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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

The prognostic role of radiotherapy and radiotherapy target in cervical lymph node metastatic squamous cell carcinoma with unknown primary: a retrospective study

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Abstract

Objectives Aim to analyze the effect of radiotherapy for cervical lymph node metastatic carcinoma with unknown primary (CCUP) and compare the survival benefits between Comprehensive radiotherapy and Involved Field radiotherapy.

Materials and methods The patients diagnosed with CCUP between 2009 and 2019 in our institution were analyzed retrospectively. The categorical variables were tested by χ^2 test. Kaplan–Meier method was used for survival analysis. Log-rank test and Cox proportional hazards regression were performed with overall survival (OS) and disease-free survival (DFS) as the primary outcome variables.

Results Of 139 patients, 64.7% (90/139) of them received radiotherapy. Of the 90 patients who underwent radiotherapy, 45.6% (41/90) received Involved Field radiotherapy and the rest 49 patients received Comprehensive radiotherapy. The median follow-up of 139 patients is 69 months. The 1-year, 3-year, and 5-year OS rates are 87%, 62%, and 39%, respectively, and the DFS rates are 73%, 45%, and 29%, respectively. Multivariate analysis of 139 patients with CCUP shows that differentiation grade, N stage, radiotherapy, and the length of the largest lymph node (D_{maxLN}) are the independent prognostic factors for both OS and DFS. Subgroup analysis of 90 patients who received radiotherapy shows that the Comprehensive radiotherapy group has a better OS ($P<0.001$) and DFS ($P<0.001$) compared with Involved Field radiotherapy.

Conclusion Radiotherapy is the independent prognostic factor for CCUP. Comprehensive radiotherapy may be superior to Involved Field radiotherapy in survival benefits.

Keywords Cervical lymph node metastatic carcinoma with unknown primary · Radiotherapy · Target delineation · Prognosis

Introduction

Cervical lymph node metastatic carcinoma with unknown primary (CCUP) refers to metastatic cancer of the cervical lymph node without a definite primary after systemic detection (Wang et al. 2018). It represents approximately 2–5%

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of all head and neck cancer (Straetmans et al. 2020). This proportion has been diminished because of the advance of the diagnostic methods to locate the primary (Grau et al. 2000; Jereczek-Fossa et al. 2004). The diagnoses of CCUP included a relevant history of tumor, clinical presentation, imaging, and panendoscopy (Arosio et al. 2017). The imaging examinations such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography-Computed Tomography (PET-CT) contribute to finding the primary tumor site. Moreover, several studies also suggest that Human Papillomavirus (HPV) and Epstein–Barr virus (EBV) testing may help to indicate a possible primary site (Motz et al. 2016; Mălin et al. 2012; Faquin 2014; Jannapureddy et al. 2010; Cheol Park et al. 2017). Squamous cell carcinoma (SCC) is the most common histologic type of CCUP accounting for 75–90%, followed by adenocarcinoma and undifferentiated carcinoma (Arosio et al. 2017).

For patients with CCUP, the main treatments include surgery, radiotherapy, and chemotherapy (Strojan et al. 2013). The choice of single or combined modality treatment is according to the condition of the disease (Pfister et al. 2020). Single modality treatment is recommended for patients with N1 or N2a stage, low-volume neck disease, and without lymph node extranodal extension (ENE). For the patient with a history of biopsy (incisional or excisional) or high-volume neck disease, a multimodality treatment is favored (Martin and Galloway 2015; Pavlidis et al. 2009). Despite this, there are still dispute about the diagnosis and treatment, particularly in radiotherapy. The target of radiotherapy has been widely discussed in the pieces of literature. Some studies suggest that a more extensive target of radiotherapy not only cannot improve the local control rates and survival but also could cause serious toxicities (Straetmans et al. 2020; Grau et al. 2000; Martin and Galloway 2015; Pflumio et al. 2019; Mizuta et al. 2018; Ligey et al. 2009; Lu et al. 2009; Poon et al. 2020). On the contrary, other researchers hold that extensive targets can bring larger survival benefits to patients with CCUP (Wang et al. 2018; Jereczek-Fossa et al. 2004; Reddy and Marks 1997). The relative rarity of incidence of CCUP means it is difficult to conduct a prospective study with guiding significance for treatment (Galloway and Ridge 2015). Therefore, the radiation therapy of CCUP is a question that needs further study.

This present study aims to investigate the prognostic role of radiotherapy in CCUP and to clarify whether there is a difference in survival benefits between two different irradiation targets: Comprehensive radiotherapy and Involved Field radiotherapy.

Materials and methods

Inclusion and exclusion criteria

The patients diagnosed with CCUP between 2009 and 2019 in West China Hospital of Sichuan University were analyzed. The inclusion and exclusion criteria were as follows. The criteria of inclusion: (1) neck mass is the first manifestation; (2) the diagnosis of a malignant tumor is supported by pathology and the histological type is squamous cell carcinoma (SCC); (3) lymph node lesion locates above the cricoid cartilage; (4) no other lesions were found by systemic examination (imaging such as CT, MRI or PET-CT and panendoscopy). The criteria of exclusion: (1) patients have a history of other tumors and the history of removal of the suspicious tumor; (2) the follow-up data of the patient are incomplete. Finally, 139 patients were included.

Data collection

The relevant data we collected included the age at diagnosis, gender, the location of the involved lymph node, the length of the largest lymph node (D_{maxLN}), histology, differentiation grade, ENE, N stage, the information of the treatment, and survival outcomes. The D_{maxLN} was determined by imaging (CT, MRI, or PET-CT). The N stage of disease was determined by the American Joint Committee on Cancer (AJCC) TNM Staging System for Cervical Lymph Nodes and Unknown Primary Tumors of the Head and Neck (8th ed., 2017). The treatment-related data contained information on surgery (neck dissection), radiotherapy, and chemotherapy.

Grouping method

Patients who received radiotherapy were divided into two groups: the group of Involved Field radiotherapy and the group of Comprehensive radiotherapy. The target of Involved Field radiotherapy only included the neck on the involved side. Besides the neck in the involved side, the target in Comprehensive radiotherapy also included the neck in another side or putative primary mucosa or both of them.

Endpoints and statistics analysis

The primary endpoints are overall survival (OS) and disease-free survival (DFS). OS is defined as the time from the date of initial diagnosis to the date of death from any cause or patient censoring at the last follow-up. DFS is measured from the date of curative treatment until death, relapse, or second primary tumor, whichever occurred first.

The categorical variables were tested by χ^2 test. Survival was calculated by the Kaplan–Meier method and compared by the Log-rank test. Multivariate Cox proportional hazards model was used to identify independent factors. Statistical analysis was performed using R (version 4.0.1; http://www.r-project.org/). The two-side $P < 0.05$ is defined as statistically significant.

Results

Patient characteristics

The characteristics of the 139 patients in this study are summarized in Table 1. Most of them inadvertently found the neck mass as the first clinical manifestation, and the rest of them found the neck mass by routine checkups. The median follow-up was 69 months. 69.8% (97/139) patients were male. Most patients had unilateral cervical mass (74.8%; 104/139). 84.2% (117/139) patients had a poor tumor differentiation level and others were all moderately and well-differentiated tumors. ENE Positive was identified in 33.1% (46/139) patients. 42.4% (59/139) patients underwent the surgery (neck dissection). All patients received chemotherapy, and the chemotherapy regimen of them was platinum-based chemotherapy, with a different combination of taxanes, 5-fluorouracil, and platinum-based drugs. 64.7% (90/139) received radiotherapy. Of the 90 patients who underwent radiotherapy, 48 (53.3%) patients received neoadjuvant chemotherapy, 77 (85.6%) patients received chemotherapy simultaneously, and a small part of patients (20; 22.2%) received chemotherapy after radiotherapy.

The characteristics of patients who received radiotherapy are summarized in Table S1. 90 patients were classified into

Table 1 Characteristics of patients

Characteristics	Overall ($n=139$)	No radiotherapy ($n=49$)	Radiotherapy ($n=90$)	*P* value
Age				
< 50	59 (42.4)	18 (36.7)	41 (45.6)	0.409
≥ 50	80 (57.6)	31 (63.3)	49 (54.4)	
Gender				
Male	97 (69.8)	34 (69.4)	63 (70.0)	1
Female	42 (30.2)	15 (30.6)	27 (30.0)	
Differentiation				
Poorly differentiated	117 (84.2)	40 (81.6)	77 (85.6)	0.717
Moderately and well differentiated	22 (15.8)	9 (18.4)	13 (14.4)	
N[a]				
≤ N2b	42 (30.2)	10 (20.4)	32 (35.6)	0.096
> N2b	97 (69.8)	39 (79.6)	58 (64.4)	
Lesion				
Unilateral	104 (74.8)	35 (71.4)	69 (76.7)	0.635
Bilateral	35 (25.2)	14 (28.6)	21 (23.3)	
D_{maxLN}				
≤ 3 cm	73 (52.5)	26 (53.1)	47 (52.2)	1
> 3 cm	66 (47.5)	23 (46.9)	43 (47.8)	
ENE				
Negative	93 (66.9)	32 (65.3)	61 (67.8)	0.915
Positive	46 (33.1)	17 (34.7)	29 (32.2)	
Surgery				
No	80 (57.6)	9 (18.4)	71 (78.9)	< 0.001
Yes	59 (42.4)	40 (81.6)	19 (21.1)	
Chemotherapy				
No	0 (0.0)	0 (0.0)	0 (0.0)	
Yes	139 (100.0)	49 (100.0)	90 (100.0)	

[a]N stage of disease was determined by the American Joint Committee on Cancer (AJCC) TNM Staging System for Cervical Lymph Nodes and Unknown Primary Tumors of the Head and Neck (8th ed., 2017)

D_{maxLN} the length of the largest lymph node, *ENE* lymph node extranodal extension

two groups according to the target of radiotherapy. 45.6% (41/90) patients received Involved Field radiotherapy. In patients who received Comprehensive radiotherapy, 12.2% (6/49) of patients included the neck in the healthy side in the target additionally. 28.6% (14/49) of patients included the putative primary mucosa in the target additionally. 59.2% (29/49) of patients included both neck in the healthy side and putative primary mucosa in the target additionally. Among these 90 patients, 44% (40/90) of them were treated with Volumetric-Modulated Arc Radiotherapy (VMAT), 56% (50/90) of them were treated with Intensity Modulated Radiation Therapy (IMRT). The dose to the neck on the involved side was 50–70 Gy (involved lymph node: 70 Gy; drainage: 50–60 Gy), to the neck on the healthy side was 50–56 Gy, and to the putative primary mucosa is 60–66 Gy.

During the follow-up period, 71 (51.1%) patients exited because of death.

Survival outcomes

In all 139 patients, the 1-year, 3-year, and 5-year OS rates are 87%, 62%, and 39%, respectively (Fig. 1A), and the DFS rates are 73%, 45%, and 29%, respectively (Fig. 1B). In the 90 patients who received radiotherapy, the 1-year, 3-year, and 5-year OS rates are 94%, 74%, and 48%, respectively, and the DFS rates are 80%, 53%, and 34%, respectively. In the other 49 patients without radiotherapy, the 1-year, 3-year, and 5-year OS rates are 73%, 39%, and 22%, respectively, and the DFS rates are 61%, 31%, and 18%, respectively. The difference in survival outcomes between these two groups is statistically significant (OS: $P<0.001$; DFS: $P<0.001$).

Univariate analysis

Univariate analysis shows that differentiation grade of tumor (OS: HR = 0.38, 95% CI = 0.16–0.88, $P=0.023$; DFS: HR = 0.37, 95% CI = 0.16–0.86, $P=0.020$; Fig. 2C, L), N stage (OS: HR = 5.2, 95% CI = 2.5–11, $P<0.001$; DFS: HR = 5.6, 95% CI = 2.7–12, $P<0.001$, Fig. 2D, M), D_{maxLN} (OS: HR = 2.2, 95% CI = 1.4–3.6, $P=0.001$; DFS: HR = 2.2, 95% CI = 1.4–3.6, $P=0.001$, Fig. 2F, O), ENE (OS: HR = 1.9, 95% CI = 1.2–3.1, $P=0.008$; DFS: HR = 2, 95% CI = 1.2–3.2, $P=0.005$, Fig. 2G, P), and radiotherapy (OS: HR = 0.34, 95% CI = 0.22–0.55, $P<0.001$; DFS: HR = 0.39, 95% CI = 0.25–0.62, $P<0.001$, Fig. 2I, R) are associated with prognosis (Table S2).

Multivariate analysis

Variables with statistical significance ($P<0.05$) in univariate analysis were included into multivariate analysis, and the results summarized in Table 2. It shows that the differentiation grade of tumor (OS: HR = 0.22, 95% CI = 0.09–0.54, $P=0.001$; DFS: HR = 0.23, 95% CI = 0.09–0.56, $P=0.001$), N stage (OS: HR = 5.29, 95% CI = 2.42–11.60, $P<0.001$; DFS: HR = 5.18, 95% CI = 2.37–11.34, $P<0.001$), D_{maxLN} (OS: HR = 2.08, 95% CI = 1.28–3.39, $P=0.003$; DFS: HR = 1.93, 95% CI = 1.18–3.16, $P=0.009$) and radiotherapy (OS: HR = 0.24, 95% CI = 0.14–0.39, $P<0.001$; DFS: HR = 0.32, 95% CI = 0.19–0.53, $P<0.001$) are the independent factors for OS and DFS.

Subgroup analysis

Further investigation about the effect of different irradiation targets on the prognosis of patients with CCUP was conducted. 90 patients who received radiation therapy were included in this subgroup analysis.

In the 49 patients of Comprehensive radiotherapy group, the 1-year, 3-year and 5-year OS rates are 100%, 88% and 59%, respectively, and the DFS rates are 88%, 65% and 45%, respectively. However, the 1-year, 3-year and 5-year OS rates are 88%, 59% and 34%, respectively, and the DFS rates are 71%, 39% and 22%, respectively in the Involved

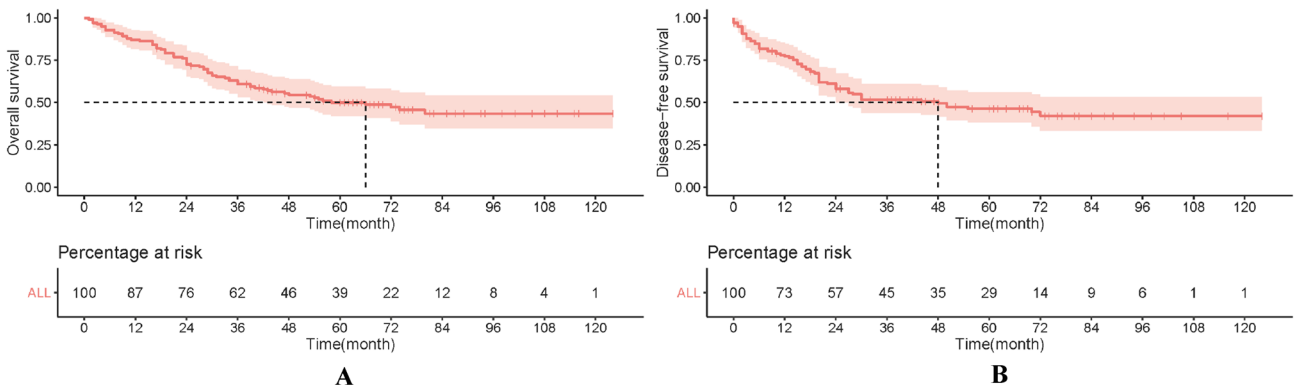

Fig. 1 The survival curves of 139 patients. **A** The overall survival (OS) of 139 patients. **B** The disease-free survival (DFS) of 139 patients

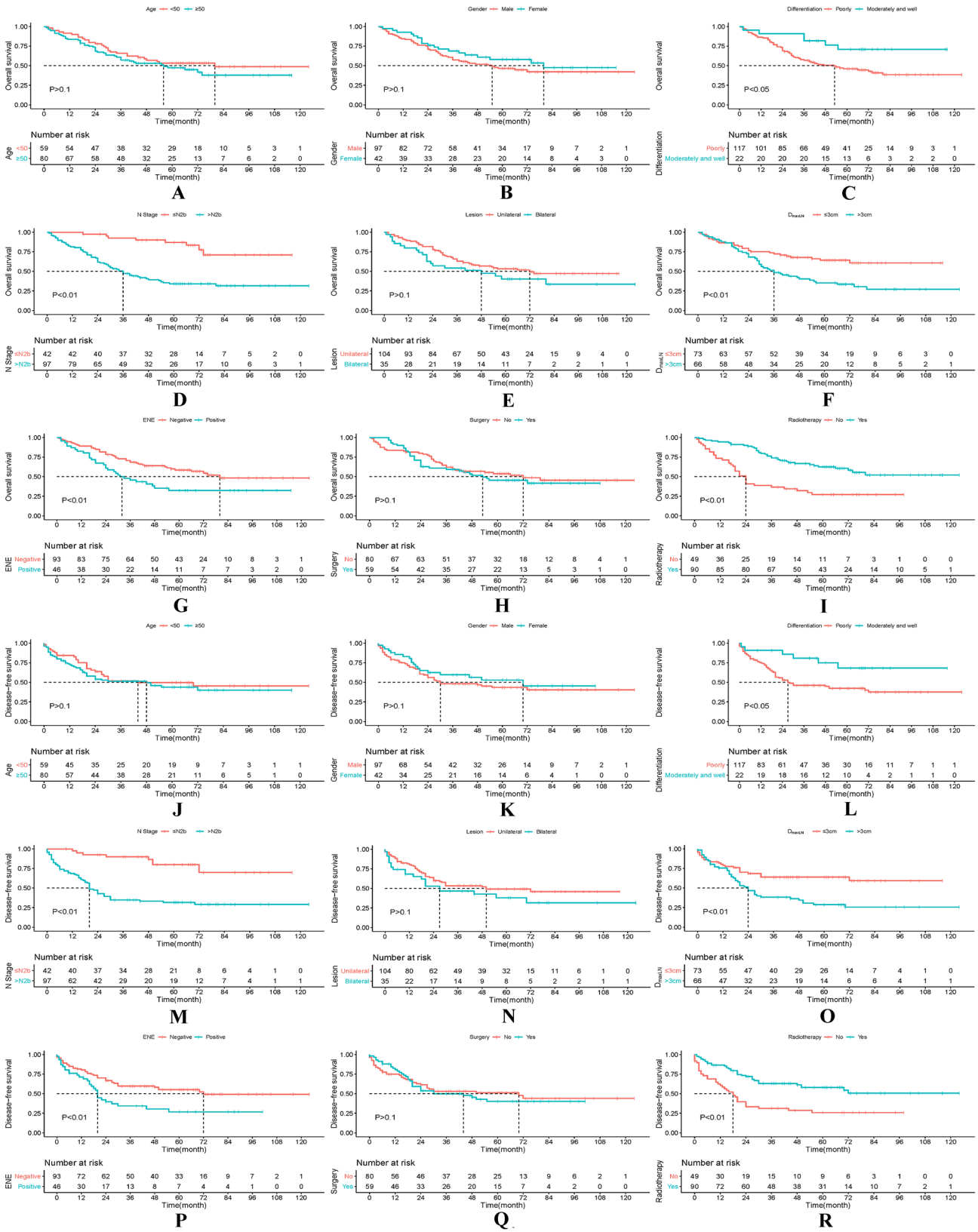

Fig. 2 The survival curves of univariate analysis. Kaplan–Meier overall survival (OS) and disease-free survival (DFS) curves for 139 patients with CCUP stratified by age (**A**, **J**), gender (**B**, **K**), differentiation (**C**, **L**), N stage (**D**, **M**), lesion (**E**, **N**), D_{maxLN} (**F**, **O**), ENE (**G**, **P**), surgery (**H**, **Q**), and radiotherapy (**I**, **R**)

Table 2 Multivariate analysis for overall survival (OS) and disease-free survival (DFS)

Variable	OS		DFS	
	HR [95% CI]	*P* value	HR [95% CI]	*P* value
Differentiation				
Moderately and well vs. poorly	0.22 [0.09, 0.54]	0.001	0.23 [0.09, 0.56]	0.001
N[a]				
> N2b vs. ≤ N2b	5.29 [2.42, 11.60]	< 0.001	5.18 [2.37, 11.34]	< 0.001
DmaxLN				
> 3 cm vs. ≤ 3 cm	2.08 [1.28, 3.39]	0.003	1.93 [1.18, 3.16]	0.009
ENE				
Positive vs. negative	1.35 [0.81, 2.26]	0.245	1.34 [0.81, 2.23]	0.260
Radiotherapy				
Yes vs. no	0.24 [0.14, 0.39]	< 0.001	0.32 [0.19, 0.53]	< 0.001

D_{maxLN} the length of the largest lymph node, *ENE* lymph node extranodal extension, *OS* overall survival, *DFS* disease-free survival, *HR* hazard ratio, *CI* confidence interval

[a]N stage of disease was determined by the American Joint Committee on Cancer (AJCC) TNM Staging System for Cervical Lymph Nodes and Unknown Primary Tumors of the Head and Neck (8th ed., 2017)

Field radiotherapy. The survival analysis shows that people who received Comprehensive radiotherapy have the better OS (HR = 0.27, 95% CI = 0.13–0.56, $P < 0.001$; Fig. 3A) and DFS (HR = 0.26, 95% CI = 0.13–0.54, $P < 0.001$; Fig. 3B).

Discussion

At present, although radiation therapy is considered one of the most effective treatments for patients with CCUP (Strojan et al. 2013; Pfister et al. 2020; Martin and Galloway 2015; Pavlidis et al. 2009), the target of radiotherapy is still controversial. Thus, this study was conducted to figure out the effect of radiotherapy and radiotherapy target on patients with CCUP, and to provide solid evidence of treatment for patients with CCUP.

The prognostic factors of CCUP have been discussed in several retrospective studies. In the study of Wang et al. the N stage, ENE, and the histological type are the independent prognostic factors of OS but not progress-free survival (PFS) (Wang et al. 2018). However, Mizuta et al. (2018) hold that the N stage is the only independent predictor of OS and disease-specific survival (DSS). Zhou et al. (2018) conclude that the P16 status, more than 10 pack-years histories of smoking, age, and N stage is related to the OS of patients with CCUP. Even though these studies differ in the prognostic factor of CCUP, they have one thing in common: all of them confirm the important role of radiotherapy in the treatment of patients with CCUP. In this study, we find that the clinical parameters such as differentiation of tumor, N stage, and D_{maxLN} are the independent prognostic factors of survival outcome,

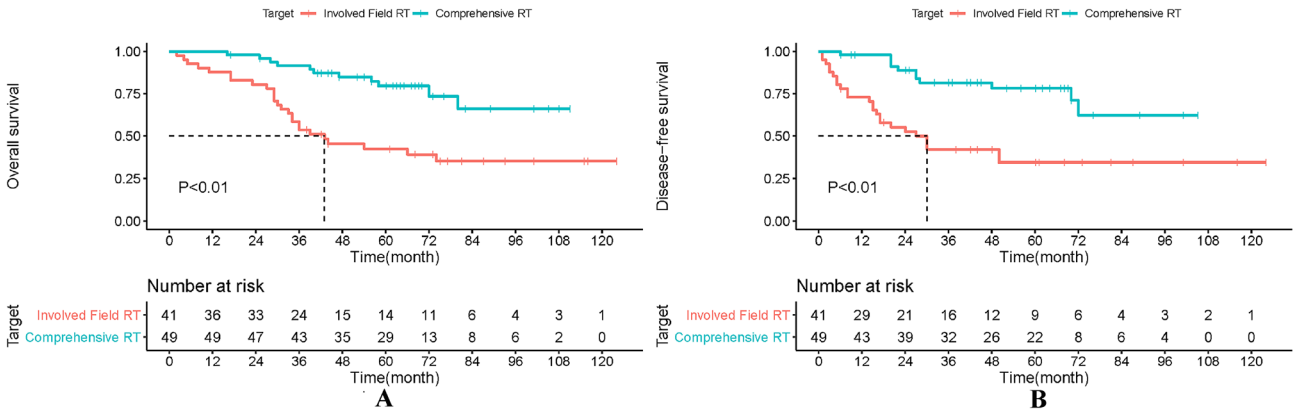

Fig. 3 The survival curves of patients with Comprehensive Radiotherapy and Involved Field Radiotherapy. **A** The overall survival (OS) of patients receiving Comprehensive RT and Involved Field RT. **B** The disease-free survival (DFS) of patients receiving Comprehensive RT and Involved Field RT

and the radiotherapy correlated the better survival with significance.

Many studies have discussed the prognostic influence of different radiotherapy targets. Pflumio et al. (2019) compared unilateral and bilateral irradiation of the neck, in patients with CCUP, and showed that bilateral irradiation of the neck not only did not improve the outcome but also caused more serious adverse events. The study from Mizuta et al. (2018) yields a consistent result. They found that there were no benefits from bilateral irradiation. Again, Grau et al. (2000) suggested that no statistically significant survival benefits from additional mucosal radiation compared with cervical irradiation alone. Other studies have come to the same conclusion: more extensive irradiation did not mean a better prognosis (Martin and Galloway 2015; Ligey et al. 2009; Lu et al. 2009; Poon et al. 2020). Other studies, however, suggest otherwise. Reddy held that expanding the extent of radiation target (bilateral neck plus mucosal irradiation vs. ipsilateral neck irradiation) can significantly improve the outcome of patients (Reddy and Marks 1997). Similar results were also found in a literature review published in 2004 (Jereczek-Fossa et al. 2004) and in a retrospective study by Wang et al. (2018), whose subgroup analysis of patients treated with radiotherapy showed that the irradiation of suspicious mucosa had improved OS. These are consistent with the results of this present study. In this present study, we divided patients who received radiotherapy into two groups according to the volume of target: Involved Field radiotherapy group and Comprehensive radiotherapy group. In addition, it shows that the patients who underwent Comprehensive radiotherapy have a better outcome.

Primary tumors not originated from the head and neck such as lung cancer and gastric cancer, could also appear cervical lymph node metastases and may not as sensitive as head and neck cancer to radiation (Tang et al. 2018). The inclusion of patients with these tumors in the study might cause the efficacy of Comprehensive radiotherapy underestimated. To minimize such errors, the "Inclusion and exclusion criteria" in this study were more rigorous. The patients in this study all have the involved lymph node located above the cricoid cartilage and the histologic type is all SCC. These suggest that compared with other studies, the patients in this study are more likely to have primary in the head and neck (Arosio et al. 2017). Furthermore, there are several advantages to exclude patients with distant metastasis. First, there is no clear definition of distant metastasis in AJCC TNM Staging System for Cervical Lymph Nodes and Unknown Primary Tumors of the Head and Neck (8th ed., 2017). The metastatic carcinoma of the non-regional lymph node is one of the situations of distant metastasis. However, it is hard for physicians to make a judgment for regional lymph nodes because of the occult primary. Second, limited to other factors such as clinical techniques, biopsy, and pathologic diagnosis might be impracticable in patients with distant metastasis (Strojan et al. 2013). It makes it difficult for physicians to distinguish the metastasis tumor from the primary tumor.

As a retrospective study, this study has its limitations. Besides, the sample size of this study is relatively small because of the low incidence of CCUP. Furthermore, the testing of HPV and EBV performed for the CCUP patients was not regularly conducted in the recruited institution. The number of patients who received testing was not enough for us to conduct further research. Previous studies have shown that the detection results of HPV and EBV may indicate the primary site (Motz et al. 2016; Mălin et al. 2012; Faquin 2014; Jannapureddy et al. 2010; Cheol Park et al. 2017). The primary lesion may be located in the oropharynx in HPV-Positive patients, and it may be located in the nasopharynx in patients with EBV high replication (Jannapureddy et al. 2010). Other studies also held that the contribution to locating primary may help to treatment de-escalation (Strojan et al. 2013; Schroeder et al. 2017; Chen et al. 2018), and reduce the treatment-related toxicities. The AJCC TNM Staging System (8th ed., 2017) and The National Comprehensive Cancer Network Head and Neck Cancer Clinical Practice Guidelines in Oncology (version 2.2020) (Pfister et al. 2020) also mentioned the importance of HPV testing. However, Pflumio et al. (2019) believe that the value of HPV testing is overestimated, and it should be tested selectively according to the location of lymph nodes, such as patients whose involved lymph nodes are located in level II or III. The study of Bussu et al. (2015) also found there are no significant correlations between the detection of HPV and EBV virus and clinicopathologic parameters or prognosis. Currently, most institutions do not systematically test HPV and EBV in patients with CCUP (Pflumio et al. 2019). There is no definitive conclusion on this issue, and studies with a larger sample size are needed.

Conclusion

Radiotherapy is the independent prognostic factor for CCUP, and the survival benefits of Comprehensive radiotherapy are superior to Involved Field radiotherapy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00432-021-03724-1.

Author contributions Conceptualization and funding acquisition: XP; methodology and resources: XP, LH, and RL; data curation: RL, LH, XM, and LY; software and formal analysis: RL, KL, and YH; supervision and investigation: RL, ZW, and KL; validation: RL, ZL, and JW; visualization: RL, ZW, and YH; writing—original draft and writing—review and editing: RL, KL, and LH; project administration: XP and LH.

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Availability of data and materials The datasets generated analyzed during the current study are not publicly available.

Code availability All statistical analyses were performed using R statistical software (version 4.0.1; http://www.r-project.org/), and the "survival" R package was used for survival analysis. The code can be obtained by contacting the corresponding author, with reasonable requests.

Declarations

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

Ethical approval This retrospective study complies with the ethical standards of the institution, and follows the principles of the Helsinki Declaration. Approval was granted by the Ethics Committee of West China Hospital of Sichuan University.

Consent to participate Because of the retrospective nature of this study, consent to participate for inclusion was waived.

Consent to publish Because of the retrospective nature of this study, consent to publish was waived.

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