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UFUR maintenance therapy significantly improves survival in locally advanced head and neck squamous cell carcinoma following definitive chemoradiotherapy

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Abstract

Background Head and neck squamous cell carcinoma (HNSCC) presents significant therapeutic challenges, particularly in patients with advanced disease. Despite advancements in treatment, high recurrence rates and poor overall survival (OS) remain major concerns. This study evaluates the impact of tegafur-uracil (UFUR) maintenance therapy on survival outcomes in patients with advanced HNSCC following definitive chemoradiotherapy.

Methods A cohort of 424 advanced HNSCC patients treated with definitive chemoradiotherapy were analyzed, with a median follow-up of 25 months. Patients were stratified into UFUR (+) and UFUR (-) groups, with baseline characteristics balanced across both arms. Oncologic outcomes, including recurrence-free survival (RFS), OS, locoregional recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS) were compared between these groups.

Results UFUR maintenance therapy significantly reduced recurrence rates (34% vs. 47%, $p < 0.002$), driven primarily by improving locoregional control (23% vs. 37%, $p < 0.001$). While distant metastasis rates were similar between groups, UFUR (+) patients demonstrated a markedly improved median OS (51.6 months vs. 24.3 months, $p < 0.001$). The UFUR (+) group also showed superior median LRFS (36.9 months vs. 20.2 months, $p = 0.003$) and DMFS (44.0 months vs. 23.5 months, $p = 0.010$). Subgroup analysis confirmed the benefits of UFUR maintenance across different stages of disease. Multivariate analysis identified UFUR maintenance, gender, and T stage as independent predictors of survival.

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Conclusion UFUR maintenance therapy significantly improves survival outcomes in patients with advanced HNSCC following definitive chemoradiotherapy, particularly through enhanced locoregional control, and should be considered a key component of personalized treatment strategies.

Keywords UFUR, HNSCC, Maintenance therapy, Recurrence-free survival, Overall survival

Introduction

Head and neck squamous cell carcinoma (HNSCC) represents a major global health burden, especially in regions where high-risk behaviours such as tobacco use, alcohol consumption, and betel quid chewing are prevalent [1]. HNSCC is a heterogeneous group of malignancies that can arise from various anatomical sites within the head and neck, including the oral cavity, oropharynx, hypopharynx, and larynx [2]. Despite significant advancements in surgical techniques, radiation therapy, and systemic treatments, the prognosis for patients diagnosed with advanced stages of HNSCC remains dire [3]. These patients often face a high likelihood of disease recurrence and a substantial risk of mortality, even after aggressive treatment. Managing HNSCC in elderly patients and those with comorbidities adds further complexity to treatment decisions [4]. Elderly patients are particularly vulnerable to the toxic effects of conventional chemotherapy regimens, which can exacerbate existing health conditions and diminish the quality of life [5]. As a result, there is a critical need for treatment strategies that are both effective in controlling the disease and tailored to the specific needs of these patients, minimizing toxicity while maintaining or enhancing therapeutic efficacy.

In recent years, maintenance treatment with oral chemotherapy has emerged as a promising approach in the treatment of various cancers, including HNSCC [6, 7]. This regimen involves the continuous administration of chemotherapeutic agents at low, minimally toxic doses, to inhibit tumour angiogenesis, modulate the immune response, and prevent tumour regrowth [8, 9]. Tegafur-uracil (UFUR), an oral prodrug of 5-fluorouracil (5-FU), has been at the forefront of this approach [10–12]. UFUR offers the advantage of sustained drug exposure with reduced toxicity, making it particularly suitable for long-term maintenance therapy in elderly and frail patients. Previous studies have confirmed the use of UFUR in combination with cisplatin and cetuximab for elderly patients with recurrent or metastatic HNSCC [10]. This highlights the potential of UFUR to reduce the incidence of severe treatment-related adverse effects while achieving comparable oncologic outcomes to more aggressive regimens [10]. The findings suggested that UFUR-based therapy could be a viable alternation for patients who are unable to tolerate the standard high-dose chemoradiotherapy due to age or comorbidities [13, 14].

The real-world efficacy of UFUR maintenance in patients with locally advanced HNSCC had been investigated in several studies [13, 15]. Conducting in a larger cohort with a substantial follow-up period, this provided robust evidence regarding the benefits of UFUR as a maintenance therapy after radical surgery and adjuvant chemoradiotherapy [16]. The results demonstrated significant improvements in recurrence-free survival (RFS) and overall survival (OS) in patients receiving UFUR maintenance therapy compared to those who did not [17]. However, little was known regarding the impact of UFUR maintenance in patients with inoperable HNSCC. Hence, we conducted a multi-institutional retrospective study to investigate the maintenance role of UFUR in locally advance HNSCC patients treated with definitive concurrent chemoradiotherapy (CCRT).

Materials and methods

Patient selection

This retrospective observational study included patients aged 18 years and older who were diagnosed with pathologically confirmed locally advanced HNSCC between 2018 and 2023. Patients were treated at five major medical centers: Keelung Chang Gung Memorial Hospital, Linko Chang Gung Memorial Hospital, Tri-Service General Hospital, China Medical University Hospital, and E-Da Cancer Hospital. Inclusion criteria required that all patients received definitive chemoradiotherapy without surgical intervention and demonstrated a complete response, partial response, or stable disease after completing chemoradiotherapy with a platinum-based regimen. Patients were excluded from the study if they met any of the following criteria: history of radical surgery either before or after chemoradiotherapy, presence of de novo recurrent or metastatic HNSCC, evidence of progressive disease following chemoradiotherapy, initiation of UFUR maintenance therapy more than 3 months after the completion of chemoradiotherapy and loss of follow-up during the study period. Patients were stratified into two groups based on the administration of UFUR maintenance therapy following chemoradiotherapy. (1) UFUR (+) Group: Patients who received UFUR maintenance therapy within 3 months after completing chemoradiotherapy were labelled as UFUR (+). The prescribed dose was oral tegafur 200 mg twice daily, accompanied by oral leucovorin 100 mg twice daily. Dose adjustments were permitted based on the patient's comorbidities and any treatment-related adverse effects, as determined by the treating physician. The UFUR maintenance therapy was continued in patients with responding or stable disease

until tumor progression, death, intolerable toxicities or to the maximum of 2 years if no disease progression. (2) UFUR (-) Group: Patients who did not receive UFUR maintenance therapy after completing chemoradiotherapy were labelled as UFUR (-).

Data collection

Patient characteristics, including demographic information, tumor location, stage, treatment details, and clinical outcomes, were retrospectively extracted from medical records. This study was conducted following the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of E-Da Hospital (EMPR18113N), the Institutional Review Board of Chang Gung Memorial Hospital (202500269B0), the Institutional Review Board of China Medical University Hospital (CMUH114-REC2-077), and the Institutional Review Board of Tri-service General Hospital (B202405200). Due to the retrospective design of the study, the requirement for informed consent was waived.

Statistical analysis

The baseline characteristics of the patients were summarized and compared between the UFUR (+) and UFUR (-) groups using chi-square tests for categorical variables. Oncologic outcomes, including recurrence-free survival (RFS), overall survival (OS), locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and recurrence rates, were analyzed. RFS was defined as the time from the last day of chemoradiotherapy to the date of tumor recurrence or the last follow-up. OS was calculated from the last day of chemoradiotherapy to the date of death from any cause or the last follow-up. LRFS was referred to the time from the last day of chemoradiotherapy to the date of tumor with locoregional recurrence or the last follow-up. DMFS was indicated as the time from the last day of chemoradiotherapy to the date of tumor with distant metastasis or the last follow-up. Kaplan–Meier survival curves were generated to illustrate survival outcomes over time. Cox proportional hazards regression analysis was performed using the "enter" method to identify independent predictors of survival and adjust for potential confounders. All statistical analyses were conducted using SPSS software, with a two-sided P value of less than 0.05 considered statistically significant.

Table 1 Basic characteristics of 424 patients with R/M HNSCC, stratified by UFUR maintenance

	UFUR (+) *N* = 212		UFUR (-) *N* = 212		*p*
Gender					0.620
Male	201	95%	196	92%	
Female	11	5%	16	8%	
Age					0.263
> 60	90	42%	76	36%	
≤ 60	122	58%	136	64%	
Primary tumor					0.189
Oropharynx	93	44%	77	36%	
Oral cavity	26	12%	36	17%	
Hypopharynx	77	36%	88	42%	
Larynx	16	8%	11	5%	
Initial T stage					0.766
T1-T2	83	39%	86	41%	
T3-T4	129	61%	126	59%	
Initial N stage					0.107
N0-N1	79	37%	64	30%	
N2-N3	133	63%	148	70%	
Initial stage					0.689
stage I-II	20	9%	23	11%	
stage III-IVB	192	91%	189	89%	
P16					0.369
positive	5	2%	12	6%	
negative	71	33%	94	44%	
unknow	136	65%	106	50%	

R/M HNSCC, recurrent or metastatic head and neck squamous cell carcinoma; UFUR, tegafur/uracil

Results

Patients' characteristics

A total of 424 patients were enrolled in our study to evaluate oncologic outcomes, with a median follow-up period of 25 months. The median age of the participants was 57 years. Baseline characteristics are detailed in Table 1. The majority of patients were male (94%) and under 60 years old (61%). The most common primary tumor sites were the oropharynx (40%) and hypopharynx (39%), followed by the oral cavity and larynx. Nearly 90% of the patients presented with stage III-IVB disease at diagnosis, and all were treated with definitive chemoradiotherapy with curative intent. Patients were stratified based on UFUR maintenance therapy, with 212 patients in the UFUR (+) group and 212 in the UFUR (-) group. In the UFUR (+) group, the median duration of UFUR treatment was 217 days, with a median tegafur dose of 400 mg per day. The two treatment arms were well balanced in terms of baseline characteristics, including gender, age, primary tumor location, initial stage, and P16 status.

Survival outcomes

The oncologic outcomes between the UFUR (+) and UFUR (-) groups are summarized in Table 2. Patients in the UFUR (+) group had a significantly lower recurrence rate compared to those in the UFUR (-) group, with rates of 34% versus 47%, respectively ($p < 0.002$). When stratified by recurrence pattern, the locoregional recurrence rate was significantly better in the UFUR (+) group compared to the UFUR (-) group, with rates of 23% versus 37% ($p < 0.001$). However, the difference in distant

Table 2 Oncologic outcomes of 424 patients with R/M HNSCC patients, stratified by UFUR maintenance

	UFUR (+) $N=212$	UFUR (-) $N=212$	p
Recurrence rate	34%	47%	0.002
Local recurrence rate	23%	37%	< 0.001
Distant metastasis rate	15%	19%	0.210
Expire rate	45%	76%	< 0.001
Recurrence-free survival	30.8 m	20.1 m	0.006
Overall survival	51.6 m	24.3 m	< 0.001
LRFS	36.9 m	20.2 m	0.003
DMFS	44.0 m	23.5 m	0.010

R/M HNSCC, recurrent or metastatic head and neck squamous cell carcinoma; UFUR, tegafur/uracil; LRFS, locoregional recurrence-free survival; DMFS, distant metastatic-free survival

metastasis recurrence rates between the two groups was not statistically significant, with rates of 15% in the UFUR (+) group and 19% in the UFUR (-) group ($p=0.210$). The median LRFS was 36.9 months in the UFUR (+) group compared to 20.2 months in the UFUR (-) group ($p=0.003$), while the median DMFS was 44.0 months in the UFUR (+) group versus 23.5 months in the UFUR (-) group ($p=0.010$).

By the end of the study, fewer patients in the UFUR (+) group had succumbed to cancer compared to those in the UFUR (-) group, with mortality rates of 45% versus 76%, respectively ($p<0.001$). Survival outcomes were also compared between the two groups, revealing that both median RFS and OS were significantly longer in the UFUR (+) group. The median RFS was 30.8 months in the UFUR (+) group compared to 20.1 months in the UFUR (-) group ($p=0.006$), while the median OS was 51.6 months in the UFUR (+) group versus 24.3 months in the UFUR (-) group ($p<0.001$).

Regardless of the recurrence pattern, both LRFS and DMFS were significantly better in the UFUR (+) group. The median LRFS was 36.9 months in the UFUR (+) group compared to 20.2 months in the UFUR (-) group ($p=0.003$), while the median DMFS was 44.0 months in the UFUR (+) group versus 23.5 months in the UFUR (-) group ($p=0.010$). The survival curves for progression-free survival (PFS) and OS are illustrated in Fig. 1.

Subgroup analysis was performed with stage. UFUR maintenance provided better tumor control across all stages. For patients with stage I-II, the median RFS were not reached (NR) in UFUR (+) and 22.9 months in UFUR (-) ($p=0.167$), while the median OS were NR months in UFUR (+) and 22.9 months in UFUR (-) ($p=0.030$). For patients with stage I-II, the median RFS were 28.3 in UFUR (+) and 18.9 months in UFUR (-) ($p=0.019$), while the median OS were 50.1 months in UFUR (+) and 24.3 months in UFUR (-) ($p=0.002$). The survival curves of RFS and OS are plotted in Fig. 2, stratified by stage.

Multivariate regression analysis

Cox regression analyses with survival for potential prognostic factors were performed. Hazzard ratio (HR) with 95% confidence intervals (CIs) was depicted in Table 3. Multivariate analysis with RFS showed gender (HR: 0.38, 95% CI: 0.22–0.69, $p=0.001$), T stage (HR: 0.64, 95% CI: 0.50–0.81, $p=0.001$) and UFUR maintenance (HR: 0.73, 95% CI: 0.58–0.92, $P=0.009$) were strongly correlated with survival. Multivariate analysis with OS demonstrated that gender (HR: 0.45, 95% CI: 0.25–0.83, $p=0.010$), T stage (HR: 0.62, 95% CI: 0.48–0.80, $p<0.001$) and UFUR maintenance (HR: 0.61, 95% CI: 0.47–0.79, P = < 0.001) were independent predictors associated with survival.

Discussion

To our best knowledge, this is the first study to demonstrated the prognostic role of UFUR maintenance for patients with HNSCC treated with definitive CCRT. Previous studies all focused on the survival benefits of adjuvant UFUR maintenance for patients with HNSCC following radical surgery. Our study confirmed that HNSCC patients receiving UFUR maintenance after definitive CCRT had longer survival than those patients without UFUR maintenance. Local regional recurrence is usually developed in the future because of a lots of carcinogenesis, including tobacco use, alcohol consumption, and betel quid chewing [18]. Field cancerization made the treatment of HNSCC became more challenge. Despite advancements in surgical techniques, radiation therapy, and systemic treatments, the prognosis for patients diagnosed with advanced HNSCC continues to be poor, with high rates of disease recurrence and mortality [19, 20]. Hence, our study highlighted the importance of maintenance therapy to decrease recurrent rate and prolong survival.

In response to these challenges, metronomic chemotherapy has emerged as a promising therapeutic strategy, particularly in HNSCC [21]. This approach involves the continuous administration of chemotherapeutic agents at low, minimally toxic doses to inhibit tumour angiogenesis, modulate the immune response, and prevent tumour regrowth [8]. UFUR, an oral prodrug of 5-FU, has become a key agent in this approach, offering sustained drug exposure with a reduced toxicity profile, making it particularly suitable for long-term maintenance therapy in the elderly and frail patients [22].

Our findings demonstrated the advantages of UFUR maintenance therapy in improving oncologic outcomes. The recurrence rate was significantly lower in the UFUR (+) group compared to the UFUR (-) group (34% vs. 47%, $p<0.002$), primarily driven by better locoregional control, with locoregional recurrence rates of 23% in the UFUR (+) group versus 37% in the UFUR (-) group ($p<0.001$).

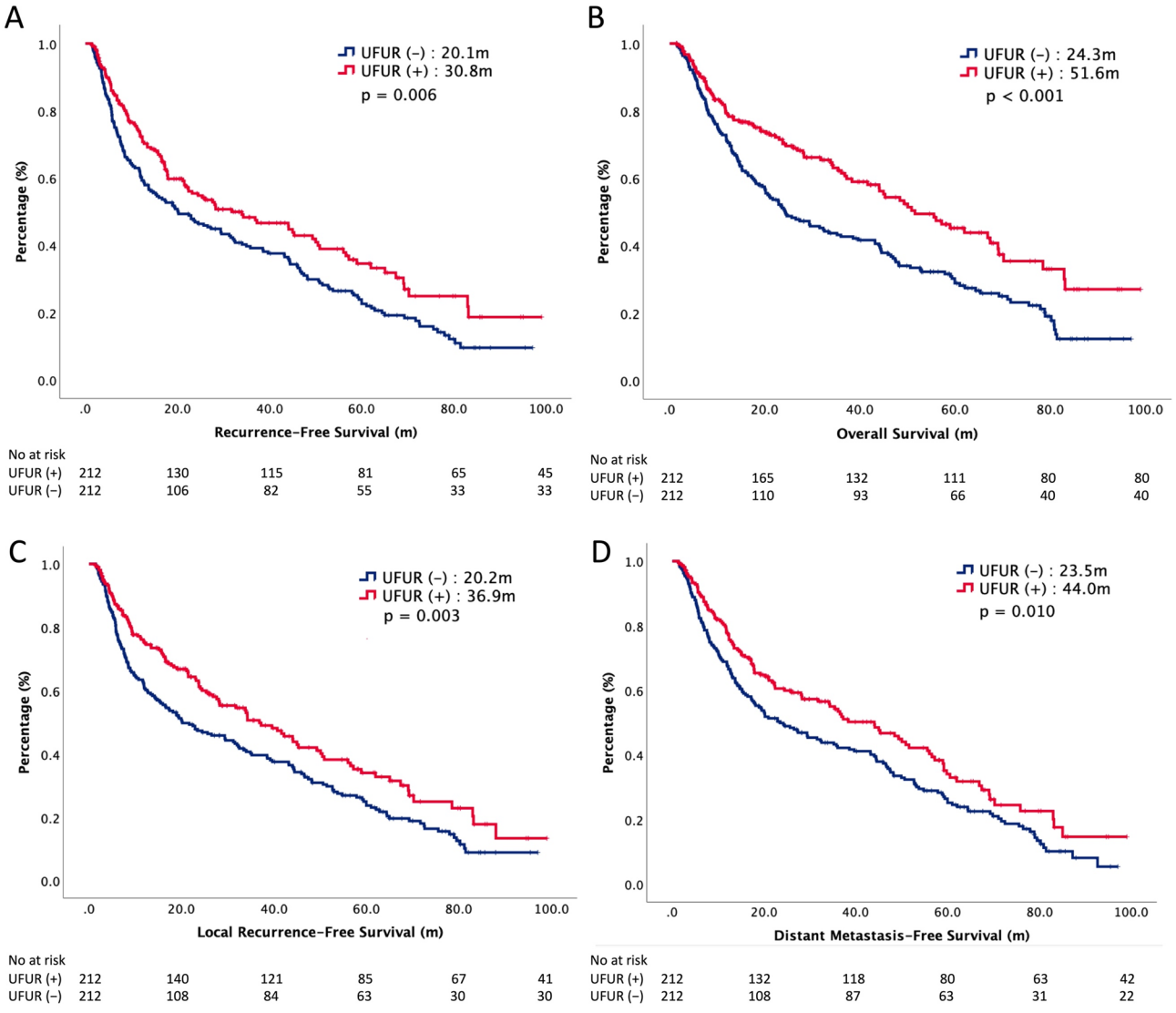

Fig. 1 Comparison of survival outcomes between the UFUR (+) and UFUR (-) groups. Survival curves for progression-free survival (PFS) and overall survival (OS) are shown, further highlighting the superior outcomes in the UFUR (+) group. The survival curves for locoregional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) demonstrate significantly improved outcomes in the UFUR (+) group. The median LRFS was 36.9 months for the UFUR (+) group, compared to 20.2 months for the UFUR (-) group ($p = 0.003$). Similarly, the median DMFS was 44.0 months in the UFUR (+) group versus 23.5 months in the UFUR (-) group ($p = 0.010$)

Given that local recurrence in head and neck cancers is often associated with poor prognosis, this improvement in locoregional control is particularly noteworthy. Although distant metastasis rates were not significantly different between the two groups (15% in UFUR (+) vs. 19% in UFUR (-), $p = 0.210$), the overall survival was markedly improved in the UFUR (+) group, with a median OS of 51.6 months compared to 24.3 months in the UFUR (-) group ($p < 0.001$). This suggests that UFUR maintenance therapy's primary impact on locoregional recurrence translates into a substantial survival benefit. Additionally, UFUR maintenance therapy provided significant improvements in both LRFS and DMFS, with a median LRFS of 36.9 months in the UFUR (+) group versus 20.2 months in the UFUR (-) group ($p = 0.003$) and median DMFS of 44.0 months versus 23.5 months, respectively ($p = 0.010$). These findings support the use of UFUR maintenance across a broad spectrum of patients with advanced HNSCC.

The results of this study have significant clinical implications. UFUR maintenance therapy, with its manageable regimen and substantial survival benefits, offers an effective strategy to improve outcomes in patients with advanced HNSCC. The marked improvement in locoregional control is particularly relevant for this patient population, where local recurrence is a major challenge. Future researches should focus on optimizing the duration and dosing of UFUR maintenance and exploring

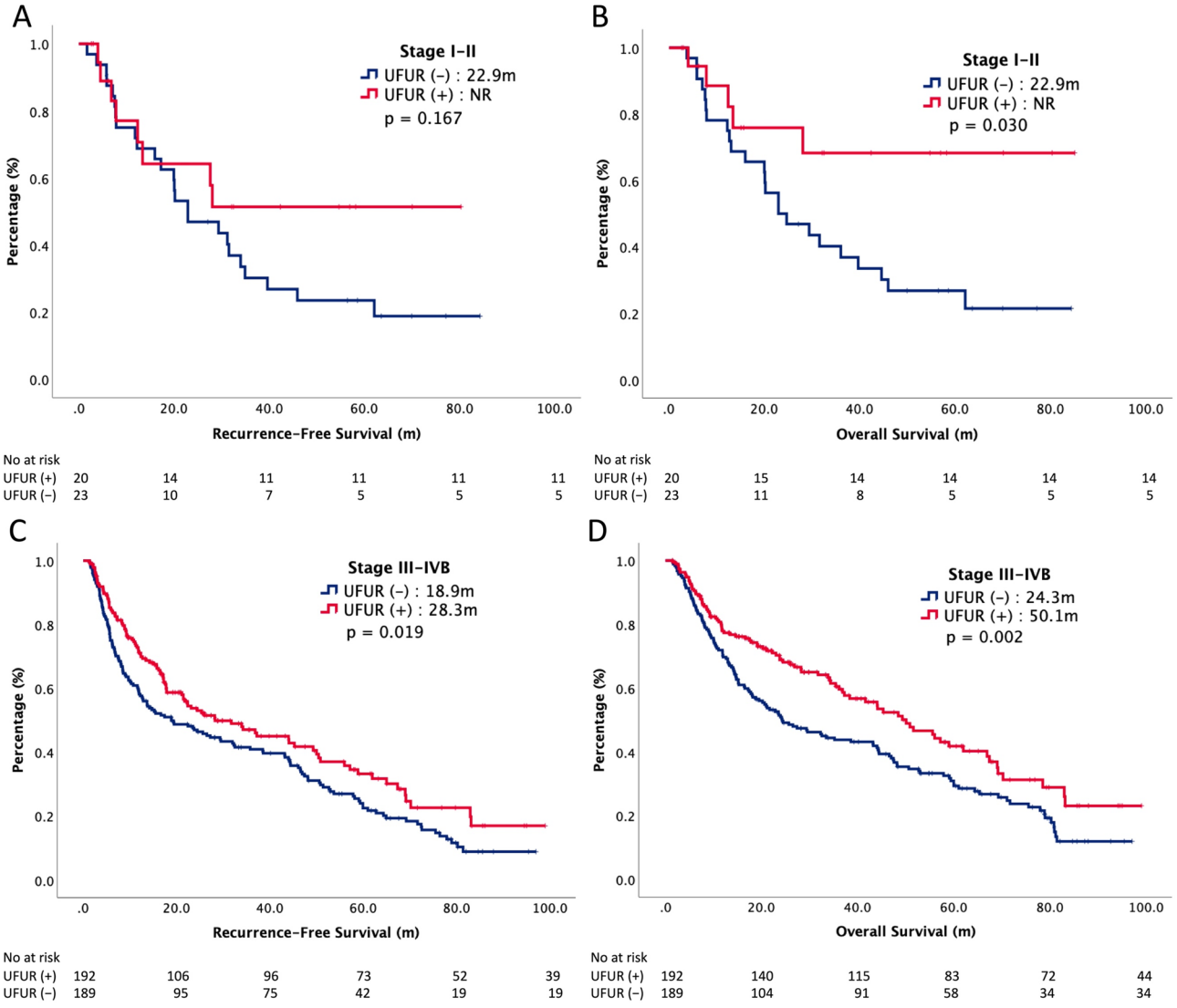

Fig. 2 Subgroup analysis of survival outcomes stratified by stage, comparing UFUR (+) and UFUR (-) groups. UFUR maintenance therapy demonstrated improved tumor control across all stages. For patients with stage I-II disease, the median recurrence-free survival (RFS) was not reached (NR) in the UFUR (+) group and 22.9 months in the UFUR (-) group ($p = 0.167$), while the median overall survival (OS) was NR in the UFUR (+) group compared to 22.9 months in the UFUR (-) group ($p = 0.030$). For patients with stage III-IV disease, the median RFS was 28.3 months in the UFUR (+) group versus 18.9 months in the UFUR (-) group ($p = 0.019$), and the median OS was 50.1 months in the UFUR (+) group compared to 24.3 months in the UFUR (-) group ($p = 0.002$). The survival curves for progression-free survival (PFS) and OS are illustrated, highlighting the stage-specific benefits of UFUR maintenance therapy

its integration with other therapeutic modalities, such as targeted therapies or immunotherapy. Additionally, identifying biomarkers that predicted response to UFUR maintenance could enable more personalized treatment approaches, further enhancing the efficacy and tolerability of HNSCC management.

There were several inevitable biases in our study, which were inherent to any retrospective observational studies. First, this was not a randomized controlled study. The choice of UFUR maintenance or not were at the physician's discretions. This will be a major bias in this study. Second, the intensity of CCRT were also variable between these two groups. Patients with older ages and poor performance status might receive CCRT with less treatment intensity. This will also influence the validity of our study. Finally, irregular follow-up interval, inconsistent adjuvant treatment and different subsequent treatments would also limit the power of our study. Nonetheless, our study demonstrated that UFUR maintenance provided a better outcome in HNSCC patients treated with definitive CCRT. Further prospective randomized control studies were warranted to validate our conclusions.

Table 3 Multivariate analysis with survival of 424 R/M HNSCC patients

	RFS		OS	
Gender, Female vs. male	0.38 (0.22–0.69)	0.001	0.45 (0.25–0.83)	0.010
Age, ≤ 60 vs. > 60	0.95 (0.75–1.22)	0.701	0.99 (0.76–1.28)	0.940
Primary tumor, oropharynx vs. non-oropharynx	0.82 (0.65–1.05)	0.110	0.80 (0.62–1.03)	0.087
T stage, T1-2 vs. T3-4	0.64 (0.50–0.81)	0.001	0.62 (0.48–0.80)	< 0.001
N stage, N0-1 vs. N2-3	0.92 (0.72–1.17)	0.486	0.95 (0.73–1.24)	0.715
Stage, I-II vs. III-IVB	0.92 (0.64–1.32)	0.645	0.99 (0.68–1.46)	0.975
P16, yes vs. no	0.89 (0.76–1.05)	0.159	0.66 (0.36–1.24)	0.399
UFUR maintenance, yes vs. no	0.73 (0.58–0.92)	0.009	0.61 (0.47–0.79)	< 0.001

R/M HNSCC, recurrent or metastatic head and neck squamous cell carcinoma; UFUR, tegafur/uracil; RFS, recurrence-free survival; OS, overall survival

Conclusion

In conclusion, UFUR maintenance therapy significantly improves survival outcomes in patients with advanced head and neck squamous cell carcinoma, particularly through enhanced locoregional control. The strong correlation between UFUR maintenance and improved overall survival underscores its potential as a key component in the personalized treatment of HNSCC. These findings support the continued integration of UFUR into treatment protocols and highlight the need for further researches to optimize its use, particularly in combination with other therapeutic modalities and in specific patient subgroups. Further prospective randomized control studies were ongoing to confirmed our conclusions.

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Author contributions
Study design: MCH and JHC. Data collection, analysis and interpretation: CHH, MYL and PHC. Patient follow-up: HMW, KYY, CLH and CYH. Drafting of the manuscript: CHH, MYL, PHC, MCH and JHC. Critical revision of the manuscript: HMW, KYY, CLH and CYH. Approval of the final version for publication: all co-authors.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was conducted following the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of E-Da Hospital (EMPR18113N), the Institutional Review Board of Chang Gung Memorial Hospital (202500269B0), the Institutional Review Board of China Medical University Hospital (CMUH114-REC2-077), and the Institutional Review Board of Tri-service General Hospital (B202405200). Due to the retrospective design of the study, the requirement for informed consent was waived.

Competing interests
The authors declare no competing interests.

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