Journal of Dental Sciences 21 (2026) 515–523

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jds.com

Original Article

Adjuvant metronomic tegafur-uracil is associated with poorer outcomes and unfavorable histopathologic progression in oral squamous cell carcinomas

Kai-Feng Hung [a,b], Yi-Ping Wang [c,d,e], Yi-Chen Sun [f,g], Zhi-Qian Lin [b], Cheng-Hsien Wu [a,h], Peter Mu-Hsin Chang [i,j], Julia Yu-Fong Chang [c,d,e*]

[a] *Department of Dentistry, School of Dentistry, National Yang Ming Chiao Tung University, Taipei, Taiwan*
[b] *Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan*
[c] *Department of Dentistry, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan*
[d] *Graduate Institute of Clinical Dentistry, School of Dentistry, National Taiwan University, Taipei, Taiwan*
[e] *Graduate Institute of Oral Biology, School of Dentistry, National Taiwan University, Taipei, Taiwan*
[f] *Department of Ophthalmology, Taipei Tzu Chi Hospital, The Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan*
[g] *School of Medicine, Tzu-Chi University, Hualien, Taiwan*
[h] *Department of Stomatology, Taipei Veterans General Hospital, Taipei, Taiwan*
[i] *Institute of Biopharmaceutical Sciences, National Yang Ming Chiao Tung University, Taipei, Taiwan*
[j] *Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan*

Received 15 October 2025
Available online 12 November 2025

KEYWORDS
Oral squamous cell carcinoma;
Metronomic chemotherapy;
Tegafur-uracil;

Abstract *Background/purpose:* Tegafur-uracil (UFUR) is widely prescribed as metronomic adjuvant chemotherapy for oral squamous cell carcinoma (OSCC) in East Asia, though its long-term benefit remains unclear. This study aimed to evaluate the oncologic and pathological impact of adjuvant UFUR in a large real-world OSCC cohort spanning three decades.
Materials and methods: This retrospective, single-institution cohort included 2048 patients with histopathologically confirmed OSCC treated at a tertiary medical center in Taiwan (1990–2020). All underwent curative-intent surgery with or without postoperative

* Corresponding author. Department of Dentistry, National Taiwan University Hospital, College of Medicine, National Taiwan University, No. 7, Chung Shan S. Rd., Zhongzheng Dist., Taipei 100, Taiwan.
E-mail address: jyfchang@ntu.edu.tw (J.Y.-F. Chang).

https://doi.org/10.1016/j.jds.2025.10.023

UFUR;
Disease-free survival;
Spindle-cell transformation

radiotherapy or concurrent chemoradiotherapy (CCRT). Among them, 878 patients received adjuvant metronomic UFUR for ≥12 months. Survival outcomes were analyzed using Kaplan—Meier and Cox proportional hazards models, and clinicopathologic associations were assessed using chi-square and Wilcoxon tests.

Results: Adjuvant UFUR did not improve disease-free survival (DFS) across cancer stages and was associated with significantly poorer DFS in early-stage diseases. Hazard ratios (HRs) for DFS in stages I—III were 1.523, 1.616, and 1.441, respectively (all $P < 0.01$). UFUR-treated patients also exhibited higher rates of recurrence, earlier onset of second primary cancers, and more frequent spindle-cell transformation, particularly among poorly-differentiated OSCCs.

Conclusion: Adjuvant metronomic UFUR provided no survival advantage and was associated with unfavorable histopathologic evolution in OSCCs. These findings warrant re-evaluation of UFUR as routine adjuvant therapy and support risk-adapted, molecularly guided postoperative strategies in oral cancer management.

Introduction

Oral squamous cell carcinoma (OSCC) remains a significant clinical burden, with 5-year survival stagnant at approximately 50 % despite treatment advances.[1—3] Early-stage OSCC is potentially curable with surgery, but advanced-stages OSCCs require surgery followed by adjuvant cisplatin-based concurrent chemoradiotherapy (CCRT).[4,5] However, locoregional recurrence, distant metastasis, or second primary cancers remain common,[2,6,7] underscoring the need for better adjuvant therapies.

Metronomic adjuvant chemotherapy entails continuous low-dose (typically 1/10 to 1/3 of the maximum tolerated dose) of cytotoxic agents.[8—12] One commonly used regimen is tegafur and uracil (UFUR), a 1:4 M combination,[13] in which tegafur is a 5-fluorouracil (5-FU) prodrug,[14] and uracil inhibits dihydropyrimidine dehydrogenase to reduce 5-FU degradation.[15] UFUR has shown promise, particularly in elderly or frail patients, and has been associated with longer progression-free and overall survival in various cancers when used as maintenance or combination therapy.[16,17]

Metronomic UFUR has also attracted interest in oral cancers, mainly as maintenance therapy for the late-stage or locally advanced disease. It is used for recurrent, metastatic, or inoperable tumors; for patients intolerant of standard chemotherapy; and for those with high-risk pathological features.[18—22] While many studies report benefit, others show no improvement in disease-free survival (DFS) or overall survival (OS),[23,24] and most are limited by small, narrowly defined cohorts and short follow-up time. In the absence of guidelines, UFUR is often used empirically in high-risk patients. These gaps motivate us to evaluate a large, long-term OSCC cohort across all stages after curative surgery (with or without adjuvant therapy) and identification of pathological features that may justify UFUR use.

We therefore conducted a retrospective analysis of a large, long-term, all-stage OSCC cohort after curative surgery to assess the prognostic impact, benefits, and risks of adjuvant metronomic UFUR.

Materials and methods

Subjects

This was an observational, retrospective, single-center study conducted at National Taiwan University Hospital (NTUH). The study cohort included patients who were histopathologically diagnosed with OSCC and received their initial treatment at NTUH between January 1990 and December 2020. Patients with a prior history of surgical resection, radiotherapy (RT), or chemotherapy at other institutions were excluded. As part of the institutional treatment protocol, eligible patients received radiotherapy or CCRT when indicated, with a total radiotherapy dose ranging from 60 Gy to 70 Gy. The TNM classification and clinical staging were determined according to the 7th edition of the American Joint Committee on Cancer (AJCC) guidelines, based on histopathological findings. Patients in the UFUR group received oral UFUR as adjuvant metronomic chemotherapy following surgery, with or without adjuvant RT or chemoradiotherapy, at a daily dose of 100—400 mg for at least 12 months after completion of standard treatment. This retrospective study utilized data from the Integrative Medical Database (NTUH-iMD), which was established under general informed consent provided by patients and institutional quality-assurance protocols.[25,26] The study protocol was reviewed and approved by the Institutional Review Board of NTUH (IRB No. 202201038RINA) and was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Descriptive statistics were used to summarize patients' demographic and clinical characteristics, including age, cancer stage, treatment modality, and pathological features. Categorical variables (such as clinical stage, treatment modality, pathological differentiation, surgical margin status, perineural invasion [PNI], lymphovascular

Table 1 Baseline clinicopathological characteristics of patients with oral squamous cell carcinoma (OSCC) stratified by adjuvant UFUR treatment. Data summarize demographic, clinical, and pathological variables of 2048 OSCC patients categorized by UFUR exposure (UFUR vs. No UFUR). Continuous data are presented as mean ± SD and categorical data as number (percentage).

	Total	No UFUR	UFUR	*P*-value
Patients	2148	1540	878	
Age, years (mean ± SD)	56.46 ± 12.82	56.98 ± 12.68	54.48 ± 11.66	
Personal habits				
Alcohol	2035 (84.16 %)[a]	1293 (83.96 %)[b]	742 (84.51 %)[c]	0.7722
Betel nut	1969 (81.43 %)[a]	1248 (81.04 %)[b]	721 (82.12 %)[c]	0.5498
Smoking	2124 (87.84 %)[a]	1337 (86.82 %)[b]	787 (89.64 %)[c]	0.1285
Primary tumor site				
Buccal mucosa	832 (34.41 %)[a]	529 (34.35 %)[b]	303 (34.51 %)[c]	0.9866
Tongue	605 (25.02 %)[a]	392 (25.45 %)[b]	213 (24.26 %)[c]	
Gingiva	277 (11.46 %)[a]	176 (11.43 %)[b]	101 (11.50 %)[c]	
Lip	60 (2.48 %)[a]	35 (2.27 %)[b]	25 (2.85 %)[c]	
Palate	176 (7.28 %)[a]	110 (7.14 %)[b]	66 (7.52 %)[c]	
Retromolar	113 (4.67 %)[a]	71 (4.61 %)[b]	42 (4.78 %)[c]	
Mouth floor	82 (3.39 %)[a]	51 (3.31 %)[b]	31 (3.53 %)[c]	
Oropharynx	273 (11.29 %)[a]	176 (11.43 %)[b]	97 (11.05 %)[c]	
Stage (AJCC 7th edition)				
I	341 (14.10 %)[a]	237 (69.50 %)[b]	104 (30.50 %)[c]	0.1197
II	364 (15.05 %)[a]	225 (61.81 %)[b]	139 (38.19 %)[c]	
III	324 (13.40 %)[a]	202 (62.35 %)[b]	122 (37.65 %)[c]	
IV	1389 (57.44 %)[a]	876 (63.07 %)	513 (36.93 %)	
IVa	1093 (45.20 %)[a]	697 (63.77 %)[b]	396 (36.23 %)[c]	
IVb	230 (9.51 %)[a]	131 (56.96 %)[b]	99 (43.04 %)[c]	
IVc	66 (2.73 %)[a]	48 (72.73 %)[b]	18 (27.27 %)[c]	
Tumor differentiation				
Well differentiated	839 (34.70 %)[a]	570 (37.01 %)[2]	269 (30.64 %)[c]	0.0016
Moderately differentiated	786 (32.51 %)[a]	425 (27.60 %)[2]	361 (41.12 %)[c]	<0.001
Poorly differentiated	120 (4.96 %)[a]	57 (3.70 %)[2]	63 (7.18 %)[c]	<0.001
Unspecified	673 (27.83 %)[a]	488 (31.69 %)[2]	185 (21.07 %)[c]	<0.001
Primary treatment modality				
Stage I				
Surgery alone	184 (53.96 %)[d]	155 (65.40 %)[e]	29 (27.88 %)[f]	
Sugery and RT	56 (16.42 %)[d]	35 (14.77 %)[e]	21 (20.19 %)[f]	<0.001
Surgery and CCRT	101 (29.62 %)[d]	47 (19.83 %)[e]	54 (51.92 %)[f]	
Stage II				
Surgery alone	160 (43.96 %)[d]	123 (54.67 %)[e]	37 (26.62 %)[f]	
Sugery and RT	86 (23.63 %)[d]	50 (22.22 %)[e]	36 (25.90 %)[f]	<0.001
Surgery and CCRT	118 (32.42 %)[d]	52 (23.11 %)[e]	66 (47.48 %)[f]	
Stage III				
Surgery alone	100 (30.86 %)[d]	80 (39.60 %)[e]	20 (16.39 %)[f]	
Sugery and RT	77 (23.77 %)[d]	50 (24.75 %)[e]	27 (22.13 %)[f]	<0.001
Surgery and CCRT	147 (45.37 %)[d]	72 (35.64 %)[e]	75 (61.48 %)[f]	
Stage IVa				
Surgery alone	308 (28.18 %)[d]	240 (34.43 %)[e]	68 (17.17 %)[f]	
Sugery and RT	278 (25.43 %)[d]	175 (25.11 %)[e]	103 (26.01 %)[f]	<0.001
Surgery and CCRT	507 (46.39 %)[d]	282 (40.46 %)[e]	225 (56.82 %)[f]	
Stage IVb				
Surgery alone	54 (23.48 %)[d]	31 (23.66 %)[e]	23 (23.23 %)[f]	
Sugery and RT	54 (23.48 %)[d]	36 (27.48 %)[e]	18 (18.18 %)[f]	0.2135
Surgery and CCRT	122 (53.04 %)[d]	64 (48.85 %)[e]	58 (58.59 %)[f]	
Stage IVc				
Surgery alone	23 (34.85 %)[d]	18 (37.50 %)[e]	5 (27.78 %)[f]	
Sugery and RT	16 (24.24 %)[d]	10 (20.83 %)[e]	6 (33.33 %)[f]	0.5424
Surgery and CCRT	27 (40.91 %)[d]	20 (41.67 %)[e]	7 (38.89 %)[f]	

[a] Percentage calculated from the total number of patients in each column (Total, No UFUR, UFUR).
[b] Percentage of patients within the No UFUR group.
[c] Percentage of patients within the UFUR group.
[d] Percentage of all patients at a given clinical stage.
[e] Percentage of No UFUR patients receiving the specified treatment modality.
[f] Percentage of UFUR patients receiving the specified treatment modality.

invasion [LVI], recurrence, second primary cancer, and spindle-cell transformation) were presented as frequencies and percentages, whereas continuous variables (such as age and follow-up duration) were expressed as means with standard deviations. Comparisons of continuous variables between groups were performed using the independent two-sample t-test or the Wilcoxon rank-sum test, depending on the normality of data distribution. Differences in categorical variables were assessed using the chi-square test or Fisher's exact test, where appropriate. Disease-free survival (DFS) was defined as the time from diagnosis to the first documented recurrence, disease progression, or death. Time-to-event outcomes, including DFS, time to recurrence, and time to second primary cancer, were estimated using the Kaplan–Meier method, and differences between groups were compared using the log-rank test. To identify prognostic factors associated with survival outcomes, Cox proportional hazards regression models were applied to estimate hazard ratios (HRs) and corresponding 95 % confidence intervals (CIs). All statistical tests were two-tailed, and a P-value <0.05 was considered statistically significant.

Results

From 1990 to 2020, a total of 8122 patients with OSCC were identified in the NTUH database (Supplemental Fig. 1A). We excluded 4594 patients who received initial treatment elsewhere or had incomplete medical records, 379 patients who died from non-cancer-related causes, and 1001 patients with carcinoma in situ or unclear TNM staging. The final analytic cohort comprised 2048 eligible patients. All patients underwent curative-intent surgery, with or without adjuvant RT or CCRT.

Among them, 878 patients (42.9 %) received adjuvant metronomic UFUR for more than 12 months following completion of standard treatment. Clinicopathologic features, including age, personal habits, primary tumor site, pathological stage, tumor differentiation, and primary treatment modality are summarized in Table 1. The mean ages of the patients receiving and not receiving UFUR were 54.5 ± 11.7 and 57.0 ± 12.8 years, respectively. There were no statistical differences between the UFUR and No UFUR groups regarding age, personal habits, primary tumor site, or other comorbidities.

The cohort included 341 (14.1 %), 364 (15.1 %), 324 (13.4 %), and 1398 (57.4 %) patients with stage I, II, III, and IV disease, respectively, according to the 7th AJCC classification, with stage IV further divided into IVa (1093; 45.2 %), IVb (230; 9.5 %), and IVc (66; 2.7 %). UFUR was administered to 30.5 %, 38.2 %, 37.7 %, and 36.9 % of patients in stages I–IV, respectively, with no significant difference in distribution among stages (chi-square test, $P = 0.1197$), suggesting that UFUR was not administered preferentially based on the tumor stage. However, tumor differentiation showed a significant association with UFUR use: patients with well-differentiated OSCCs were less likely to receive UFUR (30.6 % vs. 37.0 %, $P = 0.0016$), while those with moderately- or poorly-differentiated OSCCs were more likely to receive UFUR (41.1 % vs 27.6 % and 7.2 % vs. 3.7 %, both $P < 0.001$). Across treatment modalities, UFUR was prescribed significantly more often in patients undergoing surgery + CCRT and less often in those treated by surgery alone, particularly in stages I–IVa (all $P < 0.001$). No significant differences were observed in stages IVb or IVc ($P = 0.2135$ and $P = 0.5424$, respectively).

The median follow-up period was 31.6 months (range, 3.4–267.3 months). Kaplan–Meier analysis demonstrated a progressive decline in DFS with increasing clinical stage (Supplemental Fig. 1B). Across all stages, adjuvant UFUR was not associated with improved DFS. In contrast, patients receiving UFUR exhibited significantly poorer DFS in stages I–III. The HRs for DFS associated with UFUR were 1.523 (95 % CI 1.139–2.036) in stage I, 1.616 (95 % CI 1.185–2.202) in stage II, 1.441 (95 % CI 1.100–1.887) in stage III, and 1.083 (95 % CI 0.955–1.229) in stage IV (Fig. 1).

Median DFS for UFUR vs. No UFUR groups were 66.7 vs. 104.7 months ($P = 0.0020$) for stage I, 62.4 vs 112.3 months ($P = 0.0016$) for stage II, 39.9 vs. 63.6 months ($P = 0.0051$) for stage III, and 28.5 vs. 32.8 months ($P = 0.2070$) for stage IV, respectively (Fig. 1).

Among stage I patients without UFUR, those treated with surgery alone had significantly superior DFS (median 138.7 months) compared with those receiving surgery + RT (48.2 months) or surgery + CCRT (74.2 months) ($P < 0.0001$, Fig. 2A, left). However, among UFUR-treated stage I patients, DFS did not significantly differ across treatment modalities ($P = 0.1995$, Fig. 2A, right). Similarly, within each treatment subgroup (surgery alone, surgery + RT, surgery + CCRT), no significant DFS differences were observed between UFUR and No UFUR recipients ($P = 0.1504$, 0.5682, and 0.5693, respectively, Fig. 2B).

In stage II OSCC patients, No UFUR patients receiving surgery alone achieved longer DFS (median 155.2 months) compared with surgery + RT (59.9 months, $P = 0.0011$) or surgery + CCRT (83.9 months, $P = 0.0159$, Fig. 3A, left). Among UFUR recipients, no significant differences were found across modalities (Fig. 3A, right). When comparing UFUR vs. No UFUR groups within the same modality, surgery-alone patients without UFUR showed superior DFS (155.2 vs. 76.0 months, $P = 0.0039$), whereas no significant differences were observed in the RT or CCRT subgroups ($P = 0.2274$ and 0.0939, respectively, Fig. 3B).

To explore whether poorer outcomes reflected underlying histopathologic risk, we compared surgical margin

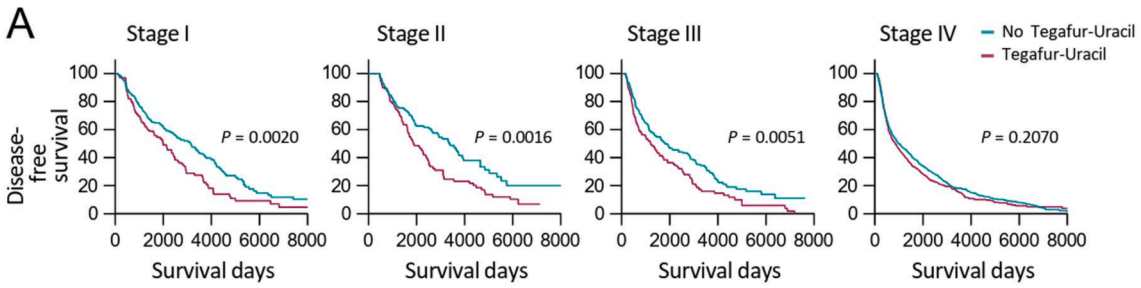

Figure 1 Adjuvant metronomic UFUR was not associated with improved disease-free survival (DFS) in OSCCs. Kaplan–Meier curves compared DFS between patients receiving UFUR (magenta) and those without UFUR (teal), stratified by clinical stage. UFUR treatment correlated with significantly poorer DFS in stages I, II, and III ($P = 0.0020$, 0.0016, and 0.0051, respectively), while no difference was observed in stage IV ($P = 0.2070$). Time scale in days.

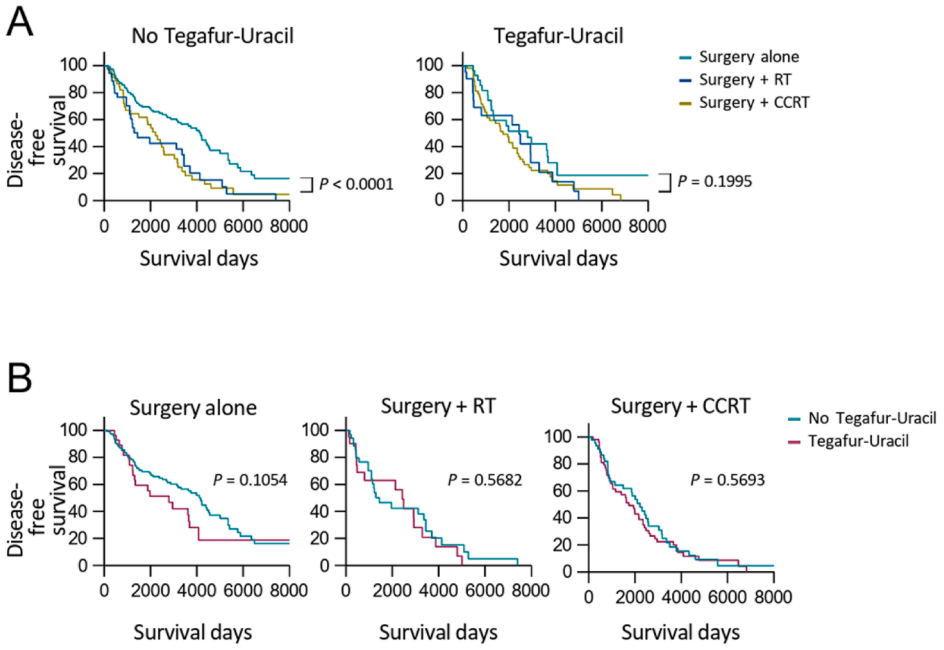

Figure 2 Stage I patients receiving surgery alone had superior DFS compared to those with UFUR as adjuvant chemotherapy across treatment modalities. (A) Kaplan–Meier curves for stage I patients without UFUR (left) and with UFUR (right), stratified by treatment modality: surgery alone (teal), surgery + RT (navy), or surgery + CCRT (yellow). The DFS significantly differed by modality in the No UFUR group ($P < 0.0001$) but not in the UFUR group ($P = 0.1995$). (B) Comparison between UFUR and No UFUR patients within each modality showed no significant DFS difference ($P = 0.1054$, 0.5682, and 0.5693, respectively). Time in days. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

status, perineural invasion (PNI), and lymphovascular invasion (LVI) between groups. Early-stage patients receiving UFUR combined with postoperative CCRT were significantly more likely to exhibit adverse pathological features. In stage I, UFUR recipients showed higher rates of close/dysplastic margins ($P = 0.0286$) and LVI ($P = 0.0107$, Supplemental Fig. 2). In stage II, PNI ($P = 0.0296$) and LVI ($P = 0.0400$) were also significantly more frequent among UFUR recipients (Supplemental Fig. 3). In stages III–IV, no significant pathological differences were observed between UFUR and No UFUR groups (Supplemental Fig. 4).

Next, we analyzed the interval from surgery to first recurrences and to second primary cancer, defined as a new malignancy at the original or another site occurring more than 5 years after completion of initial curative treatment. UFUR treatment was associated with a modest delay in recurrence among early-stage patients, but also a higher cumulative incidence of second primary cancers (Fig. 4). Recurrence intervals were longer in stage I and II UFUR recipients, whereas stage III and IV patients exhibited shorter recurrence intervals with minimal difference between groups (Fig. 4A). Conversely, UFUR-treated patients tended to develop second primary cancers earlier than those without UFUR (Fig. 4B). Among No UFUR patients, recurrence rates increased from 11.4 % (stage I) to 38.9 % (stage IV), and second primary rates from 6.3 % to 16.9 %. In contrast, UFUR-treated patients showed markedly higher early-stage recurrence (33.7 % and 37.4 % for stages I and II patients, respectively) and second primary rates (26.0 % and 22.3 %, respectively), while differences in advanced stages were non-significant (Fig. 4C; Table 2).

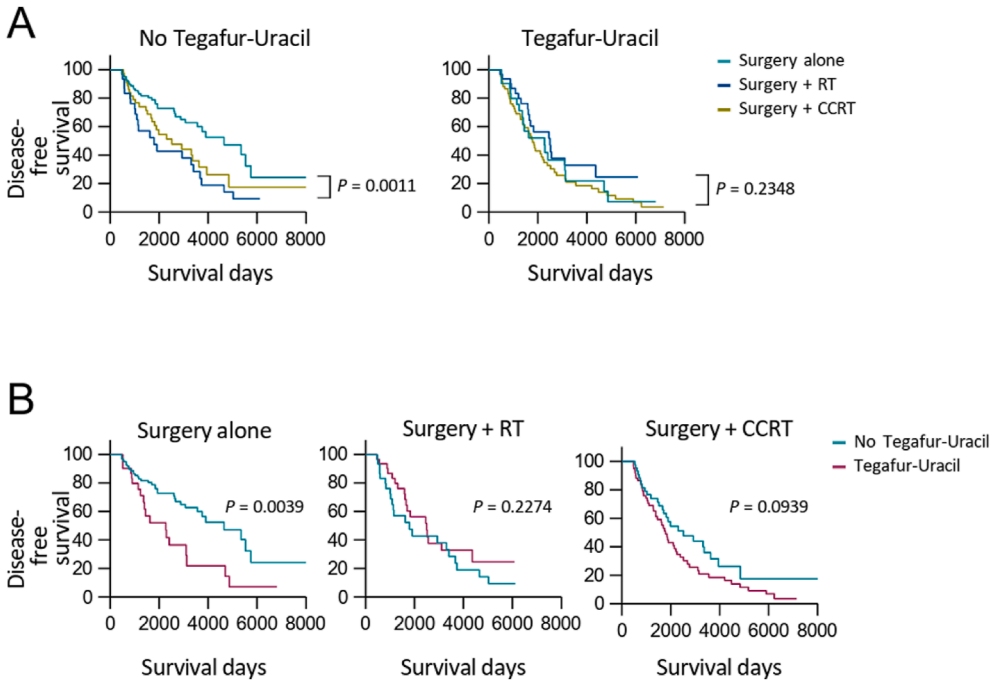

Figure 3 Stage II patients without UFUR demonstrated superior DFS across treatment modalities. (A) Kaplan—Meier curves for stage II OSCC patients without (left) or with UFUR (right), stratified by modality. The DFS differed by modality in No UFUR patients ($P = 0.0011$) but not in UFUR recipients ($P = 0.2348$). (B) UFUR was associated with significantly poorer DFS among patients receiving surgery alone ($P = 0.0039$), but not in those receiving adjuvant RT or CCRT ($P = 0.2274$ and 0.0939, respectively). Time in days.

Spindle-cell transformation, indicating aggressive tumor progression, was more frequent in UFUR-treated patients (Fig. 5). The spindle-cell transformation occurred in 6.0 % of stage IV patients receiving UFUR vs. 4.2 % without UFUR, compared to 0.96 % vs. 0.42 % in stage I (Fig. 5A; Supplemental Table 1). Advanced-stage patients more often had moderately- or poorly-differentiated OSCCs (Fig. 5B, left). Across all stages, poorly differentiated tumors were more likely to undergo spindle-cell transformation. Importantly, UFUR exposure further increased this tendency among patients with poorly-differentiated primary OSCCs (Fig. 5B, right), suggesting that prolonged metronomic UFUR may contribute to histologic dedifferentiation in recurrent disease.

Discussion

In this 30-year, all-stage OSCC cohort, adjuvant UFUR demonstrated limited survival benefit, particularly among early-stage patients, in whom UFUR use was paradoxically associated with significantly poorer DFS. This finding may, in part, reflect a clinical selection bias, whereby early-stage patients with adverse pathological features were more likely to receive postoperative UFUR. Although recurrence appeared modestly delayed, UFUR use correlated with higher recurrence rates, earlier onset of second primary cancers, and an increased risk of spindle-cell transformation, especially in poorly-differentiated OSCCs.

Previous studies have reported heterogeneous outcomes for adjuvant or maintenance UFUR in head and neck cancers. Several previous investigations demonstrated potential survival benefits in advanced, recurrent, or high-risk OSCCs, as well as in patients intolerant of standard chemotherapy.[18—21,23,24,27] For example, Lin et al.[28] reported superior 4-year DFS with postoperative UFUR versus surgery alone (84.6 % vs. 60.9 %; $P = 0.02$), while Yeh et al.[18] found improved OS, DFS, and distant-metastasis—free survival following metronomic UFUR maintenance after definitive therapy. Similarly, Huang et al. observed reduced distant metastasis and improved DFS (adjusted HR 0.51; $P = 0.006$) in patients with pathologic extranodal extension (pENE+), with greater benefit among those receiving longer maintenance therapy.[22] In contrast, Lam et al. reported no long-term survival advantage for UFUR-levamisole, despite a trend toward improved distant control and minimal toxicity.[23] These divergent findings likely stem from differences in disease stage, treatment setting, concomitant therapies, eligibility criteria, sample size, and follow-up duration across different studies.

A key distinction of our study lies in the inclusion of a large number of early-stage OSCC patients, a group typically underrepresented in previous UFUR research. We observed that UFUR recipients in this subgroup exhibited a higher prevalence of adverse pathological features, particularly when postoperative CCRT was administered, suggesting that clinicians empirically selected UFUR for patients perceived to be at higher risk. Nevertheless, even among early-stage patients treated with surgery alone—those generally expected to have minimal risk factors—UFUR was still associated with worse outcomes, implying that its use may have an intrinsically unfavorable

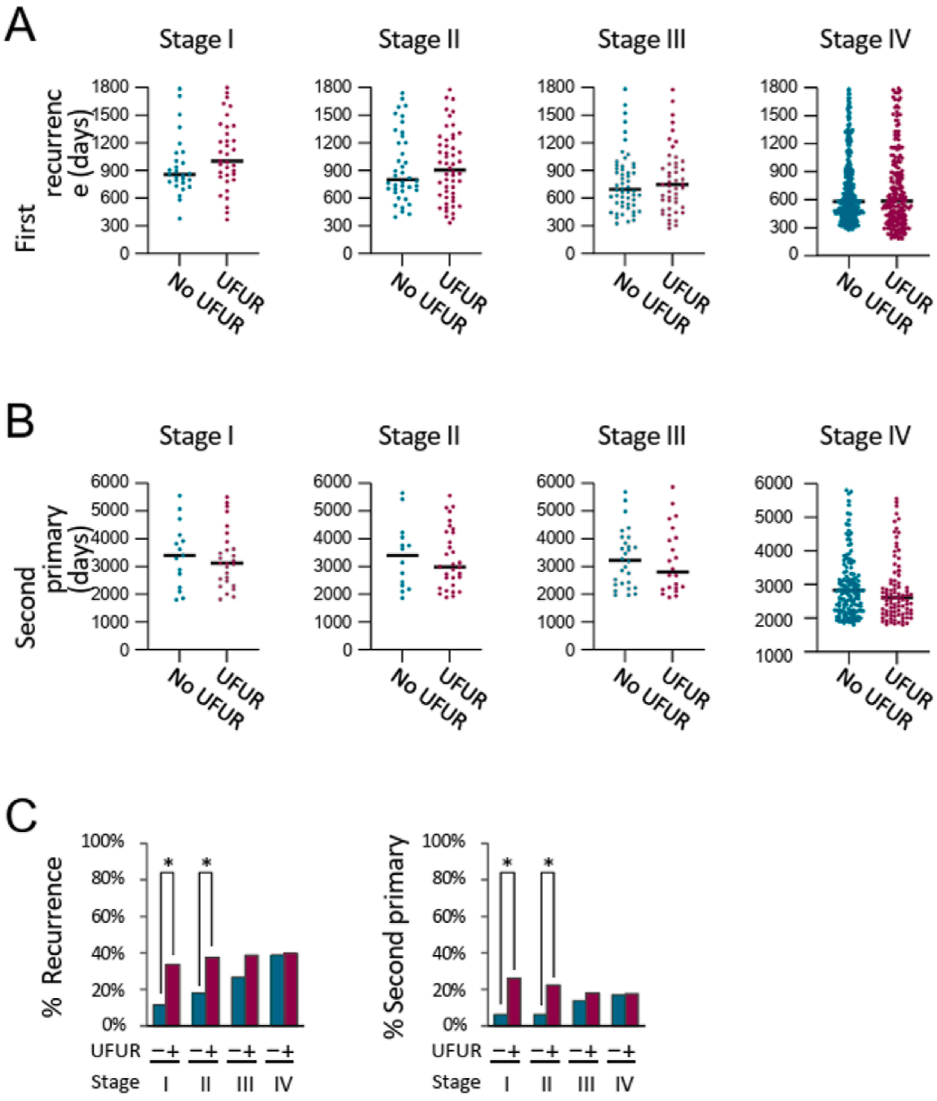

Figure 4 UFUR treatment delayed recurrence yet increased second primary cancers in early-stage OSCC patients. (A) Dot plots demonstrated time to first recurrence (days from surgery) by stage and UFUR status showed modestly delayed recurrence in stages I–II and minimal difference in stages III–IV patients. (B) Time to second primary cancer was shorter among UFUR-treated patients, notably in stage IV patients. (C) Bar plots summarized recurrence (left) and second primary (right) rates by stage and treatment. UFUR-treated stage I–II patients exhibited significantly higher recurrence and second primary rates. Error bars = SEM. Asterisks (*) indicate $P < 0.05$.

Table 2 Recurrence and second primary cancer rates by clinical stage and with or without UFUR treatment.

	Stage I		Stage II		Stage III		Stage IV	
	No UFUR	UFUR	No UFUR	UFUR	No UFUR	UFUR	No UFUR	UFUR
Total patients	237	104	235	139	202	122	876	513
Recurrence	27 (11.39 %)	35 (33.65 %)	40 (17.78 %)	52 (37.41 %)	54 (26.73 %)	47 (38.52 %)	341 (38.93 %)	204 (39.77 %)
Second primary cancer	15 (6.33 %)	27 (25.96 %)	14 (6.22 %)	31 (22.30 %)	28 (13.86 %)	22 (18.03 %)	148 (16.89 %)	91 (17.74 %)

effect rather than a confounding by indication alone. The pattern of delayed but ultimately increased recurrence and earlier second primary cancers among UFUR-treated early-stage patients raises the possibility that metronomic UFUR may suppress disease temporarily but fail to prevent the long-term recurrence.

Moreover, our study revealed a higher incidence of spindle-cell transformation, a histopathologic indicator of

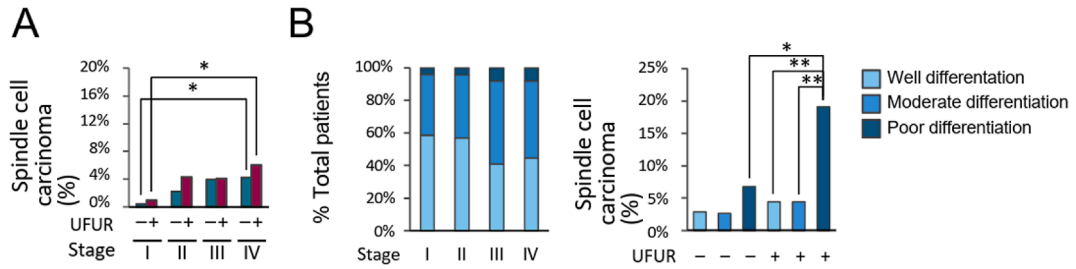

Figure 5 Spindle-cell transformation correlated with advanced stage, poor differentiation, and UFUR exposure. (A) Frequency of spindle-cell carcinoma in recurrent or second primary cancers by stage and UFUR status. Stage IV and UFUR-treated patients showed higher spindle-cell transformation rates than stage I or non-UFUR groups. (B, left) Distribution of tumor differentiation (well, moderate, poor) across stages I–IV demonstrates a shift toward poorer differentiation in later stages. (B, right) Poorly-differentiated tumors had the highest spindle-cell transformation rate, further increased by UFUR. *$P < 0.05$; **$P < 0.01$.

aggressive behavior, in recurrent or second primary cancers of UFUR-treated patients, particularly in advanced stages and poorly-differentiated primary OSCCs. Prolonged metronomic exposure to DNA/RNA-modifying agents such as UFUR may promote genomic instability and selective pressure, leading to the emergence of chemoresistant or mesenchymal-like tumor subclones. This phenomenon parallels observations in other malignancies, where long-term exposure to low-dose agents such as etoposide or temozolomide has been associated with secondary leukemias and mutagenic risks.[29,30] These findings warrant caution in the empirical use of metronomic UFUR, especially in poorly-differentiated or genomically-unstable cancers, where the propensity for aggressive transformation may be amplified.

Despite the robust sample size and extended follow-up, several limitations must be acknowledged. The 30-year study span inherently encompasses changes in surgical technique, adjuvant RT protocols, and staging guidelines, which may dilute treatment effects.[31,32] The retrospective, single-institution design introduces unavoidable selection bias and limits generalizability, and detailed data on UFUR adherence, toxicity, and molecular tumor profiles were unavailable. Nonetheless, the long observation period allowed comprehensive assessment of delayed recurrence, second primary cancer development, and histologic transformation, offering rare insights into the long-term impact of metronomic chemotherapy in real-world OSCC management.

In conclusion, adjuvant UFUR failed to improve prognosis in this large, all-stage OSCC cohort and was associated with adverse survival outcomes in early-stage patients, higher rates of second primary cancers, and increased spindle-cell transformation. These findings underscore the need for careful patient selection, individualized risk stratification, and integration of molecular diagnostics when considering UFUR in clinical practice. Future prospective studies should elucidate the molecular determinants of UFUR response and identify subsets that might derive genuine benefit from metronomic fluoropyrimidine therapy.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

We thank the staff of the Department of Medical Research, National Taiwan University Hospital for the Integrative Medical Database (NTUH-iMD). We also thank the grant support from NTUH (NTUH: 114-SS0024 and 114-S0258) and the grant support from National Science and Technology Council of Taiwan (NSTC 112-2314-B-002-090-MY3 and NSTC 113-2314-B-002-070).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2025.10.023.

References

1. Chaubal TV, Bapat RA. Squamous-cell carcinoma of the mouth. *N Engl J Med* 2017;377:1188.
2. Chow LQM. Head and neck cancer. *N Engl J Med* 2020;382:60–72.
3. Uppaluri R, Haddad RI, Tao Y, et al. Neoadjuvant and adjuvant pembrolizumab in locally advanced head and neck cancer. *N Engl J Med* 2025;393:37–50.
4. Colevas AD, Cmelak AJ, Pfister DG, et al. NCCN guidelines (R) insights: head and neck cancers, version 2.2025. *J Natl Compr Cancer Netw* 2025;23:2–11.
5. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. *Nat Rev Dis Primers* 2020;6:92.
6. Getz KR, Bellile E, Zarins KR, et al. Statin use and head and neck squamous cell carcinoma outcomes. *Int J Cancer* 2021;148:2440–8.
7. Noble AR, Greskovich JF, Han J, et al. Risk factors associated with disease recurrence in patients with stage III/IV squamous cell carcinoma of the oral cavity treated with surgery and postoperative radiotherapy. *Anticancer Res* 2016;36:785–92.
8. Bandini A, Calabro PF, Banchi M, Orlandi P, Bocci G. Metronomic chemotherapy in elderly patients. *Curr Oncol Rep* 2024;26:359–76.
9. Pasquier E, Kavallaris M, Andre N. Metronomic chemotherapy: new rationale for new directions. *Nat Rev Clin Oncol* 2010;7:455–65.
10. Bocci G, Kerbel RS. Pharmacokinetics of metronomic chemotherapy: a neglected but crucial aspect. *Nat Rev Clin Oncol* 2016;13:659–73.

11. Ghiringhelli F, Menard C, Puig PE, et al. Metronomic cyclophosphamide regimen selectively depletes CD4+CD25+ regulatory T cells and restores T and NK effector functions in end stage cancer patients. *Cancer Immunol Immunother* 2007;56:641—8.
12. Natale G, Bocci G. Does metronomic chemotherapy induce tumor angiogenic dormancy? A review of available preclinical and clinical data. *Cancer Lett* 2018;432:28—37.
13. Maehara Y, Kakeji Y, Ohno S, Baba H, Sugimachi K. Scientific basis for the combination of tegafur with uracil. *Oncology (Williston Park)* 1997;11(9 Suppl 10):14—21.
14. Ikeda K, Yoshisue K, Matsushima E, et al. Bioactivation of tegafur to 5-fluorouracil is catalyzed by cytochrome P-450 2A6 in human liver microsomes in vitro. *Clin Cancer Res* 2000;6:4409—15.
15. Takechi T, Uchida J, Fujioka A, Fukushima M. Enhancing 5-fluorouracil cytotoxicity by inhibiting dihydropyrimidine dehydrogenase activity with uracil in human tumor cells. *Int J Oncol* 1997;11:1041—4.
16. Simsek C, Esin E, Yalcin S. Metronomic chemotherapy: a systematic review of the literature and clinical experience. *J Oncol* 2019;2019:5483791.
17. Colevas AD, Amrein PC, Gomolin H, et al. A phase II study of combined oral uracil and ftorafur with leucovorin for patients with squamous cell carcinoma of the head and neck. *Cancer* 2001;92:326—31.
18. Yeh TJ, Chan LP, Tsai HT, et al. The overall efficacy and outcomes of metronomic tegafur-uracil chemotherapy on locally advanced head and neck squamous cell carcinoma: a real-world cohort experience. *Biology* 2021;10:168.
19. Chen SC, Chang PM, Yang MH. Cisplatin/tegafur/uracil/irinotecan triple combination therapy for recurrent/metastatic head and neck squamous cell carcinoma: a phase I/II clinical study. *Oncologist* 2016;21:537—8.
20. Hsieh MC, Wang CC, Yang CC, et al. Tegafur-uracil versus 5-fluorouracil in combination with cisplatin and cetuximab in elderly patients with recurrent or metastatic head and neck squamous cell carcinoma: a propensity score matching analysis. *Biology* 2021;10:1011.
21. Hsieh JC, Lien MY, Chang PH, et al. UFUR maintenance therapy significantly improves survival in locally advanced head and neck squamous cell carcinoma following definitive chemoradiotherapy. *Cancer Cell Int* 2025;25:187.
22. Huang PW, Lin CY, Lee LY, et al. Maintenance tegafur-plus-uracil after adjuvant concurrent chemoradiotherapy may improve outcome for resected oral cavity squamous cell carcinoma with extranodal extension. *Front Oncol* 2022;12:866890.
23. Lam P, Yuen AP, Ho CM, Ho WK, Wei WI. Prospective randomized study of post-operative chemotherapy with levamisole and UFT for head and neck carcinoma. *Eur J Surg Oncol* 2001;27:750—3.
24. Patil V, Noronha V, Menon N, et al. Metronomic adjuvant chemotherapy evaluation in locally advanced head and neck cancers post radical chemoradiation - a randomised trial. *Lancet Reg Health Southeast Asia* 2023;12:100162.
25. Lee YC, Chao YT, Lin PJ, et al. Quality assurance of integrative big data for medical research within a multihospital system. *J Formos Med Assoc* 2022;121:1728—38.
26. Yang YY, Juan YC, Lee YC. Medical big data value creation: role of the hospital-based research database. *J Formos Med Assoc* 2023;122:809—11.
27. Lien CF, Hwang TZ, Lin TM, et al. Prognostic impact of cortactin in patients with hypopharyngeal cancer and its role for tegafur-uracil maintenance after adjuvant chemoradiotherapy. *Am J Cancer Res* 2023;13:5504—12.
28. Lin JS, Cheng CY, Liu CJ. Oral uracil and tegafur as postoperative adjuvant metronomic chemotherapy in patients with advanced oral squamous cell carcinoma. *J Dent Sci* 2015;10:408—13.
29. Le Deley MC, Vassal G, Taibi A, Shamsaldin A, Leblanc T, Hartmann O. High cumulative rate of secondary leukemia after continuous etoposide treatment for solid tumors in children and young adults. *Pediatr Blood Cancer* 2005;45:25—31.
30. De Vita S, De Matteis S, Laurenti L, et al. Secondary Ph+ acute lymphoblastic leukemia after temozolomide. *Ann Hematol* 2005;84:760—2.
31. Alterio D, Marvaso G, Ferrari A, Volpe S, Orecchia R, Jereczek-Fossa BA. Modern radiotherapy for head and neck cancer. *Semin Oncol* 2019;46:233—45.
32. Li Y, Jiang Y, Qiu B, Sun H, Wang J. Current radiotherapy for recurrent head and neck cancer in the modern era: a state-of-the-art review. *J Transl Med* 2022;20:566.