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Survival outcome differences based on treatments used and knowledge of the primary tumour site for patients with cancer of unknown and known primary in Ontario

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ABSTRACT

Introduction Patients with cancer of unknown primary (cup) have pathologically confirmed metastatic tumours with unidentifiable primary tumours. Currently, very little is known about the relationship between the treatment of patients with cup and their survival outcomes. Thus, we compared oncologic treatment and survival outcomes for patients in Ontario with cup against those for a cohort of patients with metastatic cancer of known primary site.

Methods Using the Ontario Cancer Registry and the Same-Day Surgery and Discharge Abstract databases maintained by the Canadian Institute for Health Information, we identified all Ontario patients diagnosed with metastatic cancer between 1 January 2000 and 31 December 2005. Ontario Health Insurance Plan treatment records were linked to identify codes for surgery, chemotherapy, or therapeutic radiation related to oncology. Multivariable Cox regression models were constructed, adjusting for histology, age, sex, and comorbidities.

Results In 45,347 patients (96.3%), the primary tumour site was identifiable, and in 1743 patients (3.7%), cup was diagnosed. Among the main tumour sites, cup ranked as the 6th largest. The mean Charlson score was significantly higher ($p < 0.0001$) in patients with cup (1.88) than in those with a known primary (1.42). Overall median survival was 1.9 months for patients with cup compared with 11.9 months for all patients with a known-primary cancer. Receipt of treatment was more likely for patients with a known primary site ($n = 35,012$, 77.2%) than for those with cup ($n = 891$, 51.1%). Among patients with a known primary site, median survival was significantly higher for treated than for untreated patients (19.0 months vs. 2.2 months, $p < 0.0001$). Among patients with cup, median survival was also higher for treated than for untreated patients (3.6 months vs. 1.1 months, $p < 0.0001$).

Conclusions In Ontario, patients with cup experience significantly lower survival than do patients with metastatic cancer of a known primary site. Treatment is associated with significantly increased survival both for patients with cup and for those with metastatic cancer of a known primary site.

Key Words Cancer of unknown primary, cup, Ontario Cancer Registry, Ontario Health Insurance Plan, administrative data, survival analyses

INTRODUCTION

In most patients with metastatic cancer, the primary tumour is identified during a standard or extensive diagnostic work-up. But identification is not the case for an estimated 3%–5% of all incident cancers, which are termed "cancer of unknown primary" (cup)[1]. Currently, the widely accepted definition of cup requires the tumour at the metastatic site to be histologically confirmed[2]. Patients with cup have a poor prognosis, with survival estimates often being less than 1 year[3–5].

Although population studies of cup are common, data about the relationship between treatment and patient outcomes are limited[4–7]. A Canadian study of a cup population

found that 55% of patients did not receive any treatment, with younger age being significantly associated with treatment receipt[8]. In a U.S. cup population, most patients with cup (79.7%) did not receive any treatment; however, use of radiation therapy in those patients was associated with longer survival [hazard ratio (HR): 0.68; $p < 0.001$ compared with patients who did not receive radiation therapy]. A recent study undertaken by Australia's Department of Veterans' Affairs found that 30% of patients with cup compared with 70% of those with a known primary received treatment, experiencing a median survival of 37 days compared with 310 days respectively[9]. The literature comparing treatment and survival outcomes for patients with cup with those for patients with a known primary tumour is scarce.

Current clinical guidelines recommend wide-spectrum empiric chemotherapy for almost all cup patients[3,10–12]. However, a synthesis of clinical trials involving patients with cup questioned the therapeutic benefit of that approach, finding no evidence to support chemotherapy over best supportive care, no evidence for platinum-based chemotherapy over non-platinum-based chemotherapy, and no evidence to support a multi-agent chemotherapy regimen over single-agent treatment[3].

Given the limited information about the association between treatment for cup and survival, we investigated the relationship. Using a cup population previously identified in Ontario, we compared survival outcomes for that population with outcomes for a cohort of Ontario patients with metastatic cancer of known primary site[13]. Using administrative data related to treatment, we stratified both populations based on the type of treatment received, and we investigated potential differences in survival outcomes.

METHODS

Data Sources
The Ontario Cancer Data Linkage project "cd-link" is a collaborative data-release program between the Institute for Clinical Evaluative Sciences (ICES) and Cancer Care Ontario that provides research access to Ontario health administrative databases. Through a data use agreement, we gained access to data from OHIP (the Ontario Health Insurance Plan), the Same-Day Surgery (SDS) and Discharge Abstract (DAD) databases maintained by the Canadian Institute for Health Information, and the Ontario Cancer Registry (OCR) for all Ontario patients diagnosed with cancer between 1 January 2000 and 31 December 2005. All data were linked and de-identified by ICES. Table I shows the datasets and corresponding data used for cohort selection and analysis. Ethics approval was obtained from the University of Western Ontario Research Ethics Board before the databases were accessed.

Study Cohorts
Two cohorts were studied: a previously identified population of patients with cup[13] and a population of patients with metastatic cancer of known primary site. The methods used to identify the cup population have already been described[13]. A similar algorithm was used to identify the Ontario population of patients with metastatic cancer of

known primary site. A unique patient identifier was used to link hospitalization records from the SDS database and the DAD with patient records from the OCR. Diagnosis codes (International Classification of Diseases, revision 10) were cross-validated between the databases. We used a flag for metastatic disease from the SDS database and the DAD to further validate the diagnosis code. Patients were removed if histology was missing or if the primary tumour diagnosis changed within 60 days of the initial diagnosis. Histology codes in the OCR were grouped using the International Classification of Diseases for Oncology (3rd edition).

Treatment Data
To obtain patient-specific treatment data, both study populations were linked with the OHIP database, which includes all claims made by physicians and other health care providers for insured services to residents of the province. The resulting dataset was sorted to identify codes for surgery, chemotherapy, and therapeutic radiation related to oncology. Those codes were obtained from the OHIP Schedule of Benefits for Physician Services (Table II).

Comorbidities
Hospitalization records from the SDS database and the DAD were used to identify comorbidities diagnosed from 1 year before the cancer diagnosis to 6 months after the diagnosis date. Comorbidity scores were calculated using the Charlson comorbidity index[14]. The comorbidities included were myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes without complications, diabetes with complications, paraplegia and hemiplegia, renal disease, moderate or severe liver disease, and AIDS or HIV infection.

Statistical Analysis
All statistical analyses were performed using the SAS software application (version 9.3: SAS Institute, Cary, NC, U.S.A). The Kaplan–Meier method was used to generate survival curves. We obtained 5-year survival data for all patients. The date of cancer diagnosis was the start date for the survival analysis, and the primary endpoint of that analysis was overall survival. The log-rank test was used to assess differences between the survival curves, stratified by site and histology. Multivariable Cox regression analyses adjusted for age, sex, histology, and comorbidities were used to calculate HRs and 95% confidence intervals. A forward-selection approach was used to construct the models. Time-dependent variables were used to test the proportional hazards assumption. All statistical tests were two-tailed and were conducted at the 5% significance level. Cell sizes of fewer than 5 patients are not reported, as required by the cd-link data use agreement.

RESULTS

Table III summarizes patient and tumour characteristics. From January 2000 to December 2005, 47,090 patients were diagnosed with histologically confirmed metastatic cancer. Of those patients, 45,347 (96.3%) had an identifiable

TABLE I Ontario administrative databases and data used for cohort selection and analysis

Data source	Data used
Ontario Cancer Registry	Origin site of malignancy,[a] age, sex, tumour histology,[b] diagnosis date, diagnostic confirmation, date of last contact with patient, death date
Same Day Surgery and Discharge Abstract Database	Date of hospital admission, primary tumour site,[a] metastatic cancer
OHIP Claims Database	Physician services,[c] date provided

[a]   International Classification of Diseases, 10th revision.
[b]   International Classification of Diseases for Oncology.
[c]   OHIP Schedule of Benefits.
OHIP = Ontario Health Insurance Plan.

TABLE II Fee codes associated with oncologic chemotherapy, radiation, and surgery from the Ontario Health Insurance Plan Schedule of Benefits for Physician Services

Treatment	Fee code
Chemotherapy	G381, G281, G345, G359
Radiation	X310, X311, X312, X313, X323, X302
Surgery	E165, E166, E167, E168, E172, E300, E382, E383, E386, E525, E529, E540, E542, E635, E688, E695, E720, E751, E781, E792, E823, E901, E902, E903, E906, E925, E931, E977, E981 M058, M105, M106, M135 N102, N103, N113, N151, N152, N153, N203, N211, N286, N295, N548, N549, N550, N553, N554, N560, N561 R010, R018, R019, R020, R031, R032, R033, R037, R040, R041, R048, R049, R050, R051, R081, R094, R107, R108, R109, R111, R114, R117, R118, R119, R120, R142, R143, R144, R146, R147, R148, R149, R156, R214, R216, R226, R246, R253, R266, R272, R293, R294, R295, R330, R505, R513, R514, R546, R591, R592, R641, R714, R796, R920 S093, S116, S291, S301, S312, S316, S400, S431, S432, S482, S483, S490, S590, S715, S795 Z117, Z353, Z354, Z522, Z570, Z571, Z753, Z754, Z755, Z761, Z784, Z785, Z632, Z633, Z634, Z857, Z858

primary tumour site, and 1743 (3.7%) were diagnosed with CUP. Patients with CUP were, on average, older (69.4 years) than the patients with a known primary (63.7 years) and more likely to be male (49.7% and 44.0% respectively, $p < 0.0001$). Among the main primary tumour types, CUP ranked 6th behind gastrointestinal ($n = 16{,}308$), respiratory ($n = 12{,}166$), breast ($n = 8453$), gynecologic ($n = 2637$), and urologic ($n = 2230$) cancers. The mean Charlson score was significantly higher ($p < 0.0001$) for patients with CUP (1.88) than for patients with a known primary (1.42), and the distribution of Charlson scores differed significantly between the two groups ($p < 0.0001$).

Figure 1 shows survival for all patients over a 5-year period. The median overall survival was 1.9 months for patients with CUP compared with 11.9 months for all patients a known primary cancer (Table III). Among the known primary sites, median survival was lowest for metastatic liver cancer (2.9 months) and highest for breast cancer (censored, >60 months).

Table IV shows the characteristics of the patients with CUP and with metastatic cancer of known primary. Receipt of treatment of any type was more likely for patients with a known primary site ($n = 35{,}012$, 77.2%) than for patients with CUP ($n = 891$, 51.1%). Patients with CUP were most likely to receive a single type of treatment (73.1%); patients with a known primary were more likely to receive two or three different types of treatment (55.3%). Of the patients with CUP, those who received treatment were younger on average (67.7 years) than those who did not receive treatment (71.2 years,

$p < 0.0001$). Squamous-cell histology was more common in patients with CUP who received treatment (16.2%) than in those who did not receive treatment (3.4%).

Receiving any treatment was associated with longer median survival in both patient populations. Patients with a known primary tumour who received any treatment type had a median survival of 19.0 months; those who received no treatment had a median survival of 2.2 months. A similar trend was observed in patients with CUP: treated patients had a median survival of 3.6 months, and untreated patients had a median survival of 1.1 months.

For each treatment type, 2-year HRs and survival curves were constructed (Table V, Figure 2). Patients with CUP who received no treatment were considered the reference for each set of comparisons, and these trends were observed:

- First, receiving any treatment was associated with a better survival outcome. For patients WITH CUP, the reference group in each treatment block had the highest HR, and untreated patients with a known primary had the highest HR observed in each treatment block for the relevant patient population.
- Increasing intensity of treatment was associated with a lower HR in all patients. In the patients with CUP who received radiation, the HR declined from 0.42 ($p < 0.0001$) for 1–2 treatments, to 0.40 ($p < 0.0001$) for 3–4 treatments, and to 0.34 ($p = 0.0084$) for 5 or more treatments.
- Even with comparable treatment, survival outcomes were worse for patients with CUP than for patients

TABLE III   Characteristics of patients with metastatic tumours of a known or unknown primary

Characteristic	Patient group				*p* Value
	Known primary		Unknown primary		
	Value	Median survival (months)	Value	Median survival (months)	
Patients *(n)*	45,347 (100)	11.9	1,743 (100)	1.9	
Mean age (years)	63.7		69.4		<0.0001[a]
Age group [*n* (%)]					
<39 Years	2,045 (4.5)		31 (1.8)		<0.0001[a]
40–49 Years	5,109 (11.3)		109 (6.3)		
50–59 Years	9,165 (20.2)		235 (13.5)		
60–69 Years	11,814 (26.1)		399 (22.9)		
70–79 Years	11,998 (26.5)		575 (33.0)		
>80 Years	5,216 (11.5)		394 (22.6)		
Sex [*n* (%)]					
Men	19,946 (44.0)		867 (49.7)		<0.0001[a]
Women	25,401 (56.0)		876 (50.3)		
Year of diagnosis [*n* (%)]					
2000	8,960 (19.8)		341 (19.6)		0.230[a]
2001	7,789 (17.2)		279 (16.0)		
2002	7,432 (16.4)		291 (16.7)		
2003	7,063 (15.6)		304 (17.4)		
2004	7,758 (17.1)		304 (17.4)		
2005	6,345 (14.0)		224 (12.9)		
Histology [*n* (%)]					
Adenocarcinoma	32,450 (71.6)		939 (53.9)		<0.0001[a]
Squamous cell carcinoma	3,452 (7.6)		173 (9.9)		
Other[b]	9,445 (20.8)		631 (36.2)		
Diagnostic method [*n* (%)]					
Autopsy	46 (0.1)		<5[c]		<0.0001[a]
Cytology	3,900 (8.6)		341 (19.6)		
Histology	39,653 (87.4)		1,075 (61.7)		
Operation	725 (1.6)		194 (11.1)		
Other[d]	1,023 (2.3)		133 (7.6)		
Main primary site [*n* (%)]					
Gastrointestinal	16,308 (36.0)	11.8			
Respiratory	12,166 (26.8)	3.7			
Breast	8,453 (18.6)	Censored (>60)			
Gynecologic	2,637 (5.8)	19.6			
Urologic	2,230 (4.9)	9.8			
Head and neck	1,049 (2.3)	25.1			
Endocrine	722 (1.6)	20.8			
Sarcoma	697 (1.5)	9.2			
Lymphoma	574 (1.3)	10.0			
Melanoma of the skin	416 (0.9)	22.5			
Leukemia	30 (0.1)	5.0			
Brain	14 (0.0)	4.6			
All other[e]	51 (0.1)	5.7			

TABLE III   Continued

Characteristic	Patient group				*p* Value
	Known primary		Unknown primary		
	Value	Median survival (months)	Value	Median survival (months)	
Mean score on the CCI	1.42		1.88		<0.0001[f]
CCI score group [*n* (%)]					
0	15,342 (33.8)		475 (27.3)		<0.0001[f]
1	13,179 (29.1)		429 (24.6)		
2	7,797 (17.2)		309 (17.7)		
3	4,475 (9.9)		223 (12.8)		
4	2,330 (5.1)		141 (8.1)		
5–8	2,138 (4.7)		151 (8.7)		
>9	86 (0.2)		15 (0.9)		

[a]   By Fisher exact test.
[b]   Unspecified carcinoma, undifferentiated, sarcoma, lymphoma, other hematologic, melanoma, and other specified carcinoma.
[c]   Cells representing fewer than 5 patients are not reported in accordance with the cd-link data user agreement. "Diagnostic Method–Autopsy" has been included as part of "Other" for patients with unknown primary.
[d]   Unknown and pathology report outside of the country. Includes autopsy for patients with unknown primary.
[e]   Bone, joints, soft tissue, heart, eye adnexa, and ill-defined sites.
[f]   By *t*-test.
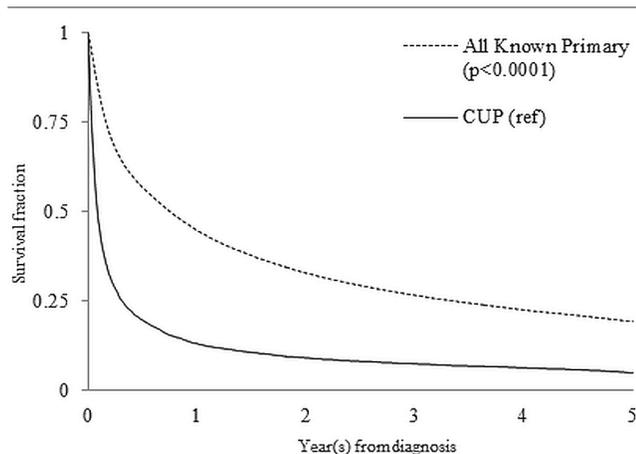CCI = Charlson comorbidity index.

FIGURE 1   Kaplan–Meier 5-year survival curves for patients with a cancer of unknown primary (CUP) and with known primary tumours.

with a known primary site. For example, patients who received no surgery, a single surgery, or 2 or more surgeries were compared. The resulting 2-year HRs were 1.00 (reference), 0.82 (*p* = 0.0077), and 0.48 (*p* < 0.0001) for patients with CUP and 0.51 (*p* < 0.0001), 0.34 (*p* < 0.0001), and 0.25 (*p* < 0.0001) for patients with a known primary.

■   Survival outcomes associated with the use of more than one type of therapy were also investigated. Compared with the use of any single therapy, the addition of a second therapy was associated with further survival benefit. All 3 therapies used in tandem were no worse than any 2 therapies. For patients with a known primary site, the 2-year HR trend was similar to that observed for patients with CUP.

The time of initial treatment relative to initial diagnosis was examined in both patient populations. Figure 3 shows the proportions of patients allocated to these 3 groups: treatment received within 6 months of diagnosis, treatment received 6 months or more after diagnosis, or no treatment received. Patient survival was then plotted for those subpopulations in 6-month increments. The surviving proportion of patients with a known primary who received no treatment declined from more than 60% up to 6 months to just 5% at more than 60 months. The increase in the proportion of patients who received treatment within 6 months of diagnosis largely accounted for that change, starting at 34.2% for 6-month survival and rising to 85.6% for more than 60-month survival. For patients with CUP, survival did not appear to have any relation with first treatment date. The proportion of patients with CUP who received no treatment remained above 50% for most survival durations.

DISCUSSION

Using health administrative databases from Ontario, we identified a population of patients diagnosed with metastatic cancer of known primary origin between January 2000 and December 2005. We described differences in the use of treatment for that population and for a previously identified population of patients with CUP, summarizing chemotherapy, radiation therapy, and surgeries received by both cohorts. We found that, in Ontario, patients with

cup experience significantly decreased survival and are less likely than patients with metastatic cancer of a known primary to receive treatment of any type. Compared with their untreated counterparts, patients with cup who received treatment of any type experienced superior survival.

Early treatment was associated with extended survival in patients with a known primary, but a parallel gain in survival was largely absent in patients with cup.

The increased survival observed in patients having metastatic cancer of known primary site compared with

TABLE IV   Characteristics of patients with metastatic tumours of known or unknown primary, by whether they received or did not receive treatment with surgery, chemotherapy, or radiation

Characteristic	Received treatment					
	Yes			No		
	Known primary [*n* (%)]	Unknown primary [*n* (%)]	*p* Value	Known primary [*n* (%)]	Unknown primary [*n* (%)]	*p* Value
Patients	35,012	891		10,335	852	
Mean age (years)	62.0	67.7	<0.0001[a]	69.5	71.2	<0.0001[a]
Age group						
<39 Years	1,787 (5.1)	17 (1.9)		258 (2.5)	14 (1.6)	
40–49 Years	4,626 (13.2)	76 (8.5)		483 (4.7)	33 (3.9)	
50–59 Years	7,866 (22.5)	143 (16.1)		1,299 (12.6)	92 (10.8)	
60–69 Years	9,348 (26.7)	213 (23.9)		2,466 (23.9)	186 (21.8)	
70–79 Years	8,446 (24.1)	267 (30.0)		3,552 (34.4)	308 (36.2)	
>80 Years	2,939 (8.4)	175 (19.6)		2,277 (22.0)	219 (25.7	
Sex			<0.0001[a]			0.0270[a]
Women	20,374 (58.2)	428 (48.0)		5,027 (48.6)	448 (52.6)	
Men	14,638 (41.8)	463 (52.0)		5,308 (51.4)	404 (47.4)	
Histology			<0.0001[b]			<0.0001[b]
Adenocarcinoma	25,846 (73.8)	472 (53.0)		6,604 (63.9)	467 (54.8)	
Squamous cell carcinoma	2,487 (7.1)	144 (16.2)		965 (9.3)	29 (3.4)	
Other	6,679 (19.1)	275 (30.9)		2,766 (26.8)	356 (41.8)	
Mean score on the CCI	1.3	1.8	<0.0001[a]	1.7	2.0	<0.0001[a]
CCI score group						
0	12,608 (36.0)	269 (30.2)	<0.0001[b]	2,734 (26.5)	206 (24.2)	<0.0001[b]
1	10,242 (29.3)	224 (25.1)		2,937 (28.4)	205 (24.1)	
2	5,816 (16.6)	140 (15.7)		1,981 (19.2)	169 (19.8)	
3	3,217 (9.2)	111 (12.5)		1,258 (12.2)	112 (13.2)	
4	1,614 (4.6)	68 (7.6)		716 (6.9)	73 (8.6)	
5-8	1,455 (4.2)	73 (8.2)		683 (6.6)	78 (9.2)	
>9	60 (0.2)	6 (0.7)		26 (0.3)	9 (1.1)	
Median survival (months)	19.0	3.6		2.2	1.1	
Treatment type						
None	Not applicable		<0.0001[b]	10,335 (100)	852 (100)	
Surgery only	6,237 (17.8)	372 (41.8)				
CTx only	6,503 (18.6)	141 (15.8)				
RT only	2,889 (8.3)	138 (15.5)				
CTx and RT	3,533 (10.1)	44 (4.9)		Not applicable		
Surgery and RT	2,356 (6.7)	107 (12.0)				
Surgery and CTx	7,009 (20.0)	65 (7.3)				
Surgery, RT, and CTx	6,485 (18.5	24 (2.7)				

[a]   By *t*-test.
[b]   By Fisher exact test.
CCI = Charlson comorbidity index; CTx = chemotherapy; RT = radiation therapy.

TABLE V   Hazard ratios (HRs) at 2 years for patients with metastatic tumours of known or unknown primary, by type of treatment received[a]

Treatment (frequency or combination)	Known primary					
	Yes (*n* = 35,012)		*p* Value[b]	No (*n* = 891)		*p* Value[b]
	[*n* (%)]	HR		[*n* (%)]	HR	
Radiation (RT)						
0	30,084 (66.3)	0.42	<0.0001	1,430 (82.0)	Reference	
1–2	13,138 (29.0)	0.31	<0.0001	274 (15.7)	0.42	<0.0001
3–4	1,638 (3.6)	0.29	<0.0001	33 (1.9)	0.40	<0.0001
>5	487 (1.1)	0.26	<0.0001	6 (0.3)	0.34	0.0084
Chemotherapy (CTx)						
None	21,817 (48.1)	0.59	<0.0001	1,469 (84.3)	Reference	
Single agent	2,877 (6.3)	0.36	<0.0001	55 (3.2	0.47)	<0.0001
Multi-agent	20,653 (45.5)	0.30	<0.0001	219 (12.6)	0.60	<0.0001
Surgery						
0	23,260 (51.3)	0.51	<0.0001	1,175 (67.4)	Reference	
1	6,469 (14.3)	0.34	<0.0001	207 (11.9)	0.82	0.0077
>2	15,618 (34.4)	0.25	<0.0001	361 (20.7)	0.48	<0.0001
Combination						
None	10,335 (22.8)	0.55	<0.0001	852 (48.9)	Reference	
Surgery only	6,237 (13.8)	0.26	<0.0001	372 (21.3)	0.54	<0.0001
CTx only	6,503 (14.3)	0.25	<0.0001	141 (8.1)	0.42	<0.0001
RT only	2,889 (6.4)	0.39	<0.0001	138 (7.9)	0.36	<0.0001
CTx and RT	3,533 (7.8)	0.20	<0.0001	44 (2.5)	0.25	<0.0001
Surgery and RT	2,356 (5.2)	0.19	<0.0001	107 (6.1)	0.22	<0.0001
Surgery and CTx	7,009 (15.5)	0.16	<0.0001	65 (3.7)	0.35	<0.0001
Surgery, RT, and CTx	6,485 (14.3)	0.14	<0.0001	24 (1.4)	0.22	<0.0001

[a]   Models adjusted for age, sex, histology, and comorbidities.
[b]   Values reflect comparisons between the reference for each treatment type and the treatment group.

patients having CUP could be attributable to several factors. Knowledge of the primary site might significantly alter clinical decision-making[3], and treatment might be more common in patients with a known primary site if oncologists and patients are more willing to accept available treatment when the primary tumour is known[15]. Second, compared with patients having a known primary, patients having CUP tended to be older and to have more comorbidities. Those factors might have led to those patients being less thoroughly investigated, resulting in a diagnosis of CUP and a corresponding reluctance to seek treatment. Alternatively, the comorbidities in patients with CUP might have lowered the likelihood of therapeutic intervention. Finally, a large percentage of the known primary tumours were breast cancers, and compared with other cancer types, were associated with the best survival. However, the favourable survival of breast cancer patients might be attributable to the inclusion of patients whose metastases were limited to lymph nodes (a potential result of ascertaining metastasis information from hospital abstracts, given that information about cancer staging was unavailable in the OCR for the study accrual period).

Our estimate of the proportion of patients with metastatic cancer of known primary not receiving treatment is similar to estimates described elsewhere. A study of 8 common solid tumour types recorded in the U.S. National Cancer Database found that 20.6% of all patients (*n* = 159,284) with those types of tumours received no treatment[16]. The authors attributed most nontreatment to poor functional status, comorbidities, and patient preference. We also observed that a larger proportion of patients with CUP than of patients with a known primary site had higher scores on the Charlson comorbidity index, suggesting that comorbidities might be a key factor for nontreatment in both patient cohorts.

Methodologically, the present work is similar to an Australian comparison between patients with CUP and those with known primary tumours[9]. The main difference between the two studies is that our cohort was drawn from the general population and the Australian study surveyed Australia's Department of Veterans' Affairs. Despite that difference, key findings were similar: Both studies found that patients with CUP are less likely than patients with a known primary to be treated and that survival outcomes
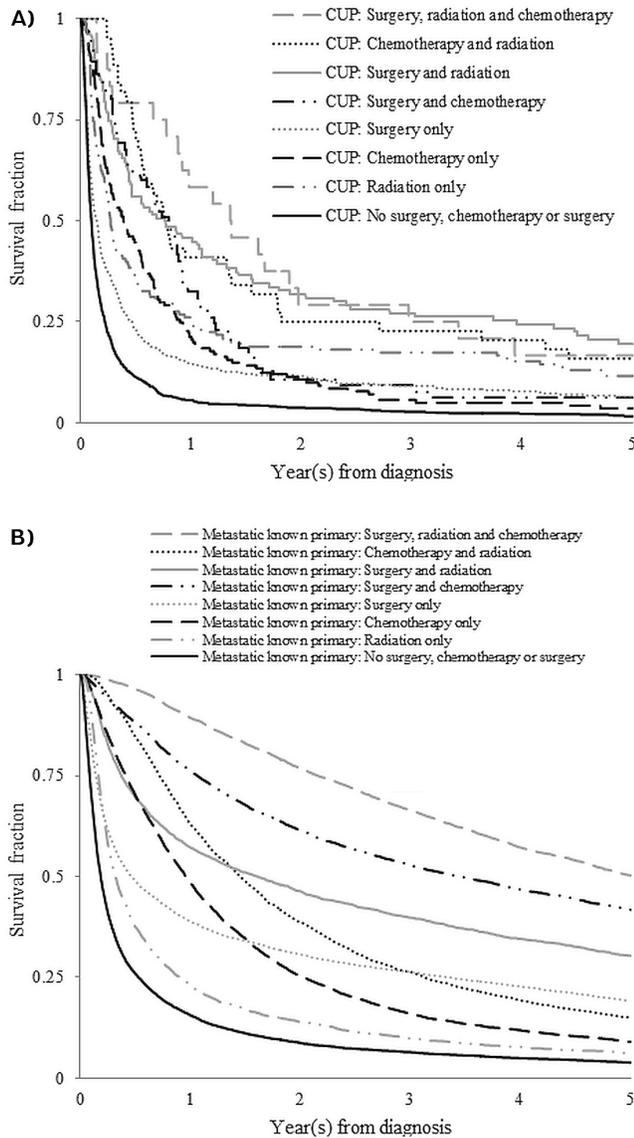
FIGURE 2 Kaplan–Meier 5-year survival curves for patients (A) with a cancer of unknown primary (CUP) by type of treatments received and (B) with metastatic tumours of known primary by type of treatments received.
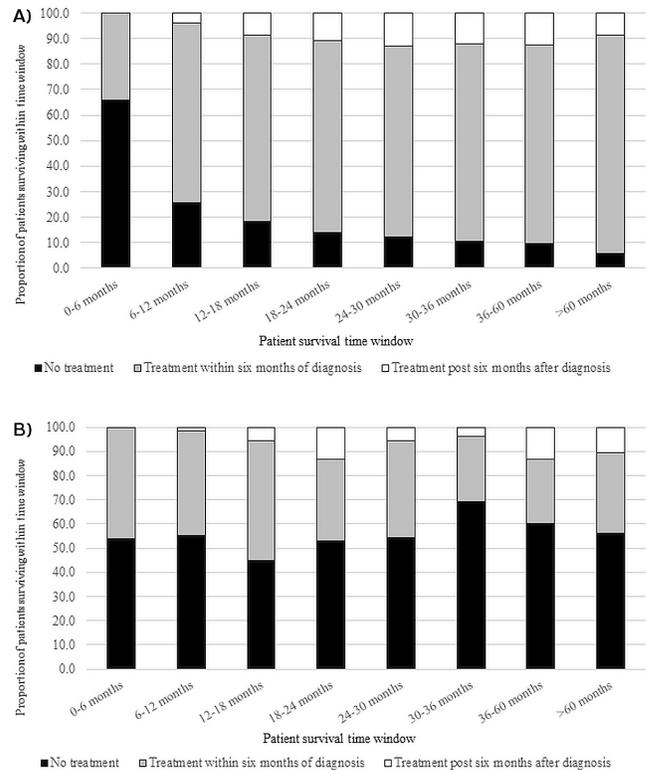

FIGURE 3 Observed 5-year survival for patients (A) with a known primary and (A) with a cancer of unknown primary, both stratified by commencement of treatment within 6 months of diagnosis, commencement of treatment at least 6 months after diagnosis, or no treatment received.

are poorer for patients with CUP than for patients with a known primary tumour.

Some discussion has arisen about the role of chemotherapy in the treatment of patients with CUP. Clinical guidelines recommend the use of empiric platinum-based combination therapies for most patients with CUP[10–12]. When such patients are treated with combination chemotherapy, they experience an estimated median survival of 9–13 months[17]. Our analyses show a significant reduction in the 2-year survival HRs in patients treated with single-agent chemotherapy. We observed no additional survival benefit associated with multi-agent chemotherapy regimens in patients with CUP. That observation is consistent with conclusions from another study that patients with CUP receiving carboplatin–paclitaxel, cisplatin–gemcitabine,

or gemcitabine monotherapy showed no significant differences in survival by treatment type[18]. However, the limited number of administrative codes for chemotherapy make it difficult to determine whether a single combination therapy or several different combination therapies were used in sequence for patients with CUP.

The benefit of treatment has been described in the CUP literature, but those results have been limited to single therapy types[2,18,19]. We found that patients receiving chemotherapy in addition to radiation therapy or surgery (or both) experienced a further survival benefit. However, we did not measure the intensity of radiation therapy, only whether a patient received radiation therapy. We are not aware of any other study that has looked at the survival benefit associated with multiple treatment types for patients with CUP. The clinical significance of our finding could be minimal, because the addition of surgery or radiation might not be tenable in some patients.

Although we found strong associations for knowledge of the primary tumour with treatment and survival outcomes, we are unable to prove causation. The choice to treat a patient—especially a patient without a primary tumour site—could be related to patient health. Alternatively, patients with CUP who receive treatment might be fundamentally different from those who do not. There are some indications that such fundamental differences

might be present in our population. First, of the patients with cup who received treatment, 16.2% had squamous cell carcinoma; of cup patients who did not receive treatment, just 3.4% had squamous histology tumours. Squamous histology represents a favourable subgroup in cup, and prior studies have found median survival to be as high as 20.4 months in that subgroup[13]. Second, the proportion of patients with cup who received no treatment did not change dramatically with patient survival, but the proportion of patients with a known primary site who were not treated decreased sharply.

Although the present work describes the use of the most common types of therapy associated with cup, other modalities, including immunotherapy and targeted therapy, are available. However, we believe that our analysis describes the treatment received by a significant proportion of patients with cup largely because current clinical guidelines rarely recommend treatment outside of chemotherapy, surgery, or radiation therapy[10–12]. The most recent cup guideline from the European Society for Medical Oncology indicates the use of chemotherapy, radiation, or surgery in 7 of the 8 classifications of favourable cup cases and for all classifications of unfavourable cup cases[18]. Furthermore, for patients for whom targeted treatment is recommended, the use of surgery, chemotherapy, or radiation is also prescribed.

CONCLUSIONS

The present work shows that, in cup, a survival benefit is associated with all treatment types analyzed. The observed increase in survival was not uniform across patient groups. Compared with their cup counterparts, patients with a metastatic tumour of known primary were far more likely to receive treatment and experienced a greater survival benefit from that treatment. The direct relationship between treatment and survival remains less clear for cup patients. Advancing clinical guidelines for cup patients toward specific and specialized care, while also expanding treatment to those who would normally go untreated, is vital for this patient population.

CONFLICT OF INTEREST DISCLOSURES
We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: PKR is a co-founder of Cytognomix Inc.; SMM has received unrestricted research grants from Merck, GlaxoSmithKline, Sanofi Pasteur, Pfizer, and Roche–Assurex for unrelated studies, and has also received fees as an advisory board member for Sanofi Pasteur; EW has received fees as an advisory board member from Amgen, Bayer, Eisai, Merck, and Roche, and EW's institution receives funding from AstraZeneca, Bristol–Myers Squibb, Eisai, Merck, and Roche for trials in which he is a co-investigator; GSZ has received fees as an advisory board member for Amgen and GlaxoSmithKline, and executive education fees from Bayer; the remaining authors have no conflicts to disclose.

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