University of Nevada, Reno

Patterns of Care Associated with Timely and Definitive Diagnosis of Cancer of Unknown Primary (CUP)

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Abstract

The purpose of this dissertation was to perform a systematic review of recent population-based studies to summarize evidence on effective CUP diagnostic evaluation practices and examine how definitive and timely diagnosis and diagnostic guideline adherent care of metastatic pancreatic cancer affects survival in older patients who initially present with CUP. Guideline adherent, definitive and timely diagnosis of stage 3 and 4 pancreatic cancer in patients who initially presented with CUP had higher odds of occurring in patients who were a race other than White or Black with fewer or no comorbidities using logistic regression. Guideline adherent, definitive and timely diagnosis had lower odds of occurring in older patients with epithelial/unspecified histology. Survival analyses shared similarities with logistic regression results regarding age, comorbidities, and histology. Definitive diagnosis of stage 3 or 4 pancreatic cancer in those who were initially diagnosed with CUP was associated with a 72% reduction in hazard of death, while diagnostic guideline adherence was associated with a 52% reduction in hazard of death. These findings indicate transition from CUP to metastatic cancer of a known site, diagnosis prior to three months, and utilization of recommended diagnostic guidelines can make a significant impact on the life of the patient. Furthermore, if a patient were Black, Latino, and/or rural-residing, this resulted in statistically significant increased hazard of death. Future research should focus on the patterns of care associated with race, ethnicity, and social determinants of health in patients diagnosed with CUP and pancreatic cancer. By assessing current epidemiological studies on CUP diagnosis in the systematic review, we gained a broader understanding of how patients initially present

with CUP and what healthcare utilization looks like for this population. The SEER-Medicare outcomes highlighted elucidate the real-world value of making a definitive and timely diagnosis in the survival of patients with CUP and metastatic pancreatic cancer, as well as the value of evaluating their complex diagnosis utilizing recommended diagnostic guidelines. Furthermore, health disparities identified, namely for older, Black, Latino, and rural-residing patients with multiple comorbidities, require further study to ascertain health care delivery and diagnosis improvement in cancer health services.

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Chapter 1: Introduction

Background. Cancer of unknown primary (CUP), also known as occult cancer, accounts for approximately 3-5% of all cancers and is the fourth most common cause of mortality due to cancer in the U.S. (NCI, 2017; Pavlidis & Pentheroudakis, 2012). CUP is defined as a case of metastatic cancer where the origination site cannot be determined (NCI, 2017). Median survival after CUP diagnosis is approximately 3-4 months, with less than 25% of patients alive after one year (NCI, 2017; Pavlidis & Pentheroudakis, 2012). The uncertainty in origin is due to several factors, such as: the inability of screening techniques to identify the primary tumor (for example, the tumor may be too small), the tumor may disappear after metastasis, the tumor was unknowingly removed in surgery for another condition, and/or the immune system already eradicated the tumor by the time of CUP diagnosis (NCI, 2017). The biology of CUP is not well understood and there is a lack of consensus on appropriate diagnostic tools (Stella et al., 2012; Varadhachary & Raber, 2014). When a patient receives a metastatic cancer diagnosis, the first step is to identify the primary site, as this directs treatment options (Pavlidis & Pentheroudakis, 2012; Stella et al., 2012; Varadhachary & Raber, 2014). The initial investigation can identify major histological groups (for example, adenocarcinoma or squamous cell carcinoma). When initial diagnostic tools are unsuccessful, and the primary site cannot be diagnosed with confidence, the cancer is described as CUP (Pavlidis & Pentheroudakis, 2012; Stella et al., 2012; Varadhachary & Raber, 2014). Some patients will receive a CUP diagnosis because the primary site cannot be found after extensive investigations; and others will receive a CUP diagnosis because they are too frail to receive in-depth

diagnostic tests or treatments. An absence of consensus on guideline expectancy and the diagnostic complexity and timing involved in making a definitive diagnosis, can put the patient at further risk of metastasis or even death. By understanding which tests clinicians typically order and how these decisions affect survival and timely diagnosis, we can focus efforts on increasing CUP patient survival and quality of life.

Relatedly, pancreatic cancer accounts for approximately 3% of all cancers and is the third most common cause of mortality due to cancer in the U.S. (ACS, 2020; Henrikson et al., 2019). The most critical prognostic factor for pancreatic cancer is stage at diagnosis (Khalaf et al., 2020). Median survival time after stage 1 and stage 2 pancreatic cancer diagnosis is 4 months, with stage 3 and stage 4 pancreatic cancer decreasing survival time to 2-3 months (Zhang et al., 2016). Approximately 53% of pancreatic cancer patients are diagnosed after metastasis has occurred (ACS, 2020). Since CUP and metastatic pancreatic cancer are comparable in prevalence and survival outcome, definitive pancreatic cancer diagnosis is a useful endpoint to assess the impact of timely diagnosis on survival of patients initially diagnosed with CUP. Definitive and timely diagnosis is crucial to survival for patients diagnosed with CUP, but studies examining the impact of these outcomes on survival and factors improving diagnosis, such as guideline adherence, remain under-investigated (Sève et al., 2009; Pentheroudakis et al., 2008; Smith-Gagen et al., 2019).

Hypothesis and Rationale. The long-term goal of this research is to use epidemiological methods to improve patterns of care for patients with CUP, thereby increasing survival and quality of life for this difficult-to-treat diagnosis. The overall objective of this dissertation is to expand knowledge on how clinicians detect and diagnose CUP and

determine if definitive and timely diagnosis, as well as diagnostic guideline adherence, affect survival rate of metastatic pancreatic cancer in older patients in the U.S. who initially present with CUP. The central hypothesis is adherent, timely diagnosis of patients with CUP positively affects their survival rate and definitive diagnosis of a known cancer site. The rationale is CUP is a diagnosis of exclusion; patients go through a prolonged and frustrating diagnostic process that can end up with no definitive diagnosis. Current literature supports the conclusion that CUP is fraught with clinical uncertainty (Varadhachary & Raber, 2014; Stella et al., 2012). When cancer biology is uncertain, clinician decision-making and complex diagnostic processes play a greater role in determining site-specific cancer treatment, thereby determining length of patient survival.

Specific Aims.

Aim 1. Perform a systematic review of recent population-based studies to summarize available evidence on effective CUP diagnostic evaluation practices, including adherence to clinical practice guidelines (CPGs).

Premise for Aim 1. Patients with CUP receive significantly less treatment yet use more health services when compared to patients with metastatic cancer of a known site (Schaffer et al., 2015). Current scientific literature maintains that adherent care, or care abiding by a prescribed set of CPGs, in CUP diagnosis is underutilized. One of the major barriers for guideline adherence is a lack of guideline expectancy, or that guidelines will not lead to the desired outcome (Kok et al., 2015; Pentheroudakis et al., 2008). Furthermore, it is unclear which diagnostic procedures and processes most efficaciously diagnosis CUP and how the diagnostic complexity of each case affects clinician ability to do so timely (Cabana et al., 1999). Adherence to CPGs is crucial for their effectiveness,

but studies examining the effect of adherence on survival and factors improving timely diagnosis in patients with CUP remain under-investigated (Sève et al., 2009; Pentheroudakis et al., 2008). Therefore, it is necessary to summarize and review epidemiological studies on CUP-related diagnostic practices and CPG utilization.

Aim 2. Examine how definitive and timely diagnosis of metastatic pancreatic cancer affects survival in older patients who initially present with CUP. Surveillance, Epidemiology, and End Results (SEER)-Medicare data will be utilized to (a) analyze the demographic characteristics of patients who receive a definitive and timely diagnosis of stage 3 or stage 4 pancreatic cancer after being initially diagnosed with CUP and patients diagnosed with stage 3 or stage 4 pancreatic cancer only, (b) assess the association between patient factors and definitive and timely diagnosis, and (c) calculate the association between survival and definitive and timely diagnosis.

Premise for Aim 2. The diagnostic complexity of CUP is fraught with clinical uncertainty. Although the definition of CUP is accurate for general purposes, this definition also underestimates the true burden of disease because it excludes incidence of cancers which were not microscopically identified or had poor differentiation, which relates to up to 60% of patients with CUP (Rassy & Pavlidis, 2019). As discussed in the premise for Aim 1, this highlights further the lack of consensus on CUP diagnostic guidelines and the variability in diagnostic application among a variety of patient populations (Rassy & Pavlidis, 2019; Conway et al., 2019). Diagnostic recommendations are the initial components of CPGs. With the presentation of uncertain metastatic cancer, guidelines provide an algorithmic pathway to accurate and timely diagnosis. A study by Neal et al. (2014) comparing cancer diagnostic intervals before and after implementation

of NICE guidelines concluded that guideline implementation created statistically significant reductions in diagnosis time for various cancers. Furthermore, as clinicians move past solely utilizing the traditional identification of tumor classification by biopsy into molecular and immunological profiles of individual patients, diagnostic complexity of CUP is ever present (Conway et al., 2019). With these findings in mind, the patient's characteristics become more important in establishing favorable and unfavorable profiles of CUP cases. By evaluating these dimensions utilizing logistic regression and survival analysis, I can establish where health disparities exist for those diagnosed with CUP to improve health care delivery and overall patient survival.

Aim 3. Examine how diagnostic guideline adherent care of metastatic pancreatic cancer affects survival in older patients who initially present with CUP. SEER-Medicare data will be utilized to assess the association between (a) patient characteristics and adherence and (b) survival and adherence.

Premise for Aim 3. Clinician decision-making in CUP diagnosis is influenced by CPGs. A study by Dillmon et al. (2012) reported that 77% of American Society of Clinical Oncology (ASCO)-member oncologists use some set of guidelines in cancer care and 81% value evidence-based guidelines. In cases of CUP, however, Karapetis et al. (2017) concluded only 62% of sampled clinicians preferred to estimate the primary tumor site as opposed to utilizing prescribed CPGs. Organizations including ASCO, NCI, European Society for Medical Oncology (ESMO), and National Institute of Health and Care Excellence (NICE) published best practice CPGs for CUP and pancreatic cancer (Ducreux et al., 2015; Kok et al., 2015; Pentheroudakis et al., 2008; Sohal et al., 2020). Patterns of care, primarily receipt of guideline adherent care, in patients initially

diagnosed with CUP who received a definitive diagnosis of metastatic pancreatic cancer can provide a real-world view on health care delivery, patient quality of life, and next steps for treatment and palliative care.

Chapter 2: Methods

Study Population. This study uses 2010-2016 SEER-Medicare data, a national population-based cancer registry linked to Medicare claims. The cohort consisted of patients identified in the SEER dataset diagnosed with CUP, International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes C80.9 and those diagnosed with stage 3 and stage 4 pancreatic cancer (ICD-O-3 codes C250-C259), between January 1, 2010 and December 31, 2016 (Klabunde et al., 2002). Patients had to be continuously enrolled in Medicare fee-for-service (both Part A and B) beginning 1 year prior to diagnosis through the observation period. Only the first reported primary cancer for each patient was included, that is, this was the first time the patients had been diagnosed with any type of cancer. Exclusion criteria were used to maximize patients whose claims data were complete: patients were excluded if enrolled in Medicare due to chronic disability, as well as those diagnosed only on a death certificate, at autopsy, or in a nursing home as their care was likely dissimilar to other patients. Only claims paid by Medicare were included so as to avoid erroneous billing codes. The final cohort consisted of 68,146 patients, of which 17,565 were initially diagnosed with CUP prior to a pancreatic cancer diagnosis.

Descriptive Characteristics. Patient characteristics included gender, age in four groups (65 or younger, 66-74, 75-84, 85 and older), race (White, Black, and Other), ethnicity

(Latino or Non-Latino), area of residence (rural or urban), and histology of the primary tumor (adenocarcinoma, squamous cell carcinoma, epithelial/unspecified, and other). Comorbidity was assessed utilizing the Klabunde adaptation of the Charlson comorbidity score where each condition is assigned a weight according to its influence on mortality (Klabunde et al., 2002). Each patient receives an integer score and a higher score indicates a greater burden of comorbid disease (Klabunde et al., 2002).

Definitive and Timely Diagnosis. The adjusted odds ratio of characteristics of patients who received definitive and timely diagnosis by patient factors was assessed using logistic regression. The outcome was definitive and timely diagnosis of pancreatic cancer (yes or no) and exposure variables included patient demographics and histology. Two logistic regression analyses were performed to compare the characteristics of patients who received definitive and timely diagnosis between two subsets of the study population; the first model analyzed patients with an initial CUP diagnosis followed by a final diagnosis of stage 3 or stage 4 pancreatic cancer and the second model analyzed patients with a diagnosis of stage 3 or stage 4 pancreatic cancer only. Diagnosis was considered timely if definitive diagnosis occurred within three months and untimely if more than three months. The three-month cut-off point was chosen as it coincides with median time of survival for patients diagnosed with CUP and/or metastatic pancreatic cancer. The definitive and timely diagnosis hazard ratio by patient factors in those initially diagnosed with CUP was assessed using Cox proportional hazards regression. The outcome was survival time and exposure variables included patient demographics and histology. The proportional hazards assumption was tested for all variables using log(-log(survival)) versus log of survival time graphical plots. As clinicians may delay

diagnosis due to clinical uncertainty, survival time was measured from the date of the first claim associated with the cancer, death, or the end of the study, whichever occurred first. All statistical analyses were performed using SAS, version 9.4 (Cary, NC).

Adherence. Adherence to initial pancreatic cancer diagnostic procedures uses consistent elements among the diagnostic guidelines from ESMO, NICE, ASCO and others, a priori (Ducreux et al., 2015; Sohal et al., 2020). All guidelines include at least one laboratory assessment, at least one computed tomography (CT) scan and/or positron emission tomography (PET) scan to allow for clinician preference and suspicion of the primary tumor, and a biopsy within a 3-month window before and after the SEER diagnosis date. Adherent diagnostic care is receipt of all three diagnostic procedures (receipt of labs, scans and biopsy). In turn, non-adherent diagnostic care is a patient missing any one of the three procedures. Adherent care will be analyzed using logistic regression and reported as odds ratios, where Y = receipt of adherent care (yes or no) and X = patient demographic and tumor variables. Receipt of adherent care on patient survival will be analyzed using Cox proportional hazards regression, where Y = survival time and X = receipt of adherent care, patient and tumor characteristics. The following confounders were controlled for: gender, age, race, ethnicity, area of residence, histology, and Charlson comorbidity score. The proportional hazards assumption was tested for all variables using log(-log(survival)) versus log of survival time graphical plots. As clinicians may delay diagnosis due to clinical uncertainty, survival time was measured from the date of the first claim associated with CUP. All analyses were conducted using SAS, version 9.4 (Cary, NC).

Chapter 3: Manuscripts

Manuscript #1: A Systematic Review of Patterns of Care and Cancer of Unknown Primary (CUP) Diagnosis

Introduction

Cancer of unknown primary (CUP), also known as occult cancer, accounts for approximately 3-5% of all cancers and is the fourth most common cause of mortality due to cancer in the U.S. (NCI, 2017; Pavlidis & Pentheroudakis, 2012). CUP is defined as a case of metastatic cancer where the origination site cannot be determined (NCI, 2017). Median survival after CUP diagnosis is approximately 3-4 months, with less than 25% of patients alive after one year (NCI, 2017; Pavlidis & Pentheroudakis, 2012).

Patients with CUP receive significantly less treatment yet use more health services when compared to patients with metastatic cancer of a known site (Schaffer et al., 2015). Evidence-based clinical practice guidelines (CPGs) provide an opportunity to bridge the gap between the variability between health policy, medical practice, and provider and patient decision-making (Kredo et al., 2016). Current scientific literature maintains that adherent care, or care abiding by a prescribed set of CPGs, in CUP diagnosis is underutilized. One of the major barriers for guideline adherence is a lack of guideline expectancy, or that guidelines will not lead to the desired outcome (Kok et al., 2015; Pentheroudakis et al., 2008). Furthermore, it is unclear which diagnostic procedures and processes most efficaciously diagnosis CUP and how the diagnostic complexity of each case affects clinician ability to do so timely (Cabana et al., 1999). Adherence to CPGs is crucial for their effectiveness, but studies examining the effect of adherence on survival and factors improving timely diagnosis in patients with CUP remain under-investigated

(Sève et al., 2009; Pentheroudakis et al., 2008). Therefore, we sought to systematically review recent observational and epidemiological studies on CUP patient characteristics, diagnostic practices, and CPG adherence.

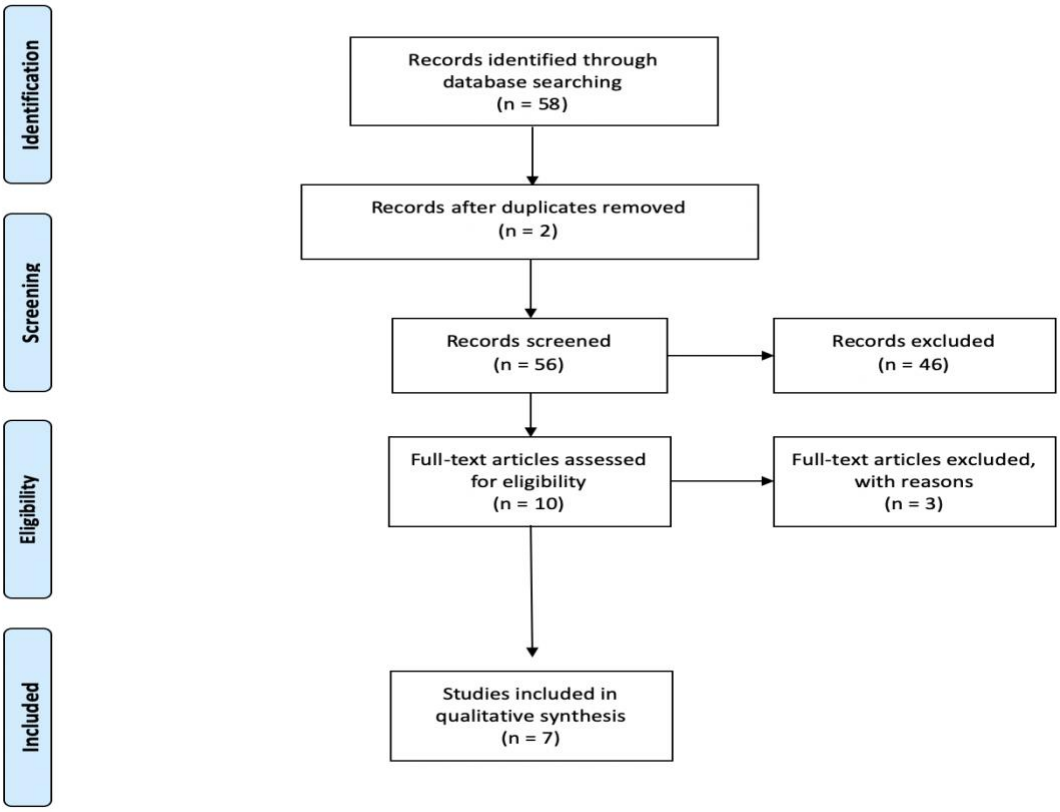
Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was applied to this review (Moher et al., 2009). The systematic review process was based on four phases according to the PRISMA statement: identification, screening, eligibility, and included (Moher et al., 2009). Table 1 provides an overview of the search inclusion criteria and Figure 1 shows the PRISMA flow diagram.

Table 1. Search criteria used on PubMed and MEDLINE

Search terms	"cancer of unknown primary" OR "cancer of unknown primary site" OR "occult cancer" OR "unknown primary" OR "carcinoma of unknown primary" OR "occult carcinoma" AND "diagnosis" OR "diagnostic" OR "evaluation" AND "population-based" OR "epidemiological"
Filters	English language, full text online, peer-reviewed publications and journal articles, and publication date between 2015-2020

Figure 1. PRISMA flow diagram



The articles were classified according to whether they: (1) met the search inclusion criteria; (2) potentially met the inclusion criteria, in which additional reading was required; or (3) did not meet the inclusion criteria. For the purposes of this systematic review, we reviewed publications which focused primarily on CUP through an epidemiological or population-based lens as these studies provide a real-world perspective of clinical practice and health care delivery. Articles were included if published within the past five years to account for the recent growth in CUP-related scientific research and literature. The initial search produced 58 articles during the identification phase. After records were screened based on title and abstract, 46 articles were excluded. Articles were excluded if the studies were case reports or randomized controlled trials, studies on metastases of specific location, and studies solely assessing novel diagnostic approaches. Publications studying CUP as an ancillary exposure or outcome were also excluded. Articles which potentially met the inclusion criteria were then reviewed further to determine eligibility. After a full-text evaluation, three articles were removed because their primary endpoint was treatment rather than diagnostic evaluation. Following this evaluation, seven articles were selected for final analysis.

Results

All seven studies sourced data from national registries (including patient and cancer registries) or electronic medical records. The median age of patients with CUP ranged from 65-84 and there were reportedly no statistically significant differences between gender (Table 2).

Median survival time from date of CUP diagnosis ranged 33-129 days. Prognosis was poorer in patients with comorbid conditions, with the highest CUP incidence occurring in

those diagnosed with hypertension, gastric acid disorders, or cardiac arrhythmia disorders. Socioeconomic status (SES) and related measures of social advantage did not show a statistically significant difference between groups in Australia (AU), Denmark (DK), and the United States (US). For patients with known histology, adenocarcinoma (AC) was the most frequent (ranging from 25%-62%), followed by squamous cell carcinoma (4%-49%; SCC), and other morphologies (2%-10%). Histology not otherwise specified (NOS) accounted for 36%-67% of patients with CUP (Table 3).

Between 50%-92% of patients with CUP did not have any prior cancer diagnosis. Those diagnosed with CUP were less likely to be hospitalized prior to diagnosis compared to patients with a known primary, but more likely to visit the emergency department once diagnosed (Hazard Ratio (HR) range 1.63-1.86).

Table 2. Study population characteristics

	CUP (N)	Median Age	Gender	Country
Dyrvig et al (2017)	542	65	51% (M) 49% (F)	DK
Jones et al (2017)	7,599	75	46% (M) 54% (F)	UK
Schaffer et al (2015)	252	84	64% (M) 36% (F)	AU
Schaffer et al (2020)	327	76	46% (M) 54% (F)	AU
Smith-Gagen et al (2019)	10,575	79	42% (M) 58% (F)	US
Vajdic et al (2015)	281	84	65% (M) 35% (F)	AU
Varghese et al (2017)	333	65	53% (M) 47% (F)	US

Table 3. Patient diagnostic characteristics

	CUP (N)	Histology[a]	Diagnostic Testing[b]
Dyrvig et al (2017)	542	N/A	98.2% (Radiology) 81% (Biopsy)
Jones et al (2017)	7,599	24.8% (AC) 4.3% (SCC) 67% (NoS) 3.8% (Oth)	N/A
Schaffer et al (2015)	252	20% (AC) 12% (SCC) 67% (NoS) N/A (Oth)	N/A
Schaffer et al (2020)	327	30.3% (AC) N/A (SCC) 12.1% (NoS) 8.5% (Oth)	65.1% (Radiology) 48.9% (Biopsy) 41.6% (Cytology)
Smith-Gagen et al (2019)	10,575	28.1% (AC) 8.2% (SCC) 54.3% (NoS) 9.4% (Oth)	94.8% (Radiology) 62.6% (Biopsy) 86.4% (Cytology)

Vajdic et al (2015)	281	62% (AC) 36% (SCC) N/A (NoS) N/A (Oth)	89.7% (Radiology) 55.8% (Biopsy) 41.3% (Cytology)
Varghese et al (2017)	333	46% (AC) 16% (SCC) 28% (NoS) 10% (Oth)	85% (Molecular Alteration)

[a]Histology includes adenocarcinoma (AC), squamous cell carcinoma (SCC), epithelial or unspecified (NoS), other types (Oth), and not applicable (N/A) if the study did not report within those categories.

[b]Diagnostic testing includes radiology (X-ray, computerized tomography [CT], ultrasound, magnetic resonance imaging [MRI], positron emission tomography [PET], and others), biopsy (histopathology), cytology (laboratory assessment), molecular alteration (genomics and genetic testing), and not applicable (N/A) if the study did not report within those categories.

Of the studies who directly assessed diagnostic procedures, 81%-88% of patients with CUP received a biopsy, 51%-98% received at least one diagnostic imaging procedure (computed tomography (CT), magnetic resonance imaging (MRI), X-ray, bone scan, or ultrasound), 15%-60% received a PET scan, 6%-39% received further diagnostic evaluation in medical oncology (e.g., exploratory surgery, endoscopy, etc.), and 8%-18% received either cytology or histopathology with immunohistochemistry testing (Table 3). Varghese et al. (2017) was the only study reviewed to incorporate genomics, reporting 85% of tumors in CUP cases had an actionable molecular alteration.

Discussion

According to Rassy & Pavlidis (2020), the recommended diagnostic workup for CUP includes a thorough physical examination, blood analyses, evaluation of tumor biomarkers (through biopsy and other means), and diagnostic imaging. It is clear from the diagnostic perspective, biopsies are utilized consistently in each study reviewed. However, there are wide differentials in the use of diagnostic imaging, nuclear medicine, pathological testing of biomarkers, and other oncological procedures. This variability may be due several factors. CUP is prematurely diagnosed in patients who undergo suboptimal evaluation due to (a) frailty and (b) severity of illness and this can explain the variability in testing. Karapetis et al. (2017) surveyed medical oncologists on their diagnostic approach to CUP and reported clinical uncertainty and poor prognosis as mitigating factors in variability of CPG adherence and diagnosis.

CPGs are utilized for a variety of reasons, including, but not limited to, improving efficacy, effectiveness, and quality of health care, standardization of clinical practices, and decreasing negative health care outcomes (Kredo et al., 2016). Moreover, CPGs are

utilized to improve upon current practice, develop benchmarks, and evaluate health outcomes based on their usage. Modern CUP diagnosis may benefit from precision-based clinical approaches, such as molecular profiling, which entails immunohistochemistry (IHC) and next-generation sequencing (NGS) of the tumor or serum biomarkers (Malone et al., 2020; Varghese et al., 2017). Future research in this area should focus on the evaluation of CPGs to identify gaps in knowledge regarding CUP diagnosis and how we can improve standardization and quality of care for this population. For example, evaluation of secondary, less invasive diagnostic procedures, such as liquid biopsy, so patients diagnosed with CUP who are too frail or ill can complete a rigorous diagnostic investigation, potentially improving their overall survival and quality of life (Bai & Zhao, 2018).

This systematic review has several limitations. CUP is a diagnosis of exclusion and as such, the study population includes a combination of those who received a thorough investigation as well as those who received minimal evaluation. This is a central feature of CUP's diagnostic complexity. The reviewed studies also utilized registry data sources, which can increase the risk of misclassification. Furthermore, race/ethnicity and residential status were only reported in two of the articles reviewed, which limits discussion and investigation of population health disparities within CUP diagnosis.

By assessing current epidemiological studies on CUP diagnosis, we gain a broader understanding of how patients initially present with CUP and what healthcare utilization looks like for this population. Further studies are needed in the U.S. to examine how patterns of care affect survivorship and timely and definitive diagnosis in patients with CUP. By understanding which tests clinicians typically order and how these decisions

affect survival and timely diagnosis, we can focus efforts on increasing patient survival and quality of life.

Manuscript #2: Impact of Definitive and Timely Diagnosis on Survival of Metastatic Pancreatic Cancer in Patients with Initial Diagnosis of Cancer of Unknown Primary (CUP)

Introduction

Cancer of unknown primary (CUP), also known as occult cancer, accounts for approximately 3-5% of all cancers and is the fourth most common cause of mortality due to cancer in the U.S. (NCI, 2017; Pavlidis & Pentheroudakis, 2012). CUP is defined as a case of metastatic cancer where the origination site cannot be determined (NCI, 2017). Median survival after CUP diagnosis is approximately 3-4 months, with less than 25% of patients alive after one year (NCI, 2017; Pavlidis & Pentheroudakis, 2012). Patients with CUP receive significantly less treatment yet use more health services when compared to patients with metastatic cancer of a known site (Schaffer et al., 2015). Relatedly, pancreatic cancer accounts for approximately 3% of all cancers and is the third most common cause of mortality due to cancer in the U.S. (ACS, 2020; Henrikson et al., 2019). The most critical prognostic factor for pancreatic cancer is stage at diagnosis (Khalaf et al., 2020). Median survival time after stage 1 and stage 2 pancreatic cancer diagnosis is 4 months, with stage 3 and stage 4 pancreatic cancer decreasing survival time to 2-3 months (Zhang et al., 2016). Approximately 53% of pancreatic cancer patients are diagnosed after metastasis has occurred (ACS, 2020). Since CUP and metastatic pancreatic cancer are comparable in prevalence and survival outcome, definitive pancreatic cancer diagnosis is a useful endpoint to assess the impact of timely diagnosis

on survival of patients initially diagnosed with CUP. Definitive and timely diagnosis is crucial to survival for patients diagnosed with CUP, but studies examining the impact of these outcomes on survival and factors improving diagnosis remain under-investigated (Sève et al., 2009; Pentheroudakis et al., 2008; Smith-Gagen et al., 2019). Moreover, there is evidence to support reduction in diagnosis time in pancreatic cancer patients leads to improved prognosis (Lukács et al., 2019; Neal et al., 2014). Therefore, we sought to examine how definitive and timely diagnosis of metastatic pancreatic cancer affects survival in older patients who initially present with CUP compared to those diagnosed with metastatic pancreatic cancer only.

Methods

This study uses 2010-2016 SEER-Medicare data, a national population-based cancer registry linked to Medicare claims. The cohort consisted of patients identified in the SEER dataset diagnosed with CUP, International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes C80.9 and those diagnosed with stage 3 and stage 4 pancreatic cancer (ICD-O-3 codes C250-C259), between January 1, 2010 and December 31, 2016 (Klabunde et al., 2002). Patients had to be continuously enrolled in Medicare fee-for-service (both Part A and B) beginning 1 year prior to diagnosis through the observation period. Only the first reported primary cancer for each patient was included, that is, this was the first time the patients had been diagnosed with any type of cancer. Exclusion criteria were used to maximize patients whose claims data were complete: patients were excluded if enrolled in Medicare due to chronic disability, as well as those diagnosed only on a death certificate, at autopsy, or in a nursing home as their care was likely dissimilar to other patients. Only claims paid by Medicare were

included so as to avoid erroneous billing codes. The final cohort consisted of 68,146 patients, of which 17,565 were initially diagnosed with CUP prior to a pancreatic cancer diagnosis.

Patient Characteristics. Patient characteristics included gender, age in four groups (65 or younger, 66-74, 75-84, 85 and older), race (White, Black, and Other), ethnicity (Latino or Non-Latino), area of residence (rural or urban), and histology of the primary tumor (adenocarcinoma, squamous cell carcinoma, epithelial/unspecified, and other). Comorbidity was assessed utilizing the Klabunde adaptation of the Charlson comorbidity score (Rothman & Greenland, 2005).

Definitive and Timely Diagnosis. Characteristics of patients who received definitive and timely diagnosis was analyzed using logistic regression and reported as adjusted odds ratios (AOR) with accompanying 95% confidence intervals (CI), where Y = receipt of definitive and timely stage 3 or stage 4 pancreatic cancer diagnosis (yes or no) and X = patient demographic and tumor variables. Two logistic regression analyses were performed to compare the characteristics of patients who received definitive and timely diagnosis between two subsets of the study population; the first model analyzed patients with an initial CUP diagnosis followed by a final diagnosis of stage 3 or stage 4 pancreatic cancer and the second model analyzed patients with a diagnosis of stage 3 or stage 4 pancreatic cancer only. Initial CUP diagnosis is defined by the date of the first biopsy or date of ICD-O-3 diagnosis, whichever comes first. Receipt of definitive diagnosis on patient survival in patients initially diagnosed with CUP was analyzed using Cox proportional hazards regression, where Y = survival time and X = receipt of definitive and timely diagnosis, patient and tumor characteristics. The following

confounders were controlled for: gender, age, race, ethnicity, area of residence, histology, and Charlson comorbidity score. The proportional hazards assumption was tested for all variables using log(-log(survival)) versus log of survival time graphical plots. As clinicians may delay diagnosis due to clinical uncertainty, survival time was measured from the date of the first claim associated with CUP. All analyses were conducted using SAS, version 9.4 (Cary, NC).

Results

Approximately 26% of patients who received a definitive and timely diagnosis of stage 3/4 pancreatic cancer started with an initial diagnosis of CUP (n=17,565). Of these cases, 53.4% were female, 37.3% were between the ages of 75-84, 81.6% were White, 92.3% were non-Latino, 59.1% lived in an urban area, 42.6% had a Charlson comorbidity score of 2 or higher, and 60.7% were histologically confirmed as adenocarcinoma (table 1). Of the cases diagnosed only with stage 3/4 pancreatic cancer, characteristics were generally similar to those initially diagnosed with CUP, however, 29.9% were between the ages of 75-84 and 31.9% had a Charlson comorbidity score of 2 or higher.

The adjusted odds of definitive and timely pancreatic cancer diagnosis in patients initially diagnosed with CUP (table 2) were 10% lower for patients between the ages of 75-84 (AOR 0.90 [0.83, 0.97]) compared to patients 85 years or older; 15% and 20% lower for those with a Charlson comorbidity score of 0 (AOR 0.85 [0.79, 0.91]) or 1 (AOR 0.80 [0.74, 0.85]) compared to a score of 2 or higher, respectively; and 24% lower for epithelial/unspecified histology compared to other histology cases (AOR 0.76 [0.71, 0.82]). The adjusted odds of definitive and timely pancreatic cancer diagnosis in patients

initially diagnosed with CUP was 27% higher for patients who are a race other than White or Black (AOR 1.27 [1.13, 1.43]).

The adjusted odds of definitive and timely diagnosis in patients only with pancreatic cancer were 6% lower for patients between the ages of 75-84 (AOR 0.94 [0.89, 1.00]) compared to patients 85 years or older and 6% lower for patients who are Black (AOR 0.94 [0.88, 1.00]). The adjusted odds of definitive and timely diagnosis in patients only with pancreatic cancer were 45% higher for patients 65 years or younger (AOR 1.45 [1.34, 1.57]) compared to patients 85 years or older; 15% higher for patients who are a race other than White or Black (AOR 1.15 [1.05, 1.25]); 90% and 25% higher for those with a Charlson comorbidity score of 0 (AOR 1.90 [1.81, 2.00]) or 1 (AOR 1.25 [1.19, 1.32]) compared to a score of 2 or higher, respectively; and 34% higher for epithelial/unspecified histology compared to other histology cases (AOR 1.34 [1.28, 1.41]).

A definitive and timely diagnosis of stage 3/4 pancreatic cancer in those who were initially diagnosed with CUP was associated with a 72% reduction in hazard of death (HR 0.28 [0.25, 0.31]) compared to those who did not receive a final pancreatic cancer diagnosis. Patients 65 years or younger were associated with a 63% reduction in hazard of death (HR 0.37 [0.33, 0.40]), patients between the ages of 66-74 had a 38% reduction in hazard of death (HR 0.62 [0.58, 0.66]), and patients between the ages of 75-84 had a 21% reduction in hazard of death (HR 0.79 [0.75, 0.85]) when compared to patients 85 years or older. Patients with a Charlson comorbidity score of 0 or 1 had a 19% (HR 0.81 [0.77, 0.86]) and 13% reduction in hazard of death (HR 0.87 [0.82, 0.92]), respectively, when compared to patients with a score of 2 or higher. Female patients were associated

with a 10% increase in hazard of death compared to males (HR 1.10 [1.05, 1.15]). Black patients were associated with a 15% increase in hazard of death compared to White patients (HR 1.15 [1.08, 1.23]). Patients of Latino ethnicity had a 19% increase in hazard of death compared to non-Latinos (HR 1.19 [1.10, 1.29]). Patients who resided in rural areas were associated with a 6% increase in hazard of death compared to patients in urban areas (HR 1.06 [1.02, 1.11]). Patients where histology was epithelial/unspecified had an 85% increase in hazard of death (HR 1.85 [1.76, 1.95]) when compared to cases with other histology.

Table 1: Descriptive characteristics of definitive and timely pancreatic cancer diagnosis in those initially diagnosed with CUP compared to those diagnosed only with pancreatic cancer, SEER-Medicare, 2010-2016

Demographic Variable	Number (Percent)	
	CUP-Pancreas (n = 17,565)	**Pancreas** (n = 50,581)
Gender		
Female	9,387 (53.4%)	25,897 (51.2%)
Male	8,178 (46.6%)	24,684 (48.8%)
Age at Diagnosis		
<= 65	2,025 (11.5%)	12,038 (23.8%)
66-74	6,031 (34.3%)	16,237 (32.1%)
75-84	6,553 (37.3%)	15,123 (29.9%)
85+	2,956 (16.9%)	7,183 (14.2%)
Race		
White	14,329 (81.6%)	41,122 (81.3%)
Black	2,123 (12.1%)	5,564 (11.0%)
Other	1,113 (6.3%)	3,895 (7.7%)
Ethnicity		
Non-Latino	16,212 (92.3%)	46,180 (91.3%)
Latino	1,353 (7.7%)	4,401 (8.7%)
Urban		
Yes	10,379 (59.1%)	30,602 (60.5%)
No	7,186 (40.9%)	19,979 (39.5%)
Charlson Comorbidity Score		
0	5,337 (30.4%)	21,649 (42.8%)
1	4,748 (27.0%)	12,797 (25.3%)
2+	7,480 (42.6%)	16,135 (31.9%)
Histology		
Adenocarcinoma	10,661 (60.7%)	29,843 (59.0%)
Epithelial/Unspecified	3,627 (20.6%)	11,077 (21.9%)
Other Histology	3,070 (17.5%)	9,105 (18.0%)
Squamous Cell Carcinoma	207 (1.2%)	556 (1.1%)

Table 2. Odds ratios of definitive and timely pancreatic cancer diagnosis in those initially diagnosed with CUP compared to those diagnosed only with pancreatic cancer by patient factors, SEER-Medicare, 2010-2016

Patient Factors	**OR (95% CI)**	
	CUP-Pancreas (n = 17,565)	**Pancreas (n = 50,581)**
Gender		
Female	1.01 (0.95, 1.07)	0.97 (0.93, 1.01)
Male	Reference	Reference
Age at Diagnosis		
<= 65	1.09 (0.98, 1.23)	**1.45 (1.34, 1.57)**
66-74	1.03 (0.94, 1.12)	1.04 (0.97, 1.11)
75-84	**0.90 (0.83, 0.97)**	**0.94 (0.89, 1.00)**
85+	Reference	Reference
Race		
White	Reference	Reference
Black	1.04 (0.95, 1.13)	**0.94 (0.88, 1.00)**
Other	**1.27 (1.13, 1.43)**	**1.15 (1.05, 1.25)**
Ethnicity		
Non-Latino	Reference	Reference
Latino	1.03 (0.93, 1.15)	1.05 (0.97, 1.13)
Urban		
Yes	Reference	Reference
No	0.99 (0.93, 1.05)	1.04 (0.99, 1.08)
Charlson Comorbidity Score		
0	**0.85 (0.79, 0.91)**	**1.90 (1.81, 2.00)**
1	**0.80 (0.74, 0.85)**	**1.25 (1.19, 1.32)**
2+	Reference	Reference
Histology		
Epithelial/Unspecified	**0.76 (0.71, 0.82)**	**1.34 (1.28, 1.41)**
Other Histology	Reference	Reference

Table 3. Impact of receiving a definitive and timely pancreatic cancer diagnosis on survival in those initially diagnosed with CUP controlling for patient factors, SEER-Medicare, 2010-2016 (n = 17,565)

Patient Factors	Hazard Ratio (95% CI)
Receipt of definitive and timely diagnosis	**0.28 (0.25, 0.31)**
Gender	
Female	**1.10 (1.05, 1.15)**
Male	Reference
Age at Diagnosis	
<= 65	**0.37 (0.33, 0.40)**
66-74	**0.62 (0.58, 0.66)**
75-84	**0.79 (0.75, 0.85)**
85+	Reference
Race	
White	Reference
Black	**1.15 (1.08, 1.23)**
Other	1.00 (0.91, 1.09)
Ethnicity	
Non-Latino	Reference
Latino	**1.19 (1.10, 1.29)**
Urban	
Yes	Reference
No	**1.06 (1.02, 1.11)**
Charlson Comorbidity Score	
0	**0.81 (0.77, 0.86)**
1	**0.87 (0.82, 0.92)**
2+	Reference
Histology	
Epithelial/Unspecified	**1.85 (1.76, 1.95)**
Other Histology	Reference

Discussion

To our knowledge, this is the first population-based study focusing on metastatic pancreatic cancer in patients initially diagnosed with CUP. This study examined how definitive and timely diagnosis of metastatic pancreatic cancer affects survival in older patients who initially present with CUP.

Definitive and timely diagnosis of stage 3 or stage 4 pancreatic cancer in patients who initially presented with CUP was favorable in patients who were a race other than White or Black with fewer or no comorbidities. Unfavorable characteristics for definitive and timely diagnosis included patients in older age groups and histology confirmed as epithelial/unspecified. Patients with comorbidities may receive health services more often than patients without comorbidities, thus are more likely to come in contact with the health care system (DHPOI, 2012). However, older patients with comorbidities may be unable to complete the diagnostic workup necessary to make a definitive and/or timely diagnosis (Massarweh et al., 2011). Unfavorable characteristics for definitive and timely diagnosis of CUP including older age, epithelial/unspecified histology, and higher comorbid burden of disease correspond with current scientific literature on CUP patterns of care, namely population-based studies focusing on patient characteristics and healthcare utilization (Schaffer et al., 2020; Jones et al., 2017; Schaffer et al., 2015), adherence and diagnostic guidelines, (Smith-Gagen et al., 2019), and risk factors and clinical management (Rassy & Pavlidis, 2020; Pavlidis et al., 2019).

In patients diagnosed with stage 3 or stage 4 pancreatic cancer only, definitive and timely diagnosis was similar to CUP patients by race, however, this subpopulation was younger and had fewer comorbidities overall. Furthermore, the comorbidity score and whether

histology was epithelial/unspecified were not barriers to definitive and timely diagnosis for the pancreatic cancer only group, suggesting there are imbalances in delivery of care compared to patients initially diagnosed with CUP. This is likely due to the complexity of identifying the primary tumor site in CUP, whereas in identification of pancreatic cancer, the clinician at least has a point from which to begin a well-informed diagnostic process. The survival analysis corresponds with the logistic regression results, primarily regarding age and comorbidities. Definitive and timely diagnosis of stage 3 or stage 4 pancreatic cancer in those who were initially diagnosed with CUP was associated with a 72% reduction in hazard of death, indicating (1) transition in diagnosis from CUP to metastatic cancer of a known site and (2) definitive diagnosis within three months can make a significant impact on the life of the patient. These findings support the hypothesis that delays in diagnosis and access to care for those with metastatic cancers, especially in complex cases such as CUP, are detrimental to patient survival. A French population-based study by Jooste et al. (2016) reported patient delay in access to care for onset of pancreatic cancer symptomology was longer than one month in 46% of patients and this was associated with poor prognosis. Furthermore, Black, Latino, rural-residing, and cases with epithelial/unspecified histology resulted in increased hazard of death.

These findings further elucidate the health disparities evident in CUP and pancreatic cancer diagnoses. Scientific literature on cancer health disparities report higher incidence of metastatic pancreatic cancer among Black and Latino patients, as well as lower occurrence of treatment (primarily surgical intervention), poor access to quality health care, and higher rates of overall morbidity and mortality (Noel & Fiscella, 2019; Tavakkoli et al., 2020; Zhou et al., 2017). An area of future research should focus on the

patterns of care associated with race, ethnicity, and social determinants of health (to include socioeconomic status) in patients diagnosed with CUP and pancreatic cancer. While SEER-Medicare data provided a robust sample size, there are limitations in this study. Our study population was limited to patients 65 years and older and did not include patients with private insurance coverage. However, the age range of an average patient with CUP is 80 years or older and the vast majority of patients 65 years and older are insured through Medicare (FIF, 2015). This study only investigated patients with a final metastatic pancreatic cancer diagnosis. Further research of other CUP-primary site cancers, for example ovarian and lung cancers, would be beneficial to the growing scientific literature on the diagnostic complexity of CUP. There is a potential limitation in studies focusing on timely diagnosis and length time bias, where ill-defined dates of diagnoses may skew the data. However, SEER-Medicare data contains the date of the first histological or cytological confirmation of malignancy, which is an appropriate variable to ascertain time of cancer diagnosis, thereby decreasing effects of length time bias (Weller et al., 2012; Neal et al., 2014). It is also important to note clinicians may need to report a definitive diagnosis to justify treatment for insurance claims. Claims data for administrative and billing purposes might be inaccurate from a biological or clinical disease perspective.

This study assesses favorable and unfavorable patient characteristics, as well as overall survival associated with the definitive and timely diagnosis of metastatic pancreatic cancer in patients who initially presented with CUP based on a large and representative population-based cohort. Our findings reflect the importance of reaching a definitive and

timely diagnosis in the survival of patients with CUP, especially for older, female, Black, Latino, and rural-residing patients with multiple comorbidities.

Manuscript #3: Impact of Diagnostic Guideline Adherence on Survival of Metastatic Pancreatic Cancer in Patients with Initial Diagnosis of Cancer of Unknown Primary (CUP)

Introduction

Cancer of unknown primary (CUP) accounts for approximately 3-5% of all cancers and is the fourth most common cause of mortality due to cancer in the U.S. (NCI, 2017; Pavlidis & Pentheroudakis, 2012). CUP is defined as a case of metastatic cancer where the origination site cannot be determined (NCI, 2017). Median survival after CUP diagnosis is approximately 3-4 months, with less than 25% of patients alive after one year (NCI, 2017; Pavlidis & Pentheroudakis, 2012). Pancreatic cancer accounts for approximately 3% of all cancers and is the third most common cause of mortality due to cancer in the U.S. (ACS, 2020; Henrikson et al., 2019). Median survival time after stage 1 and stage 2 pancreatic cancer diagnosis is 4 months, with stage 3 and stage 4 pancreatic cancer decreasing survival time to 2-3 months (Zhang et al., 2016). Approximately 53% of pancreatic cancer patients are diagnosed after metastasis has occurred (ACS, 2020). Since CUP and metastatic pancreatic cancer are comparable in prevalence and survival outcome, definitive pancreatic cancer diagnosis is a useful endpoint to assess the impact of diagnostic guideline adherence on survival of patients initially diagnosed with CUP. Clinician decision-making in CUP diagnosis is influenced by diagnostic guidelines. A study by Dillmon et al. (2012) reported that 77% of American Society of Clinical Oncology (ASCO)-member oncologists use some set of guidelines in cancer care and

81% value evidence-based guidelines. Evidence-based clinical practice guidelines (CPGs) provide an opportunity to bridge the gap between the variability between health policy, medical practice, and provider and patient decision-making (Kredo et al., 2016). In cases of CUP, however, Karapetis et al. (2017) concluded only 62% of sampled clinicians preferred to estimate the primary tumor site as opposed to utilizing prescribed diagnostic guidelines. Organizations including ASCO, National Cancer Institute (NCI), European Society for Medical Oncology (ESMO), and National Institute of Health and Care Excellence (NICE) published best practice guidelines for CUP and pancreatic cancer (Ducreux et al., 2015; Kok et al., 2015; Pentheroudakis et al., 2008; Sohal et al., 2020). Patterns of care, primarily receipt of guideline adherent care, in patients initially diagnosed with CUP who receive a definitive diagnosis of metastatic pancreatic cancer can provide a real-world view on health care delivery practices and quality of life for this population. We sought to examine how diagnostic guideline adherent care of metastatic pancreatic cancer affects survival in older patients who initially present with CUP.

Methods

This study uses 2010-2016 SEER-Medicare data, a national population-based cancer registry linked to Medicare claims. The cohort consisted of patients identified in the SEER dataset diagnosed with CUP, International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes C80.9 and those diagnosed with stage 3 and stage 4 pancreatic cancer (ICD-O-3 codes C250-C259), between January 1, 2010 and December 31, 2016 (Klabunde et al., 2002). Patients had to be continuously enrolled in Medicare fee-for-service (both Part A and B) beginning 1 year prior to diagnosis through the observation period. Exclusion criteria were used to maximize patients whose claims

data were complete: patients were excluded if enrolled in Medicare due to chronic disability, as well as those diagnosed only on a death certificate, at autopsy, or in a nursing home as their care was likely dissimilar to other patients. Only claims paid by Medicare were included so as to avoid erroneous billing codes. The final cohort consisted of 68,146 patients, of which 17,565 were initially diagnosed with CUP prior to a pancreatic cancer diagnosis. Initial CUP diagnosis is defined by the date of the first biopsy or date of ICD-O-3 diagnosis, whichever comes first.

Descriptive Characteristics. Descriptive characteristics included gender, age in four groups (65 or younger, 66-74, 75-84, 85 and older), race (White, Black, and Other), ethnicity (Latino or Non-Latino), area of residence (rural or urban), and histology of the primary tumor (adenocarcinoma, squamous cell carcinoma, epithelial/unspecified, and other). Comorbidity was assessed utilizing the Klabunde adaptation of the Charlson comorbidity score (Rothman & Greenland, 2005).

Adherence. Adherence to initial pancreatic cancer diagnostic procedures uses consistent elements among the diagnostic guidelines from ESMO, NICE, ASCO and others, a priori (Ducreux et al., 2015; Sohal et al., 2020). First, since all guidelines include laboratory assessment, we assess if the patient received at least one laboratory code within a 3-month window before and after the SEER diagnosis date. Second, since all guidelines recommend computed tomography (CT) scans and some recommend positron emission tomography (PET) scans, we include at least one scan to allow for clinician preference and suspicion of the primary tumor. Third, a biopsy is included because all guidelines recommend a biopsy. Adherent diagnostic care is receipt of all three diagnostic procedures (receipt of labs, scans and biopsy). In turn, non-adherent diagnostic care is a

patient missing any one of the three procedures. Characteristics of patients who received adherent care was analyzed using logistic regression and reported as odds ratios, where Y = receipt of adherent care (yes or no) and X = patient demographic and tumor variables. Receipt of adherent care on patient survival will be analyzed using Cox proportional hazards regression, where Y = survival time and X = receipt of adherent care, patient and tumor characteristics. The following confounders were controlled for: gender, age, race, ethnicity, area of residence, histology, and Charlson comorbidity score. The proportional hazards assumption was tested for all variables using log(-log(survival)) versus log of survival time graphical plots. As clinicians may delay diagnosis due to clinical uncertainty, survival time was measured from the date of the first claim associated with CUP. All analyses were conducted using SAS, version 9.4 (Cary, NC).

Results

The study population consisted of 53.4% female patients, 37.3% were between the ages of 75-84, 81.6% were White, 92.3% were non-Latino, 59.1% resided in an urban area, 42.6% had a Charlson comorbidity score of 2 or higher, 60.7% were histologically confirmed as adenocarcinoma, 97.4% had at least one laboratory assessment, 85.3% had at least one diagnostic scan/imaging, and 55.8% had at least one biopsy (table 1).

The adjusted odds of adherent pancreatic cancer diagnosis in patients initially diagnosed with CUP (table 2) were 45% higher for patients who are a race other than White or Black (AOR 1.45 [1.09, 1.92]); 42% higher for patients who are Latino (AOR 1.42 [1.09, 1.92]); 19% lower for those with a Charlson comorbidity score of 1 (AOR 0.81 [0.65, 0.99]) compared to a score of 2 or higher; and 60% lower for epithelial/unspecified histology compared to other histology cases (AOR 0.40 [0.31, 0.51]).

Guideline adherent diagnosis of stage 3/4 pancreatic cancer in those who were initially diagnosed with CUP was associated with a 52% reduction in hazard of death (HR 0.48 [0.46, 0.50]) compared to those who received non-adherent care. Patients 65 years or younger were associated with a 40% reduction in hazard of death (HR 0.60 [0.57, 0.62]), patients between the ages of 66-74 had a 21% reduction in hazard of death (HR 0.79 [0.76, 0.81]), and patients between the ages of 75-84 had a 7% reduction in hazard of death (HR 0.93 [0.90, 0.96]) when compared to patients 85 years or older. Patients with a Charlson comorbidity score of 0 or 1 had a 6% (HR 0.94 [0.92, 0.96]) and 4% reduction in hazard of death (HR 0.96 [0.94, 0.99]), respectively, when compared to patients with a score of 2 or higher. Patients where histology was epithelial/unspecified had a 13% decrease in hazard of death (HR 0.87 [0.85, 0.90]) when compared to cases with other histology. Female patients were associated with a 9% increase in hazard of death compared to males (HR 1.09 [1.07, 1.11]). Black patients were associated with a 9% increase in hazard of death compared to White patients (HR 1.09 [1.05, 1.12]). Patients of Latino ethnicity had an 11% increase in hazard of death compared to non-Latinos (HR 1.11 [1.07, 1.15]). Patients who resided in rural areas were associated with a 3% increase in hazard of death compared to patients in urban areas (HR 1.03 [1.01, 1.05]).

Table 1: Descriptive characteristics of patients with pancreatic cancer who were initially diagnosed with CUP, SEER-Medicare, 2010-2016 (n=17,565)

Demographic Variable	Number (Percent)
Gender	
Female	9,387 (53.4%)
Male	8,178 (46.6%)
Age at Diagnosis	
<= 65	2,025 (11.5%)
66-74	6,031 (34.3%)
75-84	6,553 (37.3%)
85+	2,956 (16.9%)
Race	
White	14,329 (81.6%)
Black	2,123 (12.1%)
Other	1,113 (6.3%)
Ethnicity	
Non-Latino	16,212 (92.3%)
Latino	1,353 (7.7%)
Urban	
Yes	10,379 (59.1%)
No	7,186 (40.9%)
Charlson Comorbidity Score	
0	5,337 (30.4%)
1	4,748 (27.0%)
2+	7,480 (42.6%)
Histology	
Adenocarcinoma	10,661 (60.7%)
Epithelial/Unspecified	3,627 (20.6%)
Other Histology	3,070 (17.5%)
Squamous Cell Carcinoma	207 (1.2%)
Diagnostic Tests (not mutually exclusive)	
Laboratory Assessment	17,107 (97.4%)
Imaging	14,975 (85.3%)
Biopsy	9,796 (55.8%)

Table 2. Adjusted odds ratios of patients with guideline adherent pancreatic cancer diagnosis who were initially diagnosed with CUP, SEER-Medicare, 2010-2016

Patient Factors	**AOR (95% CI)**
Gender	
Female	1.10 (0.94, 1.30)
Male	Reference
Age at Diagnosis	
<= 65	1.32 (0.96, 1.83)
66-74	1.26 (0.96, 1.66)
75-84	1.24 (0.95, 1.62)
85+	Reference
Race	
White	Reference
Black	0.87 (0.67, 1.15)
Other	**1.45 (1.09, 1.92)**
Ethnicity	
Non-Latino	Reference
Latino	**1.42 (1.10, 1.85)**
Urban	
Yes	Reference
No	1.15 (0.98, 1.35)
Charlson Comorbidity Score	
0	0.89 (0.74, 1.07)
1	**0.81 (0.65, 0.99)**
2+	Reference
Histology	
Epithelial/Unspecified	**0.40 (0.31, 0.51)**
Other Histology	Reference

Table 3. Impact of receiving guideline adherent pancreatic cancer diagnosis on survival controlling for patient factors in those initially diagnosed with CUP, SEER-Medicare, 2010-2016

Patient Factors	Hazard Ratio (95% CI)
Receipt of guideline adherent diagnosis	**0.48 (0.46, 0.50)**
Gender	
Female	**1.09 (1.07, 1.11)**
Male	Reference
Age at Diagnosis	
<= 65	**0.60 (0.57, 0.62)**
66-74	**0.79 (0.76, 0.81)**
75-84	**0.93 (0.90, 0.96)**
85+	Reference
Race	
White	Reference
Black	**1.09 (1.05, 1.12)**
Other	1.01 (0.97, 1.05)
Ethnicity	
Non-Latino	Reference
Latino	**1.11 (1.07, 1.15)**
Urban	
Yes	Reference
No	**1.03 (1.01, 1.05)**
Charlson Comorbidity Score	
0	**0.94 (0.92, 0.96)**
1	**0.96 (0.94, 0.99)**
2+	Reference
Histology	
Epithelial/Unspecified	**0.87 (0.85, 0.90)**
Other Histology	Reference

Discussion

This study examined how diagnostic guideline adherent care of metastatic pancreatic cancer affects survival in older patients who initially present with CUP. Guideline adherent diagnosis of stage 3 or stage 4 pancreatic cancer in patients who initially presented with CUP occurred with patients who were a race other than White or Black and those who were Latino. Non-adherent care occurred in patients with fewer comorbidities and confirmed epithelial/unspecified histology. These results correspond with current scientific literature on CUP, namely studies focusing on patterns of care (Schaffer et al., 2020; Jones et al., 2017; Schaffer et al., 2015), adherence and diagnostic guidelines, (Smith-Gagen et al., 2019), and risk factors and clinical management (Rassy & Pavlidis, 2020; Pavlidis et al., 2019).

Diagnostic guideline adherent care of stage 3 or stage 4 pancreatic cancer in those who were initially diagnosed with CUP was associated with a 52% reduction in hazard of death, indicating guideline adherent care can make a significant impact on the life of the patient. Furthermore, female, Black, Latino, and rural-residing patients had an increased hazard of death.

These findings reflect the importance of guideline-recommended care. CPGs are utilized for a variety of reasons, including, but not limited to, improving efficacy, effectiveness, and quality of health care, standardization of clinical practices, and decreasing negative health care outcomes (Kredo et al., 2016). Moreover, CPGs are utilized to improve upon current practice, develop benchmarks, and evaluate health outcomes based on their usage.

These findings also reflect apparent health inequities evident in CUP and pancreatic cancer cases. Scientific literature on cancer health disparities report higher incidence of

metastatic pancreatic cancer among Black and Latino patients, as well as lower occurrence of treatment (primarily surgical intervention), poor access to quality health care, and higher rates of overall morbidity and mortality (Noel & Fiscella, 2019; Tavakkoli et al., 2020; Zhou et al., 2017). An area of future research should focus on the patterns of care associated with race, ethnicity, and social determinants of health (to include socioeconomic status) in patients diagnosed with CUP and pancreatic cancer. This study only determined diagnostic guideline adherence of CUP patients with definitive metastatic pancreatic cancer. Future research of other CUP-primary site cancers, for example ovarian and lung cancers, would also be beneficial to the growing scientific literature on the diagnostic complexity of CUP. Furthermore, supplementary diagnostic testing specific to metastatic pancreatic cancer, to include esophagogastroduodenoscopy (EGD), endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), and molecular profiling would more substantially elucidate the extent of diagnostic investigation which occurred for this population (Ducreux et al., 2015; Sohal et al., 2020). Future research in CPGs should also focus on evaluating secondary, less invasive diagnostic procedures, such as liquid biopsy, so patients who are too frail or ill can complete a rigorous diagnostic investigation, potentially improving their overall survival and quality of life (Bai & Zhao, 2018). Although a primary strength of this study is the robust sample size, there are limitations to note. Our study population was limited to patients 65 years and older and did not include patients with other forms of health insurance coverage. However, the age range of an average patient with CUP is 80 years or older and the majority of patients 65 years and older in the U.S. are insured through Medicare (FIF, 2015). By limiting the cohort to

patients surviving three months or longer, the bias would be toward the null, resulting in a conservative estimate of the hazard ratios. We could also not identify diagnostic procedures refused by patients and it is important to note some patients may have been too frail to undergo all recommended diagnostic procedures. Another potential limitation to consider with this dataset is claims data for billing purposes can be clinically inaccurate.

This study assessed patient characteristics and overall survival associated with diagnostic guideline adherent care of metastatic pancreatic cancer patients who initially presented with CUP. This study utilized a large and generalizable population-based cohort. The results highlight the real-world value of evaluating guideline adherent care in the diagnosis and survival of patients with CUP, especially for older, female, Black, Latino, and rural-residing patients with multiple comorbidities.

Chapter 4: Discussion

The purpose of this dissertation was to (a) perform a systematic review of recent population-based studies to summarize available evidence on effective CUP diagnostic evaluation practices, including adherence to CPGs and examine how (b) definitive and timely diagnosis (c) and diagnostic guideline adherent care of metastatic pancreatic cancer affects survival in older patients who initially present with CUP.

The systematic review elucidated several key components regarding CUP diagnostic practices. The recommended diagnostic workup for CUP includes a thorough physical examination, blood analyses, evaluation of tumor biomarkers (mainly through biopsies), and diagnostic imaging. Moreover, current scientific literature showcased clinical inconsistencies in the use of diagnostic imaging, nuclear medicine (e.g., positron emission tomography [PET]), pathological testing of biomarkers (e.g., molecular profiling and immunohistochemistry testing), and other oncological procedures in CUP cases. I hypothesize these variations in clinical diagnostic evaluation may in part be due to low CPG adherence in suboptimal cases where CUP is prematurely diagnosed. Future research in CPGs should focus on evaluating secondary, less invasive diagnostic procedures, such as liquid biopsy, so patients who are too frail or ill can complete a rigorous diagnostic investigation, potentially improving their overall survival and quality of life (Bai & Zhao, 2018).

The systematic review had several limitations however. CUP is a diagnosis of exclusion and as such, the chosen articles contained variability in study populations (i.e., a combination of patients who received a thorough investigation as well as those who received minimal evaluation). The reviewed studies also utilized registry data sources,

which can increase the risk of misclassification. Furthermore, race/ethnicity and residential status were only reported in two of the articles reviewed, which limits corresponding discussion of cancer health disparities within this dissertation and in the broader field of CUP research. However, a particular strength of this dissertation are the inclusion of race/ethnicity and residential setting (as a proxy for health care access) variables in the original research outlined in the second and third studies.

The second and third studies, to my knowledge, encompass the first population-based studies focusing on definitive metastatic pancreatic cancer in patients initially diagnosed with CUP. Both definitive diagnosis and timely diagnosis of stage 3 and stage 4 pancreatic cancer in patients who initially presented with CUP had higher odds of occurring in patients who were a race other than White or Black with fewer or no comorbidities in logistic regression modeling. Furthermore, both definitive diagnosis and timely diagnosis had lower odds of occurring in older patients with confirmed epithelial/unspecified histology. Historically, patients with comorbidities receive health services more often than patients without comorbidities, coming into regular contact with the health care system (DHPOI, 2012). However, multiple comorbidities also make it difficult for both clinician and patient to complete the necessary diagnostic workup (Massarweh et al., 2011). In the group diagnosed with pancreatic cancer only, comorbidity score and histology were not obstacles to definitive and timely diagnosis, further suggesting there are inherent barriers to adequate care for patients initially diagnosed with CUP. These barriers could include timeliness to care, ability for the patient to complete a diagnostic workup, patient survival time, clinician guideline adherence, clinician difficulty in establishing a primary site, and many others. The

survival analyses shared similarities with the logistic regression results, primarily regarding age, comorbidities, and histology, but also introduced findings on the impact of definitive and timely diagnosis on survival and the health inequities for this patient population. Definitive and timely diagnosis of stage 3 or stage 4 pancreatic cancer in those who were initially diagnosed with CUP was associated with a 72% reduction in hazard of death, while guideline adherent care was associated with a 52% reduction in hazard of death. These findings indicate transition from CUP to metastatic cancer of a known site, diagnosis prior to three months, and utilization of recommended diagnostic guidelines can make a significant impact on the life of the patient. Furthermore, if a patient were Black, Latino, and/or rural-residing, this resulted in statistically significant increased hazard of death overall.

Scientific literature on cancer health disparities report higher incidence of metastatic pancreatic cancer among Black and Latino patients, as well as lower occurrence of treatment (primarily surgical intervention), poor access to quality health care, and higher rates of overall morbidity and mortality within these populations (Noel & Fiscella, 2019; Tavakkoli et al., 2020; Zhou et al., 2017). Future research should focus on the patterns of care associated with race, ethnicity, and social determinants of health (e.g., socioeconomic status) in patients diagnosed with CUP and pancreatic cancer. The inclusion of social determinants of health in epidemiological research, as well as race/ethnicity, will be necessary to progress the field of health services research, primarily the specialty of cancer epidemiology, forward. Furthermore, supplementary diagnostic testing specific to metastatic pancreatic cancer, to include esophagogastroduodenoscopy (EGD), endoscopic ultrasound (EUS), endoscopic

retrograde cholangiopancreatography (ERCP), and molecular profiling would more substantially elucidate the extent of diagnostic investigation which occurred for this population (Ducreux et al., 2015; Sohal et al., 2020).

Limitations. While SEER-Medicare data provided a robust sample size, there were limitations. The study population was limited to patients 65 years and older and did not include patients with private insurance coverage. However, the age range of an average patient with CUP is 80 years or older and the vast majority of patients 65 years and older are insured through Medicare (FIF, 2015). These studies only investigated patients with a final metastatic pancreatic cancer diagnosis. Further research of other CUP-primary site cancers, for example ovarian and lung cancers, would be beneficial to the growing scientific literature on the diagnostic complexity of CUP. It is important to note clinicians may need to report a definitive diagnosis to justify treatment for insurance claims and there is no way to identify if patients refused diagnostic testing or were too frail to undergo a substantial diagnostic work-up. Moreover, claims data for administrative and billing purposes might be inaccurate from a biological or clinical disease perspective. These studies do not include biospecimen and/or genomics data, which limits the evaluation of innovative diagnostic approaches for CUP, including biomarkers and molecular alteration. There is also a potential limitation in studies focusing on timely diagnosis and length time bias, where ill-defined dates of diagnoses may skew the data. However, SEER-Medicare data contains the date of the first histological confirmation of malignancy, which is an appropriate variable to ascertain time of cancer diagnosis, thereby decreasing effects of length time bias (Weller et al., 2012; Neal et al., 2014).

Conclusion. By assessing current epidemiological studies on CUP diagnosis in the systematic review, we gained a broader understanding of how patients initially present with CUP and what healthcare utilization looks like for this population. The SEER-Medicare studies assessed favorable and unfavorable patient characteristics, as well as overall survival associated with guideline adherent, definitive and timely diagnosis of metastatic pancreatic cancer in patients who initially presented with CUP based on a large and representative population-based cohort. The outcomes highlighted in this dissertation elucidate the real-world value of making a definitive and timely diagnosis in the survival of patients with CUP and metastatic pancreatic cancer and evaluating their complex diagnosis utilizing recommended diagnostic guidelines. Furthermore, health disparities identified, namely for older, Black, Latino, and rural-residing patients with multiple comorbidities, require further study to ascertain health care delivery and diagnosis improvement in cancer health services.

References

1) American Cancer Society [ACS]. (2020, January 8). *Key statistics for pancreatic cancer*. American Cancer Society. https://www.cancer.org/cancer/pancreatic-cancer/about/key-statistics.html#references
2) Bai, Y. & Zhao, H. (2018). Liquid biopsy in tumors: Opportunities and challenges. *Annals of Translational Medicine*, *6*(Suppl 1), S89. doi: https://dx.doi.org/10.21037%2Fatm.2018.11.31
3) Cabana, M. D., Rand, C. S., Powe, N. R., Wu, A. W., Wilson, M. H., Abboud, P. A., & Rubin, H. R. (1999). Why don't physicians follow clinical practice guidelines? A framework for improvement. *Journal of the American Medical Association*, *282*(15), 1458-65.
4) Conway, A.-M., Mitchell, C., & Cook, N. (2019). Challenge of the unknown: How can we improve clinical outcomes in cancer of unknown primary? *Journal of Clinical Oncology*, *37*(23), 2089-2090. doi: 10.1200/JCO.19.00449
5) Department of Health Pharmaceutical Oncology Initiative [DHPOI]. (2012). *The impact of patient age on clinical decision-making in oncology*. London Department of Health.
6) Dillmon, M., Goldberg, J. M., Ramalingam, S. S., Mayer, R. J., Loehrer, P., & Van Poznak, C. (2012). Clinical practice guidelines for cancer care: Utilization and expectations of the practicing oncologist. *Journal of Oncology Practice*, *8*(6), 350-353.
7) Ducreux, M., Cuhna, A. S., Caramella, C., Hollebecque, A., Burtin, P., Goéré, D., Seufferlein, T., Haustermans, K., Van Laethem, J. L., Conroy, T., & Arnold, D on

behalf of the ESMO Guidelines Committee. (2015). Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, *26*(Supplement 5), v56-v68. doi: 10.1093/annonc/mdv295

8) Dyrvig, A., Yderstræde, K. B., Gerke, O., Jensen, P. B., Hess, S., Høilund-Carlsen, P. F., & Green, A. (2017). Cancer of unknown primary: Registered procedures compared with national integrated cancer pathway for illuminating external validity. *Medicine*, *96*(16), e6693.
9) Federal Interagency Forum [FIF] on Aging-Related Statistics. (2015). *Older Americans: Key indicators of well-being.* U.S. Government Printing Office.
10) Henrikson, N.B., Aiello Bowles, E. J., Blasi, P. R., et al. (2019). Screening for pancreatic cancer: Updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA, 322*(5), 445–454. doi:10.1001/jama.2019.6190
11) Jones, W., Allardice, G., Scott, I., Oien, K., Brewster, D., & Morrison, D. S. (2017). Cancers of unknown primary diagnosed during hospitalization: A population-based study. *BMC Cancer*, *17*(85). https://doi.org/10.1186/s12885-017-3083-1
12) Jooste, V., Dejardin, O., Bouvier, V., Arveux, P., Maynadie, M., Launoy, G. & Bouvier, A.-M. (2016). Pancreatic cancer: Wait times from presentation to treatment and survival in a population-based study. *International Journal of Cancer*, *139*, 1073-1080. https://doi.org/10.1002/ijc.30166
13) Karapetis, C. S., Guccione, L., Tattersall, M. H. N., Gooden, H., Vajdic, C. M., Lambert, S., Robotin, M., Mileshkin, L. & Schofield, P. (2017). Perceptions of cancer

of unknown primary site: A national survey of Australian medical oncologists. *Internal Medicine Journal*, *47*(4), 408-414.

14) Khalaf, N., El-Serag, H. B., Abrams, H. R., & Thrift, A. P. (2020). Burden of pancreatic cancer: From epidemiology to practice. *Clinical Gastroenterology and Hepatology*, *In press.*

15) Klabunde, C. N., Warren, J. L., & Legler, J. M. (2002). Assessing comorbidity using claims data: An overview. *Medical Care*, *40*(8 Suppl), IV-26-35.

16) Kok, S. M. J., van Laarhoven, H. W. M., Lemmens, V. E. P. P., & Schroten, C. (2015). International variation in diagnostic and treatment guidelines for carcinoma unknown primary. *International Journal of Cancer Research*, *49*(2), 1711-1722.

17) Kredo, T., Bernhardsson, S., Machingaidze, S., Young, T., Louw, Q., Ochodo, E., & Grimmer, K. (2016). Guide to clinical practice guidelines: The current state of play. *International Journal for Quality in Health Care*, *28*(1), 122-128. doi: https://dx.doi.org/10.1093%2Fintqhc%2Fmzv115

18) Lukács, G., Kovács, Á., Csanádi, M., Moizs, M., Repa, I., Kaló, Z., Vokó, Z., & Pitter, J. G. (2019). Benefits Of timely care in pancreatic cancer: A systematic review to navigate through the contradictory evidence. *Cancer Management and Research*, *11*, 9849-9861. https://doi.org/10.2147/CMAR.S221427

19) Malone, E. R., Oliva, M., Sabatini, P. J. B., Stockley, T. L., & Siu, L. L. (2020). Molecular profiling for precision cancer therapies. *Genome Medicine*, *12*(8). https://doi.org/10.1186/s13073-019-0703-1

20) Massarweh, N. N., Park, J. O., Bruix, J., Yeung, R. S., Etzioni, R. B., Symons, R. G., Baldwin, L. M., & Flum, D. R. (2011). Diagnostic imaging and biopsy use among

elderly Medicare beneficiaries with hepatocellular carcinoma. *Journal of Oncology Practice, 7*, 155-60.

21) Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & The PRISMA Group. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. *Journal of Clinical Epidemiology, 62*(10), 1006-1012. doi:10.1016/j.jclinepi.2009.06.005

22) National Cancer Institute [NCI]. (2017). *Cancer of unknown primary – Health professional version*. National Cancer Institute. https://www.cancer.gov/types/unknown-primary/hp

23) Neal, R. D., Din, N. U., Hamilton, W., Ukoumunne, O. C., Carter, B. Stapley, S., & Rubin, G. (2014). Comparison of cancer diagnostic intervals before and after implementation of NICE guidelines: Analysis of data from the UK General Practice Research Database. *British Journal of Cancer, 110*(3), 584-592. doi: 10.1038/bjc.2013.791

24) Noel, M. & Fiscella, K. (2019). Disparities in pancreatic cancer treatment and outcomes. *Health Equity, 3*(1), 532-540. http://doi.org/10.1089/heq.2019.0057

25) Pavlidis, N. & Pentheroudakis, G. (2012). Cancer of unknown primary site. *The Lancet, 379*(9824), 1428-1435. doi: 10.1016/S0140-6736(11)61178-1

26) Pavlidis, N., Rassy, E., & Smith-Gagen, J. (2019). Cancer of unknown primary: Incidence rates, risk factors and survival among adolescents and young adults. *International Journal of Cancer, 146*(6), 1490-1498. https://doi-org.unr.idm.oclc.org/10.1002/ijc.32482

27) Pentheroudakis, G., Stahel, R., Hansen, H., & Pavlidis, N. (2008). Heterogeneity in cancer guidelines: Should we eradicate or tolerate? *Annals of Oncology, 19*(12), 2067-2078. doi: 10.1093/annonc/mdn418

28) Qaseem, A., Usman, N., Jayaraj, J. S., Janapala, R. N., & Kashif, T. (2019). Cancer of unknown primary: A review on clinical guidelines in the development and targeted management of patients with the unknown primary site. *Cureus, 11*(9), e5552. https://dx-doi-org.unr.idm.oclc.org/10.7759%2Fcureus.5552

29) Rassy, E. & Pavlidis, N. (2019). The currently declining incidence of cancer of unknown primary. *Cancer Epidemiology, 61*, 139-141.

30) Rassy, E. & Pavlidis, N. (2020). Progress in refining the clinical management of cancer of unknown primary in the molecular era. *Nature Reviews Clinical Oncology*.

31) Rothman, K. J. & Greenland, S. (2005). Causation and causal inference in epidemiology. *American Journal of Public Health*, *95*(suppl 1), S144–S150.

32) Schaffer, A. L., Pearson, S. A., Dobbins, T. A., Er, C. C., Ward, R. L., & Vajdic, C. M. (2015). Patterns of care and survival after a cancer of unknown primary (CUP) diagnosis: A population-based nested cohort study in Australian Government Department of Veterans' Affairs clients. *Cancer Epidemiology, 39*(4), 578-584.

33) Schaffer, A. L., Pearson, S., Perez-Concha, O., Dobbins, T., Ward, R. L., van Leeuwen, M. T., . . . Vajdic, C. M. (2020). Diagnostic and health service pathways to diagnosis of cancer-registry notified cancer of unknown primary site (CUP). *PLoS One*, *15*(3).

34) Sève, P., Mackey, J., Sawyer, M., Lesimple, T., de La Fouchardière, C., Broussolle, C., … Ray-Coquard, I. (2009). Impact of clinical practice guidelines on the

management for carcinomas of unknown primary site: A controlled “before-after” study. *Bulletin du Cancer, 96*(4), E7-E17. doi: 10.1684/bdc.2009.0870

35) Smith-Gagen, J., Drake, C. M., White, L. L., & Pinheiro, P. S. (2019). Extent of diagnostic inquiry among a population-based cohort of patients with cancer of unknown primary. *Cancer Reports and Reviews, 3*(3).

36) Sohal, D. P. S., Kennedy, E. B., Cinar, P., Conroy, T., Copur, M. S., Crane, C. H., Garrido-Laguna, I., Lau, M. W., Johnson, T., Krishnamurthi, S., Moravek, C., O’Reilly, E. M., Philip, P. A., Pant, S., Shah, M. A., Sahai, V., Uronis, H. E., Zaidi, N., & Laheru, D. (2020). Metastatic pancreatic cancer: ASCO guideline update. *Journal of Clinical Oncology, 38*(27), 3217-3230.

37) Stella, G. M., Senetta, R., Cassenti, A., Ronco, M., & Cassoni, P. (2012). Cancers of unknown primary origin: Current perspectives and future therapeutic strategies. *Journal of Translational Medicine, 10*(12), 1-11. doi: 10.1186/1479-5876-10-12

38) Tavakkoli, A., Singal, A. G., Waljee, A. K., Elmunzer, B. J., Pruitt, S. L., McKey, T., Rubenstein, J. H., Scheiman, J. M., & Murphy, C. C. (2020). Racial disparities and trends in pancreatic cancer incidence and mortality in the United States. *Clinical Gastroenterology and Hepatology, 18*(1), 171-178.e10.

39) Vajdic, C. M., Perez-Concha, O., Rhee, J. J., Dobbins, T., Ward, R. L., Schaffer, A. L., van Leeuwen, M. T., Laaksonen, M. A., Craigen, G., & Pearson, S. A. (2019). Health-related predictors of cancer registry-notified cancer of unknown primary site (CUP). *Cancer Epidemiology, 61*, 1-7.

40) Vajdic, C. M., Schaffer, A. L., Dobbins, T. A., Ward, R. L. Er, C. C., & Pearson, S. (2015). Health service utilization and investigations before diagnosis of cancer of

unknown primary (CUP): A population-based nested case-control study in Australian Government Department of Vetereans' Affairs clients. *Cancer Epidemiology, 39*(4), 585-592.

41) Varadhachary, G. R. & Raber, M. N. (2014). Cancer of unknown primary site. *The New England Journal of Medicine, 371*(8), 757-765. doi: 10.1056/NEJMra130391

42) Varghese, A. M., Arora, A., Capanu, M., Camacho, N., Won, H. H., Zehir, A., Gao, J., Chakravarty, D., Schultz, N., Klimstra, D. S., Ladanyi, M., Hyman, D. M., Solit, D. B., Berger, M. F., & Saltz, L. B. (2017). Clinical and molecular characterization of patients with cancer of unknown primary in the modern era. *Annals of Oncology, 28*(12), 3015-3021. https://doi.org/10.1093/annonc/mdx545

43) Weller, D., Vedsted, P., Rubin, G., Walter, F. M., Emery, J., Scott, S., Campbell, … Neal, R. D. (2012). The Aarhus statement: Improving design and reporting of studies on early cancer diagnosis. *British Journal of Cancer, 106*(7), 1262-1267. doi: 10.1038/bjc.2012.68

44) Zhang, Q., Zeng, L., Chen, Y., Lian, G., Qian, C., Chen, S., Li, J., & Huang, K. (2016). Pancreatic cancer epidemiology, detection, and management. *Gastroenterology Research and Practice,* 8962321. https://doi.org/10.1155/2016/8962321

45) Zhou, H., Zhang, Y., Wei, X., Yang, K., Tan, W., Qiu, Z., Li, S., Chen, Q., Song, Y., & Gao, S. (2017). Racial disparities in pancreatic neuroendocrine tumors survival: A SEER study. *Cancer Medicine, 6*(11), 2745- 2756.