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Survival outcomes and treatment utilization among patients with known and unknown primary tumours in Ontario.

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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(Thesis format: Integrated Article)

by

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Abstract

I identify two cohorts of cancer patients with known and unknown primary tumours. Cancer of unknown primary (CUP) is defined by the presence of pathologically identified metastatic disease without clinical or radiological evidence of a primary tumour. Using the Ontario Cancer Registry, Same Day Surgery/Discharge Abstract Database and Ontario Health Insurance Plan, a novel linkage strategy was developed to cross-validate diagnoses. I found CUP patients represent a significant portion of all metastatic cancers. CUP patients with histological confirmed disease, squamous cell histology, or metastases localized to nodal regions had significantly better survival than other CUP patients. Knowledge of the primary site was associated with significantly improved overall survival. Known primary patients were more likely to receive treatment than CUP patients. Treatment was associated with prolonged survival in CUP patients. Adoption of gene profiling, emphasis on targeted therapeutics, and robust clinical guidelines are likely to improve CUP patient outcomes.

Keywords

Cancer of unknown primary, CUP, treatment utilization, metastatic, Kaplan-Meier survival, survival analysis

Co-Authorship Statement (where applicable)

This work includes material that is the result of joint research. Chapter 3 is published in the journal Acta Oncologica. This article was co-authored by Dr. Gregory Zaric, Dr. Malek Hannouf, Dr. Muriel Brackstone, Dr. Eric Winquist, Dr. Sisira Sarma, Dr. Salah Mahmud, Dr. George Rodrigues and Dr. Peter Rogan. I am the first author of this publication and was largely responsible for the research design, statistical analysis, literature review and manuscript drafting. Dr. Gregory Zaric and Dr. Malek Hannouf were involved in design of the studies, participated in statistical analyses and drafting the manuscripts.

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Chapter 1 : Introduction

1.1 Background

Cancer of unknown primary (CUP) patients present with metastatic tumours in which a primary tumour cannot be found. These patients are a heterogeneous collection of malignancies, bound by an occult primary tumour (1). Treatment of metastatic cancers are often linked to the originating neoplasm, as they are of the same biological lineage (2). Therefore, physicians will work to identify the primary tumour and categorize its cell type in order to direct future treatment. The diagnostic workup to achieve these goals can vary by region, however, a detailed medical history of the patient, a complete physical examination, a full blood count and biochemical analysis, urinalysis and stool occult blood tests, a histopathological review of the tumour biopsy with immunohistochemistry (IHC) and computed tomography (CT) scan of the abdomen, thorax and pelvis are routinely recommended (3, 4). In some cases mammography, magnetic resonance imaging (MRI) and positron emission tomography (PET) may also be employed (5). If, however, after extensive clinical and diagnostic work-up a primary tumour site cannot be found, the patient is diagnosed as a cancer of unknown primary (CUP) and treated with CUP based protocols.

While the biological mechanisms surrounding CUP are not well understood three common clinical explanations are documented in the literature (1). First, the primary tumour remains intact but is too small to be detected by conventional diagnostic procedures. Second, the primary tumour may have been destroyed by the immune system. Third, in rare cases an unrelated surgical procedure may remove the primary tumour, for instance via mastectomy. In addition to a latent primary tumour, CUP

patients are often typified by these distinct characteristics: multiple metastatic sites, atypical metastatic sites and early aggressive metastases (6). Given CUP is a heterogeneous malignancy thus historically making an exact definition of CUP difficult (6, 7). Many researchers define CUP as: ‘‘histologically confirmed metastatic cancer for which clinicians are unable to identify a primary tumour after a standard diagnostic approach’’ (8). This definition has become widely accepted, but may still be insufficient. First, a “standard diagnostic approach’’ may be anything but standard in such a group of patients. Second, population studies have observed the proportion of CUP patients without histologically examined tumours between 30.3% to 58.4% (8, 9). These points highlight the difficulty in studying this population.

1.2 Epidemiology

Estimates of cancer cases resulting in a CUP diagnosis range by country and cancer registry, however, an estimate of 3-5% of all cancer cases is often stated, while wider estimates of 2-10% have also reported (1, 10). CUP does not rank among the five most common cancer diagnoses, but due to the poor prognosis of these patients it is a leading cause of cancer death (4). Overall median survival is estimated between 6-10 months (5). Several CUP patient characteristics are commonly observed. These patients tend to be older on average when diagnosed (median age between 65-90) than other common cancer types and appear to be more common in men than in women (4, 8, 10, 11). Recently smoking was shown to be a risk factor for CUP, and was strongly associated with patients surviving less than 12 months (12).

During the course of treatment approximately 5% of patients have their primary tumour discovered (6). As many as 75% of patients who undergo an autopsy have their

primary tumour found (11, 13). These patients have shown the most common primary tumours are found in the pancreas, lung, colon or rectum and liver (3).

1.3 Classification of Cell Type

A biopsy of the metastatic tumour can provide valuable information directing treatment decisions when a primary tumour is absent. Light microscopy, immunohistochemistry (IHC) and less frequently, molecular or genetic diagnostics provide valuable information as to the lineage of the metastatic tumour (3). Routine light microscopy distinguishes CUP tumour biopsies into four broad categories: adenocarcinoma, undifferentiated carcinoma, squamous-cell carcinoma, and undifferentiated neoplasm (14). IHC can distinguish cellular identity by utilizing chemical stains specific for the following tumour types: carcinoma, lymphoma, sarcoma, melanoma, non-seminoma and seminoma.

The majority of CUP patients (50%) have moderately to well differentiated metastatic adenocarcinoma (15). The next most frequent cell type is poorly or undifferentiated carcinoma (30%). Of the remaining CUP patients, approximately 15% are diagnosed with squamous cell carcinoma and the remaining 5% of patients cannot be accurately defined and are labeled as undifferentiated neoplasm. This last category can then be potentially further classified using other diagnostic tools.

1.4 Subsets

CUP can be referred to as a diagnosis of absence, since the distinguishing characteristic is the lack of a detectable primary site. Given this fact, CUP appears to be a group of unrelated malignancies. However, this issue is not fully agreed upon in the literature. One hypothesis maintains that the biology underscoring CUP has a common basis, potentially

having genetic and molecular signatures leading to an occult primary with detectable early metastases (11). The opposing view states that CUP is a loosely associated group of clinically and biologically heterogeneous tumours, in all of which the primary tumour cannot be observed (1). There is evidence to support both claims, with the latter being more widely accepted by clinicians (6).

CUP patients can be classified as either favourable or unfavourable given clinicopathological features (5). The majority of CUP patients (>80%) belong to the unfavourable subset and present with adenocarcinoma metastatic to the liver or other organs, non-papillary malignant ascites (adenocarcinoma) or multiple metastatic sites. These patients do not respond well to treatment and median overall survival is between 6-10 months (4, 5, 16). The favourable subset responds to specified treatment regimens with median overall survival from 12-165 months (11). Characteristics of the favourable subset include: poorly differentiated carcinoma with midline distribution (extragonadal germ-cell syndrome), women with papillary adenocarcinoma of peritoneal cavity, women with adenocarcinoma involving only axillary lymph nodes, squamous cell carcinoma involving cervical lymph nodes, isolated inguinal adenopathy (squamous carcinoma), poorly differentiated neuroendocrine carcinomas, men with blastic bone metastases and elevated PSA (adenocarcinoma) and patients with a single, small, potentially resectable metastatic tumour (11, 17).

1.5 Patient Management

Directed treatment regimens exist for favourable CUP patients (4, 5). These metastatic tumours are treated with a known primary analogue in mind. For instance, isolated axillary nodal metastases in females are treated similarly to breast cancer with nodal dissection and mastectomy or irradiation of the breast and chemotherapy. For the

majority of CUP patients in the unfavourable subset, a general treatment course is suggested (18). As recommended by clinical guidelines, a wide-spectrum empiric chemotherapy utilizing platinum or platinum/taxane is often prescribed (16). A synthesis of treatment outcomes in this subset of CUP patients questioned the benefit from well established platinum based regimens over placebo/palliative care (16). No clear benefit was demonstrated for the use of chemotherapy in the unfavourable subset of CUP patients.

1.6 Overview of Thesis

In this thesis I examine two patient cohorts in Ontario with metastatic cancer. The first group does not have a primary tumour identified (CUP) and the second have a known primary tumour site. I identify, describe and compare these cohorts using patient characteristics, tumour characteristics, survival and treatment utilization. I use data from the Ontario Cancer Registry, Same Day Surgery/Discharge Abstract Database and the Ontario Health Insurance Plan, all accessed through the Ontario Cancer Data Linkage project "*cd-link*". This thesis is organized as follows:

- Chapter 2: A brief summary the research objectives and hypotheses
- Chapter 3: Identification and description of an Ontario CUP population
- Chapter 4: Identification and description of an Ontario metastatic cancer of known primary population, and survival comparison to the Ontario CUP population
- Chapter 5: Comparing the treatment utilization between Ontario metastatic cancer patients with and without known primary site
- Chapter 6: A discussion of the conclusions, contribution and impact of this work

Chapter 2 : Research Objectives and Hypothesis

2.1 Overview

In this thesis, I plan to investigate the presence of CUP patients in Ontario. Population studies have been conducted on this group of patients, but are largely limited to the European context (8, 10, 19). To date, the largest CUP population described in Canada, consisting of 442 patients, was limited to a narrow definition of CUP (20).This population excluded several ICD codes which are routinely used to identify CUP populations. Considering the number of CUP cases reported in Europe (10, 19, 21) and the poor survival outcomes associated with CUP, this is a group that should be further investigated to improve current clinical practice.

The following research objectives (RO) structured the framework and analytical decisions of this work:

RO1: To identify a cohort of patients with CUP using Ontario administrative databases

RO2: To describe survival outcomes in Ontario CUP patients

RO3: To describe treatment utilization by CUP patients

RO4: To compare treatment utilization and survival of patients with metastatic cancer of known primary to CUP patients

These research objectives will be used to test the following hypotheses:

H1: CUP patients represent a significant metastatic cancer subgroup

H2: Survival will differ upon the localization of CUP metastases

H3: CUP patient survival will be lower than in patients with a metastatic cancer of known primary

H4: CUP patients are treated less intensely than patients with a known primary tumour

Chapter 3 : Identification and survival outcomes of a cohort of patients with cancer of unknown

3.1 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 (4). 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 (5). 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 (4). While CUP accounts for approximately 3% to 5% of all incident cancers, it ranks among the top five causes of cancer deaths worldwide (1, 22).

Currently, little is known about the biology of CUP (1). Epidemiological analyses of CUP cases have identified clinicopathological features, including sex, sites of the metastatic tumour and histopathology, that predict a favourable prognosis (22-24). About 20% of CUP patients belong to favourable subsets and respond well after receiving site-

specific therapies (1, 4, 17). However, the majority of CUP patients do not fit into a favourable subset and present with metastatic cancer of major organs and multiple metastases (11). While median survival in the unfavourable subgroup is under one year, prolonged survival in the favourable subgroup can extend beyond 13 years (11, 17).

In this study, I identify a cohort of CUP patients in Ontario, Canada, using provincial registries and administrative databases. I describe patient characteristics and examine overall survival using subgroups defined by histology and metastatic site. Population based studies on CUP patients are common in the European context (8, 10, 25-27), but are less studied in Canada (20, 28).

3.2 Materials and Methods

3.2.1 Data Sources

I 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, I 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(29).

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.

3.2.2 Identification of CUP Population

I identified patients using the OCR and the SDS/DAD database. I 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). I used the SDS/DAD database to verify CUP diagnosis and inclusion in the cohort. I 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. I 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 3-1).

I 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". I obtained survival data from the OCR, spanning the study period with 5 year follow up.

3.2.3 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, the date of diagnosis was the start date for survival analysis and the primary endpoint of this analysis was overall survival (OS). I used the log-rank test to assess the difference between survival curves of metastatic site and histology. I obtained hazard ratios (HRs) and 95% confidence intervals using multivariate Cox regression analyses adjusted for age and sex. A forward selection approach was used to construct models. Time dependant variables were used to test the proportional hazards assumption. In all cases the variables returned $p>0.05$. 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.

3.3 Results

Patient and tumour characteristics are summarized in Table 3-1. 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, adenocarcimona 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 3-2). 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 3-1). 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 3-2).

Only patients with confirmed histology were subject to the following analysis. This was done in order to remove any patients who were potentially not subject to appropriate diagnostic work-up and therefore may not constitute CUP patients. The Kaplan-Meier curves of OS are shown in Figure 3-3. 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%.

I stratified OS estimates by histology (Figure 3-4). Generally, patients with squamous cell carcinoma had higher one- and three-year OS within each metastatic site (Table 3-4). 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.

3.4 Discussion

I identified a cohort of CUP patients in Ontario by cross-validating data from the OCR and the SDS/DAD database. This work revealed that CUP patients in Ontario represent a significant portion of all metastatic cancers, accounting for approximately 6.8% of the total. I analyzed five-year survival as well as one-year and three-year hazard ratios (HR) subgrouped by metastatic site and histology. I 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. This CUP cohort is smaller than those of large, European-based population studies of CUP with sample sizes ranging from 18,911 to 57,638 (10, 19, 26). However, this work encompassed a six-year period, whereas these studies included 21 (10) to 47 (26) years of observations. As a consequence, this 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 (19, 26). Even without those CUP cases, this 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 (5, 8, 26) as well as decrased survival in respiratory/digestive CUP patients (30). This 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 I observed a one-year survival of 13.7% (n=349) for unspecified site CUP patients (10). 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.

This Ontario patient population was similar to a previously described CUP population based in Alberta, Canada (28). The Alberta population had a mean age of 68, was 50% male and with 50% having well differentiated carcinomas, 31% unspecified carcinoma, 6% squamous cell carcinoma and 8 % undifferentiated. These patient characteristics are nearly identical to those found in the Ontario population. However in the Alberta study characteristics including comobidity scores, performance status and number of metastatic sites were available. The use of therapeutic treatment was also described, with 55% of CUP patients undergoing no treatment. Evaluating the treatment received by the Ontario population is natural extension of this work and will aid in understanding how current clinical practice may differ across Canada. Several different time frames have been used when calculating HRs for population based CUP cohorts. For example, Hemminki *et al.* used a 1-year window (10); Kaaks *et al.* and Schaffer *et al.* used a 2-year windows (12, 31); Seve *et al.* used a 3-year window (28) while others have used windows (30, 32, 33). For this study we choose 1 and 2 year windows, which are within ranges considered in past studies.

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 (32). 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 (1). These favourable subgroups often present in such a way that a potential originating malignancy is suggested, directing therapeutic treatment (34).

Historically, therapeutic guidelines for CUP patients have recommended the use of platinum-based chemotherapy (5, 18, 35). Although targeted treatments may be available for some subgroups of patients, platinum-based chemotherapy is often recommended to accompany such treatment (11). For the majority of CUP patients, a platinum-based doublet regimen is often prescribed (3). A recent systematic review of the unfavourable subset of CUP has raised questions about current clinical practice (16). 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 (16). Future analyses describing treatment received by this study cohort is warranted to describe the Canadian clinical practice.

Fifty-one percent of this 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 (8, 9). 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 (18). 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 (16, 36). 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 (16).

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.

Table 3-1. Characteristics of patients with cancer of unknown primary by age, gender, site of secondary malignancy, histology and method of diagnostic confirmation (n=1743)

Patient characteristic	n (%)
Age	69
Male	49.7%
Site	
Secondary and unspecified malignant neoplasm of lymph nodes (196/C77)	191 (11.0)
Secondary malignant neoplasm of respiratory and digestive systems (197/C78)	746 (42.8)
Secondary malignant neoplasm of other specified sites (198/C79)	457 (26.2)
Malignant neoplasm without specification of site (199/C80)	349 (20.0)
Histology	
Adenocarcinoma	939 (53.9)
Squamous cell carcinoma	173 (9.9)
Unspecified carcinoma	475 (27.3)
Undifferentiated	139 (8.0)
Other*	17 (1.0)
Diagnostic conformation method	
Histology	1075 (61.7)
Cytology	341 (19.6)
Operation	194 (11.1)
X-Ray	117 (6.7)
Unknown	10 (0.6)
Judgement or autopsy	6 (0.4)

*Other includes sarcoma, lymphoma, other hematologic, melanoma and other specified carcinoma

Table 3-2. One-year hazard ratio (HR) by gender and age group.

		n	HR	*P*-value
Gender				
	Male	867	1.06	0.2850
	Female	876	1.00	*ref*
Age at diagnosis				
	<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	*ref*

ref = Reference group used for hazard ratio calculation

Table 3-3. Cross-tabulation of patients secondary malignancy site by histology (n=1726)

	Nodal CUP (196/C77)	Respiratory/digestive CUP (197/C78)	Other specified sites CUP (198/C79)	Unspecified site CUP (199/C80)
Adenocarcinoma	54	504	200	181
Squamous cell carcinoma	91	16	47	19
Unspecified carcinoma	41	173	154	107
Undifferentiated	<5 ǂ	47	51	38
Total	186-191ǂ	746	457	349

ǂ Cell sizes <5 cannot be reported following cd-link guidelines

Table 3-4. One-year (1 y) three-year (3 y) survival (%) and the 1 year hazard ratio (HR) stratified by patients secondary malignancy site and histology (n=1726)

	Nodal CUP (196/C77)				Respiratory/digestive CUP (197/C78)				Other specified sites CUP (198/C79)				Unspecified site CUP (199/C80)			
	1 y	3 y	HR	*P*-value	1 y	3 y	HR	*P*-value	1 y	3 y	HR	*P*-value	1 y	3 y	HR	*P*-value
Adenocarcinoma	35.7	13	0.50	0.0002	7.9	3	1.20	0.0486	11.5	4	0.90	0.3383	13.7	5	1.00	n/a
Squamous cell carcinoma	77.7	59	0.40	0.0201	0	0	3.88	0.0025	51	26.5	1.03	0.9474	52.6	31.6	1.00	n/a
Unspecified carcinoma	33.3	31	0.40	<.0001	5.2	ǂNR	0.94	0.619	13.5	5.1	0.59	<.0001	3.7	ǂNR	1.00	n/a
Undifferentiated			ǂNR		4.3	0	0.86	0.5155	17.7	5.9	0.50	0.0027	0	0	1.00	n/a
Total	56.1	40			6.8	2.4			17.9	8			11.1	4.6		

*Other includes sarcoma, lymphoma, other hematologic, melanoma and other specified carcinoma

ǂNR = Not reported due to cd-link guidelines

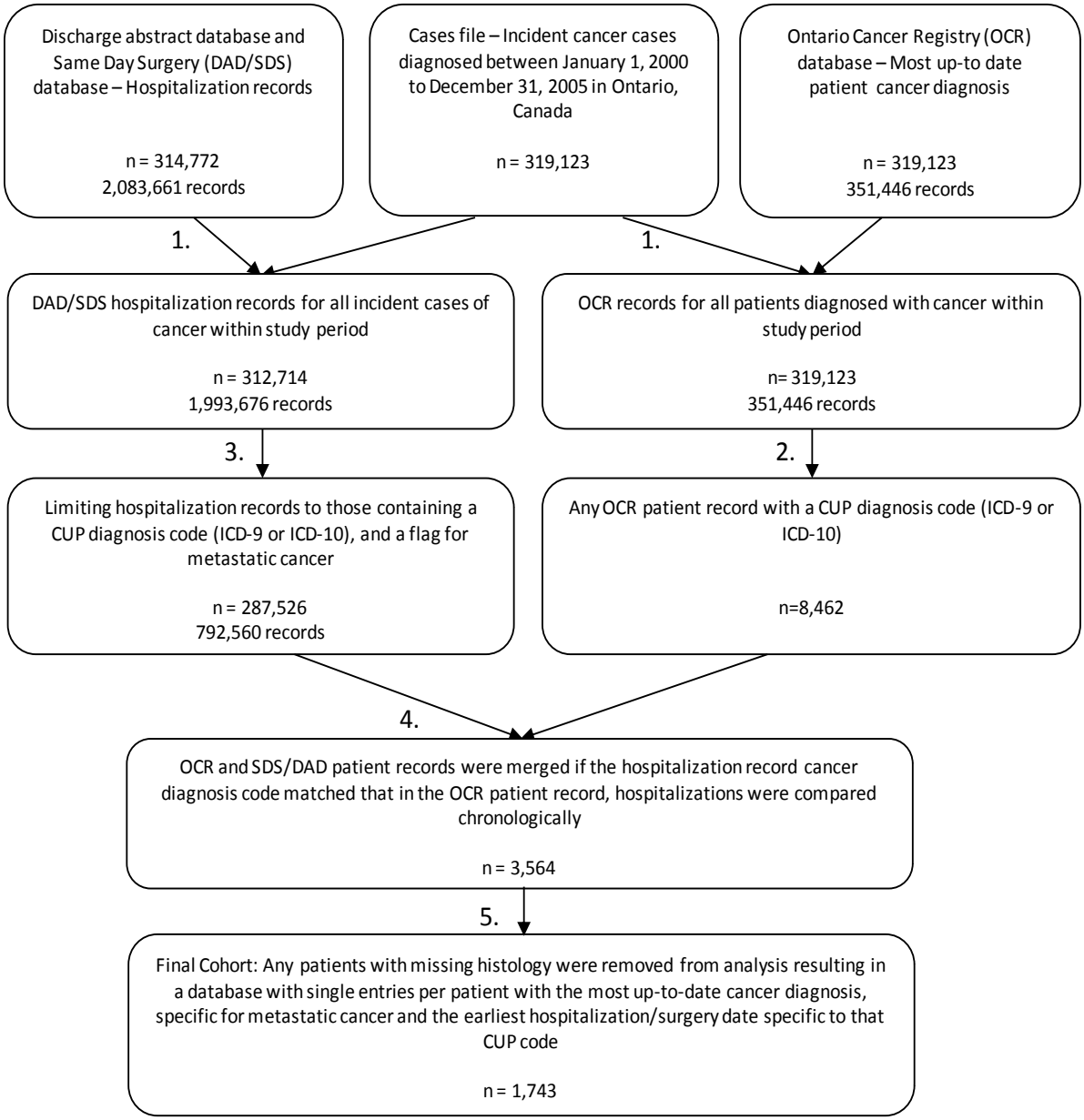

Figure 3-1. Cohort identification flowchart

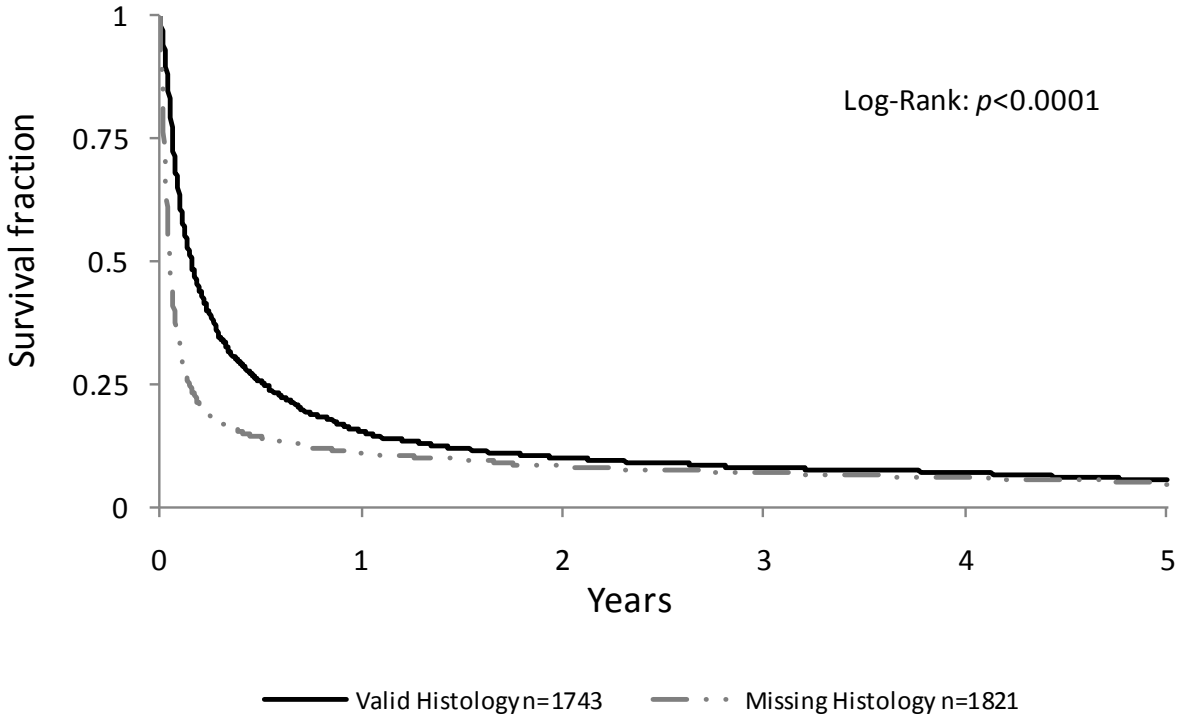

Figure 3-2. Kaplan-Meier survival curves for CUP patients with a valid histology or missing histology. CUP, cancer of unknown primary.

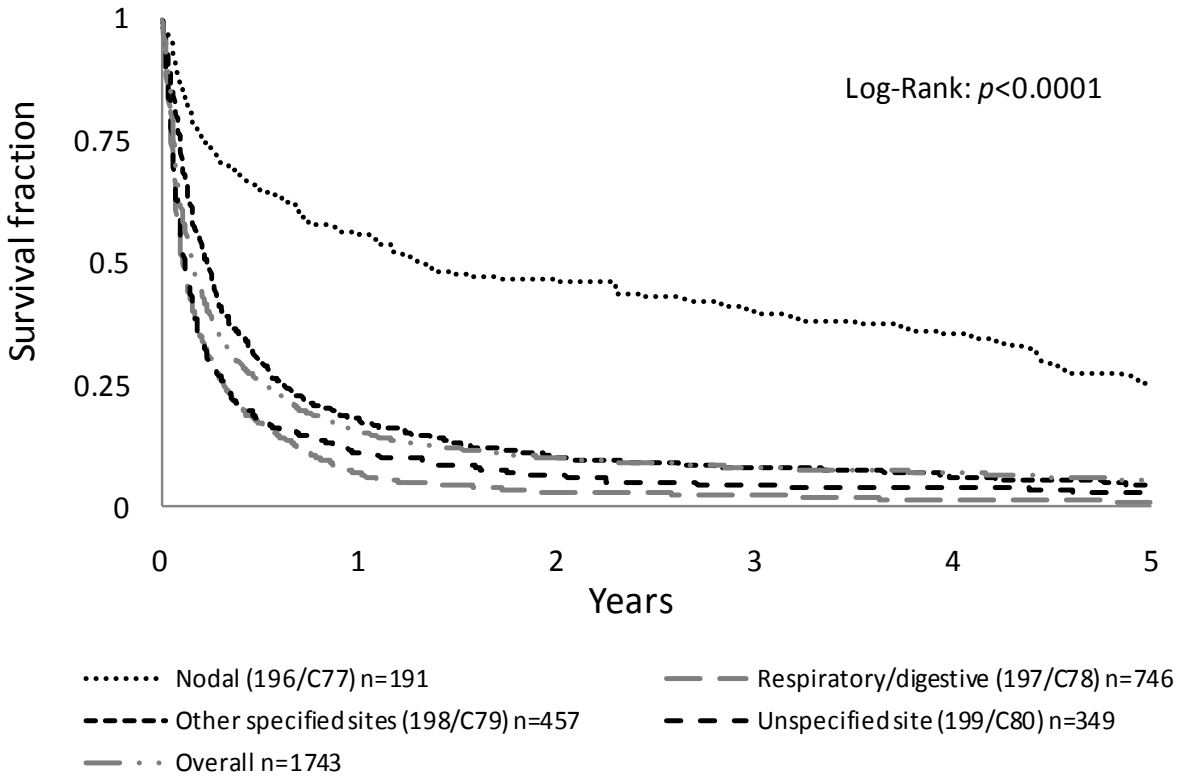

Figure 3-3. Kaplan-Meier survival curves for patients with CUP coded as 196, 197, 198 or 199. CUP, cancer of unknown primary.

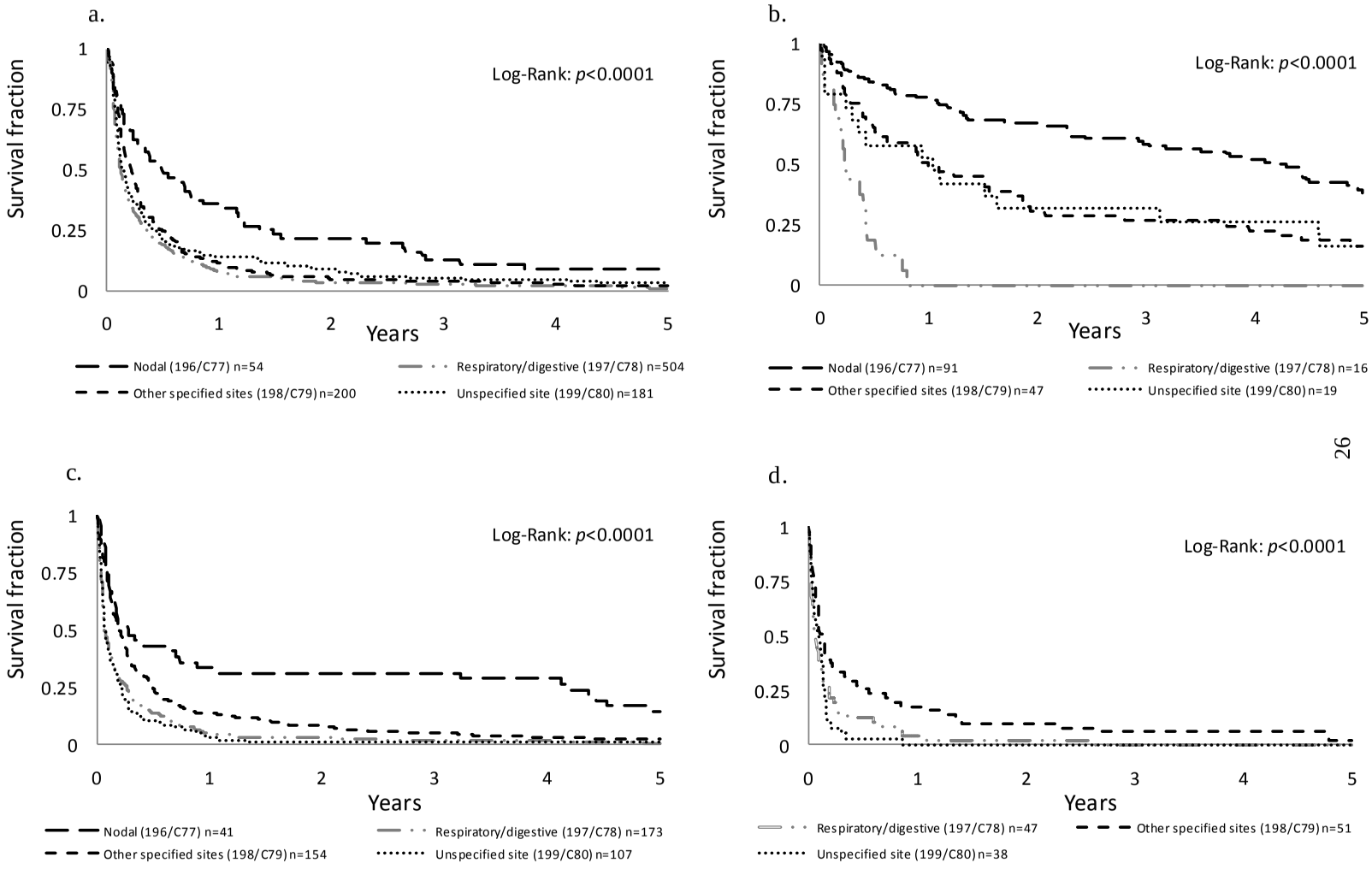

Figure 3-4. Kaplan–Meier survival curves of CUP patients with (a) adenocarcinoma, (b) squamous cell carcinoma , (c) unspecified carcinoma or (d) undifferentaied histology. CUP, cancer of unknown primary.

Chapter 4 : Comparison of survival outcomes for metastatic tumour of known primary versus cancer of unknown primary

4.1 Background

When metastatic tumours are present without an identifiable originating tumour, patients are diagnosed with a cancer of unknown primary (CUP). Ideally, patients undergo standard diagnostic workup before such a diagnosis can be made (18). Most importantly, the cancer should be histologically confirmed to be regarded as a CUP (8). One identifying characteristic in a majority of these patients is a poor prognosis and median survival is often estimated at less than 12 months (5, 10, 16). Worldwide estimates of CUP incidence vary by nation, but is generally thought to account for 3-5% of all incident cancers (4, 35).

No common underlying biological factor connects CUP patients (4). Therefore it is best described as a heterogeneous patient group categorized by an occult primary tumour. Given this loose association, methods to identify the primary tumour have been at the core of this patient population. Recently, the use of genomic assays to predict a primary tumour site has been at the forefront of CUP research. One of the largest clinical trials to date (n=252) used the predictive findings to administer assay-directed therapy (37). Overall median survival was 12.5 months, with some tumour types seeing a 29.6 month overall survival. While it is well documented CUP patients have poor survival outcomes, there is little data comparing CUP patients to metastatic cancer patients with a known primary site.

Recently I have identified a CUP population in Ontario, Canada (see Chapter 3). Metastatic tumour site was a significant predictor of survival outcomes: CUP patients in

which metastases were isolated to nodal regions had a 1-year survival of 56.1%, whereas patients with respiratory/digestive metastases had a 1-year survival of 6.8%. CUP patients with isolated nodal region metastases often fall into a subgroup deemed the favourable CUP subgroup, due to extended survival and increased treatment response (11, 18). These patients may have superior survival due to their tumour site suggesting a primary tumour, resulting in directed treatment including surgery or radiation. To investigate the survival differences between CUP and known primary metastatic cancer patients I sought to identify all metastatic cancer patients in Ontario, Canada. Using administrative databases I describe this cohort of patients and compare patient characteristics, tumour characteristics, overall and subgroup survival to an Ontario CUP population previously described (Chapter 3).

4.2 Methods and Materials

4.2.1 Data Sources

The Ontario Cancer Registry (OCR) and the Canadian Institute for Health Information (CIHI) Same-Day Surgery and Discharge Abstract Database (SDS/DAD) were used in this study. The OCR, an administrative database held by Cancer Care Ontario (CCO), combines patient information from existing CCO information, hospital pathology reports, Registrar General of Ontario and hospitalization records with a cancer diagnosis. The SDS/DAD database documents any Ontario hospital stay (DAD) or surgical procedure (SDS) performed in Ontario.

Access to these databases was granted through a Data Use Agreement (DUA) with the Ontario Cancer Data Linkage project (cd-link). This project allows academic investigators access to de-identified patient level information. The information is

processed at the Institute for Clinical Evaluative Sciences using encrypted health card numbers. Ethics approval was obtained prior to accessing these databases.

4.2.2 Ontario Cancer of Unknown Primary and Ontario Metastatic Tumour of Known Primary Population

Two distinct populations are described in this research:

1. An Ontario CUP population (Chapter 3)
2. A novel Ontario metastatic cancer of known primary site cohort.

Using the OCR, SDS/DAD and a cases database provided through cd-link a novel linkage strategy was employed to identify patients with a metastatic tumour of known primary tumour site from January 1, 2000, to December 31, 2005 (Figure 4-1). The cases database contained all individuals who were diagnosed with cancer within the study period. The SDS/DAD database was first merged with a cases database (Step 1, Figure 4-1). Using the SDS/DAD-cases database (Step 3, Figure 4-1), any patient with a hospitalization record with an ICD-10 code matching a cancer diagnosis was identified. The OCR database provided information about the primary tumour site, but did not distinguish if the malignancy was metastatic. The OCR database was also merged to the cases database (Step 2, Figure 4-1). Using the OCR-cases database (Step 4, Figure 4-1), all patients with an ICD-10 code indicating an incident cancer diagnosis during the study period were identified. Patient identification numbers that matched between these cohorts were used to cross validate their cancer diagnosis (Step 5, Figure 4-1). Only patients with matching ICD-10 codes were retained. Finally, using a metastatic cancer flag held within the SDS/DAD database, any non-metastatic cancer patients were removed from the cohort (Step 6, Figure 4-1). Patients were also removed if no histology was present or if their diagnosis changed within 60 days of their initial workup. Histological codes were

grouped using the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) from the OCR.

4.2.3 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, the date of diagnosis was the start date for survival analysis and the primary endpoint of this analysis was overall survival (OS). I used the log-rank test to assess the difference between survival curves of metastatic site and histology. I obtained hazard ratios (HRs) and 95% confidence intervals using multivariate Cox regression analyses adjusted for age and sex. A forward selection approach was used to construct models. Time dependant variables were used to test the proportional hazards assumption. In all cases the variables returned $p>0.05$. 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.

4.3 Results

I identified 47,090 patients who were metastatic at the time of diagnosis from January 2000 to December 2005 with confirmed histology and whose diagnosis remained constant during this period. Of these patients 45,347 (96.3%) had an identifiable primary site. The remaining 1,743 patients (3.7%) were diagnosed with cancer of unknown primary (CUP; Table 4-1). Among the main metastatic sites, CUP ranks as the sixth largest group behind gastrointestinal (n=16,308), respiratory (n=12,166), breast (n=8,453), gynecological (n=2,637) and urological (n=2,230).

These patients also differed significantly in their tumour specific characteristics. I found the distribution of histological cell types to differ significantly ($p<0.0001$). CUP

patients had a smaller proportion of adenocarcinoma (53.9%) and larger proportion of other histologies (36.2%) than known primary metastatic cancers (71.6%, 20.8% respectively). CUP patients also differed significantly in their distribution of diagnostic confirmation method ($p<0.0001$). These patients had fewer tumours confirmed via histology (61.7%) than known primary patients (87.4%) and many more tumours confirmed via operation (11.1% vs. 1.6%). CUP patients were the oldest group at 69.4 years at diagnosis. Known primary patient average diagnosis age ranged from 45.1 years for endocrine tumours to 67.7 years for brain tumours (Table 4-2).

Overall median survival of CUP patients was poor at 1.9 months compared to 11.9 months for all known primary cancer patients (Table 4-3). Of known primary sites, metastatic liver cancers had the lowest median survival (2.9 months) and breast cancer had the highest median survival (>60 months). I computed 2-year HR's, overall survival and survival by histology subgroup using CUP as the baseline hazard for each comparison. All known primary sites combined had a 2-year HR of 0.49 ($p<0.0001$). Nearly all main primary sites had significantly lower hazard than CUP with all histology's considered. This trend was also seen in the adenocarcinoma only comparison, however the HR's tended to be even smaller. When I compared squamous cell carcinoma only, all known primary tumours combined had a 2-year HR of 2.04 ($p<0.0001$) and no main primary site had a significantly lower HR. Known primary tumours with an other histology tended to be significantly lower than CUP patients with an other histology. Survival is shown over a 5-year period for CUP patients and all known primary tumour patients (Figure 4-2) and general primary tumour sites (Figure 4-3).

4.4 Discussion

I identified 47,090 metastatic cancer patients in Ontario, Canada. This patient population contained a CUP cohort I had previously described (Chapter 3) and the first description of all metastatic cancer patients of known primary in Ontario. I observed CUP as the sixth largest group of metastatic cancers between January 2000 and December 2005 in Ontario. I found that knowledge of the primary tumour site was associated with longer median survival, 11.9 months compared to 1.9 months when the primary site was unknown. I also described a novel linkage strategy independently surveying the OCR and the SDS/DAD.

I observed a decline in cases of metastatic cancer of known primary from a high of 8,960 patients in 2000 to a low of 6,345 patients in 2005. The American National Center for Health Statistics reported a drop in the incidence of all cancers between 1999-2005 (38). These data coupled with advances in cancer diagnostics and aggressive screening programs could explain this reduction in the number of patients who are metastatic at the time of diagnosis.

The increased survival observed in patients with metastatic cancer of known primary site versus CUP may be attributable to several factors. First, treatment may be more common in patients with a known primary site. Second, knowledge of the primary site may significantly alter clinical decision making. Third, CUP patients also tend to be older than patients with a known primary. The advanced age of CUP patients may be correlated to comorbidities, decreasing the likelihood of therapeutic intervention. Finally, a large percentage of the known primary metastatic tumours are breast cancer (n=8,453). This patient subgroup had the best survival outcome (median survival >60 months). This

is likely due to frequent screening and treatment found within this patient population (39).

Not all CUP patients had worse survival than those with a known primary site. In particular, CUP squamous cell carcinoma patients had a lower 2-year HR than all squamous cell carcinoma patients with a known primary tumour (HR=2.04, $p<0.0001$). Two factors drove this result. First, of the 3,452 patients with a known primary squamous cell carcinoma, 50.2% (n=1,771) had non-small cell lung cancer. This subgroup has been established to have poor outcomes with a five year survival of 11% (40). Second, I found metastatic cancer subgroups with a median survival above 20 months to be uncommon. However, I previously reported a median survival of 20.4 months in Ontario CUP squamous cell carcinoma patients (Chapter 3).

While I am confident in the survival differences between these two patient populations, these results cannot be directly extrapolated to CUP patients in which a primary tumour is identified. This work provides no direct evidence that identification of a primary tumour is synonymous with increased survival. However, when these results are taken together with increasing evidence found in genomic assays, this conclusion becomes plausible. As previously mentioned, the use of genomic assays in CUP patients found a median overall survival of 12.5 months (n=252), similar to the all known primary tumour overall survival of 11.9 months (n=45,347) (37). These results aid the conclusion that the identification, or alternatively, treatment based on predictive primary tumours provides survival benefit.

Overall, CUP patients have worse survival than patients with metastatic cancers of known primary site. Determining the value of identifying the putative primary tumour

site will be an important topic of research for CUP patients. Likewise, understanding fundamental differences between CUP patients and metastatic cancer of known primary patients may explain the survival differences I have observed. Investigating the role of treatment and treatment intensity may provide better insights into the key difference between these patient groups.

Table 4-1. Characteristics for patients with metastatic tumours of known primary (n=45,347) and CUP patients (n=1,743)

	All Known Primary		CUP		
	n	%	n	%	p-value
Total n	45,347	100	1743	100	
Age (average)	63.7		69.4		<0.0001*
<39	2,045	4.5	31	1.78	<0.0001**
40-49	5,109	11.3	109	6.3	
50-59	9,165	20.2	235	13.5	
60-69	11,814	26.1	399	22.9	
70-79	11,998	26.5	575	33.0	
>80	5,216	11.5	394	22.6	
Gender					
Male	19,946	44.0	867	49.7	<0.0001*
Female	25,401	56.0	876	50.3	
Year of diagnosis					
2000	8,960	19.8	341	19.6	0.230**
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					
Adenocarcinoma	32,450	71.6	939	53.9	<0.0001**
Squamous cell carcinoma	3,452	7.6	173	9.9	
Other[1]	9,445	20.8	631	36.2	
Diagnostic method					
Autopsy	46	0.1	<5[i]		<0.0001**
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[2]	1,023	2.3	132	7.6	
Main Primary Site					
Gastrointestinal	16,308	34.6	-		
Respiratory	12,166	25.8	-		
Breast	8,453	18.0	-		
Gynecological	2,637	5.6	-		
Urological	2,230	4.7	-		
Head and neck	1,049	2.2	-		
Endocrine	722	1.5	-		
Sarcoma	697	1.5	-		
Lymphoma	574	1.2	-		
Melanoma of the skin	416	0.9	-		
Leukemia	30	0.1	-		
Brain	14	0.0	-		
All other[3]	51	0.1	-		

[1]Includes: Unspecified carcinoma, undifferentiated, sarcoma, lymphoma, other hematologic, melanoma and other specified carcinoma

[2]Includes: Unknown and pathology report outside of country

[3]Includes: Bone joints, soft tissue heart, eye adnexa and ill defined sites.

[i]Cells containing less than 5 patients not reported in accordance with the cd-link DUA

*_t_-test

Table 4-2.Patient and tumour characteristics for metastatic cancer patients with known primary and CUP stratified by cell type

Primary Tumour Site	n (%)	Mean Age	Male (%)	Histology					
				Adenocarcinoma (%)		Squamous Cell (%)		Other (%)	
Gastrointestinal	**16,308**	**66.7**	**56.5**	**15,219**	**93.3**	**307**	**1.9**	**782**	**4.8**
Colorectal	10,506	67.3	54.3	10,192	97.0	55	0.5	259	2.5
Stomach	2,133	65.8	64.7	2,025	94.9	14	0.7	94	4.4
Pancreas	1,853	65.5	53.9	1,562	84.3	<5‡	0.1-0.3	286-290	15.4-15.7
Esophagus	683	64.3	78.9	413	60.5	223	32.7	47	6.9
Gall bladder	272	68.6	30.9	225	82.7	8	2.9	39	14.3
Small intestine	262	62.8	57.6	250	95.4	<5‡	0.4-1.9	11-15	4.2-5.7
Liver[1]	193	62.9	71.5	182	94.3	0	0.0	11	5.7
Other gastrointestinal[2]	406	66.0	51.2	370	91.1	<5‡	0.2-1.2	31-35	7.6-8.6
Respiratory	**12,166**	**65.8**	**56.2**	**4,694**	**38.6**	**1,77**	**14.6**	**5,701**	**46.9**
Non-small lung	9,314	65.6	56.6	4,522	48.6	1,73	18.6	3,058	32.8
Small lung	2,816	66.5	55.0	164	5.8	25	0.9	2,627	93.3
Other respiratory[3]	36	60.6	63.9	8	22.2	12	33.3	16	44.4
Breast	**8,453**	**57.8**	**0.8**	**8,291**	**98.1**	**15**	**0.2**	**147**	**1.7**
Gynecological	**2,637**	**63.4**	**0.0**	**2,206**	**83.7**	**214**	**8.1**	**217**	**8.2**
Ovarian	1,991	64.0	0.0	1,806	90.7	13	0.7	172	8.6
Uterine	379	64.9	0.0	352	92.9	6	1.6	21	5.5
Cervical	171	52.3	0.0	43	25.1	114	66.7	14	8.2
Other gynecological[4]	96	65.5	0.0	5	5.2	81	84.4	10	10.4
Urological	**2,230**	**66.4**	**80.9**	**1,450**	**65.0**	**41**	**1.8**	**739**	**33.1**
Prostate	845	73.3	99.9	737	87.2	<5‡	0.1-0.6	107-111	12.7-13.1
Kidney renal pelvis	835	63.2	66.0	683	81.8	9	1.1	143	17.1
Bladder	397	69.3	66.3	27	6.8	29	7.3	341	85.9
Other urological[5]	153	38.6	94.8	<5‡	0.7-3.3	<5‡	0.7-3.3	148	96.7
Head and neck	**1,049**	**58.9**	**75.6**	**71**	**6.8**	**910**	**86.7**	**68**	**6.5**
Pharynx	393	55.9	77.4	<5‡	0.3-1.3	341	86.8	45-49	11.5-12.5
Larynx	116	62.6	82.8	<5‡	0.9-4.3	111-	95.7-99.1	0	0.0
Other head and neck[6]	540	60.2	72.8	64	11.9	456	84.4	20	3.7
Endocrine	**722**	**45.1**	**36.8**	**507**	**70.2**	**166**	**23.0**	**49**	**6.8**
Thyroid	680	44.4	35.7	480	70.6	163	24.0	37	5.4
Other endocrine[7]	42	55.0	54.8	27	2.4-11.9	<5‡	19.0-28.6	10-14	23.8-33.3
Sarcoma	**697**	**51.3**	**47.1**	**0**	**0.0**	**0**	**0.0**	**697**	**100.0**
Lymphoma	**574**	**65.1**	**57.0**	**0**	**0.0**	**0**	**0.0**	**574**	**100.0**
Non-Hodgkin's lymphoma	527	66.7	55.4	0	0.0	0	0.0	527	100.0
Other lymphoma[8]	47	46.9	74.5	0	0.0	0	0.0	47	100.0
Melanoma of the skin	**416**	**57.2**	**63.0**	**0**	**0.0**	**0**	**0.0**	**416**	**100.0**
Leukemia	**30**	**65.0**	**63.3**	**0**	**0.0**	**0**	**0.0**	**30**	**100.0**
Brain	**14**	**67.7**	**21.4**	**<5‡**	**7.1-35.7**	**0**	**0.0**	**9-13**	**64.3-92.9**
All other[9]	**51**	**63.2**	**56.9**	**10**	**19.6**	**28**	**54.9**	**13**	**25.5**
All Known Primary	**45,347**	**63.7**	**44**	**32,450**	**71.6**	**3,45**	**7.6**	**9445**	**20.8**
CUP	**1,743**	**69.4**	**49.7**	**939**	**53.9**	**173**	**9.9**	**631**	**36.2**

[1]Includes hepatocellular and non-hepatocellular; [2]Includes biliary tract, bile duct, mesothelioma, retroperitoneum , peritoneum other and ill-defined digestive organs; [3]Includes nasal cavity, middle ear, accessory sinuses, trachea, ill-defined respiratory and mesothelioma; [4]Includes vulva, vaginal and placenta; [5]Includes testicular germcell, testicular non-germcell, ureter and other and unspecified sites of male genitals; [6]Includes salivary gland and ill-defined head and neck; [7]Includes thymus, adrenal gland and other endocrine glands; [8]Includes lymphoid and other haematopoietic; [9]Includes eye adnexa, independent (primary) multiple sites, soft tissue heart, bone and articular cartilage of limbs and other sites meninges, spinal cord, cranial nerves and other parts of the central nervous system

Table 4-3. Median survival and two year hazard ratios (HR) stratified by primary site and

Primary Tumour Site	Median survival (months)	All		Adenocarcinoma		Squamous cell carcinoma		Other	
		HR	p-value	HR	p-value	HR	p-value	HR	p-value
Gastrointestinal	**11.8**	**0.4**	**<.0001**	**0.2**	**<.0001**	**2.5**	**<.0001**	**1.0**	**0.8418**
Colorectal	20.4	0.2	<.0001	0.1	<.0001	1.5	0.0223	0.8	0.1021
Stomach	5.9	0.6	<.0001	0.4	<.0001	2.3	0.0048	0.9	0.4302
Pancreas	3.0	1.0	0.0734	0.7	<.0001	<5 ǂ		1.2	0.0007
Esophagus	4.6	0.8	0.0032	0.6	<.0001	3.0	<.0001	0.7	0.0711
Gall bladder	3.1	1.0	0.8203	0.7	<.0001	3.1	0.0033	1.2	0.1529
Small intestine	18.2	0.3	<.0001	0.2	<.0001	<5 ǂ		0.7	0.4223
Liver[1]	2.9	1.1	0.1828	0.7	0.0035	N/A*		1.3	0.3654
Other	6.7	0.6	<.0001	0.4	<.0001	<5 ǂ		0.8	0.3558
Respiratory	**3.7**	**0.7**	**<.0001**	**0.5**	**<.0001**	**2.7**	**<.0001**	**0.7**	**<.0001**
Non-small lung	3.7	0.8	<.0001	0.5	<.0001	2.8	<.0001	0.8	<.0001
Small lung	3.6	0.6	<.0001	0.3	<.0001	1.7	0.0296	0.7	<.0001
Other respiratory[3]	9.2	0.4	<.0001	0.3	0.0108	1.6	0.1486	0.4	0.0068
Breast	**N/A**	**0.1**	**<.0001**	**0.0**	**<.0001**	**0.6**	**0.3938**	**0.5**	**<.0001**
Gynecological	**19.6**	**0.3**	**<.0001**	**0.2**	**<.0001**	**1.7**	**<.0001**	**0.5**	**<.0001**
Ovarian	20.3	0.3	<.0001	0.2	<.0001	1.8	0.0819	0.4	<.0001
Uterine	18.3	0.3	<.0001	0.2	<.0001	3.4	0.0035	1.2	0.2618
Cervical	11.9	0.5	<.0001	0.2	<.0001	2.3	<.0001	0.6	0.1072
Other gynecological[4]	14.3	0.3	<.0001	0.2	0.0069	1.2	0.2567	0.4	0.0271
Urological	**9.8**	**0.4**	**<.0001**	**0.3**	**<.0001**	**2.9**	**<.0001**	**0.4**	**<.0001**
Prostate	15.3	0.2	<.0001	0.2	<.0001	<5 ǂ		0.3	<.0001
Kidney renal pelvis	5.7	0.6	<.0001	0.4	<.0001	4.9	<.0001	0.6	<.0001
Bladder	5.4	0.4	<.0001	0.7	0.2209	3.3	<.0001	0.4	<.0001
Other urological[5]	38.4	0.2	<.0001	<5 ǂ		<5 ǂ		0.2	<.0001
Head and neck	**25.1**	**0.2**	**<.0001**	**0.1**	**<.0001**	**0.9**	**0.867**	**0.2**	**<.0001**
Pharynx	36.5	0.2	<.0001	<5 ǂ		0.95	0.681	0.2	<.0001
Larynx	14.6	0.3	<.0001	<5 ǂ		1.26	0.142	0.2	<.0001
Other head and neck[6]	24.8	0.2	<.0001	0.1	<.0001	0.9	0.711	0.9	0.5669
Endocrine	**20.8**	**0.4**	**<.0001**	**0.2**	**<.0001**	**1.6**	**0.000**	**0.9**	**0.56**
Thyroid	22.6	0.4	<.0001	0.2	<.0001	1.7	0.000	0.9	0.9585
Other endocrine[7]	7.9	0.5	0.0035	0.3	<.0001	<5 ǂ		0.3	<.0001
Sarcoma	**9.2**	**0.4**	**<.0001**	**N/A***		**N/A***		**0.5**	**<.0001**
Lymphoma	**10.0**	**0.2**	**<.0001**	**N/A***		**N/A***		**0.3**	**<.0001**
Non-Hodgkin's	10.0	0.2	<.0001	N/A*		N/A*		0.4	<.0001
Other lymphoma[8]	11.5	0.3	<.0001	N/A*		N/A*		1.0	<.0001
Melanoma of the skin	**22.5**	**0.2**	**<.0001**	**N/A***		**N/A***		**0.2**	**<.0001**
Leukemia	**5.0**	**0.4**	**<.0001**	**N/A***		**N/A***		**0.4**	**0.0007**
Brain	**4.6**	**0.6**	**0.2052**	**<5 ǂ**		**N/A***		**1.0**	**0.7703**
All other[9]	**5.7**	**0.5**	**<.0001**	**0.9**	**0.7775**	**1.1**	**0.582**	**0.6**	**0.1057**
All Known Primary	**11.9**	**0.4**	**<.0001**	**0.2**	**<.0001**	**2.0**	**<.000**	**0.6**	**<.0001**
CUP	**1.9**	***ref***		***ref***		***ref***		***ref***	

[1]Includes hepatocellular and non-hepatocellular; [2]Includes biliary tract, bile duct, mesothelioma, retroperitoneum , peritoneum other and ill-defined digestive organs; [3]Includes nasal cavity, middle ear, accessory sinuses, trachea, ill-defined respiratory and mesothelioma; [4]Includes vulva, vaginal and placenta; [5]Includes testicular germcell, testicular non-germcell, ureter and other and unspecified sites of male genitals; [6]Includes salivary gland and ill-defined head and neck; [7]Includes thymus, adrenal gland and other endocrine glands; [8]Includes lymphoid and other haematopoietic; [9]Includes eye adnexa, independent (primary) multiple sites, soft tissue heart, bone and articular cartilage of limbs and other sites meninges, spinal cord, cranial nerves and other parts of the central nervous system

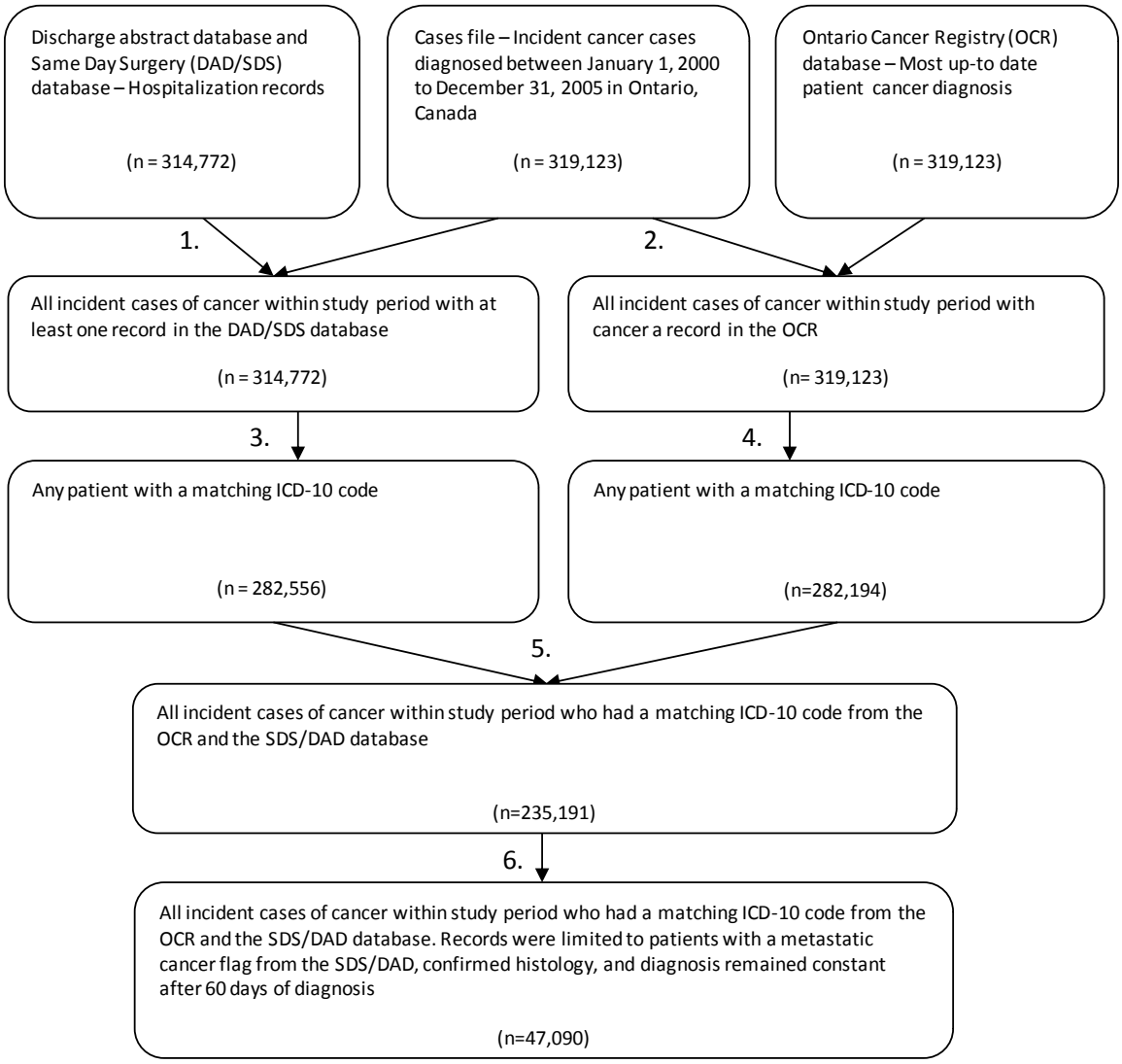

Figure 4-1. Cohort identification flowchart.

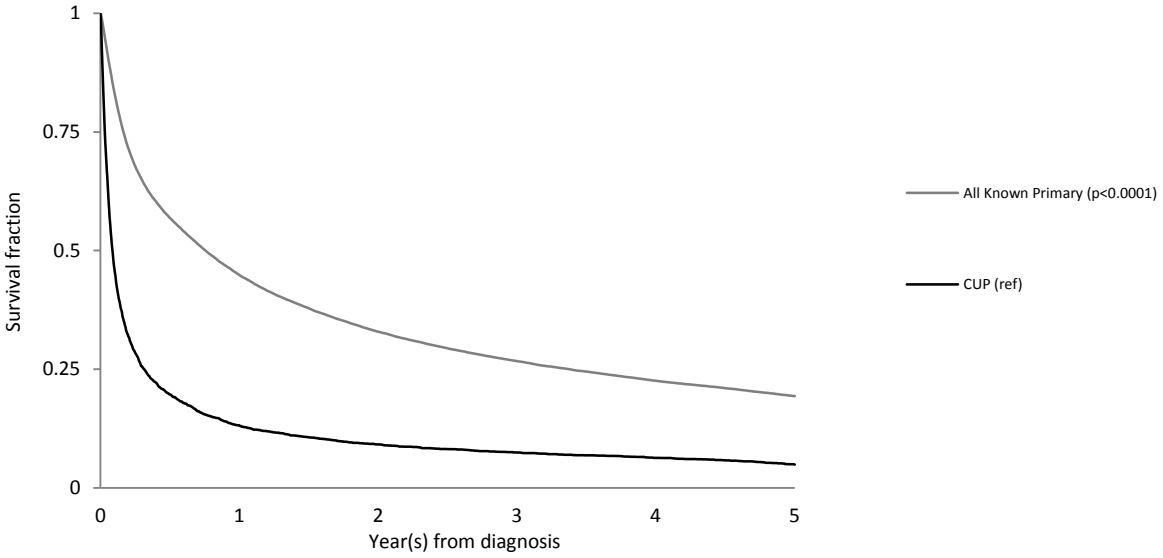

Figure 4-2. Kaplan-Meier 5 year survival curve for cancer of unknown primary (CUP) and all known primary tumour patients.

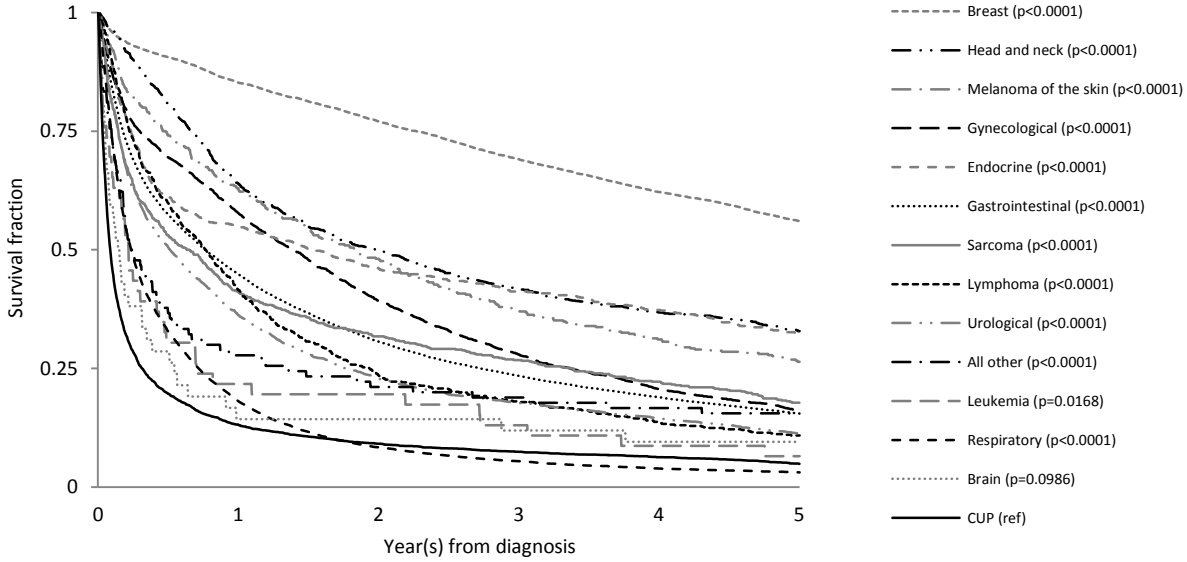

Figure 4-3. Kaplan-Meier 5 year survival curve for cancer of unknown primary (CUP) and all known primary tumour patients stratified by general primary site.

Chapter 5 : Treatment utilization and intensity for patients with metastatic cancer of known and unknown primary site

5.1 Background

In a majority of metastatic cancer patients the primary tumour is identified through the standard diagnostic workup. This is not the case for an estimated 3-5% of all incident cancers termed cancer of unknown primary (CUP) (1). Currently, the widely accepted definition of CUP requires the metastatic site tumour to be histologically confirmed (9). These patients are often typified with a poor prognosis, estimates of survival are often below one year (8, 10, 16).

Although clinical guidelines exist for this population, for an estimated 80% of patients the recommended treatment is a wide-spectrum empiric chemotherapy (5, 16, 18, 41). However, a synthesis of clinical trials involving CUP patients questioned the therapeutic benefit of chemotherapy (16). The authors found 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 multi-agent chemotherapy regimen over single agent treatment. These results are not entirely surprising as CUP is believed to represent a heterogeneous population of tumours rather than a single entity (6). The lack of progress in treatment information for the majority of CUP patients remains problematic for clinicians.

While population studies of CUP are common, the relationship between patient outcomes and treatment is scarce. A Canadian CUP population study found that 55% of patients did not receive any treatment, with younger age being significantly related to receiving treatment (28). In an American CUP population 79.7% of patients did not

receive radiation therapy and those that did were associated with longer life (9). Recently CUP patients and patients with a known primary tumour were identified from the Australian Government Department of Veterans' Affairs (DVA) (31). In this population 30% of CUP received treatment with a median survival of 37 days compared to 70% of known primary patients with a median survival of 310 days.

I attempt to address the limited information in CUP treatment by summarizing chemotherapy, radiation and surgeries undergone by Ontario metastatic cancer patients. I analyze two previously described cohorts: CUP and cancer of known primary site patients from Ontario, Canada (Chapters 3-4). I present whether or not treatment was administered, types of treatment, if multiple treatment types were used and survival/hazard ratios associated with those subgroups. I aim to identify treatment differences upon knowledge of the primary site, and how these patient groups differ in their response to various treatments.

5.2 Methods and Materials

5.2.1 Data Sources

Ontario residents diagnosed with cancer are tracked though the Ontario Cancer Registry. This database is updated annually by Cancer Care Ontario (CCO) and combines patient level data from multiple administrative sources. Tumour histology, date of death/cause (if applicable) and International Classification of Diseases 10^{th} revision code are available from this resource.

The Ontario Health Insurance Plan is a provincial health insurance plan administered by the Ministry of Health and Long-Term Care for residents of Ontario, Canada. OHIP is restricted to Canadian citizens, Permanent Residents or individuals with a work permit who solely or primarily reside in Ontario. Physician services are recorded

by OHIP on a fee-for-services basis and include consultations and visits, nuclear medicine, diagnostic imaging, radiation, treatment course planning, surgical procedures and drug administration. Fee codes are outlined in the Schedule of Benefits for Physician Services Ontario (SOB).

All Ontario hospital stays or same-day surgeries are recorded in the Canadian Institute for Health Information (CIHI) Same-Day Surgery and Discharge Abstract Database (SDS/DAD). This database records patient information and procedure/disease information for each hospital stay/surgery.

The Ontario Cancer Data Linkage project *"cd-link"* allowed us access to the aforementioned databases. Through a Data Use Agreement (DUA) I was given access to de-identified patient information processed by the Institute for Clinical Evaluative Sciences. Ethics approval was obtained prior to accessing these databases.

5.2.2 Study Population

I have previously described two metastatic cancer populations. An Ontario CUP population was identified from the OCR (Chapter 3). A second cohort of patients who were metastatic at the time of diagnosis was identified by merging the OCR and SDS/DAD hospitalization files (Chapter 4).

5.2.3 Treatment Data

Both study populations were merged with the OHIP database to obtain treatment data . I filtered this merged dataset to identify codes for surgery, chemotherapy or therapeutic radiation related to oncology.

5.2.4 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, the date of diagnosis was the start date for survival analysis and the primary endpoint of this analysis was overall survival (OS). I used the log-rank test to assess the difference between survival curves of metastatic site and histology. I obtained hazard ratios (HRs) and 95% confidence intervals using multivariate Cox regression analyses adjusted for age and sex. A forward selection approach was used to construct models. Time dependant variables were used to test the proportional hazards assumption. In all cases the variables returned $p>0.05$. 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.

5.3 Results

Table 5-1 shows characteristics of patients with a metastatic tumour of known primary (n=45,347) and CUP with confirmed histology (n=1,743). Patients with a known primary site were more likely to receive any treatment type (n=35,012; 77.2%) than patients with an unknown primary site (n= 891; 51.1%). CUP patients were most likely to receive a single type of treatment (73.1%), while known primary patients were more likely to receive two or three different types of treatment (55.3%). Patients with CUP who did or did not receive treatment were significantly older than their known primary counterparts ($p<0.0001$). CUP patients who received treatment were younger on average (67.7 years) than CUP patients who did not receive treatment (71.2 years). CUP patients who received treatment were more likely to have a squamous cell histology (16.2%) than CUP patients who did not receive treatment (3.4%).

I observed that receiving any treatment was associated with higher median survival. Patients with known primary tumours who received any treatment type had a

median survival of 19.0 months. Patients with known primary tumours who did not receive any treatment had a median survival of 2.2 months. A similar trend was observed in CUP patients with treated patients having a median survival of 3.6 months and non-treated patients having a 1.1 month median survival.

I compared two year hazard ratios (HR) for the each treatment type (Table 5-2). CUP patients who received no treatment were used as the baseline hazard for each set of comparisons. For radiation, chemotherapy and surgeries I observed the following trends. First, receiving treatment was associated with better survival for CUP and known primary patients. In all cases the HR in the untreated groups were higher than the treated groups. Second, HR's decreased with more intensive treatment. Third, even with comparable treatment, CUP patients had worse survival outcomes than patients with a known primary. For example, I compared patients who received no surgery, a single surgery or two or more surgeries. The resulting two year HR's were 1.00 (*ref*), 0.82 (p=0.0077) and 0.48 (p<0.0001) in CUP patients but 0.51 (p<0.0001), 0.34 (p<0.0001) and 0.25 (p<0.0001) in the known primary group.

I investigated survival outcomes associated with the use of more than one type of therapy. CUP patients administered any single treatment saw an increased survival over CUP patients receiving no treatment (Figure 5-1; Table 5-2).The two year HR's for surgery only 0.54 (p<0.0001), chemotherapy only 0.42 (p<0.0001), and radiation only 0.36 (p<0.0001) reflect this increase. The addition of a second therapy was associated with further survival benefit. All three therapies in tandem were no worse than any two therapies. Two year HR's followed a similar trend for patients with a known primary site, though more pronounced.

I investigated any differences when treatment was administered between these two patient populations. Figure 5-3 shows the proportion of patients divided into three groups: treatment received within 6 months of diagnosis, treatment received after 6 months of diagnosis or no treatment received. These were then plotted by patient survival groups in 6 month increments. Patients with known primary site who survived longer were more likely to receive treatment than those who died earlier. The proportion of known primary patients who received no treatment decreases from over 60% of patients surviving up to 6 months to only 5% of patients surviving more than 60 months. The increase in the proportion of patients who received treatment within 6 months of diagnosis largely accounted for this change, starting at 34.2% at 6 month survival and growing to 85.6% at over 60 month survival. Among CUP patients, survival did not appear to have any relation to first treatment date. The proportion of CUP patients who did not receive any treatment remains above 50% for the majority of patient survival length. The pre-six month treatment and post-six month treatment groups also maintain a consistent proportion over patient survival length.

5.4 Discussion

To my knowledge this work represents the first direct comparison of treatment utilization in CUP patients and metastatic cancer of known primary patients in the general population. Using two previously described patient populations, I have described the treatment received by CUP and metastatic cancer of known primary patients in Ontario, Canada (Chapter 3 and 4). Only 22.8% of metastatic cancer of known primary patients did not receive any of the treatments types studied, whereas 48.9% of CUP patients did not receive any treatment. I found that receiving any treatment was

associated with survival benefit in both patient populations. I was able to show that early treatment was correlated with extended survival in known primary patients but was largely independent of survival in CUP patients.

Our estimate of the proportion of metastatic cancer patients of known primary not receiving treatment is similar to what has been described elsewhere. A study of the American National Cancer Database for 8 common solid tumour types found 20.6% (n=159,284) of all patients across all types of tumours did not receive any treatment (42). The authors attributed most non-treatment to poor functional status, comorbidities and patient preference. Given the high proportion of CUP patients who did not receive any treatment coupled with their poor prognosis and diminished median survival, these characteristics are likely to describe a significant proportion of the CUP patient population. The addition of comorbidities in the CUP and known primary patient population would likely reveal one additional factor associated with treatment differences.

Methodologically this work is similar to an Australian comparison between CUP patients and known primary tumour patients (31). However, I obtained my cohort from the general population whereas the Australian work surveyed the Australian Government Department of Veterans' Affairs (DVA). Despite this difference, several key findings were similar. Both studies found CUP patients are less likely to be treated than patients with known primary, Schaffer *et al.* observed 30% CUP treated and 70% of known primary treated; the corresponding figures I found were 51.1% and 77.2% respectively. Both studies also observed poor survival among the CUP patients compared to those with a known primary tumour.

There has been some discussion as to the role of chemotherapy in the treatment of patients with CUP. Clinical guidelines recommend the use of platinum based combination empiric therapies for the majority of CUP patients (5, 18, 41). CUP patients treated with combination chemotherapy have an estimated median survival of 9 to 13 months (43). Whether or not this is a significant benefit over best supportive care remains in question (16). These results show significant reduction in 2-year HR's in chemotherapy treated patients. I observed no additional survival benefit associated with multi-agent chemotherapy regimens in CUP patients. This is similar to another study that found CUP patients receiving carboplatin and paclitaxel, cisplatin and gemcitabine or gemcitabine monotherapy showed no significant difference in the Log rank test (p=0.0656) (30).

The benefit of therapeutic treatment has been described in the CUP population, however these results have been limited to a single therapy type (9, 30, 44). I observed that patients receiving chemotherapy in addition to radiation, surgery or both experienced even further survival benefit. No population data to date has shown the survival benefit associated with multiple treatment types for CUP patients. However, the clinical significance of this result may be minimal as the addition of surgery or radiation may not be tenable in some patients.

PET scans are becoming increasingly utilized in the diagnostic workup of CUP patients (45). PET scans can be used in patients who cannot take iodine or who have renal insufficiency (34). In certain CUP patients PET scans are recommended including those with squamous cell lymphadenopathy of the neck (45). In these patients a primary

tumour is found approximately 50% of the time, and resulting PET image can guide therapy. The utilization of this technique may correlate with long surviving CUP patients.

Although I have found strong associations between treatment and survival, I am unable to indicate causation. Whether a patient is treated, especially those without a primary tumour site, may be related to patient health. Alternatively, CUP patients who receive treatment may be fundamentally different from those who do not. There are some potential indications this may be the case in this population. First, the proportion of squamous cell carcinoma CUP patients who received any treatment was 16.2%, and those without treatment numbered 3.4%. This histology is often associated with the favourable subgroup of CUP and I have previously shown median survival to be as high as 20.4 months in this group (Chapter 3). Second, the proportion of CUP patients who received no treatment did not change dramatically with patient survival. This same proportion decreased sharply for patients with a known primary site. This gives confidence to attribute survival benefit to treatment in known primary patients, but not in the CUP population.

While this work describes the utilization of the most common types of therapy associated with CUP, other modalities including immunotherapy and targeted therapy exist. I am confident this work describes the treatment undergone by the majority of CUP patients. This is largely due to the fact that current clinical guidelines rarely recommend treatment outside of chemotherapy, surgery or radiation (5, 18, 41). The most recent European Society of Medical Oncology CUP guideline indicates chemotherapy, radiation or surgery in 7 of the 8 classifications of favourable CUP patients and for all subtypes of unfavourable CUP patients (18). Furthermore, in patients where targeted treatment is

recommended, the use of surgery, chemotherapy or radiation is also prescribed. For example hormonal therapy is recommended for the following CUP patients: 1. male patients showing elevated PSA levels suggesting a prostate primary tumour and 2. female patients with isolated axillary nodal metastases often resulting from a breast cancer primary tumour (18). Even in the later scenario, surgery and radiation is also recommended.

I have shown there is a survival benefit associated with all treatment types surveyed in this work. The observed increase in survival benefit was not uniform across the patient groups. Patients with metastatic tumour of known primary experienced greater survival benefit than their CUP peers and were far more likely to receive treatment. The direct relationship between treatment and survival remains less clear for CUP patients than those with a known primary site. Advancing clinical guidelines for CUP patients towards specific and specialized care while also expanding treatment to those who would normally go untreated is vital for this population.

Table 5-1. Characteristics for patients with metastatic tumours of known primary receiving surgery, chemotherapy or radiation (n=35,012), cancer of unknown primary (CUP) patients receiving surgery, chemotherapy or radiation (n=891), patients with metastatic tumours of known primary receiving no surgery, chemotherapy or radiation (n=10,335) and CUP patients receiving no surgery, chemotherapy or radiation (n=852)

	Patients who received surgery, chemotherapy or radiation					Patients who did not receive surgery, chemotherapy or radiation				
	Metastatic cancer with known primary		CUP			Metastatic cancer with known primary		CUP		
	n	%	n	%	p-value	n	%	n	%	p-value
Total n	35,012		891			10,335		852		
Mean Age	62.0		67.7		<0.0001*		69.5		71.2	<0.0001*
<39	1,787	5.1	17	1.9		258	2.5	14	1.6	
40-49	4,626	13.2	76	8.5		483	4.7	33	3.9	
50-59	7,866	22.5	143	16.1		1,299	12.6	92	10.8	
60-69	9,348	26.7	213	23.9		2,466	23.9	186	21.8	
70-79	8,446	24.1	267	30.0		3,552	34.4	308	36.2	
>80	2,939	8.4	175	19.6		2,277	22.0	219	25.7	
Gender					<0.0001*					0.0270*
Female	20,374	58.2	428	48.0		5,027	48.6	448	52.6	
Male	14,638	41.8	463	52.0		5,308	51.4	404	47.4	
Cell type					<0.0001**					<0.0001**
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	
Median Survival (months)	19.0		3.6			2.2		1.1		
Treatment type										
None		N/A			<0.0001**	10,335	100	852	100	
Surgery only	6,237	17.8	372	41.8						
Chemotherapy only	6,503	18.6	141	15.8						
Radiation only	2,889	8.3	138	15.5						
Chemotherapy and radiation	3,533	10.1	44	4.9			N/A			
Surgery and radiation	2,356	6.7	107	12.0						
Surgery and chemotherapy	7,009	20.0	65	7.3						
Surgery, radiation and	6,485	18.5	24	2.7						

*t-test
**Fisher's exact test

Table 5-2. Two year hazard ratios (HR) for patients with metastatic tumours of known primary and CUP, stratified by type of treatment received. Models adjusted for age, sex and histology

	Metastatic with known primary				CUP (n=891)			
	n	**%**	**HR**	**p-value**	**n**	**%**	**HR**	**p-value**
Radiation treatments								
0	30,084	66.3	0.42	<.0001	1,430	82.0		*ref*
1-2	13,138	29.0	0.31	<.0001	274	15.7	0.42	<.0001
3-4	1,638	3.6	0.29	<.0001	33	1.9	0.40	<.0001
>5	487	1.1	0.26	<.0001	6	0.3	0.34	0.0084
Chemotherapy								
None	21,817	48.1	0.59	<.0001	1,469	84.3		ref
Single agent	2,877	6.3	0.36	<.0001	55	3.2	0.47	<.0001
Multi-agent	20,653	45.5	0.30	<.0001	219	12.6	0.60	<.0001
Surgeries								
0	23,260	51.3	0.51	<.0001	1,175	67.4		ref
1	6,469	14.3	0.34	<.0001	207	11.9	0.82	0.0077
>2	15,618	34.4	0.25	<.0001	361	20.7	0.48	<.0001
Type of treatment								
None	10,335	22.8	0.55	<.0001	852	48.9		ref
Surgery only	6,237	13.8	0.26	<.0001	372	21.3	0.54	<.0001
Chemotherapy only	6,503	14.3	0.25	<.0001	141	8.1	0.42	<.0001
Radiation only	2,889	6.4	0.39	<.0001	138	7.9	0.36	<.0001
Chemotherapy and radiation	3,533	7.8	0.20	<.0001	44	2.5	0.25	<.0001
Surgery and radiation	2,356	5.2	0.19	<.0001	107	6.1	0.22	<.0001
Surgery and chemotherapy	7,009	15.5	0.16	<.0001	65	3.7	0.35	<.0001
Surgery, radiation and	6,485	14.3	0.14	<.0001	24	1.4	0.22	<.0001

p-values reflect comparisons between the reference (*ref*) of each treatment type and the treatment group

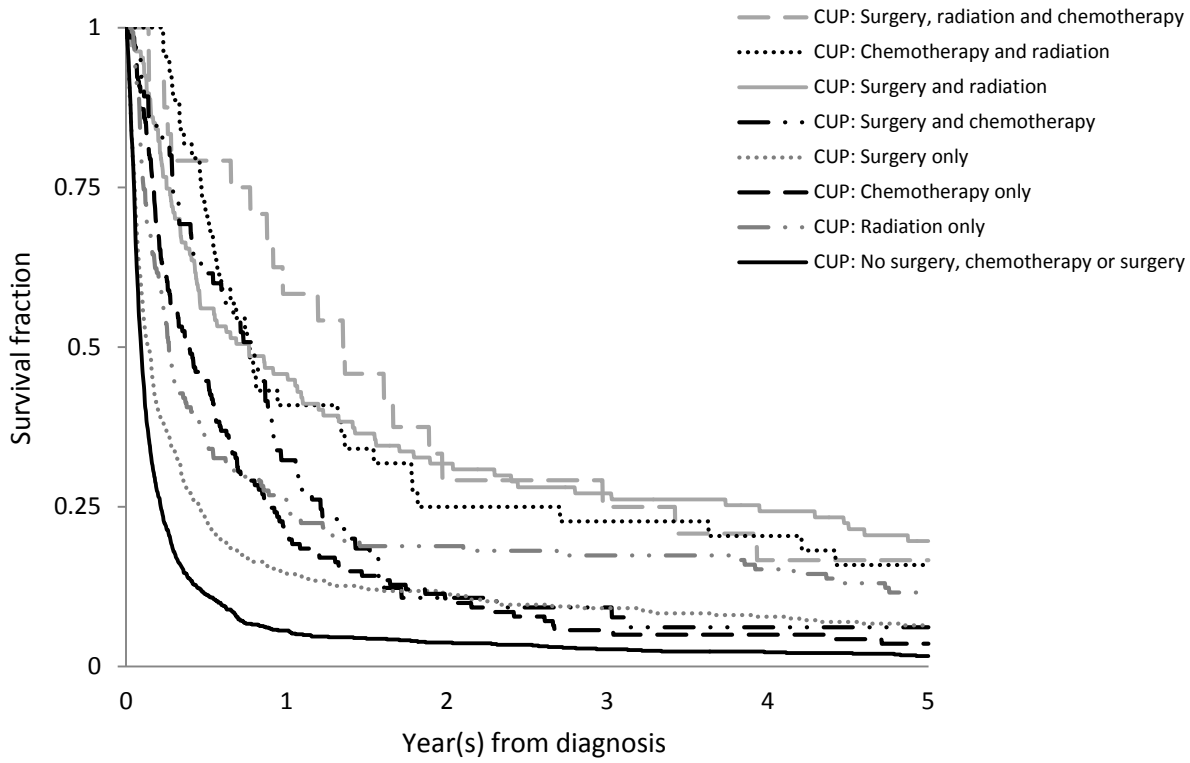

Figure 5-1. Kaplan-Meier 5 year survival curve for cancer of unknown primary (CUP) and type of treatments received.

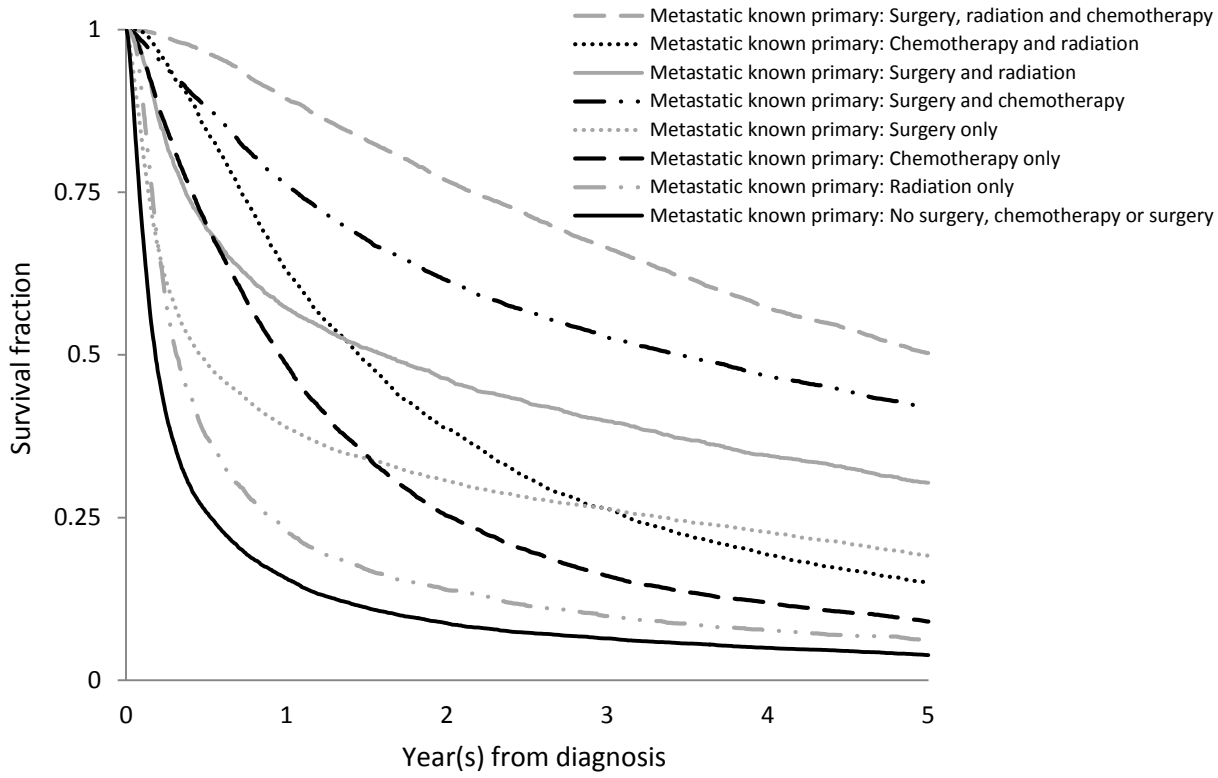

Figure 5-2. Kaplan-Meier 5 year survival curve for patients with metastatic tumours of known primary and type of treatments received.

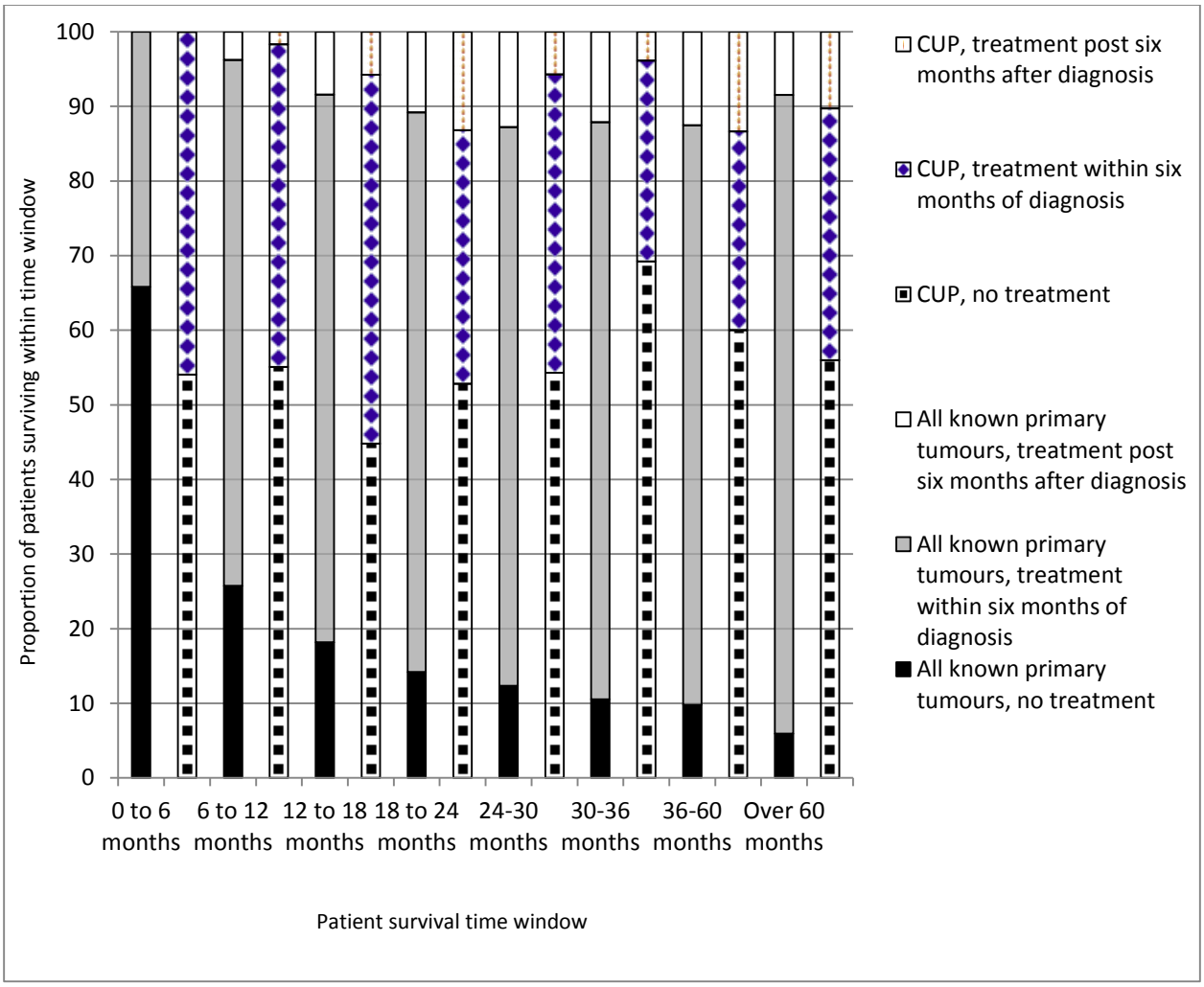

Figure 5-3. Survival over 5 years for CUP and known primary patients stratified if treatment was received within six months of diagnosis, post six months after diagnosis or no treatment was received.

Chapter 6 : Discussion

In this study I have described two novel cohorts of Ontario metastatic cancer patients. Cross-validating data from the OCR and the SDS/DAD database I identified a cohort of CUP patients and metastatic cancer of known primary site patients. To my knowledge this work represents the first description of a CUP population of this size in Canada. This study revealed that CUP patients in Ontario represent a significant portion of all metastatic cancers, accounting for approximately 6.8% of the total metastatic population. I found that CUP patient survival varied by metastatic site and histology with nodal CUP patients having better survival than any other CUP metastatic site. Overall median survival of CUP patients was poor (1.9 months) compared to overall metastatic cancer of known primary patients (11.9 months). When I aggregated chemotherapy, radiation and surgery I discovered patients with a metastatic cancer of known primary were more likely to receive treatment (77.2%) than CUP patients (51.1%).

While the description of this CUP population is novel in Canada, the patient characteristics and results largely confirm previous results in the literature. Increased survival in nodal CUP patients and patients with squamous cell histology has been described elsewhere (5, 8, 26) as well as decreased survival in respiratory/digestive CUP patients (30). These findings reinforce the factors describing unfavourable and favourable subgroups already known about CUP patients (35, 46). I did however, note Canadian specific traits in this population. In a large Swedish cohort, Hemminki *et al.* found 24% survival after one year (n=7,730), whereas I observed a one-year survival of 13.7% (n=349) for unspecified site CUP patients (10). 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.

Comparing the survival of CUP patients to patients with metastatic cancer of known primary site suggests that knowledge of the originating malignancy may be integral to survival. The use of molecular tumour profiling in addition to routine diagnostic methods appears to directly address this idea. While this method does not physically locate the primary tumour, it does suggest a site based on the tumour gene expression profile. In an experimental trial, 247 of 289 patients had a tissue of origin predicted (37). Site-specific treatment was administered to 194 patients. The overall median survival was 12.5 months. This result is encouraging especially considering that I observed an OS of 1.9 months in CUP patients, however some caution is required in interpreting this finding. When breast and ovary were the predicted primary sites, median survival was over two years. Studies estimating the primary tumour site of CUP patients using death records place breast and ovary near one year median survival (25). The advent of this technology is likely to help CUP patients but may disproportionately benefit patients with favourable outcomes.

Establishing a casual relationship between receiving treatment and survival outcomes in the CUP population is difficult. As mentioned previously those receiving treatment may be likely to have better survival outcomes. This is especially true for the favourable subgroup. These patients respond better to treatment while simultaneously having the benefit of site-specific treatment guidelines (5, 18). I did, however, observe increased survival in all CUP subgroups who received treatment. Furthermore, the

greatest reduction in HR was observed in patients receiving multiple treatments. These observations were mirrored in patients with a known primary tumour. The temporal relationship of treatment and survival was quite different in these populations. With a known primary, advanced survival coincided with early treatment, a trend not observed in the CUP population. Taken together these results may suggest CUP patients receiving treatment are fundamentally different than those who do not receive treatment. This difference may manifest as a responsiveness to treatment, but be rooted in a biologically distinct entity (47). Support for this argument can be seen in recent synthesis of unfavourable CUP patient treatment literature (16). Historically, therapeutic guidelines for CUP patients have recommended the use of platinum-based chemotherapy (5, 18, 35). Although targeted treatments may be available for some subgroups of patients, platinum-based chemotherapy is often recommended to accompany such treatment (11). For the majority of CUP patients, a platinum-based doublet regimen is often prescribed (3). 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 or single versus doublet or triplet chemotherapy regimens (16).

There are several areas of importance for future research in this field. The first is to understand the utility of molecular gene expression profiling in predicting primary tumours. If knowledge of the primary tumour site is clinically beneficial, the survival outcomes associated with this technique should reflect that idea. Secondly, clinical guidelines may need to be refined for the unfavourable population. CUP patients who are receiving empiric chemotherapy may not be experiencing survival benefit from their

treatment. This needs to be addressed. Ideally, these two research areas should coincide, the former providing a framework for treatment, and the later producing survival benefit for all CUP patients.

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Curriculum Vitae

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Education

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Scholarships/Awards

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Plant and Cell Physiology Best Poster — 2012
Molecular Plant-Microbe Interactions — Kyoto, Japan

Western Graduate Research Scholarship — 2010-2014
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Publications

Identification and survival outcomes of a cohort of patients with cancer of unknown primary in Ontario, Canada. *Acta Oncologica* 31:1-7. (2014)

TRICOT encodes an AMP1-related carboxypeptidase that regulates root nodule development and shoot apical meristem maintenance in *Lotus japonicas.* *Development* 140:353-361. (2013)

Conference Oral Presentation

Identification of a common regulator involved both in nodulation and shoot apical meristem maintenance in *Lotus japonicas*. *Molecular Plant-Microbe Interactions*. (2012). Kyoto, Japan.

Conference Poster Presentations

Identification and description of cancer of unknown primary cohort in Ontario. *Canadian Centre for Applied Research in Cancer Control*. (2014). Toronto ON Canada.

Identification of the occult tumor in cancer of unknown primary (CUP): A priority based on histology. *American Society of Clinical Oncology*. (2013). Chicago, IL, USA.

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