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Original Article

Prognostic impact of cortactin in patients with hypopharyngeal cancer and its role for tegafur-uracil maintenance after adjuvant chemoradiotherapy

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Abstract: The prognosis of patients with hypopharyngeal cancer (HPC) remains poor. Our study aims to investigate the prognostic impact of cortactin in patients with HPC and its role for tegafur-uracil (UFUR) maintenance after adjuvant chemoradiotherapy (CRT). Patients who were diagnosed to have HPC and underwent laryngopharyngectomy followed by adjuvant CRT were enrolled into our study. Immunohistochemical staining was performed for cortactin evaluation. Kaplan-Meier curves were depicted for recurrence-free survival (RFS) and overall survival (OS). A total of 157 patients were enrolled into our study. After stratified by cortactin, 53 patients were cortactin (+) and 104 patients were cortactin (-). The median RFS was 86.7 months in cortactin (-) and 10.2 months in cortactin (+) ($P < 0.001$). The median OS was 93.4 months in cortactin (-) and 16.9 months in cortactin (+) ($P < 0.001$). Patients were further classified according to UFUR maintenance or not after adjuvant CRT. In cortactin (+) patients, the median RFS and OS were 13.6 months versus 7.0 months ($P = 0.006$) and 24.0 months versus 10.0 months ($P < 0.001$) in UFUR (+) and UFUR (-), respectively. In cortactin (-) patients, the median RFS and OS were 96.0 months versus 72.2 months ($P = 0.262$) and 98.5 months versus 105.0 months ($P = 0.665$) in UFUR (+) and UFUR (-), respectively. Cortactin has a significantly impact in HPC patients. UFUR maintenance provided survival benefits in patients with cortactin (+) after adjuvant CRT.

Keywords: Cortactin, tegafur-uracil, hypopharyngeal cancer, chemoradiotherapy, prognosis, survival

Introduction

Hypopharyngeal cancer (HPC) is uncommon, accounting for 4% of all malignancies of the head and neck, and 7% of all upper aerodigestive tract malignancies [1]. HPC are aggressive and generally present as advanced disease with lymph node metastasis at presentation, and worse prognosis [2]. The gold standard treatment for HPC is total laryngopharyngectomy, followed by adjuvant chemoradiotherapy (CRT) in patients with high risk pathologic features. Meanwhile, tegafur-uracil (UFUR; TTY Biopharm, Taiwan) was used as maintenance treatment after CRT for certain higher risk patients in our local practice. However, the prognosis of HPC remains poor. The 5 year overall survival (OS) rate is approximately 35%. Although the treatment has been significantly improved, the survival has been strikingly restricted for decades [3]. As the complexity of these tumors, their surrounding structures, and the frequent comorbidities, a multidisciplinary treatment approach with risk factors stratification should be applied to achieve the best oncological outcomes [4].

As the advances of molecular medicine, several prognostications are identified. Among these, cortactin is one of the most crucial factors. A large number of evidences indicated that cortactin is overexpressed in various types of human cancers, such as head and neck, squamous carcinomas, colorectal cancer, esophageal cancer, gastric cancer, liver cancer, breast cancer, and ovarian cancers [5-8]. Cortactin overexpression has been confirmed to be associated with carcinogenesis, invasiveness, and poor prognosis in various cancers [9]. However, there are no comprehensive study focusing on the prognostic impact of cortactin in patients with HPC. The impact of cortactin expression on survival in patients with HPC remains undefined. Moreover, there are no literatures regarding the association between cortactin expression and UFUR maintenance in patients with HPC. Thus, there is an urgent unmet need to have a predictive factor in such a poor prognosis cancer like HPC. Herein, our study aims to investigate the prognostic impact of cortactin in patients with HPC and its role for UFUR maintenance after adjuvant CRT.

Materials and methods

Patients eligibility

Patients who aged older than 18 years and underwent curative laryngopharyngectomy for HPC from 2007 to 2015 at E-Da Hospital were retrospectively reviewed. Those who were treated with adjuvant CRT for high risk pathologic features were enrolled into our study. High risk pathologic features included extra-nodal extension (ENE), positive margin (PM), advanced primary tumor (T4), multiple lymph nodes metastasis (N2), lymphovascular invasion (LVI) and perineural invasion (PNI). The surgical tissue specimen was also retrieved for cortactin evaluation. Exclusion criteria were no laryngopharyngectomy, no adjuvant CRT after surgery, insufficient tissue specimens for cortactin staining or lost follow up. The patients' clinical and laboratory data were collected from medical records. This was a retrospective study, which was exempt from requiring consent. This study was approved by the E-Da Hospital Institutional Review Board (EMPR-109-089), and was conducted in accordance with the Declaration of Helsinki.

Immunohistochemistry

Consecutive surgical tissue specimens were sent for immunohistochemical staining (IHC) for cortactin examination. The method of IHC stain was introduced in our previous study [10]. The steps were summarized as below. IHC stain with anti-cortactin antibody (clone 30, from BD Transduction Laboratories, Frankline Lakes, NJ, USA) was performed on the fully automated Bond-Max system (Leica Microsystems). Slides with specimens were dried for 30 min at 60°C. The following steps were performed by the automated instrument include deparaffinization of specimen by rinse with Bond Dewax Solution at 72°C, heat-induced epitope retrieval, peroxide block placement on the slides for 5 min, incubation with mouse monoclonal anti-cortactin antibody at a dilution of 1:100 for 30 min, Bond Polymer placement on the slides for 8 min, color development with diaminobenzidine chromogen for 5 min, and hematoxylin counterstaining for 5 min. The results of IHC were evaluated by a pathologist to define the cortactin expression status in the cytoplasm and cell membrane. Cortactin (+) indicated a positive staining of cortactin higher than the intensity in the surrounding normal tissue, while cortactin (-) indicated a similar or lower expression **Figure 1**.

Statistical analysis

All the clinical and pathologic characteristics were retrieved from a medical chart review and calculated with frequencies. Chi-square methods were used to examine the differences between groups. Statistical analyses were performed using SPSS. The oncologic outcomes were presented with recurrence-free survival (RFS) and overall survival (OS). RFS was measured from the day of surgery until the date of tumor recurrence or final follow-up, while OS was calculated as the time from the day of surgery until the date of death from any cause or final follow-up. Kaplan-Meier curves were depicted for RFS and OS. We also conducted a log-rank test with Cox regression models using "enter" selection to adjust for the effects of potential confounders. After that, patients were stratified according to UFUR maintenance or not. UFUR (+) referred to UFUR maintenance and UFUR (-) referred to no UFUR maintenance.

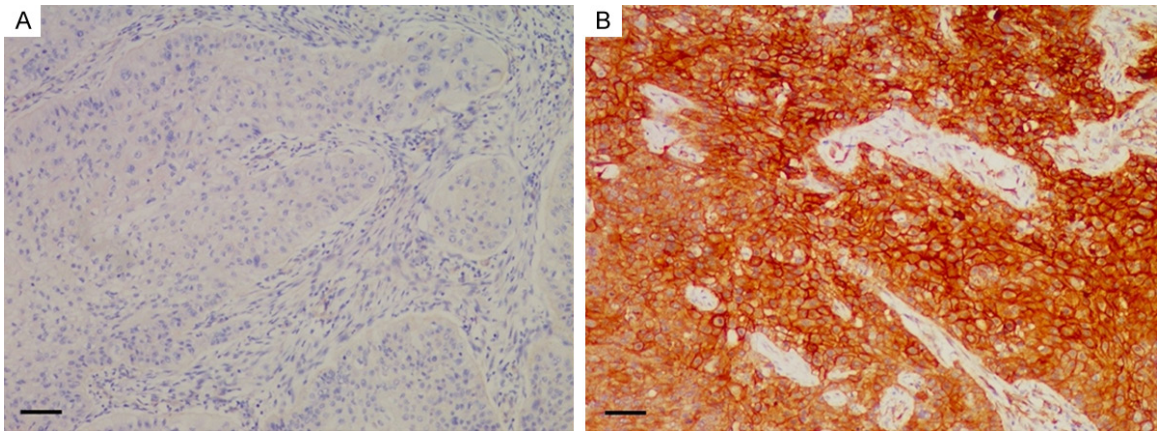

Figure 1. Immunohistochemical staining for cortactin (scale bar = 10 μm, 200× magnification). (A) Cortactin negative, (B) Cortactin positive.

RFS and OS were estimated again to investigate the impact of UFUR maintenance in patients with positive or negative cortactin expression. All *P* values were two sided and considered to be statistically significant if *p* values < 0.05.

Results

Patients characteristics

A total of 157 patients were enrolled into our study for oncologic outcomes evaluation. Baseline characteristics were presented in **Table 1**. In general, 98% patients were male in gender with a median age of 54 years. Among these patients, 84% were alcoholism, 92% were current smokers or former smokers and 69% had betel nut consumption. All patients had advanced HPC with 25% pathologic stage III and 75% pathologic stage IVA-IVB. There were 8% of our patients harboring PM and 14% harboring ENE. Nearly 60% patients received UFUR maintenance after adjuvant CRT at physician's discretion. After stratified by cortactin, 53 patients were cortactin (+) and 104 patients were cortactin (-). All basic characteristics including gender, age, alcoholism, smoking status, betel nut consumption, pathologic stage, PM, ENE, LVI, PNI and UFUR maintenance were well balanced between the two arms.

Survival outcomes

The median follow-up interval was 65 months. At the end of our study, 70% of our patient died and cancer was the main reason of their death. In terms of RFS and OS, patients with cortactin (-) had significantly better prognosis than patients with cortactin (+). The median RFS was 86.7 months in cortactin (-) and 10.2 months in cortactin (+) ($P < 0.001$). The median OS was 93.4 months in cortactin (-) and 16.9 months in cortactin (+) ($P < 0.001$). The survival curves of PFS and OS are plotted in **Figure 2**. Cox regression multivariate analyses with survival for potential prognosticators were summarized in **Table 2**. Multivariate analysis demonstrated that gender, betel nut consumption, ENE and cortactin expression were independently correlated with RFS and OS.

Impact of UFUR maintenance

Patients were further classified according to UFUR maintenance or not after adjuvant CRT. Totally, there were 92 patients received UFUR maintenance after CRT. In cortactin (+) group, there were 29 patients treated with UFUR maintenance and 24 patients without UFUR maintenance, while in cortactin (-) group, there were 63 patients treated with UFUR maintenance and 41 patients without UFUR maintenance. **Table 3** showed the basic characteristics of these patients stratified by cortactin expression and UFUR maintenance. All variables including gender, age, alcoholism, smoking status, betel nut consumption, pathologic stage, PM, ENE, LVI and PNI were well balanced between UFUR (+) and UFUR (-). The RFS and OS of UFUR (+) and UFUR (-) are depicted in **Figure 3**. UFUR maintenance significantly improved RFS and OS in cortactin (+) patients, but was insignificant in cortactin (-) patients. In

Table 1. Basic characteristics of 157 hypopharyngeal cancer patients, stratified by cortactin

	Cortactin (+) *N* = 53		Cortactin (-) *N* = 104		*P*
Gender					0.984
Male	52	98%	102	98%	
Female	1	2%	2	2%	
Age					0.292
≤ 60	36	68%	85	82%	
> 60	17	32%	19	18%	
Alcoholism					0.278
Yes	41	73%	91	87%	
Never	12	27%	13	13%	
Smoking					0.712
Yes	47	89%	97	93%	
Never	6	11%	7	7%	
Betel nut					0.167
Yes	31	58%	77	74%	
Never	22	42%	27	26%	
Pathologic T stage					0.539
pT1-2	16	30%	36	35%	
pT3-4	37	70%	68	65%	
Pathologic N stage					0.107
pN1-2	17	32%	51	49%	
pN3	36	68%	53	51%	
Pathologic Stage					0.829
III	12	23%	26	25%	
IVA-IVB	41	77%	78	75%	
PM					0.618
Yes	4	8%	4	4%	
No	49	92%	100	96%	
ENE					0.372
Yes	11	21%	11	11%	
No	42	79%	93	89%	
LVI					0.144
Yes	24	45%	30	29%	
No	29	55%	74	71%	
PNI					0.622
Yes	11	21%	18	17%	
No	42	79%	86	83%	
UFUR maintenance					0.414
Yes	29	55%	63	61%	
No	24	45%	41	39%	

PM, positive margin; ENE, extra-nodal extension; LVI, lymphovascular invasion; PNI, perineural invasion; UFUR, tegafur-uracil.

cortactin (+) patients, the median RFS and OS were 13.6 months versus 7.0 months (P = 0.006) and 24.0 months versus 10.0 months (P < 0.001) in UFUR (+) and UFUR (-), respectively. In cortactin (-) patients, the median RFS and OS were 96.0 months versus 72.2 months (P = 0.262) and 98.5 months versus 105.0 months (P = 0.665) in UFUR (+) and UFUR (-), respectively.

Discussion

To our best knowledge, this is the first study investigating the prognostic impact of cortactin in HPC patients with high risk pathologic features and its role for UFUR maintenance after adjuvant CRT. Our study demonstrated that cortactin had a significant prognostic impact on survival in HPC patients. Patients with cortactin (+) were significantly inferior to those with cortactin (-), in terms of RFS and OS. Our study also indicated the clinical implication of cortactin for UFUR maintenance after adjuvant CRT. The RFS and OS were statistically better in UFUR (+) than in UFUR (-) among patients with cortactin (+), while there were no different in RFS and OS between UFUR (+) and UFUR (-) among patients with cortactin (-). Previous literature showed cortactin overexpression has consistently associated with carcinogenesis, invasiveness, and poor prognosis in various malignancies [9]. Our results were consistent with preceding literatures and confirmed the prognostic value and clinical significance of cortactin in HPC. Cortactin could be a reliable prognostic biomarker and had a clinical implication for patients with HPC. These results were clinically useful for outcomes anticipation and risk stratification, as well as patients counseling.

Cortactin is encoded by the CTTN gene, also called EMS1, which is located on chromosome 11q13 [11]. It is an F-actin binding protein that recruits Arp2/3 complex proteins to F-actin to regulate actin nucleation, and cytoskeletal assembly and adhesion [12]. Cortactin has been recognized for its association with cell motility and invasion [13, 14]. It can be phosphorylated by tyrosine and serine/threonine kinases and then binds to sites of dynamic actin assembly in cellular protrusions, such as in lamellipodia and invadopodia [15]. Moreover, cortactin regulates membrane trafficking and enhances the secretion of extracellular matrix (ECM)-degrading proteinases, resulting in tumor cell metastasis. For example, cortactin overexpression was clinically validated to be associated with increased incidence of

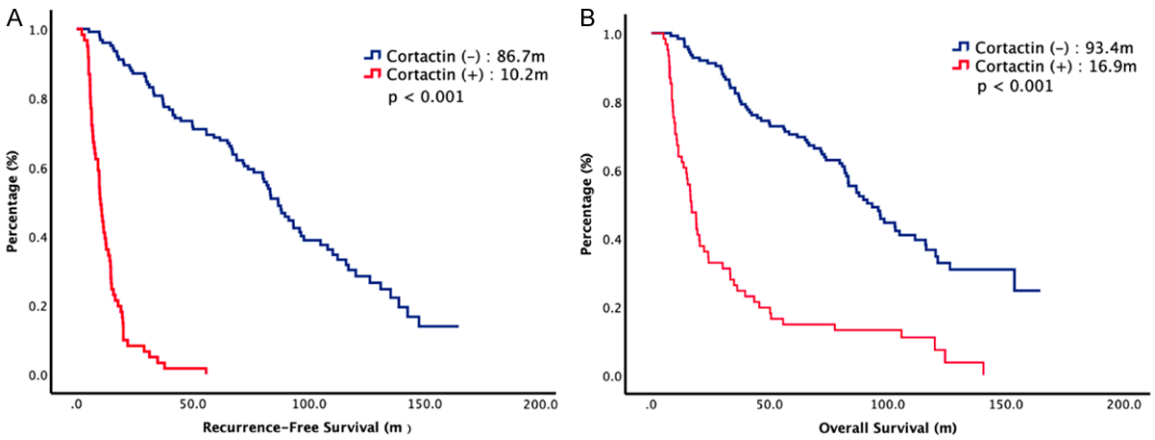

Figure 2. Survival of 157 patients with hypopharyngeal cancer, stratified by cortactin expression. (A) Recurrence-free survival, (B) Overall survival.

Table 2. Cox regression analysis of parameters associated with survival

Variables	RFS		OS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender, Male vs. Female	0.31 (0.10-0.99)	0.049*	0.22 (0.07-0.71)	0.012*
Age, ≤ 60 vs. > 60	0.90 (0.62-1.32)	0.601	0.86 (0.58-1.26)	0.436
Alcoholism, no vs. yes	0.81 (0.52-1.24)	0.329	0.65 (0.43-1.01)	0.054
Smoking, no vs. yes	0.75 (0.44-1.29)	0.296	0.82 (0.47-1.43)	0.478
Betel nut, no vs. yes	0.66 (0.47-0.93)	0.019*	0.69 (0.48-0.99)	0.041*
Pathologic T stage, 1-2 vs. 3-4	0.87 (0.63-1.22)	0.425	0.84 (0.60-1.19)	0.332
Pathologic N stage, 0-1 vs. 2-3	0.78 (0.56-1.09)	0.145	0.65 (0.42-1.00)	0.050
Pathologic stage, 1-2 vs. 3-4	0.68 (0.44-1.08)	0.100	0.88 (0.55-1.42)	0.604
PM, no vs. yes	0.89 (0.42-1.54)	0.491	0.95 (0.44-2.02)	0.884
ENE, no vs. yes	0.55 (0.37-0.83)	0.004*	0.52 (0.34-0.79)	0.002*
LVI	0.96 (0.62-1.48)	0.836	0.90 (0.57-1.41)	0.639
PNI	0.71 (0.43-1.17)	0.179	0.66 (0.40-1.10)	0.108
UFUR maintenance, yes vs. no	0.88 (0.64-1.22)	0.451	0.83 (0.59-1.17)	0.286
Cortactin, (-) vs. (+)	0.06 (0.04-0.10)	< 0.001*	0.25 (0.17-0.35)	< 0.001*

RFS, recurrence-free survival; OS, overall survival; HR, hazzard ratio; CI, confidence interval; PM, positive margin; ENE, extra-nodal extension; UFUR, tegafur-uracil. *Meaningful *P* value.

second esophageal neoplasm [10]. For patients with breast cancer, high-level expression with phosphorylation of cortactin has an unfavorable prognosis [16]. In stage II-III colorectal cancer, the expression of cortactin is an independent prognostic factor for survival [17]. Overexpression of cortactin in gastric cancer will up-regulated epidermal growth factor receptor leading to proliferation, invasion, and cell migration [18]. More recently, overexpression of cortactin in different types of leukemia, similar to solid tumors, has been associated with a worse outcome for these patients, suggesting that determining cortactin levels may help stratify high-risk patients and optimize their treatments [19]. Aforementioned literatures have proved its prognostication in several cancers, except HPC. Our study confirmed the prognostic role of cortactin in HPC. Further prospective studies are warranted to validate our results.

In our local practices, UFUR was widely used as maintenance treatment after curative therapy. UFUR is an oral form of fluoropyrimidine which composed of tegafur and uracil in a 1:4 molar ratio. Tegafur is an orally bioavailable prodrug of 5-FU and uracil is an orally fluoropyrimidine inhibitor of dihydropyrimidine dehydrogenase, which can enhance the efficacy of 5-FU and

Table 3. Basic characteristics of 157 hypopharyngeal cancer patients, stratified by UFUR

	Cortactin (+)			Cortactin (-)		
	UFUR (+) N = 29	UFUR (-) N = 24	*P*	UFUR (+) N = 63	UFUR (-) N = 41	*P*
Gender			0.605			0.951
Male	29 (100%)	23 (96%)		62 (99%)	40 (98%)	
Female	0 (0%)	1 (4%)		1 (1%)	1 (2%)	
Age						0.724
≤ 60	21 (73%)	15 (63%)	0.316	51 (81%)	32 (78%)	
> 60	8 (27%)	9 (37%)		12 (19%)	9 (22%)	
Alcoholism			0.301			1.000
Yes	21 (73%)	20 (83%)		55 (87%)	36 (87%)	
Never	8 (27%)	4 (17%)		8 (13%)	5 (13%)	
Smoking			0.865			0.814
Yes	26 (90%)	21 (88%)		59 (94%)	38 (92%)	
Never	3 (10%)	3 (12%)		4 (6%)	3 (8%)	
Betel nut			0.553			0.850
Yes	16 (55%)	15 (62%)		47 (75%)	30 (73%)	
Never	13 (45%)	9 (38%)		16 (25%)	11 (27%)	
Pathologic T stage			0.701			0.526
pT1-2	8 (28%)	8 (33%)		24 (38%)	12 (30%)	
pT3-4	21 (72%)	16 (67%)		39 (62%)	29 (70%)	
Pathologic N stage			0.616			0.867
pN1-2	10 (34%)	7 (29%)		31 (49%)	20 (48%)	
pN3	19 (66%)	17 (71%)		32 (51%)	21 (52%)	
Pathologic Stage			0.224			0.436
1-2	8 (28%)	4 (17%)		18 (29%)	8 (20%)	
3-4	21 (72%)	20 (83%)		47 (71%)	31 (80%)	
PM			0.594			0.304
Yes	3 (10%)	1 (4%)		0 (0%)	4 (10%)	
No	26 (90%)	23 (96%)		63 (100%)	37 (90%)	
ENE			0.632			0.235
Yes	7 (24%)	4 (17%)		4 (6%)	7 (17%)	
No	22 (78%)	20 (83%)		59 (94%)	34 (83%)	
LVI			0.888			0.476
Yes	13 (45%)	11 (46%)		16 (25%)	14 (34%)	
No	16 (55%)	13 (54%)		47 (75%)	27 (66%)	
PNI			0.983			0.592
Yes	6 (21%)	5 (21%)		12 (19%)	6 (15%)	
No	23 (79%)	19 (79%)		51 (81%)	35 (85%)	

UFUR, tegafur-uracil; PM, positive margin; ENE, extra-nodal extension; LVI, lymphovascular invasion; PNI, perineural invasion.

diminish the toxicity [20]. The maintenance role of UFUR has been demonstrated in various solid malignancies, including colon cancer [21] and nasopharyngeal cancer [22]. A more recent study demonstrated that UFUR maintenance significantly improved survival in patients with non-distant metastatic stage IV oral cavity cancer after CRT [23]. Nonetheless, there were no predictors found in these aforementioned studies. As for HPC patients, there are no clear evidences evaluating the maintenance role of UFUR following CRT. Our study illustrated cortactin is a promising predictive factor for UFUR maintenance in HPC patients. UFUR maintenance significantly improved RFS and OS in cortactin (+) patients, but was insignificant in cor-

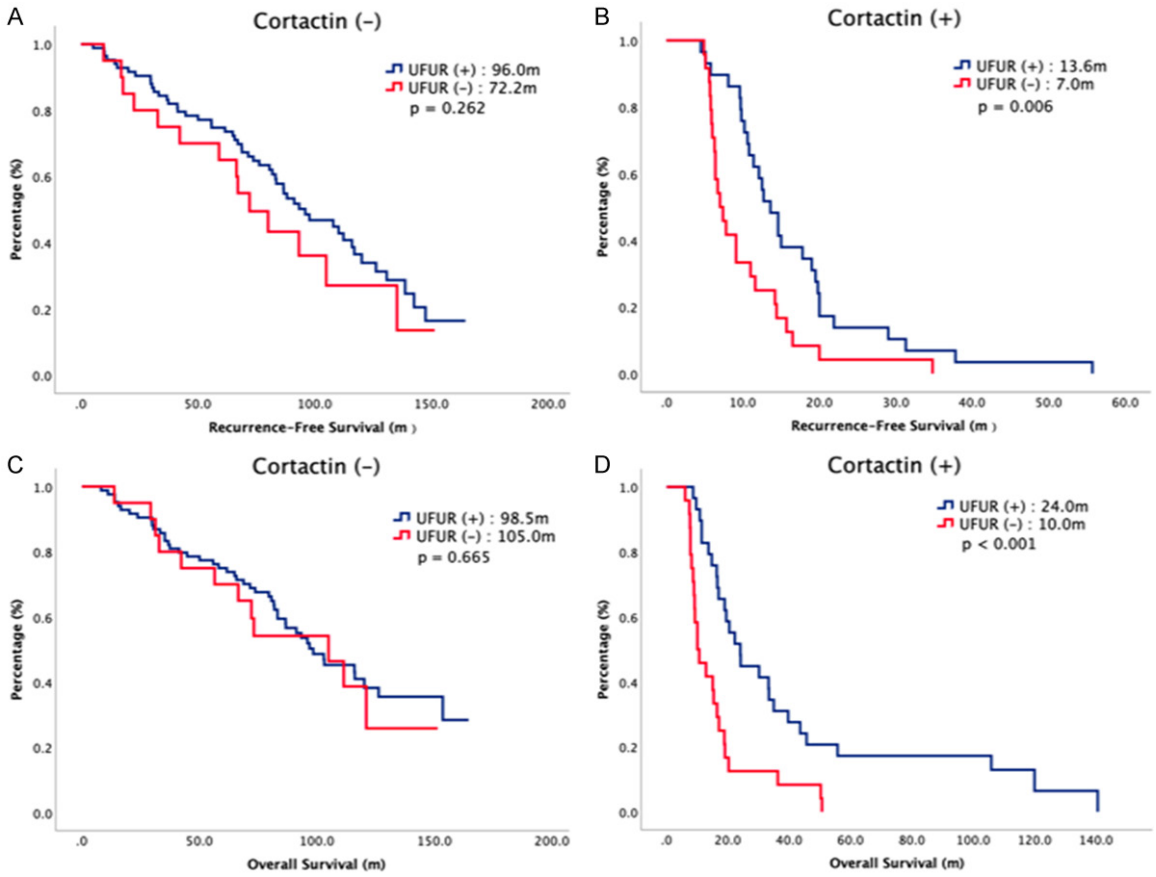

Figure 3. Survival of 157 patients with hypopharyngeal cancer, stratified by cortactin expression and UFUR maintenance. (A) Recurrence-free survival of cortactin (-), (B) Recurrence-free survival of cortactin (+), (C) Overall survival of cortactin (-), (D) Overall survival of cortactin (+).

tactin (-) patients. The reasons why UFUR maintenance can improve survival in HPC patients with cortactin (+) are unclear. The hypothesis will be that overexpressed cortactin can regulate cell cycles via RhoA to decrease expression of Cip/Kip cyclin-dependent kinase inhibitors and activate Skp2 as a downstream effector for RhoA. Cortactin overexpression force head and neck cancer cells enter into cell cycles, resulting in proliferation, progression and metastasis [24]. UFUR is a prodrug of 5-FU, which is an antimetabolite chemotherapy. 5-FU acts via G1-S-phase cell cycle arrest with apoptosis [25]. This process prohibits cell cycles and prevents cell progression which is activated by overexpressed cortactin. Thus, UFUR maintenance plays an important role in patients with cortactin (+).

There are several potential limitations in our work. First, the retrospective and non-randomized study design may be a major bias in this study. UFUR maintenance was decided at physician's discretion, rather than randomly. This may influence the generalizability of the results. Second, a single institutional experience and a small sample size may limit the statistical power of our study. Finally, the evaluation of cortactin expression is subjectively reviewed by single pathologist. There were no standardized criteria for cortactin scoring at present. Given that our retrospective study has several inevitable selection biases, our study remains clinically valuable.

Conclusion

To date, little is known regarding the prognostic impact of cortactin in HPC patients with high risk pathologic features and its role for UFUR maintenance after adjuvant CRT. Our study confirmed that the prognosis of patients with cortactin (-) were significantly better than those with cortactin (+) in terms of OS and RFS. Meanwhile, our study also concluded that UFUR maintenance significantly improved RFS and

OS in cortactin (+) patients, but was insignificant in cortactin (-) patients. Multivariate analysis showed gender, betel nut consumption, ENE and cortactin expression were independently correlated with RFS and OS. Based on our results, cortactin (+) was an indicator of poor prognosis and UFUR maintenance should be suggested in HPC patients with cortactin (+) after adjuvant CRT. Further prospective randomized controlled trials with larger cohort are warranted to validate our results.

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Disclosure of conflict of interest

None.

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