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TUMOUR REVIEW

Liver metastases from cancer of unknown primary (CUPL): A retrospective analysis of presentation, management and prognosis in 49 patients and systematic review of the literature

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Summary
Aim: Patients with liver metastases from cancer of unknown primary (CUPL) have a dismal prognosis. We retrospectively analysed their management and outcome and performed a systematic review of CUPL series published in the literature.
Patients and methods: Electronic data from 49 CUPL patients referred to Hellenic Cooperative Oncology Group (HeCOG) centers were retrospectively studied for characteristics of clinical presentation, diagnostic workup, management, outcome and prognostic factors. A systematic literature review was undertaken in PubMed and EmBase databases.
Results: All our patients (males: 31, females: 18; median age: 65) underwent a computed tomography scan (CT) of the abdomen, 71% a thoracic CT, 53% gastroscopy and 47% colonoscopy. The commonest histologic subtypes encountered were adenocarcinoma ($N = 34$) or undifferentiated carcinoma ($N = 12$). The liver was the only metastatic site in 38% of patients, while it was accompanied with other metastatic sites in 62% (the commonest: lung, bone and lymph nodes). Forty-seven patients received first-line chemotherapy (42 platinum based) and 16 second-line. An objective response was observed in six patients (12%), median survival being 10 months (95% CI, 7–13). In univariate analysis, good performance status and normal baseline serum CEA levels were correlated with superior survival, while in multivariate analysis only

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age < 55 (HR 0.16, $p = 0.02$) and the absence of extrahepatic disease (HR 0.21, $p = 0.007$) predicted for a better outcome. Published data from four relevant series (total patients = 662) parallel our findings.

Conclusions: Patients with liver metastases from CUP are resistant to conventional types of treatment and carry a poor prognosis. Understanding the molecular biology of CUP is essential for the development of new, targeted effective therapies.

Introduction

Cancer of unknown primary site (CUP) is defined as histologically confirmed metastases in the absence of identifiable primary tumor despite a standardized diagnostic approach.[1] Clinical and laboratory data required to define a patient as having CUP are: histologically confirmed metastatic cancer, histopathology review with use of immunohistochemistry, detailed medical history, complete physical examination (including pelvic and rectal examination), full blood count and biochemistry, urinalysis, stool occult blood testing, chest radiography, computed tomography of the abdomen and pelvis, mammography and PET scan (in selected cases).[2,3] Fundamental characteristics of CUP are early dissemination and unpredictable metastatic pattern[4,5] coupled to dormancy or regression of the primary tumor,[6–8] and aggressive biologic behaviour. CUP accounts for 2.3—4.2% of cancer in both sexes and is marginally more frequent in males than in females. The median age for occurrence is 60 years.[9–14] Therapy is usually ineffective and median survival ranges from 6 to 11 months.[15,16] Therefore, the challenge for the treating physician and patient alike is both diagnostic — how extensive should the exploration for the primary be — and therapeutic.

Among the most important advances in understanding CUP biology was the identification of favourable clinicopathologic subsets affecting 10—20% of patients with CUP. Appropriate diagnosis of such cases is of great importance as they warrant specific treatment, which is frequently effective. These are young patients with poorly differentiated carcinoma of midline distribution (extragonadal germ cell syndrome), women with papillary carcinoma of the peritoneal cavity, women with adenocarcinoma involving only axillary lymph nodes, patients with squamous cell carcinomas involving cervical lymph nodes, poorly differentiated neuroendocrine carcinomas, men with blastic bone metastases and elevated PSA (adenocarcinoma), isolated inguinal adenopathy (squamous carcinoma) and patients with a single, small, potentially resectable tumor. These patients respond to antineoplastic therapy and occasionally enjoy long-term disease control. Unfortunately, more than 80% of CUP patients do not fall in one of these categories and belong to the poor-prognosis subset. No chemotherapeutic regimen has been established as a standard one, despite variable response rates ranging from 0% to 50% with median patient survival of 4 to less than 12 months.[17]

Among poor-prognosis CUP patients, metastases to the liver are frequent, being present in 20—30% of them.[7] After lymph node enlargement, hepatic involvement is the second leading mode of presentation of unknown primary carcinoma.[18] Patients with hepatic metastases from an unknown primary site have been considered to harbour aggressive, high-volume and resistant disease with a grim outcome. Still, anecdotal evidence is the basis for this perception in most cases and retrospective or prospective data are scant and infrequently updated. We report presentation, management and outcome data of 49 patients diagnosed with liver metastases of unknown primary (CUPL) and compare them with data from other published CUPL patient series identified via a systematic review of the literature.

Patients and methods

From 1999 until 2007 patients with multiple unresectable liver metastases from an unknown primary tumor, with or without deposits in other organ sites were treated with cytotoxic chemotherapy either in the context of prospective clinical trials organized by HeCOG or according to off-trial cooperative group protocols in HeCOG participating centres. These patients had detailed clinical data recorded in a regularly updated electronic database. Common eligibility criteria for administration of chemotherapy included histologic or cytologic confirmation of malignancy, adequate bone marrow, hepatic (serum bilirubin <1.5 times the upper limit of normal ULN, AST and ALT <5 times ULN) and renal (glomerular filtration rate >40 ml/min by the Cockroft—Gault formula) reserves, presence of measurable/evaluable disease, absence of significant morbidities and adequate performance status (ECOG PS 0—3). Tumor response was assessed at all malignant deposits (not solely in the liver) according to the World Health Organization (WHO) criteria. The National Cancer Institute Common Toxicity Criteria version 2.0 were used to report toxicity.

The relevant digitalized clinical data were retrospectively collected, reviewed and analyzed in January 2008. Studied parameters included patient and tumor epidemiologic data, first-line chemotherapeutic management data, response to treatment, time to progression and overall survival times. Patient characteristics and studied parameters are shown in detail in Tables 1 and 2. All clinical parameters were examined for potential prognostic significance for overall survival by univariate and multivariate analysis. The objectives of this retrospective study were to depict the epidemiological profile of patients with irresectable hepatic involvement from CUP, study the chemotherapeutic regimens used and examine their activity, as well as report the time to progression after first-line chemotherapy and overall survival of these patients.

Overall survival (OS) was measured from the date of tissue diagnosis until death from any cause. Surviving patients were censored at the date of last contact. Time to disease progression (TTP) was measured from the date of start of

Table 1 Baseline examinations

	Patients	%
Baseline examinations N = 49		
Abdominal CT/MRI	49	100
Thoracic CT	35	71.4
Pelvic CT	20	40.8
Colonoscopy	23	46.9
Gastroscopy	26	53.1
Bone scintigraphy	18	36.7
Brain CT/MRI	8	16.3
Thyroid ultrasound	1	2
ENT	1	2
Proctoscopy	5	10.2
Colposcopy	4	8.2
Laparoscopy	2	4
Laparotomy	5	10.2

ENT: ear—nose—throat panendoscopy.

chemotherapy administration until progression or death. Time to event distributions were estimated using Kaplan—Meier curves. Univariate analysis of prognostic significance of various parameters for survival was done with the Log-rank test, a $p < 0.05$ (two-tailed) being considered significant. The Cox proportional hazards regression model was implemented for multivariate analysis. In order to assess the strength of association of OS with various variables, a backward selection procedure with removal criterion $p > 0.10$, identified the subclass of significant variables among the following: gender, age at diagnosis (up to 55 versus 56—65 versus more than 65), performance status (0—1 versus 2—3), histology, grade of differentiation, metastatic sites (liver only versus liver and one other metastatic organ site versus liver and two or more other sites), type of first-line treatment (oxaliplatin-based versus non-oxaliplatin-based), brain metastases (presence versus absence), markers (all markers normal versus one at least abnormal). The Wald x2 test and the corresponding p-values < 0.05 were used to determine statistical significance. Logistic regression analysis was applied in order to examine potential predictive significance of the variables described above for disease response to first-line chemotherapy.

Results

Patient and tumor characteristics

From 1999 to 2007, a total of 49 patients fulfilling the criteria of CUPL were registered with the HeCOG electronic database. Detailed patient, tumor and management data are shown in Table 2. Median age at diagnosis was 65. There was a preponderance of men (63.2%). Adenocarcinoma was the prevalent histologic type accounting for 69% of the cases, followed by undifferentiated carcinoma (24%).The most commonly associated metastatic sites were lung, bone and lymph nodes. Liver was the only metastatic site in 38% of cases, associated to one organ metastatic site in 26%, two in 20% and more than two other metastatic sites in 14% of the cases. Seventeen (34%) patients had a WHO performance status of 0 at diagnosis, while 31 patients were mildly to moderately symptomatic (62%).

Table 2 Patient and tumor characteristics/treatment

	Patients	%
Characteristics	*N = 49*	
Gender		
Male/female	31/18	63/37
Age at diagnosis		
Median (range)	65 (36—78)	
WHO performance status at diagnosis		
0	17	34
1	20	40
2	11	22,4
3	1	2
Histology		
Adenocarcinoma	34	69
Undifferentiated carcinoma	12	24
Neuroendocrine	3	6
Number of metastatic sites		
Liver only	19	38
1	13	26
2	10	20
3	5	10
4	2	4
Associated metastatic sites		
Lung	13	26.5
Lymph nodes	12	24.5
Bone	9	18.4
Peritoneum	4	8.1
Spleen	3	6.1
Adrenals	1	2
Brain	1	2
Treatments		
Patients treated by chemotherapy	47	96
Number of patients who received		
1 line	29	59.2
2 lines	16	32.6
3 lines	2	4.1
Protocols administered first line		
With platinum salt	42	85.7
Oxal/irrinotecan	33	67.3
Carbo/TXT	9	18.4
Without platin salt	4	8.2

Baseline examinations

An abdominal computed tomography scan (CT) was carried out in all patients (Table 1). A thoracic CT took place in 35 (71.4%) patients while 20 patients (40.8%) underwent a pelvic CT. Colono- and gastroscopy was carried out in 46.9% and 53.1% of the patients retrospective, driven by suspicious signs, symptoms or laboratory tests. Bone scintigraphy was done in 18 (36.7%) of the cases, while a brain CT/

magnetic resonance (MRI) in 8 (16.3%). Other baseline examinations that took place were thyroid ultrasound (2%), ear—nose—throat panendoscopy (ENT) (2%), proctoscopy (10%), colposcopy (8%), laparoscopy (4%) and laparotomy in 10.2%. CA 19-9, CA125, CA 15-3 and CEA were the most common markers utilized. All markers were normal in nine patients (18%), while 35 patients (70%) had at least one serum marker level abnormal at baseline. Serum marker levels were determined at baseline in order to identify surrogate markers of response that are more easily followed-up, rather than to suggest the primary tumor.

Treatment efficacy and toxicity

Of the 49 patients of this series, 47 (96%) were managed with first-line chemotherapy, while two did not because of rapid deterioration due to progression of malignancy (Table 2). The high rate of management with chemotherapy is interpreted by the fact that only patients fit enough for such therapy were recorded in the HeCOG protocol registry. Only two patients (4.1%) were operated for liver metastases and four (8.2%) treated with ionising radiotherapy. Twenty-nine patients did not receive salvage regimens after failure of first-line chemotherapy, 16 received a second-line chemotherapeutic regimen and only two a third-line. Protocols received as first-line chemotherapy either contained a platinum salt (considering as such the oxaliplatin as well): carboplatin/docetaxel, oxaliplatin/irinotecan and oxaliplatin/capecitabine, or did not: 5-fluorouracil (5FU)/leucovorin, docetaxel, capecitabine and 5FU/irrinotecan.

An oxaliplatin-based chemotherapy was administered in 34 (68%) patients. No response (defined as stable disease (SD) or progressive disease (PD)) was seen in 74% of the patients. An objective response (complete remission (CR) or partial remission (PR)) was observed in six patients (12%). If stabilization of disease can be considered of clinical significance, control of the disease (CR + PR + SD) was achieved in 14 patients (30%) (Table 5). Responses and disease stabilization were short-lived, as the majority of patients progressed either while on therapy or soon after its completion (56%). Patient outcome was exceptionally poor, as median TTP was 4 months and median overall survival 10 months. Only 35% of patients survived longer than one year from diagnosis, while 2-year survival was less than 10% (two patients). The most common hematologic toxicities were neutropenia and anemia (with one patient suffering grade IV febrile neutropenia), while the most frequent non-hematologic ones were constitutional and gastrointestinal.

Prognostic/predictive factors for outcome

Several clinical, histopathological and management parameters (age, gender, performance status, histology, grade, baseline serum tumor markers, number of metastatic organ sites, brain metastases and administered chemotherapy) were tested for potential utility as prognostic factors for overall survival as well as for predictive utility for response to chemotherapy (Table 3).

In univariate analysis, good performance status and normal CEA levels were significantly associated with a reduced hazard for death. Patients with PS 0—1 had a median OS of 12 months (95% CI 8—16 months) versus a median OS of 3 months (95% CI 1—6 months) for those with PS 2—3 (Logrank $p = 0.003$). Patients with normal baseline serum CEA had a median OS of 12 months (95% CI 5—18 months) versus 7 months (95% CI 3—11 months) for those with elevated serum CEA (Logrank $p = 0.03$). The absence of extrahepatic dissemination showed a trend for statistically significant association with superior survival. In the more robust multivariate analysis, young age <55 years and metastatic involvement of the liver only with absence of other organ deposits significantly predicted better outcome. Age <55 was associated with a hazard ratio (HR) for death of 0.16 (95% confidence intervals CI 0.04—0.8, $p = 0.02$) and disease confinement to the liver with a HR for death of 0.21 (95% CI 0.07—0.7, $p = 0.007$). At logistic regression, no clinical, laboratory or pathologic variable predicted for response to chemotherapy at a significance level <0.05.

Review of the literature

We performed a manual search of the Pubmed online database using the search engine: (cancer OR carcinom* OR neoplas* OR malignan* OR tumor OR tumor) AND (''unknown primary'' OR ''unknown origin'' OR ''occult primary'') AND (liver OR hepatic). Our search was limited to the English and French language. We encountered four patient series of CUPL, presented below in chronological order (Table 4).

In 1991, Mousseau et al.[7] presented a series of 91 patients with liver metastases from CUP. The liver was the only site of disease in 31% of patients. Adenocarcinomatous histology of good to moderate differentiation was seen in 78% of patients. The median overall survival did not differ between patients with liver only and patients with extrahepatic deposits and was disappointingly low (4—5 months). No clinicopathologic variable was found to carry prognostic significance for patient outcome, though patients receiving chemotherapy (80% of total) fared better than those who did not. However, this was likely to result from a selection bias as fitter patients who usually survive longer were the ones most likely to receive chemotherapy. Objective response rate was 11% with a variety of combination cytotoxic regimens incorporating 5-fluorouracil, cyclophosphamide, vinca alkaloids and anthracyclines. Responders had a median survival of 9 months, in sharp contrast to the median survival of 3.5 months seen in non-responders ($p = 0.001$). Upon disease progression, salvage chemotherapy was largely ineffective.

In 1998, Ayoub et al.[18] presented the biggest series ever published, encompassing 365 patients with liver metastases from an unknown primary tumor. The objectives of the study were to identify clinicopathologic variables with prognostic significance for patient outcome, determine the common primary tumors identified, assess the yield of specific diagnostic tests and evaluate the impact of therapy on survival. Out of 1522 patients with suspected CUP, 500 had metastases primarily to the liver and a primary tumor was identified in 135 (27%). From the 365 remaining patients with CUPL, 38% had metastases to liver only and 62% to liver and additional organ sites. The predominant histologic subtype was adenocarcinoma (61%). As in the general population of CUP patients, lymph nodes, bone and lung were

the most common additional sites of involvement. CUPL patients had a significantly higher death rate than other CUP patients, with a HR after adjusting for other prognostic factors of 1.75 (95% CI, 1.52—2.03; $p < 0.0001$). Median survival was only 7.2 months. Pathology, age and number of metastatic sites were found to be independent prognostic factors for survival. Histologic features consistent with neuroendocrine carcinoma were associated with a significantly lower death rate than patients without these, with a HR of 0.29 (95% CI, 0.18—0.47; $p < 0.0001$). A regression model with these three prognostic factors resulted in an adjusted HR for a 20-year increase in age of 1.3 (95% CI, 1.0—1.5; $p = 0.022$), for a four-unit increase in number of metastatic sites of 1.5 (95% CI, 1.0—2.1; $p = 0.04$), and for neuroendocrine histology of 0.3 (95% CI, 0.19—0.49; $p < 0.0001$). Chemotherapy was given more frequently in patients younger than 60 years compared with those older than 60 (75% versus 46%). Patients who received chemotherapy were mostly fitter and younger than the ones who did not and thus had a significantly lower death rate, with a HR of 0.52 (95% CI, 0.41—0.66; $p < 0.0001$). The effect of chemotherapy being more pronounced in patients with adenocarcinoma histology (HR 0.43; 95% CI, 0.32—0.58; $p < 0.0001$).

In 2002, Hogan et al.[19] retrospectively analysed 88 patients with a suspected CUP and liver biopsy-proven hepatic metastases over a 10-year period (time period not specified). There was a preponderance of males (58 out of a total of 88 patients), with a median age at diagnosis of 64.5. Adenocarcinoma was the prevalent histologic subtype accounting for as much as of 80% of all cases. Patients with adenocarcinoma for whom adequate survival data were available ($N = 62$) were further analysed for factors that may influence outcome. In 8/62 (11%) patients a primary tumor was identified. There was no separate statistical analysis for the two distinct subgroups: those for whom no primary tumor was identified (CUPL) and those for whom a primary was eventually identified. 16/62 patients received active treatment with either surgery, radiotherapy, single-agent chemotherapy or a combination protocol, the rest being managed with palliative care only. The median survival for treated patients (49 days) versus untreated patients (52 days) was not significantly different ($p = 0.128$). Patients <65-years-old were more likely to receive active treatment ($p = 0.006$). Age (HR 1.01, $p = 0.178$), active treatment (HR = 0.65; $p = 0.194$), identification of the primary tumor (HR = 0.60, $p = 0.213$) and male gender (HR = 0.88; $p = 0.642$) had no significant effect on survival.

In 2005, Pouessel et al.[20] conducted a retrospective study of 118 CUPL patients, over a 10-year period of time from 1993 to 2002. The most frequent histologic type was again adenocarcinoma (57.6%). Hepatic metastases were isolated in 32 patients, other metastatic sites being the lymph nodes, lung and bone. Patients (107) received at least front-line chemotherapy, 74 platinum-based. In first-line chemotherapy, overall response rates were 19.4% with administration of platinum combinations and 20% with non-platinum regimens. The median overall survival was 6.6 months, the type of chemotherapy (with or without platinum) bearing no impact on survival ($p = 0.35$). The median survival for treated patients was 7 months. In univariate analysis five variables had a statistically significant negative effect on survival: performance status > 1, liver metastasis producing the presenting manifestations, elevated serum CA 19-9 concentrations, abnormal serum alkaline phosphatase and elevated LDH. Inversely, presence of a neuroendocrine CUP and administration of chemotherapy were linked with a better prognosis. At multivariate analysis, independent factors associated with poor prognosis were elevated serum LDH and altered performance status with reported odds ratio for death of 2.4.

Discussion

CUPL is an unfavourable subset of cancer of unknown primary site which, as it is clear from the literature review we performed, is not well studied. Only five clinical series have been published with small numbers of patients (total number 711), while no controlled or prospective trials on this CUP subset exist. Opposite to what is true in most other CUP subsets in which only a slight male gender preponderance is seen, in CUPL males outnumber females by a ratio of almost 2:1. Median age at diagnosis is 61—65. There is agreement between all the published series that lung, pancreatic and colorectal primary tumors are most commonly identified in the setting of CUP patients presenting with liver metastases. In this point, it is important to comment on the extension of the clinical and laboratory tests that must take place in order to identify a primary tumor. The search for the primary must be done by meticulous history and physical examination, a CT scan of the chest, abdomen and pelvis supplemented by detailed histopathological studies (immunohistochemistry, electron microscopy and advanced molecular technology). Mammography, endoscopy (ENT panendoscopy, bronchoscopy, colonoscopy, proctoscopy and colposcopy) and other scans should only be undertaken in the presence of suspicious signs, symptoms or laboratory abnormalities or in the presence of compatible clinical presentation (isolated axillary adenopathy for mammography). Remarkably, not all the series in our review comment on the extensiveness of the diagnostic work-up. One has to bear in mind that the identification of the primary tumor is important only if a favourable clinicopathologic subset is suspected, in which case a more labored search can be justified (electron microscopy, molecular techniques and PET scan).

CUP cases (70—80%) belong to poor risk subsets, for which a more labored search for the primary tumor is not reasonable since it carries no information of prognostic or therapeutic relevance. Recently, large retrospective series have suggested that patients presenting with CUP carry different biology and natural history from tumors with known primary sites: Bishop et al.[21] found inferior outcome of patients with metastatic adenocarcinoma of unknown primary in comparison to patients with metastatic deposits from known primary tumors of the lung, breast and gastrointestinal tract. Moreover, the drug regimens used for the management of patients with known gastrointestinal (5-fluorouracil, mitomycin, irinotecan, oxaliplatin, etc.) or lung (platinum, taxanes, gemcitabine, vinorelbine, etc.) metastatic tumors seem ineffective in the equivalent unfavourable subsets of CUP patients. The lack of therapeutic impact of primary site identification in poor-risk CUP patients may change when new effective primary site-specific

Table 3 Prognostic factors for patient survival

	Univariate			Multivariate		
	OS	95% CI	*p*	HR	95%CI	*p*
Age groups						
Up to 55	15	9–21		0.16	0.04–0.8	0.02
55–65	10	3–17		1.02	0.35–2.9	0.9
>65	7	5–10	0.08		1	
PS groups						
0–1	12	8.3–15.6				
2–3	3	1–6	0.003			
Metastatic sites						
Unique	13	9.5–16.4		0.21	0.07–0.7	0.007
Multiple	7	4–10	0.09	1		
CEA						
Normal	12	5–18				
Abnormal	7	3–11	0.03			

therapies (cetuximab, bavacizumab, tyrosine kinase inhibitors, etc.) become available and establish their utility.

The most commonly involved metastatic sites in addition to hepatic involvement are similar in all series: lymph nodes, bone and lung. Adenocarcinoma is the prevalent histology (64%), followed by undifferentiated carcinoma (20%), neurondocrine (8.4%) and squamous (3%). Among the most significant contributions of our systematic review is the identification of prognostic factors that predict for patient outcome and may ultimately allow for tailored treatment according to risk of death. In Ayoub's study patients with features consistent with neuroendocrine carcinoma had a three- to fivefold better survival than those with other histologies. The longer survival of these patients may result from an inherently different disease biology. Thus, CUP patients with neuroendocrine carcinoma that involves the liver seem to harbour a tumor with biology that resembles the one of known primary counterparts (e.g., pancreatic islet cell tumors): they are relatively slow-growing tumors and are often associated with prolonged survival frequently measured in years. Neuroendocrine differentiation, when present, seems to portend a good prognosis for other primary tumors as well (breast, colon, lung cancer, etc.). Age, number of metastatic sites, LDH and performance status have all been found to be independent prognostic factors in uni- and multivariate analysis for survival in the series that we are examining. Young age and deposits in the liver only were found to be significantly associated with better outcome on multivariate analysis in our series. Interpretation of the complex mechanisms by which these variables influence clinical outcome is speculative, as they may reflect cancer biology, disease bulk, host biology, tissue perfusion, drug metabolism, clearance and drug access to tumor cells. High-volume disease may be difficult to contain or it may simply be a marker of aggressive malignant biology. Presence of metastases in multiple sites may affect pivotal organs for host biochemical functions, alter drug metabolism or seed sites inaccessible to cytotoxic chemotherapy (sanctuary sites). Performance status may have an impact on drug metabolism, drug impact on tumor cells, immune surveillance and tolerability of cytotoxic chemotherapy. Moreover, it may reflect disease virulence, host reserves and inflammation.

What is noteworthy is that several investigators claim that chemotherapy offers survival benefit in CUPL patients, in spite of overall response rates around 20% and absence of prospective patient randomisation. In Ayoub's series chemotherapy-treated patients had a lower death rate than those who were not treated with chemotherapy (hazards ratio (HR),0.52; $p < 0.0001$). In Mousseau's series, when patients were able to receive chemotherapy, median survival was better (4 months) than without (median survival 1 month; $p = 0.005$). In addition, in the case of objective response to chemotherapy, the median survival was 9 months versus 3.5 months for patients without objective response ($p = 0.001$). In Poussel's series median survival was 6.6 months for both treated and untreated patients and for the treated only patients median survival was 7 months. In Hogan's series, there was not a difference in median survival between those who were or not treated with chemotherapy. In our series (Lazaridis et al.), there is no such comparison because 47/49 patients were treated with chemotherapy (patients in HeCOG's protocols). It should be stressed that the limitations of these studies make the conclusion that chemotherapy is of benefit, unsafe. The retrospective nature of the series potentially allow for several biases. Patients who received chemotherapy may have been of better performance status compared with the ones who did not or may have harboured less aggressive tumors. The superior survival of patients responding to chemotherapy may be due to toxic effects in non-responders or to a detrimental impact of chemotherapy on survival in non-responders.

Median survival times in the series under study range from 1.7 to 10 months. This difference probably reflects the inherent heterogeneity of cancer of unknown primary. In Hogan's series only 26% of the patients received chemo-

Table 4 Clinicopathologic characteristics of all published CUPL series

	Mousseau et al. (*N* = 91)	Ayoub et al. (*N* = 365)	Hogan et al. (*N* = 88)	Pouessel et al. (*N* = 118)	Lazaridis et al. (*N* = 49)	Total (*N* = 711)
Histology						
Adenocarcinoma (%)	78	61	79.5	58	69	65
Undifferentiated (%)	12	26.5	3.5	20	24	20
Neuroendocrine (%)		9	9	14	6	8.4
Squamous (%)	6	2	4.5	4	0	3
Others (%)	4	1	3.5	3.5	NA	
Most common primary tumors	NR	Lung (18%), colorectal (17%), pancreas (16%)	Colorectal (37.5%), lung (25%)	NR	NR	
Associated metastatic sites						
Lung (%)	NR	36	NR	NR	26.5	
Bone (%)	NR	37	NR	NR	18.4	
Lymph nodes (%)	NR	46	NR	NR	24.5	
Peritoneal (%)	NR	13	NR	NR	8.1	
Adrenal (%)	NR	12	NR	NR	2	
Brain (%)		4			2	
Median survival (months)	4 months (liver-only metastases)—5 months (the others)	7.2	1.7	6.6	10	
Median age at diagnosis	61(males) 59 (females)	NR	64.5	61	65	
Prognostic factors	None	Histology (neuroendocrine, age, number of metastatic sites)	None	LDH, PS		
Gender						
Male (%)	58	NR	66	58	63	
Female (%)	42	NR	33	42	37	

Table 5 Responses to chemotherapy

	Pouessel et al.		Mousseau et al.		Lazaridis et al.	
	First line	Second line	First line	Second line	First line	Second line
Without platinum	*N* = 40	*N* = 36	*N* = 65		*N* = 4	*N* = 8
CR (%)	0	0			0	0
PR (%)	20	2.8	11	3	0	0
SD (%)	10	8.3			0	12.5
With platinum (including oxaliplatin)	*N* = 67	*N* = 10			*N* = 43	*N* = 18
CR (%)	1.5	0	NR	NR	4.7	0
PR (%)	17.9	10	NR	NR	9.3	10
SD (%)	11.9	10	NR	NR	18.6	20

therapy, while in ours 47/49 patients were treated with chemotherapy. Other contributing factors may be different selection criteria, since our series only includes patients fit enough to tolerate cytotoxic chemotherapy. No chemotherapy regimen has been found convincingly effective for the majority of CUP patients presenting with disseminated liver or multi-organ metastases. Despite some evidence of response, median survival is still in the range of 8—9 months.

Our analysis of CUPL patients confirms the overall poor prognosis generally attributed to this patient population. Nevertheless, within this unfavourable population of CUPL, small subsets of patients with a more favourable prognosis

can be identified (e.g. those harbouring neuroendocrine tumors). Breakthroughs in understanding of the molecular biology and pathophysiology of CUP are imperatively needed, in order to identify key molecular aberrations that could be targeted by smart drugs. Moreover, patient selection by means of molecular profiling would be pivotal so as to administer effective, individualised therapy that would inhibit molecular events that drive each specific patient's tumor.[22] Chemotherapy is likely to continue playing a role for chemical cytoreduction of the malignant clone. However, this is likely to prove effective only if combined with targeted agents that would reverse resistance and would suppress repopulation of metastatic deposits.

Conflict of interest statement

None declared.

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