and/or non-cohesive tumor border)	72 (61.0 %)	74 (50.7 %)	146 (55.3 %)	
Concurrent chemotherapy				<0.01
No	112 (94.9 %)	120 (82.2 %)	232 (87.9 %)	
Yes	6 (5.1 %)	26 (17.8 %)	32 (12.1 %)	
Radiotherapy, site				
Oral cavity	118 (100.0 %)		118 (44.7 %)	
Oral cavity + unilateral neck		91 (62.3 %)	91 (34.5 %)	
Oral cavity + bilateral neck		55 (37.7 %)	55 (20.8 %)	
Equivalent fractionation scheme, in case of SIB: "tumor bed"/ "neck"				
56 Gy in 28 fractions	75 (63.6 %)	7 (4.8 %)	82 (31.1 %)	
66 Gy in 33 fractions	40 (33.9 %)	0 (0 %)	40 (15.2 %)	
70 Gy in 35 fractions	3 (2.5 %)	0 (0 %)	3 (1.1 %)	
56/50 Gy in 28 fractions (SIB)	0 (0 %)	62 (42.5 %)	62 (23.5 %)	
66/54 Gy in 33 fractions (SIB)	0 (0 %)	69 (47.3 %)	69 (26.1 %)	
66/60 Gy in 33 fractions (SIB)	0 (0 %)	6 (4.1 %)	6 (2.3 %)	
70/60 Gy in 35 fractions (SIB)	0 (0 %)	1 (0.7 %)	1 (0.4 %)	
Other	0 (0 %)	1 (0.7 %)	1 (0.4 %)	

positive surgical margin. There were no differences in indication for PORT between both groups (p = 0.28). Also the amount of removed lymph nodes were equally balanced between the groups (p = 0.59).

The median follow-up was 5 years (IQR 3.57 – 7.04). The median follow-up time of patients alive was 4.5 years (IQR 3.30 – 6.59). In the whole group, 9 regional recurrences occurred, 4 in the PORT-T group and 5 in the PORT-TN group. Five out of 9 regional recurrences were in-field recurrences, respectively 1 in the PORT-T group (i.e. level 1 recurrence in the case of a floor of mouth primary tumor site) and 4 in the PORT-TN group; 3 out of 9 ipsilateral regional recurrences in the PORT-T group and 1 out of 9 contralateral recurrence in the PORT-TN group. Three out of 5 in-field recurrences were irradiated to an equivalent dose of 46 Gy in 23 fractions; one received 56 Gy in 28 fractions; and the other only 23.2 Gy in 13 fractions due to wound complications during radiotherapy. The unadjusted 5-year regional control was 96 % in both groups (Fig. 1A). No factors were found significant for regional control, except the ipsilateral lymph node yield (HR 0.46 for each doubling of the yield, Table 2). In a multivariable analysis (MVA) adjusting for the ipsilateral lymph node yield no difference was found between the PORT-T and PORT-TN groups (HR 0.75, 95 % CI 0.19–2.95, p = 0.68).

There were 23 local recurrences: 10 in the PORT-T group and 13 in

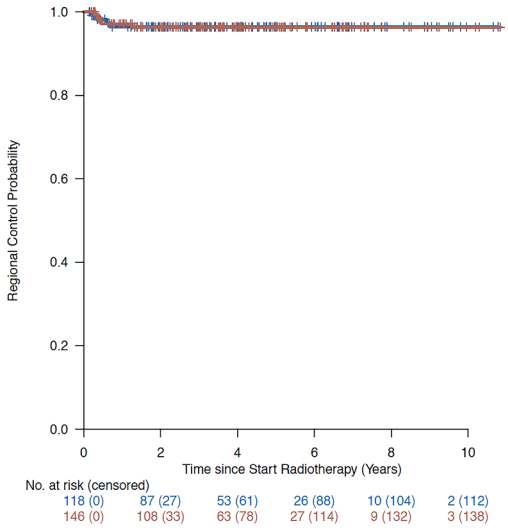

Fig. 1A. Kaplan-Meier curves of regional control.

Table 2
Univariable analysis of regional control.

		Patients	Events	HR	95 % CI	p-value
Treatment	PORT-T	118	4			
	PORT-TN	146	5	1.00	(0.27–3.73)	1
Sex	Male	149	6			
	Female	115	3	0.64	(0.16–2.56)	0.53
Age (continuous per year)		264	9	0.99	(0.93–1.05)	0.77
Concurrent chemotherapy	No	232	9			
	Yes	32	0	0.00	(0.00–Inf)	1
pT	1–2	57	4			
	3–4	207	5	0.35	(0.09–1.31)	0.12
No. of removed lymph nodes	>17	195	4			
	15–17	29	2	3.39	(0.62–18.53)	0.16
	10–14	25	1	2.03	(0.23–18.18)	0.53
	<10	14	2	8.08	(1.48–44.15)	0.02
	unknown	1	0	0.00	(0.00–Inf)	1
No. of ipsilateral lymph nodes removed	(per doubling of number of nodes)	263	9	0.46	(0.24–0.89)	0.02
No. of contralaterallymph nodes removed	(per doubling of number of nodes)	263	9	0.96	(0.65–1.41)	0.82
PORT indication	Combination of risk factors (close margin and/or pT3-4 and/or PNG and/or LVI and/or non-cohesive tumor border)	146	6			
	< 1 mm margin (positive)	67	0	0.00	(0.00–Inf)	1
	1–5 mm margin (close)	24	2	2.02	(0.41–9.99)	0.39
	pT3-4	25	1	0.99	(0.12–8.22)	0.99
	perineural growth	2	0	0.00	(0.00–Inf)	1
Primary tumor site	Buccal mucosa	10	1			
	Retromolar triangle	45	1	0.21	(0.01–3.35)	0.27
	Alveolar process of mandible	67	2	0.30	(0.03–3.36)	0.33
	Tongue	49	1	0.19	(0.01–3.09)	0.24
	Floor of mouth	93	4	0.43	(0.05–3.82)	0.45
Previous neck surgery	No	257	9			
	Yes	7	0	0.00	(0.00–Inf)	1
Previous neck radiotherapy	No	259	9			
	Yes	5	0	0.00	(0.00–Inf)	1
Center	F	45	1			
	A	11	0	0.00	(0.00–Inf)	1
	B	12	0	0.00	(0.00–Inf)	1
	C	36	0	0.00	(0.00–Inf)	1
	D	13	0	0.00	(0.00–Inf)	1
	E	7	0	0.00	(0.00–Inf)	1
	G	30	1	1.55	(0.10–24.88)	0.76
	H	19	0	0.00	(0.00–Inf)	1
	I	34	0	0.00	(0.00–Inf)	1
	J	9	1	4.76	(0.30–76.04)	0.27
	K	44	6	6.52	(0.78–54.24)	0.08
	L	4	0	0.00	(0.00–Inf)	1

the PORT-TN group, the unadjusted 5-year local control was respectively 92 % vs. 91 % (p-value > 0.05, Fig. 1B). Thirty-eight patients were diagnosed with a 2nd primary tumor (head and neck carcinoma n = 32, lung carcinoma n = 5, endometrium carcinoma n = 1). After 5 years the incidence for developing a second primary tumor was not significantly different between the PORT-T and PORT-TN group, respectively 16 % vs 12 % (p-value > 0,05). Fifteen patients developed distant metastases and 86 patients died (37 in the PORT-T group and 49 in the PORT-TN group), the unadjusted 5-year overall survival was 80 % vs 78 % for the PORT-T and PORT-TN group, respectively (p-value > 0.05, Fig. 1C). Only 1 out of 9 regional recurrences occurred simultaneously with the presence of distant metastases, while the other 8 were isolated regional recurrences (Fig. 2). No significant overall-survival difference was found in a MVA adjusting for age, pT, primary tumor site and whether prior neck surgery or radiotherapy was given (HR PORT-T vs PORT-TN 0.95, 95 %CI 0.61–1.48, p = 0.82). Adjusted overall survival curves using Inverse Probability of Treatment Weighting were largely overlapping too (figure S1).

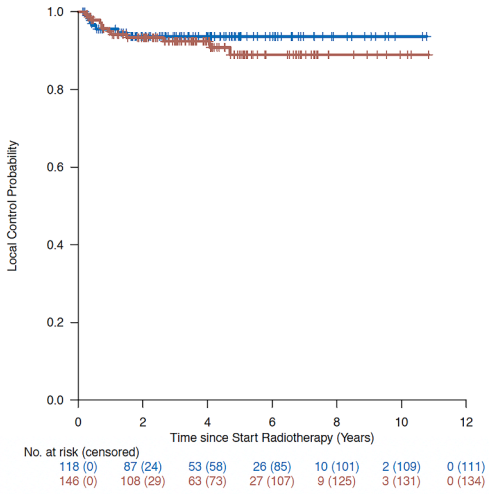

Fig. 1B. Kaplan-Meier curves of local control.

Late toxicity was documented in 194 and 192 patients for xerostomia and dysphagia, respectively (Table 3). Patients treated in the PORT-T group had less late xerostomia (p < 0.01) and dysphagia (p < 0.01) compared to the patients treated in the PORT-TN group. UVA of grade 2–3 xerostomia and dysphagia are shown in Table 4 and 5, respectively. After MVA of all statistically significant predictors in UVA adjusted for center, irradiation of the neck remained a significant predictor for grade

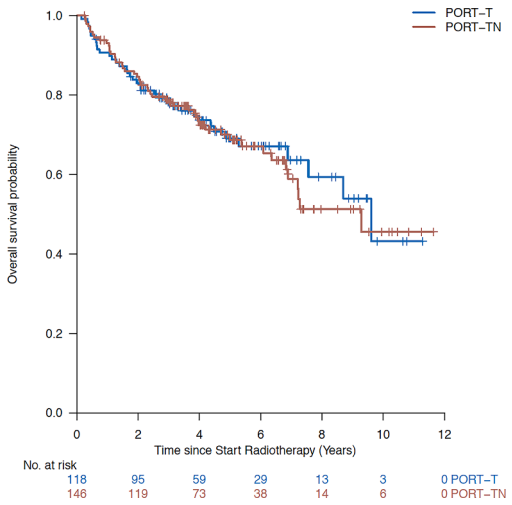

Fig. 1C. Kaplan-Meier curves of overall survival.

2–3 xerostomia (OR 4.93; 1.75–13.89, p < 0.01), the total neck dose (with the PORT-TN group) lost statistical significance (p = 0.06). For grade 2–3 dysphagia, irradiation of the neck was also a significant predictor in MVA (OR 5.29; 2.09–13.43, p < 0.01), along with pT3-4 status (OR 2.84; 1.21–6.69, p = 0.02). The observed differences in reported toxicity between centers in UVA remained significant in MVA for both grade 2–3 xerostomia and dysphagia.

Discussion

To the best of our knowledge, this nationwide retrospective observational study is the largest series to date investigating the necessity of elective irradiation of the pN0 neck in OCC patients who require adjuvant radiotherapy to the primary tumor bed only. The current study shows that regional control rates are excellent and comparable between PORT-T and PORT-TN groups. Patients irradiated to the primary tumor site plus the pN0 neck (PORT-TN) have significantly higher incidence of late grade 2–3 dry mouth (31 % vs. 15 %, p < 0.01) and dysphagia (61 % vs. 19 %, p < 0.01).

Apart from less radiation-related dysphagia and xerostomia, reduction of the radiation volume by not including the neck has several other advantages as well. First, improvement of different domains of quality of life has been reported in various randomized and prospective studies to be the result of reducing the irradiated volumes[5–7]. Secondly, reducing the irradiated volumes might subsequently reduce the incidence of a second primary tumor in the head and neck region, which is already higher in these patients than the general population[8]. Thirdly, it might also reduce the risk of ischemic cerebrovascular accidents, since several studies have shown a clear correlation between carotid exposure to radiation and the development of carotid stenosis and ischemic cerebrovascular accidents[9–11]. Fourthly, it will reduce the risk of several thyroid disorders[12]. Moreover, in case of regional recurrence or second primary tumor in the head and neck region, it offers the possibility to irradiate the radiation-naive neck to high radiation dose or to easier operate upon the neck with less risk of postoperative complications.

The data on the benefit of elective irradiation of the en bloc dissected pN0 neck is limited and published literature is conflicting. Two groups have reported treatment outcomes in less than 55 patients[13,14], suggesting that the omission of elective radiotherapy is safe while others have advocated to include the pN0 neck in elective PORT target volumes, especially in the case of positive surgical margins[15,16]. It is speculated that positive surgical margins could be an indication for the aggressiveness of the primary tumor and the presence of the tumor in the mucosal surface of the surgical specimen could cause tumor spill. Because of the rich lymphatic network in the head and neck region, elective nodal irradiation in patients with head and neck squamous cell carcinoma primarily treated with radiotherapy is shown to be very effective in reducing the risk of regional failure to less than 5 % [15,17,18]. Our study included a large number of patients (n = 264) from 12 dedicated head and neck cancer centers across the Netherlands. This report shows that there is no clear benefit of elective neck irradiation of the surgically treated pN0 neck, while both groups show 5-year

Table 3
Highest scored late toxicity.

Xerostomia	PORT-T	PORT-TN	Total
patients scored	68	126	194
Grade			
0	35 (51 %)	24 (19 %)	59 (30 %)
1	23 (34 %)	63 (50 %)	86 (44 %)
2	10 (15 %)	37 (29 %)	47 (24 %)
3	0 (0 %)	2 (2 %)	2 (1 %)
Linear-by-linear association test, p-value < 0.01			

Dysphagia	**PORT-T**	**PORT-TN**	**Total**
Patients scored	67	125	192
Grade			
0	49 (73 %)	29 (23 %)	78 (41 %)
1	5 (7 %)	20 (16 %)	25 (13 %)
2	9 (13 %)	61 (49 %)	70 (36 %)
3	4 (6 %)	15 (12 %)	19 (10 %)
Linear-by-linear association test, p-value < 0.01			

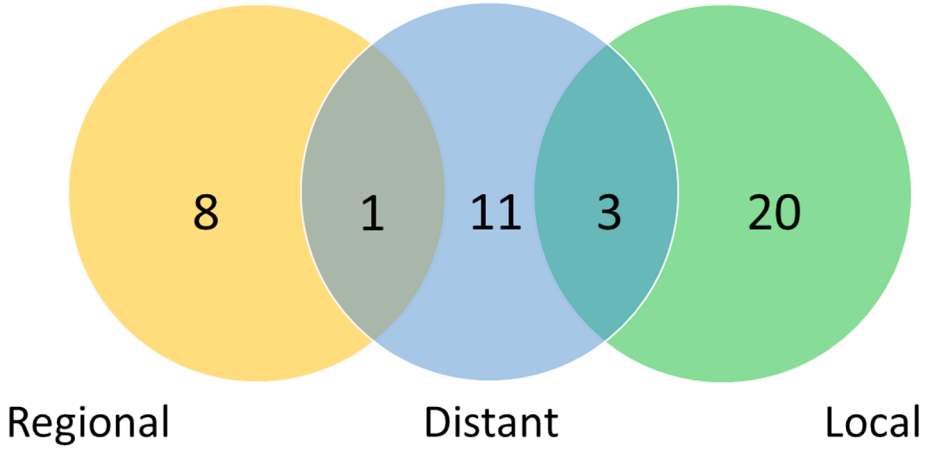

Fig. 2. Venn diagram of patterns of recurrences' distribution.

Table 4
Univariable logistic regression analyses of grade 2–3 xerostomia.

	Patients	Events	(%)	OR	95 % CI		p-value
Treatment							
PORT-T	68	10	15 %				
PORT-TN	126	39	31 %	2.60	(1.20—5.62)		0.02
pT							
1–2	46	8	17 %				
3–4	148	41	28 %	1.82	(0.78—4.23)		0.16
Neck radiotherapy							
Unilateral	80	22	28 %				
Bilateral	46	17	37 %	1.55	(0.71—3.35)		0.27
Concurrent chemotherapy							
No	166	42	25 %				
Yes	28	7	25 %	0.98	(0.39—2.48)		0.97
Total dose tumor bed							
(continuous per Gy)	194	49	25 %	0.95	(0.89—1.02)		0.15
Total neck dose							
(continuous per Gy)	126	39	31 %	0.80	(0.69—0.94)		0.01
Center							
F	39	6	15 %				
A	8	1	12 %	0.79	0.08	7.60	0.83
B	7	2	29 %	2.20	0.34	14.08	0.41
C	34	10	29 %	2.29	0.73	7.17	0.15
D	13	1	8 %	0.46	0.05	4.21	0.49
E	7	1	14 %	0.92	0.09	9.04	0.94
G	30	6	20 %	1.38	0.39	4.79	0.62
J	9	8	89 %	44.00	4.62	418.93	<0.01
K	44	14	32 %	2.57	0.87	7.53	0.09
L	3	0	0 %	0.00	0.00	Inf	0.99

Table 5
Univariable logistic regression analyses of grade 2–3 dysphagia.

	Patients	Events	(%)	OR	95 % CI		p-value
Treatment							
PORT-T	67	13	19 %				
PORT-TN	125	76	61 %	6.44	3.19	13.03	<0.01
pT							
1–2	47	14	30 %				
3–4	145	75	52 %	2.53	1.25	5.11	0.01
Neck radiotherapy							
Unilateral	80	45	56 %				
Bilateral	45	31	69 %	1.72	0.80	3.72	0.17
Concurrent chemotherapy							
No	164	78	48 %				
Yes	28	11	39 %	0.71	0.31	1.62	0.42
Total dose tumor bed							
(continuous per Gy)	192	89	46 %	1.02	0.97	1.08	0.43
Total neck dose							
(continuous per Gy)	125	76	61 %	0.95	0.83	1.07	0.38
Center							
F	40	12	30 %				
A	8	2	25 %	0.78	0.14	4.42	0.78
B	8	2	25 %	0.78	0.14	4.42	0.78
C	33	25	76 %	7.29	2.57	20.72	<0.01
D	13	0	0 %	0.00	0.00	Inf	0.99
E	7	4	57 %	3.11	0.60	16.08	0.18
G	30	23	77 %	7.67	2.60	22.65	<0.01
H	6	5	83 %	11.67	1.23	110.80	0.032
K	44	16	36 %	1.33	0.53	3.32	0.54
L	3	0	0 %	0.00	0.00	Inf	0.99

regional control of 96 %. Based on this result, the concept of tumor spill does not seem to play a notable role, since there is no increased risk of regional recurrence when the pN0 en bloc dissected neck is not adjuvantly irradiated.

An other potential risk factor for regional recurrence could be the location of the oral cancer subsite, since it has been proposed that subsites can have different biological behavior[19–21]. In our study, we identified relatively more primary tumors located in the tongue in the PORT-T group, for which we have no clear explanation. Nevertheless, we found no differences in clinical outcome between the different subsites with regard to the development op regional recurrences. We did find that tumors located on the alveolar process of the mandible had a higher incidence of developing a local recurrence and had poorer overall survival in the univariable analyses, but it lost its significance in the multivariable analyses. The lymph node yield from elective neck dissections has been associated with survival outcome[22–25]. Several cutoff levels have been proposed and most studies have determined that a cutoff value of 18 removed lymph nodes is being predictive for survival outcome[22]. Jaber et al showed that lower regional recurrence rates and improved survival outcome were seen as lymph node yield

increased for pN0 OCC[24]. We also found a clear improvement in regional control if the amount of removed lymph nodes increased, but did not see an improved overall survival. Our results show that elective radiotherapy to the pN0 neck does not influence the regional recurrence rate, but a high yield of lymph nodes does. This might possibly reflect that more than microscopic disease is left behind in the neck when a low number of lymph nodes is removed.

The limitations of the current study, including biases inherent to a retrospective analysis are well understood by the authors. Although the regional control curves closely overlap, the limited number of events may have hindered the identification of confounders necessary to account for differences in case-mix. For overall survival however there were more events (n = 86) and therefore possibilities to adjust the analysis for potential confounding. We used multivariable regression and inverse probability of treatment weighting, neither of which could detect a difference between the two treatment groups.

Prior to the initiation of this study, we conducted a survey amongst participating centers. Four centers claimed to belong to the PORT-T group, 5 centers to the PORT-TN group and in 3 centers there was no formal treatment protocol and pN0 neck irradiation was mainly left to the discretion of the physician, determined on a case-by-case basis. When analyzing the data, we found that only one department treated all their patients according to their own institutional protocol while the other departments had some exceptions to their own protocol. Therefore, we could not exclude the possibility of some selection bias. However, we did not find any contributing factors after multivariable analysis. There were significant differences in reported toxicity between centers. One possible explanation can be a difference in interpretation of de CTCAE-toxicity definition for grade 2 dysphagia and to a lesser extent for xerostomia. Another explanation could be the use of different treatment planning techniques resulting in differences in organ at risk sparing[26,27]. An in-depth plan comparison was outside the scope of this project. However, difference in toxicity between the treatment groups remained significant after adjusting for center effects. Furthermore, the reported reduction of toxicity by omitting adjuvant radiotherapy to the en bloc dissected pN0 neck might be underestimated, because accurate registration and documentation of different radiation-related toxicity items like fibrosis, laryngeal edema, hypothyroidism and incidence of fistulas, are missing in the current study. On the other hand, the strengths of our study are the multicenter setup and large sample size in a relatively homogenous group of patients focusing on one head and neck sub-site, the oral cavity.

The optimal proof to show that it is safe to omit elective postoperative radiotherapy to the pN0 neck would be if at least two randomized controlled trials confirm our results. However it is unlikely that these trials will be conducted, since the scientific debate on this topic is already very old and has yet not resulted in such trials. Perhaps this is due to the fact that these trials will need a large sample size and need a lot of centers to participate in order to accrual enough patients to answer this important question. It would also be important for these trials to accrual in a relatively short time period to be clinical relevant and economically efficient. We were able to collaborate with almost all Dutch radiotherapy departments to collect every possible patient adhering to the inclusion criteria and still needed a time period of 10 years to find 264 patients and 9 regional recurrences.

In conclusion, the current study aimed to investigate the effect of adding or excluding elective radiotherapy to the en bloc dissected pN0 neck in patients with OCC, treated in 12 dedicated head and neck cancer centers in the Netherlands. The study showed that patients irradiated to the primary tumor bed only (PORT-T) had the same excellent regional control compared to those irradiated to the primary tumor bed and the operated neck site (PORT-TN), with significantly lower incidence of late grade 2–3 xerostomia and dysphagia. Based on these results, elective irradiation of the pN0 neck can safely be omitted following local resection with en bloc neck dissection in OCC patients who require adjuvant radiotherapy to the primary tumor bed only based on local pathological risk factors.

CRediT authorship contribution statement

B. Kreike: Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **A. Al-Mamgani:** Writing – original draft, Resources. **E. van Werkhoven:** Writing – review & editing, Formal analysis, Data curation. **M. Beugeling:** Writing – review & editing, Resources. **J.H.A. M. Kaanders:** Writing – review & editing, Resources, Conceptualization. **M. van Ruler:** Writing – review & editing, Resources. **P.A.H. Doornaert:** Writing – review & editing, Resources. **M.A. de Jong:** Resources. **M.S. Koedijk:** Writing – review & editing, Resources. **M.R. Vergeer:** Writing – review & editing, Resources. **H.H.G. Verbeek:** Writing – review & editing, Resources. **F.W.R. Wesseling:** Writing – review & editing, Resources. **Joris B.W. Elbers:** Writing – original draft, Resources, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2025.110896.

Data availability

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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