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HEAD AND NECK

Tumor control of cervical lymph node metastases of unknown primary origin: the impact of the radiotherapy target volume

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Abstract

Purpose Debate on the extent of treatment of neck metastasis of cancer of unknown primary tumors (CUPs) is still ongoing. In two Dutch tertiary referral centers, the post-surgical radiation target volume changed from the bilateral neck including the pharyngeal axis to the unilateral neck only, in the course of the last decade. This study aims to investigate the outcome of patients with CUP before and after de-escalation of post-surgical radiotherapy.

Methods Data of two Dutch tertiary referral centers were merged. Disease-free survival (DFS), overall survival (OS), and regional control rate (RCR) of 80 patients diagnosed with CUP (squamous cell and undifferentiated carcinomas) between 1990 and 2009 were retrospectively analyzed.

Results Thirty patients received bilateral neck and pharyngeal axis radiotherapy and 42 patients ipsilateral radiotherapy only. In another eight patients, the postsurgical radiation target volume was expanded to the contralateral neck or to the pharyngeal axis, due to suspicious lesions on imaging. The 5-year DFS, OS and RCR were 60%, 51.2%, and 80%, respectively, in the total patient population. RCR did not differ in patients treated with ipsilateral as compared to bilateral radiotherapy nor did 5-year OS and DFS. No tumors occurred in the pharyngeal axis.

Conclusion In this study, omitting elective treatment of the contralateral neck and pharyngeal axis did not lead to a decrease in locoregional control or survival rates when treating patients with CUP.

Keywords Lymph node · Pathology · Neoplasms · Unknown primary · Neck dissection · Radiotherapy · Survival rate

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Introduction

Cervical lymph node metastases of carcinomas of unknown primary origin (CUP) represent 2–5% of all malignancies in the head and neck region [1]. Diagnostic approaches in patients with CUP are comprehensive, including a full history, a physical examination, ultrasonography (US) of the neck combined with fine needle aspiration cytology (FNAC), magnetic resonance imaging (MRI) of the head and neck region and/or computed tomography (CT) with (whole body) FDG-PET scan. The latter has been introduced in the last decades. Next, a panendoscopy is performed together with systematic biopsies of suspect regions and blind biopsies of the nasopharynx and base of the tongue, as well as an ipsilateral or bilateral tonsillectomy [1, 2].

Human papillomavirus (HPV) positivity in the lymph node metastasis is an indicator for a primary cancer originating in the oropharynx [3]. Sensitivity of diagnostic work-up may therefore be improved by testing on $p16^{INK4A}$ immunohistochemistry and HPV-16 DNA polymerase chain reaction (PCR) [4]. Correspondingly, detection of Epstein–Barr virus (EBV) nucleic acids in lymph node metastases of unknown origin suggests a nasopharyngeal primary tumor [5]. Current TNM classification (Eight Edition) has adopted special staging systems for HPV and EBV-associated lymph node metastases in CUP in which these entities have been classified as oropharyngeal or nasopharyngeal carcinoma, respectively (T-stage as T0) [6].

In literature, 5-year loco-regional disease-free survival rates and 5-year overall survival (OS) rates vary in the range of 17–85 and 22–79%, respectively, dependent on the treatment modalities applied and patient characteristics [2, 7–10]. Generally, treatment consists of primary surgery (with or without postoperative radiotherapy) or primary radiotherapy. Radiotherapy comprises uni- or bilateral neck radiation, with or without radiation of the pharyngeal axis. In the last years, chemoradiotherapy has also been applied as a treatment option for selected cases [11]. However, the optimal treatment for CUP and which tumor and patient characteristics should steer treatment decision-making, is still a matter of debate [10]. A particular issue is whether radiotherapy should include the bilateral neck and pharyngeal mucosa or only the unilateral neck. Extensive radiotherapy may prevent recurrence in the contralateral neck and outgrowth of the occult primary tumor at the mucosal site, but this is at the cost of significant increase of acute and late morbidity [7, 12–15]. Some studies suggest that there is no difference in OS between patients treated with unilateral or bilateral radiotherapy and that patients can be spared the morbidity of bilateral treatment [12, 13]. Recently, two reviews on treatment modalities in CUP also concluded that more evidence is needed regarding the extent of radiotherapy [9, 10].

The aim of this study is to determine the outcome of patients with cervical CUP in relation to the applied treatment in two Dutch head and neck clinics. Results of post-surgical unilateral versus bilateral post-operative irradiation and radiotherapy of the pharyngeal axis are compared in terms of disease-free survival (DFS), regional recurrence rate (RCR) and OS. Also, the relation of HPV detection in affected lymph nodes with outcome was investigated retrospectively.

Material and methods

Patients

Data of patients presenting with cervical CUP at the departments of Otorhinolaryngology, Head and Neck Surgery of the Maastricht University Medical Centre (Maastricht UMC: Center 1) ($n=60$) and the Radboud University Medical Center Nijmegen (Radboud UMC: Center 2) ($n=64$), the Netherlands, from 1990 until 2009 were retrospectively assessed. In- and exclusion of patients with CUP are described in Fig. 1. Approval by the ethics committee of both institutes was obtained.

All patients with CUP were discussed in the centers' multidisciplinary head and neck tumor boards: the most recent edition of the TNM classification of the International Union Against Cancer was used to determine treatment plans. In the included era, HPV and EBV were not routinely tested.

Diagnostic work-up

The diagnostic work-up included a full history, a physical examination, ultrasonography (US) of the neck combined with fine needle aspiration cytology (FNAC), magnetic resonance imaging (MRI) of the head and neck region and/or computed tomography (CT) with (whole body) FDG-PET scan, introduced in the last decade. Also, a panendoscopy was performed together with systematic biopsies of suspect regions and blind biopsies of the nasopharynx and base of the tongue, as well as an ipsilateral or bilateral tonsillectomy. The contralateral tonsil was not removed routinely. If the patient had undergone tonsillectomy in the past, only biopsies of the tonsillar fossa were obtained.

Treatment

In both centers, the protocol for treatment of CUP syndrome is based on the Dutch national guideline: "Primary tumor unknown" [16]. Initially, treatment of CUP involved an ipsilateral neck dissection with adjuvant bilateral radiotherapy including radiotherapy of the pharyngeal axis. In the course of the last decade, the radiation target volume was reduced.

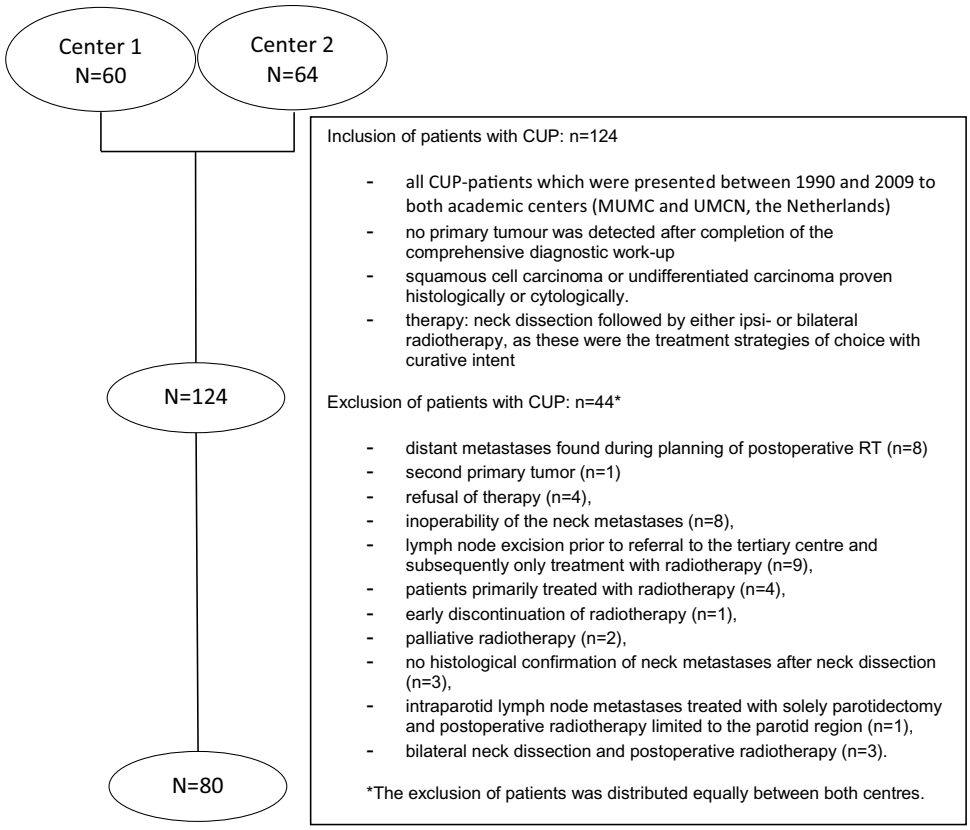

Fig. 1 In- and exclusion criteria used for selecting patients with CUP in both participating centers

The practice of adjuvant radiotherapy of the contralateral N0-neck, and radiotherapy of the pharyngeal axis were abandoned and changed to post-operative ipsilateral radiation only.

Radiotherapy in Maastricht UMC The elective radiation dose to the uninvolved neck regions and the pharyngeal axis was 46–50 Gy. The regions of the involved nodes were treated up to 66 Gy.

Radiotherapy in Radboudumc The median elective radiation dose to the uninvolved neck regions and pharyngeal axis was 50 Gy and the median dose delivered to the pathologically involved node level(s) was 64 Gy, range 56–70 Gy, depending on histopathological criteria (higher dose if extranodal growth or close or positive resection margins).

Radiation therapy was administered using techniques that were available in those periods: in the beginning of the study, patients, undergoing bilateral neck irradiation including the mucosal axis, were treated with 2-D radiation with parallel opposing beams for the upper neck and a matching anterior lower neck field. Unilateral radiation for patients receiving ipsilateral neck radiation only was given by oblique wedge-pair beams. These techniques evolved into 3-D radiation and ultimately intensity modulated radiation therapy (IMRT).

Chemoradiation as part of the treatment protocol of CUP was not used in both centers during the period of inclusion of this study. None of the included patients were therefore treated with adjuvant and/or concomitant chemotherapy.

Follow-up

Follow-up consisted of a periodic history and physical examination during 5 years in all patients and was scheduled every 2 months in the 1st year and extended to every 6 months during the 5th year after treatment of CUP. In case of suspect local, regional and/or distant failure, additional imaging tests and/or panendoscopy were performed, when considered necessary and when further treatment options were still present.

Statistics

Statistical analysis of the data was performed using SPSS software (v17.0). When comparing groups, the Pearson Chi-square test was used. Survival rates and data on disease-specific control in patients were calculated from the date of the first pathological confirmation of disease. There were no patients lost to follow-up. DFS, OS, and RCR were computed with Kaplan–Meier survival analysis.

DFS was defined as the survival until recurrence of disease locally, regionally and/or distantly. To report on the value of ipsilateral versus bilateral radiotherapy of the neck,

the RCR is used. OS was defined as survival until death. The log-rank test was used for univariate comparisons of the survival functions. Nominal two-sided p values are reported, the significance level was set at $p \leq 0.05$.

HPV status

The presence of HPV was retrospectively determined according to the algorithm described by Smeets et al. [17]. Thirty-two tumor samples in the center 1 and 40 samples in the center 2 were available in which immunohistochemical (IHC) detection of $p16^{INK4A}$, and/or HPV16 DNA polymerase chain reaction (PCR) were performed.

Results

Study population

No differences were noted regarding the diagnostic work-up in the two centers. In total, 80 patients with CUP were analyzed in this study (Table 1). They all underwent a neck dissection followed by post-operative radiotherapy with curative intent (Table 2). Bilateral radiotherapy combined with irradiation of the pharyngeal axis was performed in 30 patients (38%) and ipsilateral radiotherapy without irradiation of the pharyngeal axis in 42 (52%).

Due to suspicious lesions found on imaging—but not histologically or cytologically confirmed, postoperative ipsilateral radiotherapy was combined with treatment of the pharyngeal axis in two patients, and another five patients received radiotherapy of the bilateral neck without irradiation of the pharyngeal axis. Finally, one patient with limited pN1 disease did not receive additional radiotherapy of the ipsilateral neck, but instead the pharyngeal axis was irradiated because of a suspected lesion found by imaging (Table 2).

Outcome

Five-year DFS, OS and RCR were 60%, 51.2% and 80%, respectively (Table 3). There were no significant differences in survival between the group of patients irradiated ipsilaterally and those treated bilaterally. Also, the 5-year regional control rates did not differ between both groups, respectively, 77.3% and 82.9% ($p = 0.54$) (Fig. 2), nor did the 5-year contralateral recurrence rate ($p = 0.23$).

In both groups, no primary tumors occurred in the pharyngeal axis during follow-up. Two primary tumors, both located in the floor of the mouth outside the pharyngeal axis, emerged during follow-up in the total population (in both patients 31 months after initial treatment). The first patient was initially treated with bilateral neck irradiation without the pharyngeal axis. The second patient was treated with radiotherapy of the bilateral neck and pharyngeal axis.

Twenty-three patients developed distant metastases during follow-up. This was not related to the extent of radiotherapy used.

Table 1 Demographic data

	Total patient population $n = 80$	Center 1 $n = 43$	Center 2 $n = 37$	p value
Follow-up time (months)				
Mean	43.1	45.3	40.6	NS
Range	3–200	4–200	3–116	
Age (years)				
Mean	63.1	62,9	63.2	NS
Range	41–86	41–83	46–86	NS
Male/female	59/21	35/8	24/13	NS
Non-smoker, n (%)	1 (1.25)	1 (2.3)	0 (0)	NS
Alcohol consumption ≤ 2 U/day, n (%)	36 (45)	18 (41.86)	16 (43.2)	NS
Histopathological data				
Squamous cell carcinoma	71	36	35	
Undifferentiated carcinoma	9	7	2	
pN status (UICC version 7)				
pN1	3	3	0	NS
pN2a	17	8	9	
pN2b	40	20	20	
pN3	20	12	8	

NS not significant

Table 2 Type of treatment based on pN status

	Number of patients	%	pN1	pN2a	pN2b	pN3	*p* value
Type of neck dissection							
Radical neck dissection	43	54	1	8	22	12	
Modified radical neck dissection	22	28	1	6	12	3	
Extended radical neck dissection	10	12	0	1	4	5	
Selective neck dissection (regions I/II/III)	5	6	1	2	2	0	NS
Type of postoperative therapy							
Ipsilateral radiotherapy of the neck	44	55	2	11	21	10	NS
Radiotherapy							
Bilateral radiotherapy of the neck	35	44	0	6	19	10	NS
Radiotherapy of the pharyngeal axis	33	41	2	6	16	9	NS
Type of combined therapy							
ND + RT-ipsi	42	52	1	11	20	10	
Therapeutical strategy							
ND + RT-bilat + RT-PA	30	38	0	6	15	9	
ND + RT-ipsi + RT-PA	2	3	1	0	1	0	
ND + RT-bilat	5	6	0	0	4	1	
ND + RT-PA	1	1	1	0	0	0	NS
Total patient population	80	100	3	17	40	20	

NS not significant, *ND* neck dissection, *RT-bilat* radiotherapy of the bilateral neck, *RT-PA* radiotherapy of the pharyngeal axis

HPV status

In total, 4 out of 72 histopathological samples of cervical metastases tested positive for both $p16^{INK4A}$-expression and HPV DNA (5.7%), 3 patients of which were treated with radiotherapy of the pharyngeal axis, including the oropharyngeal mucosa. Five-year DFS, OS and RCR in the four HPV-positive patients were all 100%.

Discussion

The objective of this study was to investigate the outcome of patients with CUP before and after de-escalation of post-surgical radiotherapy applied in two Dutch tertiary referral centers. In this study, no differences were found regarding survival and regional control rate in patients with CUP treated with neck dissection and post-operative bilateral radiotherapy including radiation of the pharyngeal axis ($n = 30$) compared to patients with CUP treated with neck dissection and post-operative ipsilateral radiotherapy solely ($n = 42$). Eight patients received additional therapy of the contralateral neck or the pharyngeal axis as a consequence of radiological suspicion of disease although this was not pathologically confirmed. In addition, no primary tumors occurred in the pharyngeal axis, even though radiotherapy to the pharyngeal axis was abandoned in 47 out of 80 patients.

Unilateral versus bilateral radiotherapy

In our study, no differences in survival rates and moreover no differences in regional control rates were found between the group of CUP patients treated ipsilaterally and those treated with bilateral radiotherapy of the neck.

These results correspond with previous research by our group in which 29 patients of our cohort were compared with 22 patients with CUP in a German tertiary head and neck cancer referral center [18]. In that study, significantly more contralateral recurrences were seen in the ipsilateral radiated patients compared to the bilateral radiated patients. In the current study, the above-mentioned cohort of 29 patients was expanded to 80 patients which were homogeneously treated; the regional recurrence rate concerning contralateral relapses did not significantly differ.

In an early review of literature by Nieder et al., a median nodal relapse of 19% (range 8–45%) after comprehensive radiotherapy compared to 51.5% (range 31–63%) after ipsilateral radiotherapy was described [13]. However, regarding 5-year overall survival rates no differences were noted between both groups (50%, range 34–63%, compared to 36.5%, range 22–41%, respectively). In a more recent meta-analysis by Liu et al. of 16 studies that report outcome between bilateral versus ipsilateral radiotherapy [9], a significant reduced relative risk of 0.61 was described for nodal recurrence in patients treated with more comprehensive radiotherapy, however, no differences between both groups were found for 5-year OS and DFS. This lack of difference

Table 3 Five-year overall survival, disease-free survival and regional control rate in the total patient population and in relation with pN status and therapy

	N	Disease-free survival	Overall survival	Regional control rate
		%	%	%
Total patient population	80	60	51.2	80
pN status				
pN1	3	100	66.7	100
pN2a	17	88.2	76.5	88.2
pN2b	40	45	45	80
pN3	20	60	40	70
	p value	0.014	NS	NS
Type of neck dissection				
Radical neck dissection	43	53.5	41.9	76.7
Modified radical neck dissection	22	72.7	63.6	86.4
Extended radical neck dissection	10	40	50	70
Selective neck dissection (regions I/II/III)	5	100	80	100
	p value	0.047	NS	NS
Post-operative ispilateral				
Post-operative ipsilateral RT	44	61.4	47.7	77.3
Versus bilateral radiotherapy				
Post-operative bilateral RT	35	57.1	54.3	82.9
	p value	NS	NS	NS
Post-operative RT of the pharyngeal axis				
Included	33	60.6	54.5	81.8
Not included	47	59.6	48.9	78.7
	p value	NS	NS	NS
Therapy strategy				
ND + RT-ipsi[a]	42	61.9	50	78.6
ND + RT-bilat-PA[b]	30	60	56.7	83.3
	p value	NS	NS	NS

[a]ND + RT-ipsi: neck dissection and post-operative ipsilateral radiotherapy without radiation of the pharyngeal axis

[b]ND + RT-bilat-PA: neck dissection with post-operative radiotherapy including radiation of the pharyngeal axis

in overall survival between both treatment groups was confirmed in a recent review of Müller von der Grün et al. [10]. Our study also shows no significant differences regarding 5-year DFS and OS. Moreover, no differences were found regarding (ipsilateral and contralateral) regional control rates between both groups. In our study, the inclusion of the contralateral neck in five patients in which radiologically suspected lesions were found during radiation treatment planning without histologically or cytologically confirmation may have contributed to the lack of differences in 5-year RCR between both groups. The strict evaluation criteria of CUP and uniform treatment (all patients underwent unilateral neck dissection combined with post-operative radiotherapy) may have contributed to this favorable RCR when compared to other studies. Altogether, in our study metastatic disease ($n = 23$) was a more common reason of disease failure than locoregional failure ($n = 18$). The radiotherapy target volume was not related to the occurrence of distant metastases. This supports the current findings in literature that the possible benefit of extended volume radiotherapy on a slightly improved locoregional control, if present, cannot be translated into improved overall survival rates [10, 19].

Radiotherapy of the pharyngeal axis

In our study, no primary tumors occurred in the pharyngeal axis regardless of inclusion of the pharyngeal mucosa in the radiation target volume. Two out of 80 patients developed a primary tumor during follow-up, both located in the oral cavity, which is generally not included in the target volume of pharyngeal axis irradiation. In a review of literature by Reddy et al., a higher local (mucosal) failure is reported in patients who received treatment to the neck alone (44%) compared to those who received radiotherapy

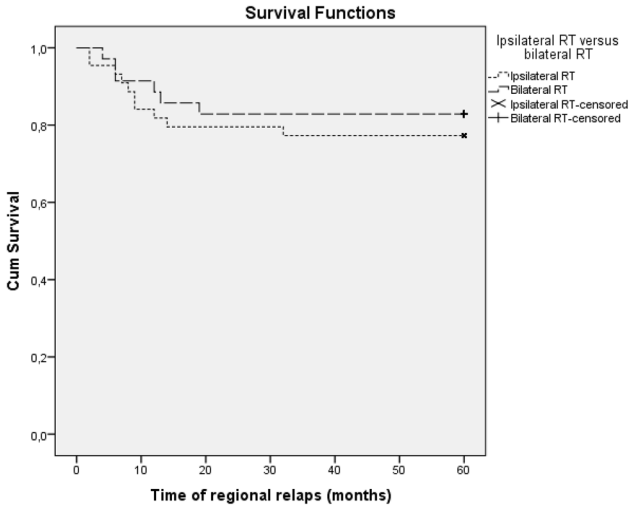

Fig. 2 Regional control rate comparing patients treated with post-operative ipsilateral ($n=44$) versus bilateral radiotherapy of the neck ($n=35$)

to the pharyngeal axis (8%) [14]. Also, lower primary tumor emergence rates were described for patients treated with bilateral radiotherapy when compared to patients treated with ipsilateral radiotherapy [7, 14]. A recent meta-analysis also reported a significantly lower 5-year primary tumor emergence rate (12%; RR = 0.44) and a lower 5-year DFS rate when comprehensive radiation volumes were used [9]. Again, the 5-year overall survival did not differ significantly for ipsilateral and comprehensive radiated patients, whereas acute severe toxicity and xerostomia were significantly increased in the latter group.

Contributing factors to the current reported low primary emergence rate might be the strict evaluation criteria of CUP in which only true CUP patients are selected, the comprehensive diagnostic work-up used in both centers in this study and the addition of radiotherapy of the pharyngeal axis in three patients in which lesions were suspected on imaging studies. The importance of a comprehensive diagnostic work-up is illustrated by the significant decrease of primary tumor emergence rates in literature after the introduction of PET-CT in the radiation treatment planning in CUP patients [7, 10, 13]. Nevertheless, the additional value of PET remains hard to quantify next to panendoscopy with blind biopsies of the base of tongue and tonsillectomy [20].

Furthermore in literature, the importance of selecting of irradiation volumes regarding the treatment of the primary site is emphasized with the introduction of IMRT, which allows preserving organs at risk (salivary tissue in particular), but on the other hand can miss the primary tumor that coincidently would have been treated with older less sophisticated techniques.

HPV and CUP

In the 8th edition of the UICC's TNM classification for CUP patients, HPV- and EBV-associated lymph node involvement is staged separately corresponding to N-staging in HPV-associated oropharyngeal and EBV-associated nasopharyngeal carcinomas. Inclusion of HPV and EBV testing in CUP may support prediction of the prognosis and the location of the primary tumor in the oropharynx and/or nasopharynx respectively [21]. The prevalence of HPV-associated head and neck carcinomas still rises and the prognosis remains more favorable as in non-HPV-associated carcinomas. As patients treated with radiotherapy of the ipsilateral neck only were more often included in the second half of this study, it was interesting to investigate the possible presence of an HPV endemic in this group and its influence on the presented outcome. Patients in our study cohort were treated before the introduction of HPV and EBV assessment to the routine diagnostic work-up and a retrospective analysis for HPV presence could be performed in 72 out of 80 patients. Nevertheless only in four patients HPV/p16^{INK4a} presence was detected. Possibly, most HPV-positive primary tumor of the oropharynx were detected by tonsillectomy or blind biopsies of the oropharyngeal region resulting in low percentages of HPV-positive true CUPs [22].

Study design

In previous research, we compared 29 patients of the currently presented cohort with 22 patients from a cohort in Germany [22]. Due to a relative heterogenous treatment strategy in both centers, this study aimed to collect a larger patient group with a more homogenous therapeutic approach. Therefore, data were merged from two Dutch tertiary referral centers in which the diagnostic and therapeutic development evolved almost identically, in the period of inclusion of more than 2 decades. This retrospective study still encountered possible limitations to investigate the impact of radiotherapy target volume of the neck and pharyngeal axis on tumor control in CUP. The number of included patients is rather small ($n=80$). However, the selected study group was derived from a collection of two cohorts which were homogenously treated in two Dutch tertiary referral centers and was the result of a meticulous exclusion of non-true CUP. The inclusion period was extended over 2 decades: in the 1st decade of inclusion, radiotherapy of the bilateral neck and the pharyngeal axis was predominantly performed, whereas post-surgical ipsilateral radiotherapy was more often applied in the 2nd decade of inclusion. This latter group experienced a higher availability of IMRT compared to 2DRT in the first group, and was also more prone to have PET-CT included in the diagnostic work-up. The chance to coincidently radiate a missed primary tumor with IMRT is nevertheless smaller

then with older less sophisticated techniques. Regarding the role of PET, de Bree et al. already mentioned the inability to quantify the additional value of PET next to a comprehensive diagnostic work-up including panendoscopy, tonsillectomy and blind biopsies of the base of tongue [19]. The influence of a possible HPV endemic in the latter half of the study was also minimalized as only 4 (out of 72) patients turned out to have HPV-associated disease. Again, the role of a comprehensive diagnostic work-up, particularly of the oropharyngeal region, may have led to this low prevalence of HPV in CUP.

To create the ideal world to compare the outcome of ipsilateral radiotherapy only with a comprehensive radiotherapeutic regime in CUP patients, Nieder et al. recommended in 2001 a randomized controlled trial [13]. It is reported that a similar trial which started in 2002 was never accomplished (EORTC-24001-22005) as a consequence of very limited patient enrollment [10]. The low prevalence of patients with CUP and the heterogeneous treatment strategies as a consequence of the lack of well-designed studies are important limiting factors to create a study design with an acceptable methodological work-up regarding this subject. A prospective multicenter approach in which homogenous therapeutic strategies are applied is considered to be feasible.

Conclusion

In this study, omitting irradiation of the pharyngeal axis in patients with cervical lymph node metastases of unknown primary origin after performing a comprehensive diagnostic work-up, including PET-CT and panendoscopy with tonsillectomy and blind biopsies of the base of tongue, did not result in the emergence of a primary tumor in the pharyngeal axis during 5 years of follow-up. This can avoid acute and late toxicity of comprehensive radiotherapy of the pharyngeal mucosa with significant improvement of long-term quality of life of these patients. Also, the absence of post-surgical radiotherapy of the contralateral neck in CUP did not lead to a decrease of regional control rates nor of survival rates. The occurrence of distant metastases was the most important reason for failure of disease-free survival in this study. The true impact of radiotherapy target volume in CUP patients still needs further investigation and at least requires a prospective multicenter approach.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Medisch Ethische Commissie Maastricht University Medical Center and Radboud University Medical Center Nijmegen, The Netherlands) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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