

11-1-2015

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## Citation of this paper:

Kim, Chong S; Hannouf, Malek B; Sarma, Sisira; Rodrigues, George B; Rogan, Peter K; Mahmud, Salaheddin M; Winquist, Eric; Brackstone, Muriel; and Zaric, Gregory S, "Identification and survival outcomes of a cohort of patients with cancer of unknown primary in Ontario, Canada." (2015). *Epidemiology and Biostatistics Publications*. 62.  
<https://ir.lib.uwo.ca/epidempub/62>

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**Identification and survival outcomes of a cohort of patients with cancer of unknown primary in Ontario, Canada.**

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**This is the pre-peer reviewed version of the following article:**

Identification and survival outcomes of a cohort of patients with cancer of unknown primary in Ontario, Canada, *Acta Oncol.* 2015 Nov;54(10):1781-7.

**which has been published in final form at:**

<http://www.tandfonline.com/doi/full/10.3109/0284186X.2015.1020965>

(doi: 10.3109/0284186X.2015).

## **Abstract**

**Background:** Cancer of unknown primary origin (CUP) is defined by the presence of pathologically identified metastatic disease without clinical or radiological evidence of a primary tumour. Our objective was to identify incident cases of CUP in Ontario, Canada, and determine the influence of histology and sites of metastases on overall survival (OS).

**Material and Methods:** We used the Ontario Cancer Registry (OCR) and the Same-Day Surgery and Discharge Abstract Database (SDS/DAD) to identify patients diagnosed with CUP in Ontario between January 1, 2000, and December 31, 2005. Patient diagnostic information, including histology and survival data, was obtained from the OCR. We cross-validated CUP diagnosis and obtained additional information about metastasis through data linkage with the SDS/DAD database. OS was assessed using Cox regression models adjusting for histology and sites of metastases.

**Results:** We identified 3,564 patients diagnosed with CUP. Patients without histologically confirmed disease (n=1,821) had a one-year OS of 10.9%, whereas patients with confirmed histology (n=1,743) had a one-year OS of 15.6%. The most common metastatic sites were in the respiratory or digestive systems (n=1,603), and the most common histology was adenocarcinoma (n=939). Three-year survival rates were 3.5%, 5.3%, 41.6% and 3.6% among adenocarcinoma, unspecified carcinoma, squamous cell carcinoma and undifferentiated histology, respectively. Three-year survival rates were 40%, 2.4%, 8.0% and 4.6% among patients with metastases localized to lymph nodes, the respiratory or digestive systems, other specified sites, and unspecified sites, respectively.

**Conclusion:** CUP patients in Ontario have a poor prognosis. Some subgroups may have better survival rates, such as patients with metastases localized to lymph nodes and patients with squamous cell histology.

## **Background**

The primary objective for physicians treating patients presenting with a metastatic cancer is to identify the tumour's site of origin. The typical diagnostic work-up includes a detailed analysis of medical history, complete physical examination, full blood count and biochemical analysis, urinalysis and stool occult blood tests, histopathological review of the metastatic tumour biopsy and computed tomography (CT) scan of the chest, abdomen and pelvis [1]. If the primary tumour remains occult, examining metastatic tumour samples with additional immunohistochemical (IHC) staining becomes crucial in establishing a potential originating tissue as well as for directing further examination [2]. Additionally, tests such as mammography, upper and lower gastro-intestinal endoscopy, magnetic resonance imaging (MRI) and positron emission tomography (PET) may be considered. If the site of the primary tumour remains unidentified after additional diagnostic work-up, then the patient is considered to have cancer of unknown primary site or origin (CUP). The overall prognosis of CUP patients is poor, with an estimated three- to 10-month median survival [1]. While CUP accounts for approximately 3% to 5% of all incident cancers, it ranks among the top five causes of cancer deaths worldwide [3, 4].

Currently, little is known about the biology of CUP [3]. Epidemiological analyses of CUP cases have identified clinicopathological features, including sex, sites of the metastatic tumour and histopathology, that predict a favourable prognosis [4-6]. About 20% of CUP patients belong to favourable subsets and respond well after receiving site-specific therapies [1, 3, 7]. However, the majority of CUP patients do not fit into a favourable subset and present with metastatic cancer of major organs and multiple metastases [8]. While median survival in the unfavourable subgroup is under one year, prolonged survival in the favourable subgroup can extend beyond 13 years [7, 8].

In this study, we identify a cohort of CUP patients in Ontario, Canada, using provincial registries and administrative databases. We describe patient characteristics and examine overall survival using subgroups defined by histology and metastatic site. Similar studies have been conducted in Europe, but we are not aware of any published data on CUP survival in Canada [9-12].

## **Materials and Methods**

### **Data Sources**

We used the Ontario Cancer Data Linkage project “*cd-link*” to obtain data from population-based administrative databases for Canada’s largest province. The *cd-link* project is a data release mechanism in which patient-level data relevant to cancer research are linked at the Institute for Clinical Evaluative Sciences using encrypted health card numbers, de-identified, and, with the protections of a comprehensive Data Use Agreement (DUA), are provided to investigators at academic institutions in Ontario. Through the *cd-link* project, we gained access to the Ontario Cancer Registry (OCR) database and the Canadian Institute for Health Information (CIHI) Same-Day Surgery and Discharge Abstract Database (SDS/DAD). Ethics approval was obtained prior to accessing these databases.

Maintained by Cancer Care Ontario (CCO), the OCR is an electronic database that tracks all incident cases of cancers and associated mortality in Ontario. The OCR contains patient information that is compiled from the following sources: hospital pathology reports with a cancer diagnosis, patient records from CCO, electronic death records from the Registrar General of Ontario and hospitalization records documenting a cancer diagnosis from SDS/DAD (CIHI). Patient data from these sources are linked using probabilistic linkage, and each patient is assigned a unique identifier. For each patient, the OCR contains patient information, including

their regional cancer centre registration date, whether an autopsy was completed, histology of biopsy, cause of death, institution of diagnosis, number of primary tumours and their first treatment date. The most up-to-date patient cancer diagnosis is recorded in the OCR database using the International Classification of Diseases 9th (ICD-9) before 2002 and ICD 10th (ICD-10) afterwards. The data quality of the OCR has been examined previously and was found to be highly accurate [13].

The SDS/DAD database contains patient-level data for acute, rehabilitation, chronic and day-surgery institutions in Ontario. Each observation in this database contains information about one hospital stay (DAD) or one same-day surgery stay (SDS). This database contains information regarding sex, date of birth, up to 25 diagnoses per hospitalization, procedures undertaken, length of stay and several variables indicating resource consumption.

### **Identification of CUP Population**

We identified patients using the OCR and the SDS/DAD database. We defined CUP cases as any Ontario resident who was registered by the OCR during the period from January 1, 2000, to December 31, 2005, with one or more of the following diagnosis codes: cancer of unknown primary with metastatic sites localized to lymph nodes (ICD-9:196/ICD-10:C77), the respiratory or digestive systems (ICD-9:197/ICD-10:C78), other specified sites (ICD-9:198/ICD-10:C79), or without specification of metastatic site (ICD-9:199/ICD-10:C80). We used the SDS/DAD database to verify CUP diagnosis and inclusion in the cohort. We included patients where there was evidence in the SDS/DAD database of metastatic disease and CUP diagnosis from two months before until two months after the initial diagnosis. We excluded patients whose CUP diagnosis was changed to any other site later in the course of the disease and those who had a previous known primary cancer diagnosis (Figure 1).

We grouped patients by histology types using the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) histology codes available from the OCR. The following ICD-O-3 codes were utilized: adenocarcinoma (8140-8580), squamous cell carcinoma (8050-8089), unspecified carcinoma (8010-8049) and undifferentiated (8000-8004). Patients with no histologically confirmed disease (i.e., ICD-O-3 9990) were grouped in one category. All remaining ICD-O-3 codes were compiled as “other”. We obtained five-year survival data from the OCR.

### **Statistical Analysis**

All statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC, U.S.A). The Kaplan-Meier method was used to generate survival curves, and the primary endpoint of this analysis was overall survival (OS). We used the log-rank test to assess the difference between survival curves of metastatic site and histology. We obtained hazard ratios (HRs) and 95% confidence intervals using Cox regression analyses adjusted for age and sex. All statistical tests were two-tailed and were conducted at the 5% significance level. Cell sizes of fewer than five patients were not reported, as required by the *cd-link* Data Usage Agreement.

### **Results**

Patient and tumour characteristics are summarized in Table 1. During the study period, 52,619 patients were diagnosed with metastatic cancer, and of those, 3,564 (6.8%) had a final diagnosis of CUP. Histological samples provided the most common method for confirming diagnosis (43.8%). Confirmation of tumour cell type via histology was missing for 1,821 (51.1%) of CUP patients. For CUP patients with confirmed histology, metastatic tumours localized to the respiratory or digestive systems were most common (42.8%). Over half of all

tumours were adenocarcinomas (n=939). There were significant variations in histology by tumour location. For example, adenocarcinoma was the most common histology for respiratory/digestive CUP (67.6%), other specified sites (43.8%) and unspecified sites (51.9%), but it only represented 23.4% of nodal CUP. Squamous cell carcinoma was the most common histology among nodal CUP (39.4%), but only represented 2.1% of respiratory/digestive CUP, 10.3% of other specified site CUP, and 5.4% of unspecified site CUP.

There was no difference in survival by gender (Table 2). Survival was better for younger patients, and this trend was consistent across all age groups. Patients lacking histology were older, on average, than those with histology (Table 1). Patients without histology were more likely to have unspecified site CUP and less likely to have nodal CUP compared to patients with confirmed histology. The overall survival of patients with known histology was significantly higher than survival among those without histology (Figure 2).

The Kaplan-Meier curves of OS are shown in Figure 3. The overall trend is similar among respiratory/digestive, other specified sites and unspecified CUP. Nodal CUP patients had a significantly higher one-year OS probability of 52.4% (log-rank  $p < 0.0001$ ) compared to all other subgroups. Patients with other specified site CUP were the next highest surviving group, with a one-year OS probability of 16.6%.

We stratified OS estimates by histology (Figure 4). Generally, patients with squamous cell carcinoma had higher one- and three-year OS within each metastatic site (Table 3). Patients with squamous cell carcinoma had a one-year OS probability of 59.5%, compared to the next highest one-year OS probability in the adenocarcinoma group at 11.3%. Nodal CUP with adenocarcinoma, squamous cell carcinoma or unspecified carcinoma histology had significantly better survival compared to similar histology tumours of other sites. In nodal CUP with

undifferentiated histology, only unspecified site CUP had significantly worse survival. Nodal CUP had significantly better survival among all comparisons for CUP patients without histology.

### **Discussion**

We identified a cohort of CUP patients in Ontario by cross-validating data from the OCR and the SDS/DAD database. Our work revealed that CUP patients in Ontario represent a significant portion of all metastatic cancers, accounting for approximately 6.8% of the total. We analyzed five-year survival as well as one-year hazard ratio (HR) subgrouped by metastatic site and histology. We found that survival varied by metastatic site and histology. Patients with nodal CUP had better survival than any other CUP metastatic site. Patients with metastases localized to either respiratory or digestive regions generally had some of the worst survival outcomes, regardless of histology. Among patients with squamous cell carcinoma, those with non-respiratory/digestive metastases had the highest survival rates.

The short time window of data collection and the large cohort size constitute the strengths of this study and likely translate into consistent diagnosis and treatment during the collection period. Our CUP cohort is smaller than those of large, European-based population studies of CUP with sample sizes ranging from 18,911 to 57,638 [9, 11, 14]. However, our work encompassed a six-year period, whereas these studies included 21 [9] to 47 [11] years of observations. As a consequence, our study did not include CUP cases from the 1990s, a period that is suggested to have been the peak of CUP incidence from European cancer registries [11, 14]. Even without those CUP cases, our sample size is comparable, given the collection window.

Our findings are consistent with previous research. Increased survival in nodal CUP patients and patients with squamous cell histology has been described elsewhere [2, 11, 15] as well as decreased survival in respiratory/digestive CUP patients [16]. Our work largely

corroborates what is currently known about CUP, but it also shows unique traits of this Canadian cohort. In a large Swedish cohort, Hemminki *et al.* found 24% survival after one year (n=7,730), whereas we observed a one-year survival of 13.7% (n=349) for unspecified site CUP patients [9]. This variation may be attributed to population differences or, more likely, to alternative diagnostic or therapeutic guidelines that occurred over the different time frames. If this observed difference can be accounted for by diagnostic or post-diagnostic treatment, it will be important to try and implement this aspect into the Canadian setting.

Among patients with squamous cell carcinoma, those with respiratory/digestive as the site had the worst survival outcomes. Lung cancer was identified as the main cause of death for extranodal squamous cell carcinoma CUP patients in Sweden [17]. Death from digestive cancers was also common. This suggests CUP involving respiratory and digestive sites are directly linked with patient outcome. Patients with non-respiratory/digestive squamous cell carcinoma may have their metastatic sites located such that treatment by radiation or surgery is possible. This is especially true for tumours located in the head and neck or inguinal area [18]. These favourable subgroups often present in such a way that a potential originating malignancy is suggested, directing therapeutic treatment [19].

Historically, therapeutic guidelines for CUP patients have recommended the use of platinum-based chemotherapy [2, 20, 21]. Although targeted treatments may be available for some subgroups of patients, platinum-based chemotherapy is often recommended to accompany such treatment [8]. For the majority of CUP patients, a platinum-based doublet regimen is often prescribed [22]. A recent systematic review of the unfavourable subset of CUP has raised questions about current clinical practice [23]. Phase II trials completed in the past 15 years have yielded inconclusive results regarding chemotherapy over best supportive care, and have not

clarified the benefit of treatment regimens with platinum-based chemotherapy over non-platinum-based chemotherapy with single versus doublet or triplet chemotherapy regimens [23]. Future analyses describing treatment received by our study cohort is warranted to describe the Canadian clinical practice.

Fifty-one percent of our sample (1,821/3,564) did not have a confirmed histology. Given that this group had poor outcomes, with a minority of patients surviving beyond a few months (Figure 2), there may be clinical and administrative factors leading to an absence of histology. For instance, these patients may not have survived long enough for pathology analyses to be conducted. Many of these patients (98%) had operation as their method of confirmation. It is possible that for this subgroup, surgery revealed a poor prognosis such that histological tests were not ordered. It is also possible that, for some members of this group, CUP diagnosis was used by the registry as a temporary diagnosis but was never updated, so that the final record shows unconfirmed histology. Two recent population registry studies reported CUP with no histological evidence to comprise 30.3% and 58.4% of CUP cases [15, 24]. While this does not prove the accuracy of the CUP diagnosis, it does show these patients represent a significant and clinically visible subset of the CUP population.

The lack of certain information known to be relevant for the CUP population represents a limitation of this study. The number of metastatic sites is known to be associated with greater disease burden [21]. Indeed, one characteristic of the favourable subset of CUP patients is a single metastatic site. Additionally, several prognostic scores have been proposed with potential factors associated with CUP patient survival. However, the OCR does not capture the number of metastatic sites or prognostic markers, such as lactate dehydrogenase (LDH) level, albumin level and performance status [23, 25]. Application and validation of a prognostic model in this large

CUP patient cohort could have important consequences in current clinical practice. Capturing the above data elements in administrative databases would significantly enhance research in this area. Treatment intensity in this cohort could prove to be valuable in establishing costs for treating patients with CUP and the relationship between survival and therapeutic procedures. This link has yet to be clearly demonstrated for CUP populations [23].

This study shows that CUP patients in Canada constitute a relatively large group of the metastatic cancer population and that this population is mainly composed of patients in the unfavourable CUP subgroup. Important differences in patient survival between this cohort and those identified in previous studies suggest a need for further study. Future research efforts should continue to explore new diagnostic tools for this population, especially those with unfavourable characteristics.

**Acknowledgments:** This study was supported by the Canadian Institutes of Health Research. SMM, PKR and GSZ are supported by the Canada Research Chairs Program.

Table 1. Demographic characteristics of the CUP cohort.

Patient characteristics	Histologically confirmed n=1,743 (%)	Missing histology n=1,821 (%)
Age (average)	69	76
<39	31 (1.8)	22 (1.2)
40-49	109 (6.3)	47 (2.6)
50-59	235 (13.5)	106 (5.8)
60-69	399 (22.9)	237 (13.0)
70-79	575 (33.0)	589 (32.3)
>80	394 (22.6)	820 (45.0)
Gender		
Male	866 (49.7)	847 (46.5)
Year of diagnosis		
2000	280 (16.1)	308 (16.9)
2001	289 (16.6)	337 (18.5)
2002	289 (16.6)	298 (16.4)
2003	307 (17.6)	315 (17.3)
2004	295 (16.9)	275 (15.1)
2005	283 (16.2)	288 (15.8)
Site		
Nodal CUP (196/C77)	191 (11.0)	42 (2.3)
Respiratory/digestive CUP (197/C78)	746 (42.8)	857 (47.1)
Other specified site CUP (198/C79)	457 (26.2)	361 (19.8)
Unspecified site CUP (199/C80)	349 (20.0)	561 (30.8)
Histology		
Adenocarcinoma	939 (53.9)	0
Squamous cell carcinoma	173 (9.9)	0
Unspecified carcinoma	475 (27.3)	0
Undifferentiated	139 (8.0)	0
Other*	17 (1.0)	0
No histological evidence	0	1821 (100)
Diagnostic conformation method		
Histology	1075 (61.7)	0
Cytology	341 (19.6)	0
Operation	194 (11.1)	1787 (98.1)
X-Ray	117 (6.7)	0
Unknown or Other	10 (0.6)	34 (1.9)
Judgement or autopsy	6 (0.4)	0

\*Includes sarcoma, lymphoma, other hematologic, melanoma and other specified carcinoma.

Table 2. One-year hazard ratio (HR) by gender and age group.

	n	HR	P-value
<b>Gender</b>			
Male	867	1.06	0.2850
Female	876	1.00	<i>Ref</i>
<b>Age at diagnosis</b>			
<39	31	0.50	0.0010
40-49	109	0.55	<.0001
50-59	235	0.66	<.0001
60-69	399	0.78	0.0007
70-79	575	0.86	0.0270
>80	394	1.00	<i>Ref</i>

*Ref* = Reference group used for hazard ratio calculation

Table 3. One-year (1 y), three-year (3 y) survival (%), median overall survival (OS, months) and one-year adjusted hazard ratios (HR) stratified by metastatic site and histology (n=1743)

	Nodal CUP (196/C77)				Respiratory/digestive CUP (197/C78)					Other specified sites CUP (198/C79)					Unspecified site CUP (199/C80)					Total		
	OS	1 y	3 y	HR	OS	1 y	3 y	HR	P-value	OS	1 y	3 y	HR	P-value	OS	1 y	3 y	HR	P-value	OS	1 y	3 y
Adenocarcinoma	6.0	35.7	13	1.00	1.4	7.9	3	2.36	<.0001	2.6	11.5	4	1.92	0.0005	1.7	13.7	5	2.10	<.0001	1.8	11.3	3.5
Squamous cell carcinoma	60.0	77.7	59	1.00	2.9	0	0	10.01	<.0001	11.3	51	26.5	2.37	0.0014	12.5	52.6	31.6	2.98	0.0076	20.4	59.5	41.6
Unspecified carcinoma	3.3	33.3	31	1.00	0.8	5.2	NR <sup>†</sup>	2.34	<.0001	2.3	13.5	5.1	1.50	0.0539	0.9	3.7	NR <sup>†</sup>	2.49	<.0001	1.4	10.1	5.3
Undifferentiated		NR <sup>†</sup>		1.00	0.9	4.3	0	6.84	0.0631	1.7	17.7	5.9	3.99	0.1801	1.2	0	0	11.09	0.0240	1.2	9.4	3.6
No histological evidence	5.2	38.1	33.3	1.00	0.6	6.9	0	2.53	<.0001	0.8	16.3	12.2	1.94	0.0015	0.5	11.6	6.8	2.12	0.0002	0.5	10.9	6.9
Total	13.9	52.4	38.2	1.00	0.9	6.7	2.8	3.93	<.0001	1.6	16.6	9.3	2.66	<.0001	0.8	11.4	6.0	3.36	<.0001	0.8	13.2	7.4

<sup>†</sup>NR = Not reported in accordance with the cd-link DUA

OS = Median overall survival in months

CUP with metastatic sites localized to lymph nodes (ICD-9:196/ICD-10:C77) used as the reference group in HR calculations

## Figures

Figure 1: Cohort identification flowchart.

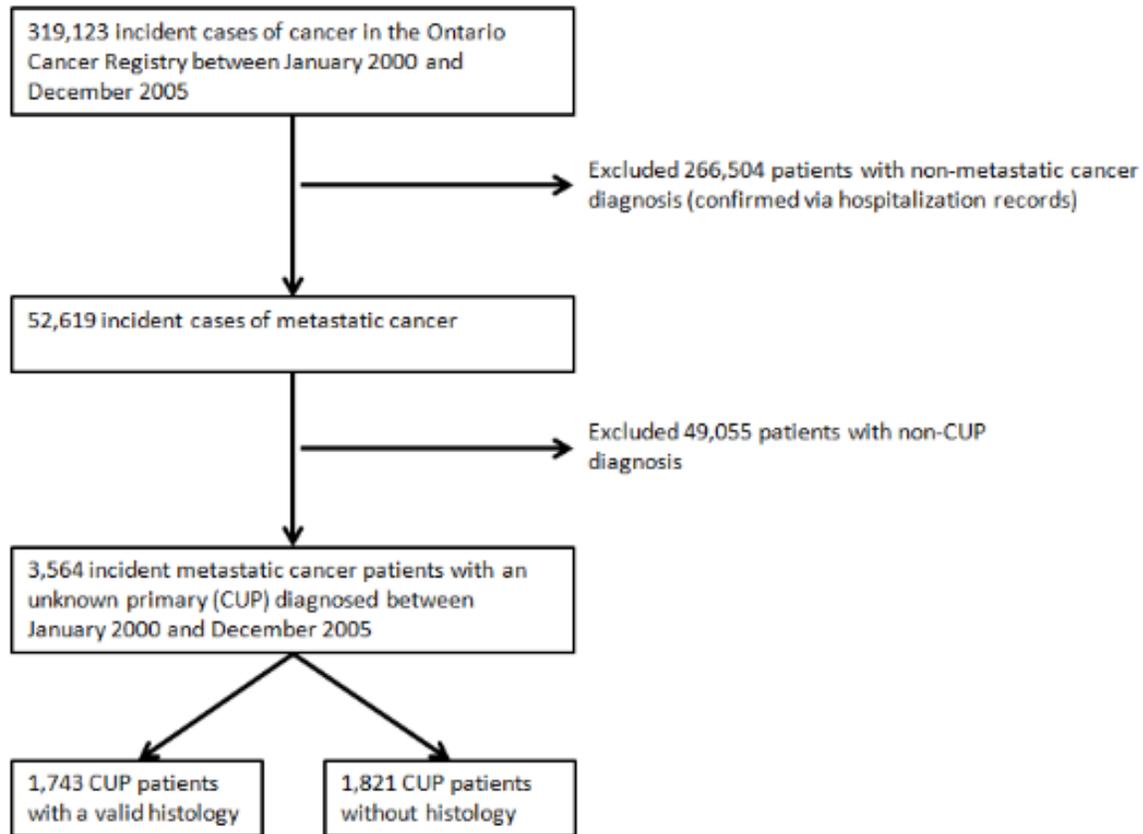


Figure 2: Kaplan-Meier survival curves for CUP patients with a valid histology or missing histology. CUP, cancer of unknown primary.

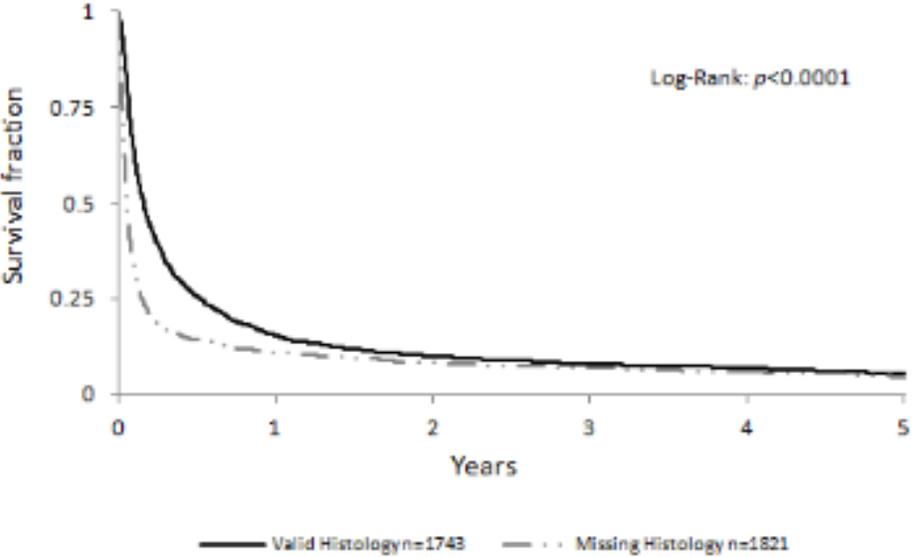


Figure 3: Kaplan-Meier survival curves for patients with CUP coded as 196, 197, 198 or 199. CUP, cancer of unknown primary.

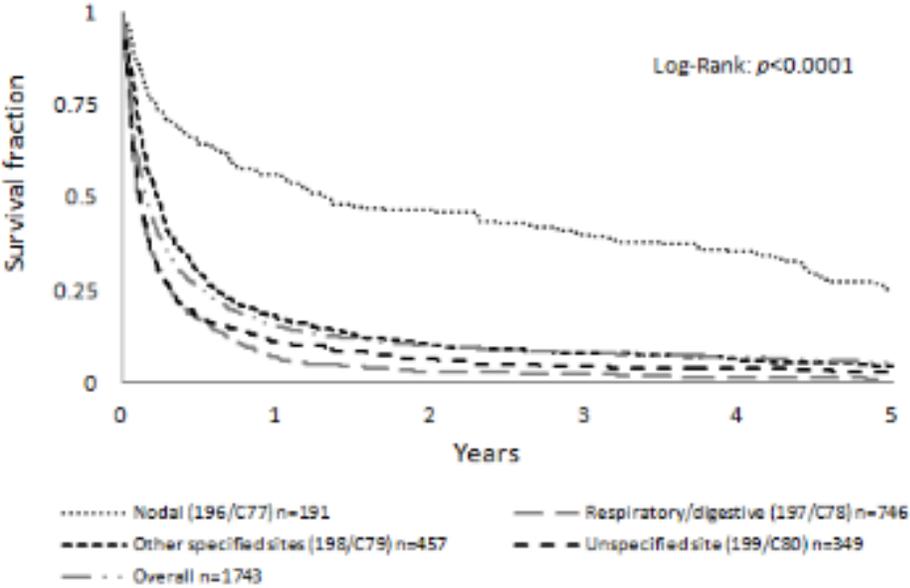
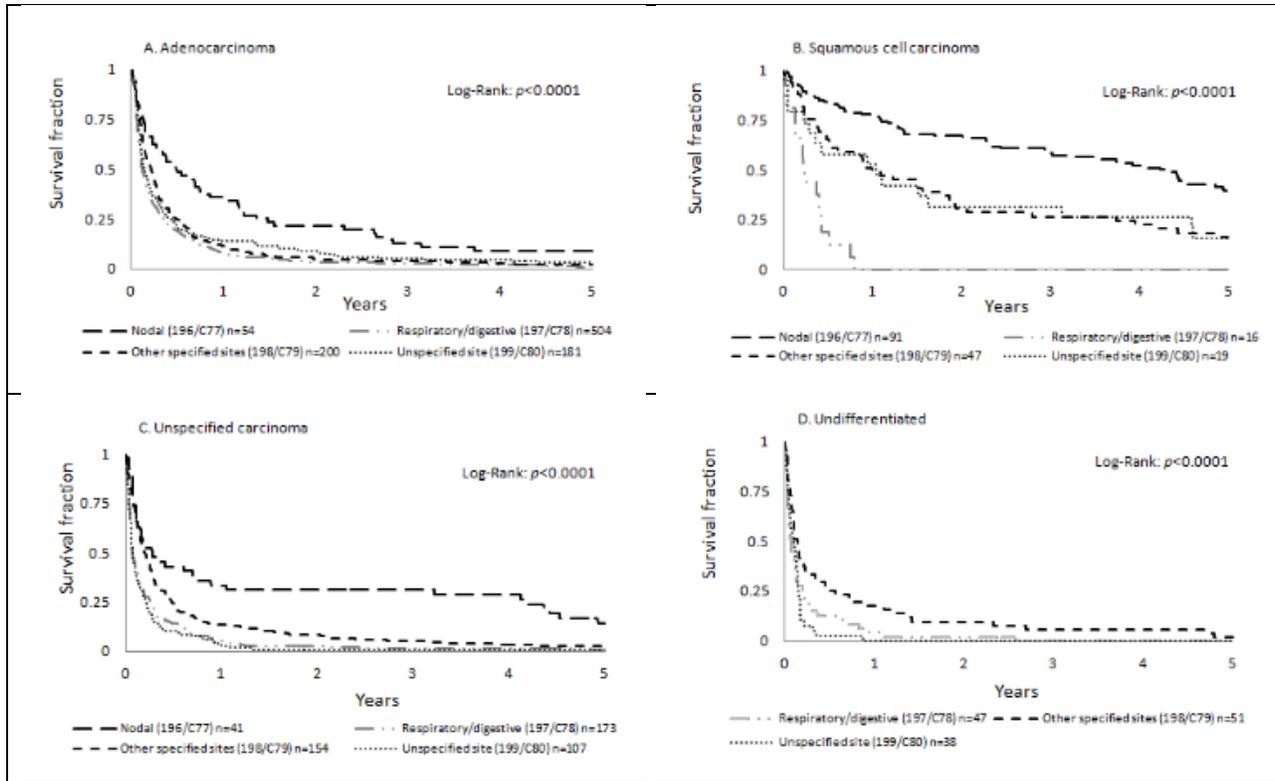


Figure 4: Kaplan-Meier survival curves of CUP patients with (A) adenocarcinoma, (B) squamous cell carcinoma, (C) unspecified carcinoma, or (D) undifferentiated histology. CUP, cancer of unknown primary.



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