Clinical Characteristics and Survival Outcomes in Patients with Cancer of Unknown Primary Site (CUP): A Retrospective Cohort Study

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Abstract

Background: Carcinoma of unknown primary (CUP) remains a heterogeneous disease, with poor survival outcomes and limited data from Thailand.

Objective: To describe clinical characteristics, clinicopathologic features, treatment patterns, progression-free survival (PFS), overall survival (OS), and to identify prognostic factors of patients with CUP.

Materials and Methods: A retrospective study was conducted on patients diagnosed with CUP between January 2012 and December 2022 at Khon Kaen Cancer Center, Khon Kaen Hospital. Patients were categorized into favorable- or unfavorable-risk subsets according to ESMO criteria.

Results: Among 102 patients, the median age was 60.7 years, and 64.7% were male. Disseminated disease was present in 86.3%, and adenocarcinoma (56.86%) was the most common histology, and favorable-risk subsets accounted for 72.5%. The median PFS for the favorable-risk groups and the unfavorable-risk group were 7 months vs. 1 month ($p<0.001$), respectively. The median OS for favorable-risk groups and unfavorable-risk groups were 17 months vs. 2 months ($p<0.001$), respectively. Most treated patients received empirical platinum-based chemotherapy, predominantly paclitaxel-platinum combinations. In multivariable analysis, disease extent (localized vs. disseminated) and smoking status (smoke vs. non-smoke) were the only independent prognostic factors for OS and PFS.

Conclusion: This real-world CUP cohort shows patients with favorable risk groups have better survival outcomes than unfavorable risk groups, with survival comparable to specialized international series. Disease extent and smoking status emerged as the only independent prognostic factors.

Keywords: Cancer of unknown primary (CUP); Clinical characteristics; Survival

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Carcinoma of unknown primary (CUP) is a heterogeneous group of histologically diverse cancers, encompassing cancer of unidentified primary origin, and represents 3% to 5% of all malignancies and establishes an unmet clinical need due to poor long-term clinical outcomes, with rates falling to 1% to 2% over the last several decades[1,2].

International guidelines are in place to provide a framework for diagnosing patients suspected of having CUP. These guidelines encompass a comprehensive patient history and physical examination, blood chemistry analysis, radiographic imaging, cytology, or tissue biopsy to establish the presence of cancer. Moreover, essential immunohistochemistry staining is required for confirmation[1,3-5]. Presentation of CUP varies widely, from a solitary site of disease to multiple

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What is already known about this topic?

CUP is an aggressive, biologically heterogeneous metastatic cancer with persistently poor survival, even when managed according to contemporary diagnostic and therapeutic guidelines. International guidelines (ESMO) stratify CUP into favorable and unfavorable subsets using simple clinicopathologic features and recommend empirical platinum-based doublet chemotherapy, yet most outcome data come from Western, high-resource settings, and robust real-world evidence from Thailand and Southeast Asia is still limited.

What does this study add?

This study provides real-world evidence on the clinical characteristics, treatment patterns, and survival outcomes of CUP patients from a resource-limited tertiary cancer center in northeastern Thailand. The relatively favorable mOS of 17 months in this cohort is largely explained by the high proportion of favorable-risk patients (72.5%) rather than treatment superiority, highlighting the critical prognostic importance of ESMO risk classification. On multivariable analysis, disease extent (localized versus disseminated) and smoking status were the only independent prognostic factors for both OS and PFS.

metastases. Frequently affected sites include the lymph node, bones, liver, and lungs[6,7].

CUP malignancies are classified into favorable and unfavorable categories based on the histological subtype, pattern of the disease, and the available treatment options, which ultimately influence the prognosis of survival[1]. A favorable CUP typically consists of histological subtypes that respond well to available systemic treatments. Introducing specific targeted therapy or immunotherapy might improve the chances of survival[8]. In contrast, managing unfavorable CUP primarily involves empirical systemic chemotherapy for patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, or focusing on symptomatic and supportive care if their ECOG status deteriorates, leading to poorer survival prospects[1]. The median overall survival (mOS) for unfavorable CUP is approximately 6 months, whereas patients with a favorable subtype could have an mOS ranging from 12 to 36 months[8].

The current understanding of the characteristics and treatment patterns of patients with CUP, as outlined in the latest international guidelines, especially from an Asian perspective, remains limited. In this retrospective cohort study, our objective was to assess the clinical characteristics, treatment patterns, and outcomes of patients diagnosed with CUP to provide valuable insights for clinical practice. Our focus centered on survival outcome mOS and mPFS within a real-world context.

Objective

This study aims to comprehensively characterize CUP, focusing on both prognostic determinants and clinically relevant outcomes. The objectives are to describe clinical characteristics, clinicopathologic features, treatment patterns, PFS, and OS, and to identify prognostic factors in patients diagnosed with CUP treated at Khon Kaen Hospital.

Materials and Methods

Study Design and Patients' Eligibility

The present study is a single center, retrospective cohort study conducted in a real world tertiary cancer center and includes all patients diagnosed with CUP at Khon Kaen Cancer Center, Khon Kaen Hospital, between January 2012 and December 2022. Eligible patients were older than 15 years, had CUP confirmed by histopathology, had complete clinical documentation, and had no identifiable primary tumor on conventional imaging (chest radiography, computed tomography, and/or magnetic resonance imaging) performed according to local practice; patients with an active first primary malignancy within the preceding 5 years were excluded.

All patients were categorized into favorable or unfavorable prognostic subsets according to the European Society for Medical Oncology (ESMO) CUP guidelines[1]. Favorable-risk CUP was defined by the presence of any of the following clinicopathologic criteria: (i) single-site or oligometastatic disease amenable to local ablative treatment, (ii) women with isolated axillary lymph node metastases with a breast immunohistochemical (IHC) profile, (iii) women with peritoneal carcinomatosis of serous papillary histology, (iv) squamous cell carcinoma involving non-supraclavicular cervical lymph nodes without an identifiable mucosal primary, (v) men with blastic bone metastases and/or PSA positivity suggesting a prostate origin, (vi) adenocarcinoma with a colorectal IHC profile, or (vii) carcinoma with a renal-cell IHC profile. All remaining patients who did not fulfill any of the above criteria were classified as unfavorable-risk CUP and managed with empirical platinum-based doublet chemotherapy or best supportive care according to performance status.

Demographic and clinical variables, tumor histology, treatment modalities, and outcomes were extracted from the electronic medical record and outpatient charts. Progression free survival (PFS) was defined as the interval from the date of CUP diagnosis to the first documented disease progression on initial therapy or death, whichever occurred first, whereas overall survival (OS) was defined as the time from diagnosis to death from any cause. Tumor response was assessed by computed tomography or magnetic resonance imaging at intervals determined by treating physicians according to routine local practice.

The study protocol was reviewed and approved by the Institutional Review Board of Khon Kaen Hospital, Khon Kaen, Thailand (KEXP68107).

Sample Size

As this study employed a retrospective cohort design, formal prospective sample size calculation based on hypothesis testing was not applicable, given that the allocation of patients to systemic chemotherapy or best supportive care was determined by clinical judgment and disease characteristics rather than controlled by the investigators. Therefore, a census-based approach was adopted: all consecutive patients diagnosed with CUP at Khon Kaen Cancer Center between January 2012 and December 2022 who fulfilled the eligibility criteria were included, yielding

a final cohort of 102 patients. This sample size is consistent with those reported in comparable real-world CUP retrospective series and provides sufficient events for Cox proportional hazards regression analysis.

Statistical Analysis

The patients' baseline characteristics were reported using descriptive statistics. The PFS and OS were presented by the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazard model was used for multivariable analyses to adjust for potential confounding factors. The results are presented as hazard ratios (HR) and 95% confidence intervals (CI). The chi-square test and Fisher's exact test were used to compare baseline characteristics among patients grouped by categorical variables. Continuous variables were compared using Student's t-test. The level of critical significance was assigned at p-value less than 0.05. The statistical analyses were performed by using IBM SPSS Statistics, version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Patients' Characteristics and Tumor Data

From January 2012 to December 2022, 102 consecutive patients with CUP were managed at Khon Kaen Cancer Center, Khon Kaen Hospital. Baseline demographic and clinical characteristics of the study cohort are summarized in Table 1.

A total of 102 patients were included, with a median age of 60.71 years and a predominance of males (64.71%). Most patients were smokers (58.82%), had no first-degree family history of cancer (72.55%), and presented with constitutional symptoms (77.50%), including marked weight loss in 69.61%. At diagnosis, 72.55% had an ECOG performance status of 0-1, and 86.27% had disseminated disease, most commonly involving the liver, lymph nodes, and intra-abdominal or pelvic masses. Fourteen patients (13.73%) presented with localized disease, confirmed by conventional imaging to have no evidence of distant metastasis. The most frequently involved sites were lymph nodes (13 patients, 92.9%) and head & neck lesions (10, 71.4%), with some patients being involved of more than one anatomical site (total site involvement: 27). The predominant histologic subtype was adenocarcinoma (56.86%), followed by poorly differentiated carcinoma (15.69%), undifferentiated malignant neoplasm (10.78%), squamous cell carcinoma (8.82%), poorly differentiated neoplasm (4.90%), and neuroendocrine carcinoma (2.94%). Seventy-four of the 102 patients (72.5%) were classified as having favorable risk disease, and 27.5% as having unfavorable risk disease according to ESMO criteria. Compared with the favorable risk group, patients in the unfavorable risk subset were more often male, older, nonsmokers, and had poorer ECOG performance status (all $p<0.001$). Unfavorable risk patients also more commonly presented with disseminated disease involving the retroperitoneum, liver, lung, and brain, whereas localized nodal and head and neck presentations occurred exclusively in the favorable risk group ($p\leq0.05$ for several sites).

Treatment and Outcomes of Patients with CUP

Among the 102 patients with CUP, 74 (72.5%) received active anticancer treatment. Of these, 4 patients (5.41%) underwent local therapy with surgery, and 15 (20.27%) received radiotherapy, while 58 (78.37%) were treated with empirical systemic chemotherapy. First-line systemic therapy was administered exclusively to patients in the favorable-risk group; the remaining favorable-risk patients received local therapy alone (surgery or radiotherapy), whereas all patients in the unfavorable-risk group received best supportive care. The most used chemotherapy regimen was paclitaxel plus platinum (PT: 27 patients, 46.55%), followed by etoposide plus platinum (EP: 11, 18.96%) and oxaliplatin based regimens (Ox: 9, 15.52%).

The median follow up for the cohort was 16 months, with a median progression free survival (mPFS) of 6 months and a mOS of 16 months (Figure 1A, B).

The mPFS by prognostic group was 7.0 months in the favorable risk group and 1.0 months in the unfavorable risk group ($p<0.001$) (Figure 1C). In univariate analysis, absence of constitutional symptoms, receipt of local radiotherapy, and localized disease were each significantly associated with longer PFS. In the multivariable model, only smoking status and disease extent remained independent prognostic factors: smokers had a higher adjusted hazard of progression than nonsmokers, and localized disease continued to be associated with longer PFS, whereas other variables lost significance after adjustment (Table 2).

The mOS was 17.0 months in the favorable risk group and 2.0 months in the unfavorable risk group ($p<0.001$) (Figure 1D). In univariate analysis, receipt of local radiotherapy and localized disease were significantly associated with improved OS, whereas disseminated disease predicted worse OS. In the multivariable model, smoking status and disease extent

Table 1. Baseline patient characteristics and tumor features in patients with cancer of unknown primary (CUP), stratified by favorable and unfavorable risk groups according to ESMO criteria

Characteristic clinical feature	Total (n=102)	Favorable risk characteristics (n=74, 72.5%)	Unfavorable risk characteristics (n=28, 27.5%)	p-value
Sex; n (%)				<0.001
Male	66 (64.71)	39 (52.70)	27 (96.43)	
Female	36 (35.29)	35 (47.30)	1 (3.57)	
Age; n (%)				<0.001
≥60 years	59 (57.84)	34 (45.95)	25 (89.29)	
<60 years	43 (42.16)	40 (54.05)	3 (10.71)	
Age (years); median (IQR)	61 (55-68)	59 (52-65)	67 (62-71)	<0.001
Smoking; n (%)				<0.001
No	42 (41.18)	18 (24.32)	24 (85.71)	
Yes	60 (58.82)	56 (75.68)	4 (14.29)	
First-degree relative cancer; n (%)				0.733
No	74 (72.55)	53 (71.62)	21 (75.00)	
Yes	28 (27.45)	21 (28.38)	7 (25.00)	
Constitutional symptom†; n (%)				0.079
No	23 (22.55)	20 (27.03)	3 (10.71)	
Yes	79 (77.45)	54 (72.97)	25 (89.29)	
Historically significant weight loss‡; n (%)				0.226
No	31 (30.39)	25 (33.78)	6 (21.43)	
Yes	71 (69.61)	49 (66.22)	22 (78.57)	
Histology; n (%)				0.064
Adenocarcinoma	58 (56.86)	42 (56.76)	16 (57.14)	
Poorly differentiated carcinoma	16 (15.69)	14 (18.92)	2 (7.14)	
Poorly differentiated neoplasm	5 (4.90)	4 (5.41)	1 (3.57)	
Undifferentiated malignant neoplasm	11 (10.78)	4 (5.41)	7 (25.00)	
Squamous cell carcinoma	9 (8.82)	7 (9.46)	2 (7.14)	
Neuroendocrine	3 (2.94)	3 (4.05)	0 (0.00)	
ECOG; n (%)				<0.001
0-1	74 (72.55)	74 (100)	0 (0.00)	
≥2	28 (27.45)	0 (0.00)	28 (100)	
Disease extent; n (%)				0.013
Localized disease	14 (13.73)	14 (18.92)	0 (0.00)	
Disseminate disease	88 (86.27)	60 (81.08)	28 (100)	
Localized disease; n (%)				
Lymph node	13 (12.75)	12 (17.57)	0 (0.00)	0.018
Intra-abdominal or pelvic mass	1 (1.35)	1 (1.35)	0 (0.00)	0.536
Bone	1 (0.98)	1 (1.35)	0 (0.00)	0.536
Head and neck lesion	10 (9.80)	10 (13.51)	0 (0.00)	0.041
Skin and soft tissue	2 (1.96)	2 (2.70)	0 (0.00)	0.380
Disseminate disease; n (%)				
Lymph node	57 (55.88)	41 (55.41)	16 (57.14)	0.875
Intra-abdominal or pelvic mass	48 (47.06)	35 (47.30)	13 (46.43)	0.937
Retroperitoneal	26 (25.49)	12 (16.22)	14 (50.00)	<0.001
Bone	25 (24.51)	16 (21.62)	9 (32.14)	.270
Liver	67 (65.69)	41 (55.41)	26 (92.86)	<0.001

IQR=interquartile range; ECOG=Eastern Cooperative Oncology Group; GI=gastrointestinal

† Constitutional symptoms were defined as the presence of one or more of the following: fever (>38°C without identifiable infectious cause), unintentional weight loss (>10% body weight within 6 months), and/or drenching night sweats.

‡ Significant weight loss was defined as unintentional loss of ≥10% of baseline body weight within the preceding 6 months prior to diagnosis.

Table 1. (continued)

Characteristic clinical feature	Total (n=102)	Favorable risk characteristics (n=74, 72.5%)	Unfavorable risk characteristics (n=28, 27.5%)	p-value
Disseminate disease (continued)				
Lung	40 (39.22)	22 (29.73)	18 (64.29)	0.001
Mediastinum	12 (11.76)	7 (9.46)	5 (17.86)	0.240
Peritoneum carcinomatosis	27 (26.47)	24 (32.43)	3 (10.71)	0.027
GI tract	17 (16.67)	13 (17.57)	4 (14.29)	0.691
Head and neck lesion	3 (2.94)	2 (2.70)	1 (3.57)	0.817
Skin and soft tissue	8 (7.84)	4 (5.41)	4 (14.29)	0.137
Brain	8 (7.84)	0 (0.0)	8 (28.57)	<0.001
Best supportive care; n (%)				<0.001
No	74 (72.54)	74 (100)	0 (0.00)	
Yes	28 (27.46)	0 (0.00)	28 (100)	
Local treatment (surgery); n (%)				0.214
No	98 (96.00)	70 (94.59)	28 (100)	
Yes	4 (3.92)	4 (5.41)	0 (0.00)	
Local treatment (radiation); n (%)				0.053
No	87 (85.30)	59 (79.72)	28 (100)	
Yes	15 (14.70)	15 (20.27)	0 (0.00)	
Systemic treatment (first line); n (%)				<0.001
Paclitaxel monotherapy	1 (1.72)	1 (1.72)	0 (0.00)	
Paclitaxel/platinum	27 (46.55)	27 (46.55)	0 (0.00)	
Etoposide/platinum	11 (18.96)	11 (18.96)	0 (0.00)	
Gemcitabine/platinum	5 (8.62)	5 (8.62)	0 (0.00)	
Oxaliplatin-based regimen	9 (15.52)	9 (15.52)	0 (0.00)	
5FU/LV	3 (5.17)	3 (5.17)	0 (0.00)	
Capecitabine	2 (3.46)	2 (3.46)	0 (0.00)	

IQR=interquartile range; ECOG=Eastern Cooperative Oncology Group; GI=gastrointestinal

† Constitutional symptoms were defined as the presence of one or more of the following: fever (>38°C without identifiable infectious cause), unintentional weight loss (>10% body weight within 6 months), and/or drenching night sweats.

‡ Significant weight loss was defined as unintentional loss of ≥10% of baseline body weight within the preceding 6 months prior to diagnosis.

Table 2. Progression-free survival outcome

Factor	Univariate analysis			Multivariable analysis		
	HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Sex: female (ref: male)	0.76	0.47 to 1.02	0.238			
Age (years): ≤60 (ref: >60)	0.82	0.50 to 1.32	0.417			
Smoking: yes (ref: no)	1.31	0.75 to 2.28	0.328	1.92	1.05 to 3.53	0.034
Constitutional symptoms: no (ref: yes)	0.54	0.31 to 0.91	0.023			
First degree relative cancer: no (ref: yes)	1.49	0.88 to 2.50	0.133			
History of significant weight loss: no (ref: yes)	0.84	0.51 to 1.37	0.495			
Local treatment (radiation): no (ref: yes)	0.51	0.28 to 0.92	0.027			
Disease extension: localized (ref: disseminated)	2.50	1.34 to 4.65	0.004	2.94	1.54 to 5.61	0.001

HR=hazard ratio; CI=confidence interval

remained the only independent prognostic factors for OS: smokers had a higher adjusted hazard of death than nonsmokers (adjusted HR 2.14, 95% CI 1.19 to 3.83, p=0.010), and localized disease continued to be strongly associated with longer OS compared with disseminated disease (adjusted HR 3.06, 95% CI 1.60 to 5.86, p=0.001) (Table 3).

Discussion

This study describes the clinical characteristics,

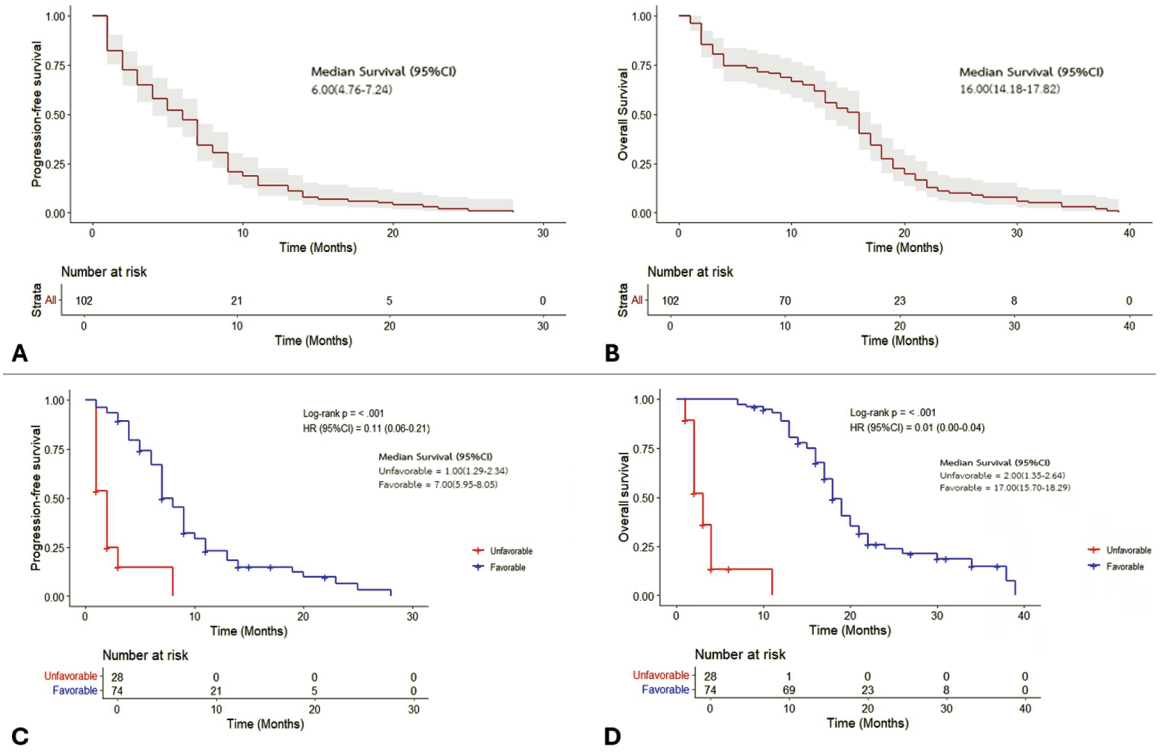

Figure 1. Kaplan-Meier curves for progression free survival (PFS) in patients with cancer of unknown primary (CUP) (A) and overall survival (OS) in patients with CUP (B), and PFS (C) and OS (D) stratified by favorable and unfavorable risk categories.

Table 3. Overall survival outcome

Factor	Univariate analysis			Multivariable analysis		
	HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Sex: female (ref: male)	0.88	0.55 to 1.40	0.599			
Age (years): ≤60 (ref: >60)	0.91	0.56 to 1.47	0.713			
Smoking: yes (ref: no)	1.50	0.86 to 2.61	0.145	2.14	1.19 to 3.83	0.010
Constitutional symptoms: no (ref: yes)	0.62	0.36 to 1.04	0.075			
First degree relative cancer: no (ref: yes)	1.22	0.72 to 2.06	0.452			
History of significant weight loss: no (ref: yes)	0.87	0.53 to 1.43	0.607			
Local treatment (Radiation): no (ref: yes)	0.54	0.29 to 0.98	0.043			
Disease extension: localized (ref: disseminated)	2.26	1.33 to 4.56	0.004	3.06	1.60 to 5.86	0.001

HR=hazard ratio; CI=confidence interval

treatment patterns, and survival outcomes of 102 patients with CUP managed at a single tertiary cancer center in Northeast Thailand over an 11-year period. CUP remains a heterogeneous and diagnostically challenging entity, historically accounting for 3% to 5% of all malignancies. The prognosis of CUP remains poor, with approximately 20% of patients surviving beyond one year[8].

The baseline demographic characteristics of our cohort are broadly consistent with published series. Our median age of 60.7 years and male predominance (64.7%) align with the Korean real-world cohort by Kang et al.[9] (median age 62 years, 62.3% male, 218 patients), the Australian multicenter study by Boys et al.[10] (median age 65 years, 52% male, 123), the Japanese series from Aichi Cancer Center by Ando et al.[11] (median age 67 years, 59% male, 407), and the Chinese cohort by Ma et al.[12] (mean age 56.6 years, 66.4% male, 107). Adenocarcinoma was the predominant histological subtype in our series (56.9%), which is in agreement with the global literature reporting adenocarcinoma in 50% to 60%

of CUP cases. The high rate of disseminated disease at presentation (86.3%) underscores the aggressive biological behavior typical of CUP.

A noteworthy finding in our study is the relatively high proportion of patients classified as favorable-risk (72.5%) according to ESMO criteria, compared with most published series where unfavorable-risk CUP accounts for 70% to 85% of cases. This difference may be attributed to several factors. First, our classification included all patients with ECOG performance status 0-1 and those with specific favorable clinicopathological presentations (e.g., cervical lymph node squamous cell carcinoma, isolated nodal disease), which are recognized as favorable subsets within the ESMO framework. Second, referral patterns at our center, which serves as a tertiary cancer facility in the region, may have resulted in a selection bias toward patients deemed fit for active treatment. In contrast, the Australian cohort classified 70% of patients as unfavorable risk, and the Japanese series reported 71% in the unfavorable-risk subgroup[10]. These differences highlight the heterogeneity of CUP populations across geographic and institutional settings and emphasize the importance of standardized classification criteria.

The mOS of 16 months in our cohort is identical to that reported by Ando et al.[11] from a specialized Japanese cancer center (mOS 16 months for confirmed CUP), and longer than the 8.3 months reported by Kang et al.[9] and 10.2 months by Boys et al[10]. The relatively favorable survival in our cohort is likely driven by the higher proportion of favorable-risk patients (72.5%), the majority of whom had ECOG performance status 0-1 (100% within the favorable-risk group) and received active anticancer treatment. This is consistent with the observation that patients with ECOG 0-1 and normal lactate dehydrogenase (LDH) have better prognoses[7]. When stratified by risk category, the stark survival difference between favorable (mOS 17 months) and unfavorable (mOS 2 months) subgroups in our study is consistent with the established dichotomy in CUP outcomes. The unfavorable risk mOS of 2 months in our cohort is notably shorter than the 12 months reported by Ando et al.[11] and the 5.5 months reported by Boys et al.[10] for non-squamous unfavorable CUP. This poor outcome may reflect the fact that all unfavorable-risk patients in our cohort received best supportive care only, without systemic chemotherapy, likely due to poor performance status (100% ECOG ≥2) and disseminated disease burden.

Among treated patients, empirical platinum-based chemotherapy was the backbone of systemic therapy, with paclitaxel plus platinum (46.6%) being the most frequently administered regimen, followed by etoposide plus platinum (19.0%) and oxaliplatin-based regimens (15.5%). This prescribing pattern aligns with ESMO guideline recommendations for empirical platinum-based doublet chemotherapy in CUP. A meta-analysis by Lee et al.[13] demonstrated that taxane-based regimens for unfavorable CUP yielded a modest but significant survival benefit (prolonged median survival by 1.52 months, p=0.03) over non-taxane regimens, although the benefit did not sustain at 2 years. Paclitaxel/carboplatin is widely regarded as a standard empirical regimen for CUP, with reported response rates of 30% to 40% and a mOS of approximately 9 months. In contrast, the Australian cohort predominantly used carboplatin/gemcitabine as empirical first-line therapy, and the Japanese cohort utilized modified FOLFOX6 for IHC-predicted gastrointestinal profiles. The choice of regimen appears to reflect regional prescribing practices and available drug access rather than evidence-based superiority of one regimen over another, as randomized trials have not clearly demonstrated superior empirical chemotherapy for CUP.

In the multivariable analysis, disease extent (localized vs. disseminated) and smoking status emerged as the only independent prognostic factors for both PFS and OS in our cohort. Localized disease was strongly associated with longer OS (adjusted HR 3.06, 95% CI 1.60 to 5.86, p=0.001) and PFS (adjusted HR 2.94, 95% CI 1.54 to 5.61, p=0.001). This finding is consistent with multiple published studies. Kang et al.[9] identified ECOG performance status 0-1 and localized disease as significantly associated with favorable survival in their multivariate analysis. Similarly, Boys et al.[10] confirmed that unfavorable risk (HR 2.9, p=0.006) and poor performance status (HR 2.8, p<0.001) were independently associated with poor survival.

In our cohort, receipt of local radiotherapy was significantly associated with longer PFS and OS in univariate analysis, although it did not retain independent significance in the multivariable model. This finding aligns with the understanding that localized treatment with surgery or radiotherapy can provide meaningful benefit for selected CUP subsets, particularly those with favorable presentations such as cervical lymph node squamous cell carcinoma or single metastatic lesions. The Chinese cohort by Ma et al.[12] similarly demonstrated significantly longer mOS in patients receiving local treatment (69 vs. 17.9 months; p=0.009). These observations reinforce

the importance of a multidisciplinary approach to identify CUP patients who may benefit from localized therapy in combination with or instead of systemic chemotherapy.

A limitation of our study is the absence of molecular profiling and immunotherapy data, reflecting the reality of resource-limited oncology practice in northeastern Thailand during the study period. In the current era, comprehensive genomic profiling (CGP) has emerged as a promising approach for CUP management[14]. These emerging data suggest that a subset of CUP patients may benefit from immunotherapy, and the integration of CGP and immunotherapy into CUP management represents a critical direction for future research, including in resource-limited settings.

Conclusion

In this single-center retrospective cohort, mOS and mPFS were 16 and 6 months, respectively, for the entire cohort. When stratified by risk group, mOS was 17 months vs. 2 months and mPFS was 7 months vs. 1 month for favorable vs unfavorable groups (both $p<0.001$). Disease extent and smoking status were the only independent prognostic factors in multivariable analysis: localized disease was strongly associated with longer survival compared with disseminated disease, while smokers had a higher risk of death than nonsmokers.

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Author Contributions

LT: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing-original draft, and writing-review and editing. The author has read and approved the final manuscript.

Clinical Trial Registration

Not applicable. This study is a single-center retrospective observational cohort study using de-identified data from existing medical records. It does not involve any prospective intervention or clinical trial; therefore, registration in a clinical trial registry is not required according to the recommendations of the International Committee of Medical Journal Editors (ICMJE) and the World Health Organization (WHO).

Conflicts of interest

The authors declare no conflict of interest.

Data Availability Statement

The datasets generated and analyzed during the current study are not publicly available due to patient confidentiality restrictions, but are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of Khon Kaen Hospital (KEXP68107).

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Use of Artificial Intelligence

AI-assisted tools were used solely for English language editing and grammar checking during manuscript revision. Specifically, ChatGPT-4o (OpenAI, 2025) and Claude Sonnet 4.5 (Anthropic, 2025) were used for sentence refinement only. All scientific content—including study design, data collection, analysis, interpretation, and conclusions—was conducted exclusively by the authors. The authors take full responsibility for the integrity and originality of all content. AI tools are not listed as authors per ICMJE criteria.

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