

## ORIGINAL RESEARCH

Treatment of head and neck carcinoma of unknown primary:  
Cracking a nut with a sledgehammer?

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## Abstract

**Objectives:** To compare the impact on survival and late radiation toxicity of patients with squamous cell carcinoma of unknown primary who were treated with ipsilateral neck dissection and ipsilateral postoperative radiotherapy (PORT) and patients treated with ipsilateral neck dissection and PORT to both sides of the neck plus the pharyngeal axis.

**Methods:** Retrospective cohort study performed at the Erasmus University Medical Center in which 78 patients with squamous cell carcinoma of unknown primary were identified. Thirty-nine patients received PORT to both sides of the neck plus the pharyngeal axis (BILAX) and another 39 patients were irradiated on the ipsilateral neck (IPSI) only. The endpoints of the present study were 3-year overall survival (OS), 3-year disease-free survival (DFS), and overall late radiation toxicity.

**Results:** The 3-year OS rate of the entire group of 78 patients was 74.2% and the 3-year DFS rate was 72.7%. The 3-year OS rates for the IPSI and the BILAX groups were 74.4% and 74.1%, respectively ( $P = .654$ ). The most common late radiation toxicity experienced was xerostomia (64.8%), which was significantly more often seen in the BILAX group than in the IPSI group (83.8% and 44.1%, respectively,  $P = .001$ ). Overall late radiation toxicity was significantly higher in the BILAX group ( $P = .003$ ).

**Conclusion:** There was no significant difference in OS and DFS rates between the IPSI and the BILAX group. Late radiation toxicity was significantly higher in the BILAX group.

**Level of Evidence:** Level 2b: Individual retrospective cohort study.

## KEYWORDS

cancer of unknown primary, head and neck carcinoma, pharyngeal axis, radiation toxicity, radiotherapy

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## 1 | INTRODUCTION

Metastatic cervical lymphadenopathy is often the first clinical manifestation of carcinomas of the head and neck. The most common histology found in cervical metastasis is squamous cell carcinoma.<sup>1</sup> However, in 3% to 9% of all head and neck squamous cell carcinoma (HNSCC), the primary tumor remains unidentified.<sup>2</sup>

In the work-up, clinical examination and extensive imaging consisting of computed tomography (CT) or magnetic resonance imaging (MRI), directed biopsies, and panendoscopies are performed to identify the primary tumor. Furthermore, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been established to be valuable in detecting the occult primary tumor site.<sup>3,4</sup> Nevertheless in 3% to 9% of all HNSCC, the primary tumor remains unidentified.<sup>2</sup> In recent years, new techniques have been established to be valuable in the identification of the primary site in head and neck carcinoma of unknown primary (HNCUP). These techniques include the transoral robotic surgery (TORS) and transoral laser microsurgery (TLM). With these techniques, identification rates up to 94% have been reported, being significantly higher in comparison to traditional examinations under anesthesia.<sup>5-7</sup>

The management of these HNCUP consists of (random) directed biopsies where areas with no visible tumor are sampled.<sup>8</sup> These areas often include the pharyngeal axis consisting of the nasopharynx, the base of tongue and the palatine tonsils,<sup>9</sup> as the primary tumor is often believed to have an origin in these regions.

Due to the low incidence, substantial heterogeneity exists between centers in regards to treatment and management of HNCUP. A large range of treatment modalities have been suggested for HNCUP, including ipsilateral and bilateral neck dissections with or without adjuvant therapy, radiotherapy, chemotherapy, targeted therapy, and combinations thereof.<sup>2,10-12</sup>

Per guidelines of the National Comprehensive Cancer Network, a frequently used approach for HNCUP is neck dissection in the form of single treatment modality for pN1 diseases without extranodal extension (ENE), whereas in pN1 with ENE, pN2 and pN3 disease adjuvant radiotherapy is given.<sup>10,13-17</sup>

Despite the apparent superior survival rates with combined treatment modalities,<sup>13,14</sup> the extent of neck dissections and radiotherapy target volumes remain controversial. As part of the radiotherapy target volume, irradiation of the contralateral neck and pharyngeal axis has traditionally been deemed to be an integral part of the radiation treatment plan in an adjuvant setting.<sup>11,15,18,19</sup> With the aim of reducing acute and late effects of the contralateral neck and the pharyngeal axis, some authors have advocated in selected cases for ipsilateral-only treatment in lieu of bilateral and pharyngeal axis radiation, as comparable survival rates have been reported for both groups.<sup>20-22</sup> Nevertheless, it remains poorly defined in the literature whether ipsilateral-only treatment also leads to significant reduction in adverse radiation effects.

In this study, we aim to compare clinical outcomes of patients treated with adjuvant radiation to the ipsilateral neck only (IPSI group) as opposed to adjuvant bilateral neck plus pharyngeal axis radiation

(BILAX group). Following this, the late radiation effects from both groups will be assessed.

## 2 | MATERIALS AND METHODS

### 2.1 | Ethical considerations

The Erasmus Medical Center Ethics Committee approved this retrospective study (MEC-2016-751). Written informed consent was obtained from all the patients at the time of admission. All data analyses were performed anonymously.

### 2.2 | Case selection

All patients diagnosed between January 01, 2006 and December 31, 2015 with HNCUP treated with curative intent were retrospectively analyzed and included in this study. HNCUP was determined by means of histologically or cytologically proven cervical metastasis with no primary tumor identified through endoscopic examination, MRI of the head and neck and/or PET-CT with random-directed biopsies. Patients with a history of prior HNSCC were excluded in this study.

Tumor-specific data and patient data were obtained from Erasmus Medical Center patient records and integrated with data from the Netherlands Comprehensive Cancer Organization (NCCO). All data were manually checked by the authors, where in case of data conflict, data from the NCCO were considered to be superior.

### 2.3 | Work-up and treatment

Up until 2013, the work-up at our center initially consisted of an MRI of the head and neck. If no tumor could be found through imaging, a panendoscopy with random-directed biopsies of the pharyngeal axis were performed with either an ipsilateral or bilateral tonsillectomy.

During this period, treatment for HNCUP was based on histologic differentiation and stage. Poorly differentiated carcinoma was treated with an ipsilateral neck dissection of neck levels 1 to 5, followed by bilateral neck irradiation plus irradiation of the pharyngeal axis.

Moderately and well-differentiated carcinomas regardless of nodal stage were treated with an ipsilateral neck dissection of levels 1 to 5. Adjuvant ipsilateral radiotherapy was given when the neck node was larger than 3 cm or in the case of multiple positive neck nodes.

Following the protocol changes of 2013, all patients underwent a PET-CT scan. Following this, areas with increased FDG uptake were then biopsied. If no areas with increased FDG uptake were found on the PET-CT scan, random-directed biopsies plus either an ipsilateral or bilateral tonsillectomy were performed.

In both protocols, if no primary tumor was found after completing the work-up, the lymph node tumor was regarded as an HNCUP.

In the new protocol, ipsilateral neck dissection of neck levels 1 to 5 was set as the cornerstone of treatment for all stages of HNCUP, regardless of differentiation. All patients were also treated with post-operative radiotherapy (PORT) of the ipsilateral neck only.

In patients with pN1 staged nodes, where ipsilateral neck dissection showed no ENE, PORT was omitted. Patients with bilateral lymphadenopathy received neck dissections and PORT to both sides of the neck, but not to the pharyngeal axis.

In our series, patients with bilateral lymphadenopathy treated with bilateral PORT were considered to be in the ipsilateral group if the pharyngeal axis was not part of the radiotherapy target volume.

Ipsilateral irradiation of the neck up to 46 Gy was performed using the intensity-modulated radiotherapy (IMRT) technique post-operatively five or six times per week in fractions of 2 Gy, after which an additional boost of 20 Gy to the involved neck levels was given, resulting in a cumulative dose of 66 Gy. Patients in the bilateral plus pharyngeal axis group were also post-operatively irradiated using the IMRT technique six times per week in fractions of 2 Gy. Both sides of the neck and the pharyngeal axis received a dose of 46 Gy, after which a boost of 20 Gy to the affected neck levels was administered, totaling a cumulative dose of 66 Gy.

## 2.4 | Endpoints and definitions

The primary endpoints were overall survival (OS) rates and disease-free survival (DFS) rates of the IPSI group and the BILAX group. OS was defined as death due to any cause between the date of diagnosis and the date of death. DFS was calculated using the date of last treatment to the date of first recurrence (local, regional or distant).

Secondary endpoints were cumulative late toxicity scores and number of patients per late toxicity category (>180 days after radiotherapy) per treatment group. Late toxicity was scored by reviewing patient records using the Common Terminology Criteria for Adverse Events v5.0 (CTCAE).

Comorbidity between the two groups prior to treatment were compared using the Adult Comorbidity Evaluation-27 (ACE-27), which scores comorbidity in nine organ systems, resulting in a total score between 0 and 3.

## 2.5 | Statistical analysis

Statistical analysis was conducted using SPSS (IBM SPSS Statistics, version 24.0.0.1). OS and DFS were estimated with the Kaplan–Meier

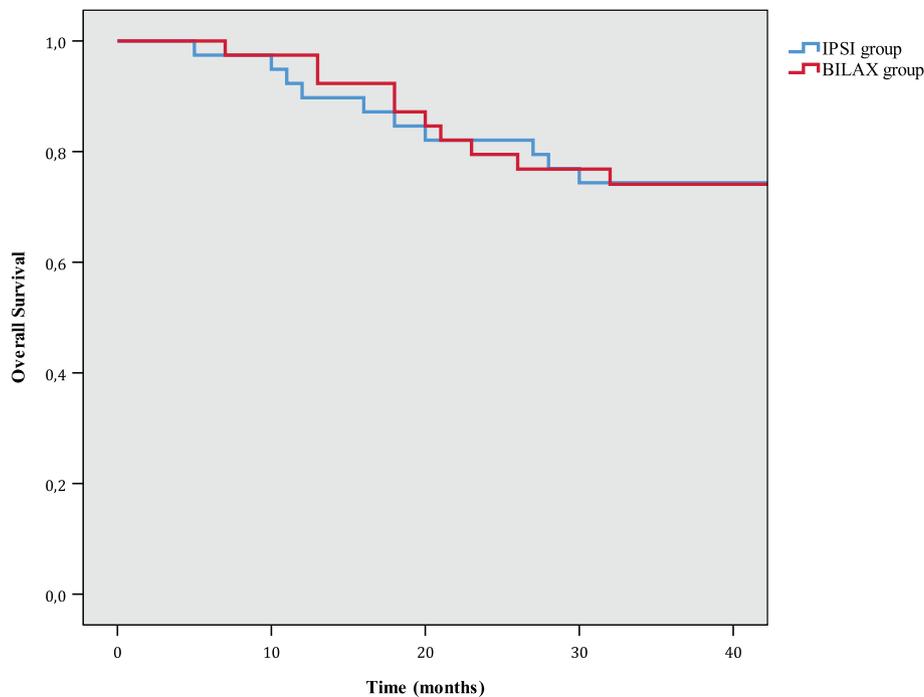
**TABLE 1** Baseline characteristics of the included patient population

Characteristic		IPSI (n = 39) (%)	BILAX (n = 39) (%)	P value
Gender	Male	23 (59.0)	26 (66.7)	.640
	Female	16 (41.0)	13 (33.3)	
Mean age at diagnosis in years ± SD		62.5 ± 8.9	59.0 ± 8.1	.759
cN-stage according to the 7th TNM				.654
	1	9 (23.1)	4 (10.3)	
	2A	6 (15.4)	6 (15.4)	
	2B	18 (46.2)	22 (56.4)	
	2C	3 (7.7)	3 (7.7)	
	3	3 (7.7)	4 (10.3)	
Histologic grade				<b>.05</b>
	1 (Well differentiated)	3 (7.7)	0	
	2 (Moderately differentiated)	20 (51.3)	4 (10.3)	
	3 (Poorly differentiated)	9 (23.1)	31 (79.5)	
	Missing	7 (17.9)	4 (10.3)	
Extranodal lymph node extension				.363
	No	24 (61.5)	19 (48.7)	
	Yes	15 (38.5)	20 (51.3)	
ACE-27 <sup>a</sup> score				.542
	0	16 (41.0)	17 (43.6)	
	1	10 (25.6)	11 (28.2)	
	2	7 (17.9)	9 (23.1)	
	3	6 (15.4)	2 (5.1)	

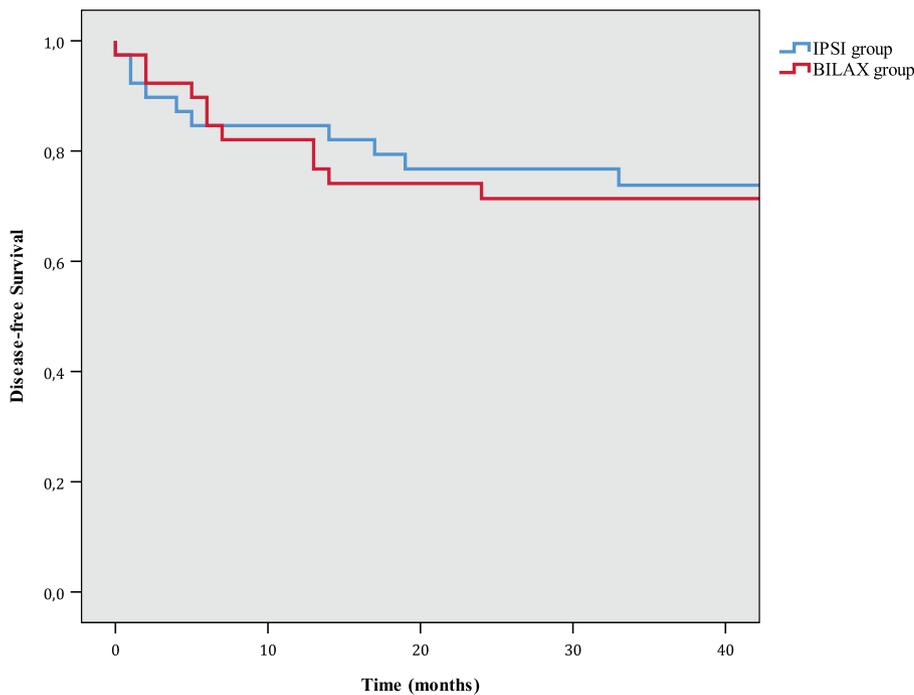
Note: Significant P values are indicated with bold numbers.

Abbreviations: BILAX, bilateral neck plus pharyngeal axis; IPSI, ipsilateral neck.

<sup>a</sup>Adult Comorbidity Evaluation-27.



**FIGURE 1** Kaplan-Meier curve of overall survival by postoperative radiotherapy (PORT) target volumes (log-rank test  $P = .654$ )



**FIGURE 2** Kaplan-Meier curve of disease-free survival by PORT target volumes (log-rank test  $P = .808$ )

method. Heterogeneity between groups were assessed using the Chi-squared test and Fisher's exact test when appropriate. Two-tailed significance levels of  $\leq 5\%$  was used for all analyzes. For frequencies and proportions descriptive statistics were used.

### 3 | RESULTS

A total of 103 patients with pathologically confirmed HNCUP treated with curative intent between January 01, 2006 and December

31, 2015 were identified. Five patients were excluded due to having a prior head and neck malignancy. Eighty-one patients received PORT after neck dissection without adjuvant chemotherapy.

PORT to the ipsilateral neck was given in 39 patients and another 39 patients underwent bilateral neck and pharyngeal axis irradiation. In 3 of the 81 patients in the neck dissection plus PORT group, radiotherapy target volume records could not be retrieved and were thus excluded in further analysis

The median follow-up duration of all 78 patients was 54 months (range 5–153 months). During this period, 26 patients died (33.3%).

Twelve patients (15.4%) developed distant metastases and 6 patients (7.7%) developed regional recurrences. The 3-year OS rate for the entire group of 78 patients was 74.2% and the 3-year DFS rate was 72.7%. The majority of the patients fell into the cN2b stage (51.3%), followed by cN1 (16.7%). Stage cN3 was observed in 9.0% of the patients. Three patients with cN2c stage were treated in the BILAX group, whereas another 3 patients with cN2c stage were treated in the IPSI group. The most common histopathologic grade found was poorly differentiated carcinoma (51.3%). Well and moderately differentiated carcinoma accounted for 34.6% of the patients. In 11 patients differentiation grade was not identified. No significant difference existed at baseline between the two groups in regards to comorbidity (ACE-27,  $P = .542$ ) and extranodal extension ( $P = .363$ , see Table 1).

**TABLE 2** Sites of recurrence by treatment group at 3-year follow-up ( $P = .779$ )

	BILAX group	IPSI group	Total
Local	1	2	3
Regional	4	2	6
Locoregional	1	0	1
Regional and distant metastasis	1	2	3
Distant metastasis only	4	4	8
Total	11	10	21

Abbreviations: BILAX, bilateral neck plus pharyngeal axis; IPSI, ipsilateral neck.

**TABLE 3** Overall late radiation-induced toxicity by treatment group as a product of cumulative score ( $P = .003$ )

	Toxicity score category			Total
	Low (0–1)	Moderate (2–3)	High ( $\geq 4$ )	
BILAX group (%)	4 (10.8)	26 (70.3)	7 (18.9)	37
IPSI group (%)	16 (47.1)	15 (44.1)	3 (8.8)	34
Total	20	41	10	71

Abbreviations: BILAX, bilateral neck plus pharyngeal axis; IPSI, ipsilateral neck.

**TABLE 4** Number of patients experiencing late radiation-induced toxicity per category by treatment group.

	BILAX group	IPSI group	Total	P value
Skin hypopigmentation	1	0	1	1.000
Skin fibrosis	23	20	43	.812
Xerostomia	31	15	46	<b>.001</b>
Telangiectasia	4	6	10	.508
Laryngeal edema	8	3	11	.190
Dysgeusia	11	6	17	.269
Hearing impairment	2	1	3	1.000
Neck edema	8	2	10	.085
Hypothyroidism	1	0	1	1.000
Total	89	53	142	

Note: Significant P values are indicated with bold numbers.

Abbreviations: BILAX, bilateral neck plus pharyngeal axis; IPSI, ipsilateral neck.

BILAX yields no significant better OS and DFS rates (log-rank test  $P = .654$ , Figure 1 and  $P = .808$ , Figure 2, respectively) compared to IPSI: the IPSI and BILAX groups had 3-year OS rates of 74.4% and 74.1%, respectively. The 3-year DFS rate in the IPSI group was 73.8%, while a 3-year DFS rate of 71.4% was reported in the BILAX group. Eleven out of 39 patients (28.2%) in the BILAX group developed a recurrence, whereas in 10 out of 39 patients (25.6%) in the IPSI group a recurrence was observed.

A subdivision of the recurrence sites into local, regional, locoregional, regional and distant, and distant metastasis only, shows no significant difference in recurrence sites between the BILAX group and the IPSI group (Table 2,  $P = .779$ ).

Three patients with only local or regional recurrences had a recurrence on the contralateral side. One patient in this group was treated with ipsilateral RT after neck dissection and subsequently developed a regional recurrence on the contralateral side. The two remaining patients developed local contralateral recurrences, of whom one belonged to the IPSI group and the other to the BILAX group.

Out of the 78 patients who underwent radiotherapy with known radiotherapy target volume records, 7 patients developed metastases or recurrences in the head and neck region within 6 months. Scoring of toxicity within the RT target volumes for the remaining 71 patients showed a significantly lower total toxicity score for patients in the IPSI group as opposed to the BILAX group (Table 3,  $P = .003$ ). In our series, 16 patients (47.1%) of the IPSI group had a low toxicity score. In contrast, 4 patients (10.8%) in the BILAX group were scored as having low radiation toxicity. The majority of the BILAX group fell into the moderate radiation toxicity group, accounting for 26 patients (70.3%),

whereas 15 patients (44.1%) of the IPSI group were classified into this same group. The BILAX group and the IPSI group had 7 (18.9%) and 3 (8.8%) patients, respectively, in the high toxicity category.

Adverse late radiotherapy effects could be divided in 9 system organ classes: skin hypopigmentation, skin fibrosis, xerostomia, telangiectasia, laryngeal edema, dysgeusia, hearing impairment, neck edema, and hypothyroidism.

Xerostomia was the most common adverse event of radiotherapy with 46 of the 71 (64.8%) patients reporting at least some degree of symptomatic xerostomia with or without dietary alterations. A significant difference existed in the distribution of xerostomia rate between the IPSI and BILAX groups. In the BILAX group, 31 patients (83.8%) reported to have some form of xerostomia as opposed to 15 patients (44.1%) in the IPSI group (Table 4,  $P = .001$ ). The second most common late radiation adverse event was skin fibrosis, with 43 patients (60.6%) in our series developing skin fibrosis after radiotherapy. No significant difference was found between the two groups ( $P = .812$ ).

## 4 | DISCUSSION

In this study, we observed 3-year OS and DFS rates of 74.2% and 72.7%, respectively, for the entire group of 98 patients. Data from other authors reveal that our survival rates are on the higher end of the spectrum, as OS rates have been reported ranging from 22% to 67%.<sup>16,20-27</sup> These reported survival rates however are 5-year survival rates, whereas we measured 3-year survival rates. Our series also did not include inoperable patients or patients treated outside protocol. A direct comparison with our observed survival rates can therefore not be fully made.

### 4.1 | IPSI or BILAX

Traditionally, bilateral neck and pharyngeal axis irradiation were deemed to be essential to prevent occult primary carcinomas developing in the pharyngeal axis. However, similar survival rates have been shown with ipsilateral irradiation only.<sup>21,22</sup> The main benefit of ipsilateral irradiation is the reduction in acute and late toxicity of the contralateral neck and pharyngeal axis. The most common late radiotherapy complications in head and neck carcinoma is xerostomia.<sup>28</sup> This is in line with what we found in our current study. In our series, 64.8% of the patients experienced some form of xerostomia 6 months post-treatment. Patients who were treated with PORT in the BILAX group were found to have significantly more often some degree of symptomatic xerostomia as opposed to patients in the IPSI group.

In this study, late toxicity was determined by scoring all categories using the CTCAE, after which a total score was obtained. A method of late toxicity scoring used by some authors is comparing the maximum toxicity scores of predefined categories, such as xerostomia or dysphagia. In our opinion, the use of a total score results in a more comprehensive overview of toxicity, as not only is the severity of the adverse events taken into account, but also the extent of the toxicity.

In the current study, we found that PORT in the BILAX group compared to PORT in the IPSI group did not result in significantly better OS and DFS rates. These findings are in line with outcomes reported by other studies.<sup>21,22</sup> The IPSI and BILAX group had OS rates of 74.4% and 74.1% ( $P = .654$ ) respectively. The DFS rate in the IPSI group was 73.8%, while a DFS rate of 71.4% was reported in the BILAX group ( $P = .808$ ). Similar outcomes were reported by Reddy and Marks<sup>22</sup> in their study regarding survival rates. In their study, Reddy and Marks compared 36 six patients irradiated to both sides of the neck and the pharyngeal axis to 16 patients irradiated with an electron beam to the ipsilateral neck only. Despite no significant difference in survival rates between both groups, they did observe significantly higher contralateral nodal failure in the ipsilateral group. Furthermore, Reddy and Marks observed a significant higher occult primary emergence rate in the ipsilateral group as opposed to the bilateral plus pharyngeal axis group.

Two occult primaries were found after treatment of HNCUP, which were determined to be of the same entity as the HNCUP through loss of heterozygosity (LOH) analysis or histomorphology examination. In these cases, one patient belonged to the BILAX group and the other patient to the IPSI group.

The patient in the BILAX group developed a bilateral locoregional recurrence. This patient initially presented with a unilateral HNCUP. Despite irradiation to the pharyngeal mucosa and the contralateral neck, 1 year after diagnosis and treatment a T4aN2cM0 oral cavity carcinoma was diagnosed. LOH analysis showed that this carcinoma and the HNCUP formed one entity. The oral cavity is in both groups outside the RT target volumes.

The patient in the IPSI group initially presented with an N2c HNCUP. This patient was treated with a bilateral neck dissection and bilateral PORT to both sides of the neck. The pharyngeal axis was in this case not part of the RT target volume. Three years after treatment a T4aN0M0 oropharyngeal carcinoma was diagnosed in this patient. Both tumors were considered to be histomorphologically identical. Due to the small numbers, no meaningful statistical information could be given regarding occult primary emergence or contralateral recurrence rates in the two groups.

In our cohort, TLM and TORS techniques were not yet used to identify the primary tumor in the work-up. Given the improved identification rates with TLM and TORS over traditional imaging and examination under anesthesia, these occult primaries could have been found in the work-up phase using these newer techniques.

A French study by Ligez et al<sup>21</sup> conducted a similar study where 59 ipsilaterally irradiated patients were compared to 36 cases of bilateral plus pharyngeal axis irradiation. In their series, no significant differences were found between the two groups regarding regional control and occult primary tumor emergence rates. Despite the fact that there was a trend observed towards higher relapse rates in the ipsilateral group as compared to the bilateral group (34% and 25%, respectively,  $P = .21$ ), 5-year OS rates were highly similar (22% and 23%, respectively,  $P = .944$ ).

A point of interest in ipsilaterally treated patients is that in case of contralateral recurrences or second primaries, the nontreated side

of the neck has a larger range of treatment options available as limits exist in reirradiation of the same target volumes. Tumor radioresistance or a significant exacerbation in radiotherapy toxicity is known to pose significant challenges to reirradiation of bilaterally irradiated patients with contralateral recurrences. For this reason, an argument could be made in favor of treatment with ipsilateral PORT only.

## 4.2 | Study strengths and limitations

A major strength of this study is that it is to our knowledge the first of its kind to compare the late radiation effects of postoperatively ipsilaterally irradiated patients to patients treated with bilateral plus pharyngeal axis irradiation. Furthermore, there was only a minimum of missing data regarding treatment given and radiotherapy target volumes.

There are, however, several study limitations. The majority of patients in the BILAX group had due to our previous treatment protocols poorly differentiated carcinomas. Prior to the 2013 treatment protocol changes, patients with poorly differentiated carcinomas were typically treated with bilateral plus pharyngeal axis irradiation after neck dissection, whereas well and moderately differentiated carcinomas were treated with neck dissections and ipsilateral irradiation to the neck. Despite the fact that the literature shows that tumor differentiation has no effects on prognosis,<sup>29,30</sup> our survival rates may have been skewed in favor of ipsilateral PORT.

Another study limitation is the fact that HPV-p16 tumor status was not taken into account, as p16 immunohistochemistry was not routinely performed at the time of treatment. Besides oropharyngeal squamous cell carcinoma, it is suggested that HPV tumor status may also play a prognostic role in HNCUP as up to 74% of HPV positivity has been reported in cases with HNCUP.<sup>31,32</sup> HPV positivity has been shown to have a beneficial prognostic effect on overall and disease free survival in HNCUP. As of now, no research has been conducted comparing ipsilateral PORT to bilateral plus pharyngeal axis PORT while taking into account HPV-p16 tumor status.

## 5 | CONCLUSION

This study shows that ipsilateral irradiation after neck dissection in patients with HNCUP does not have a negative effect on OS and DFS compared to patients who received PORT to both sides of the neck and the pharyngeal axis. Ipsilateral PORT leads to significant lower late radiation toxicity, with the greatest difference being the lower rate of xerostomia in the ipsilateral group. Further research should be conducted focusing on radiotherapy target volumes in HNCUP while taking into account the effect of HPV-p16 tumor status.

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## CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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