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Outcomes of Tumor-Directed Surgery in Cancers of Head of Pancreas, Ampulla and Extrahepatic Bile Ducts: Influence of Patient Demographics, Disease Characteristics and Geographic Factors

By

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Master of Public Health

Epidemiology

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Michael Goodman

Faculty Thesis Advisor

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Abstract

Outcomes of Tumor-Directed Surgery in Cancers of Head of Pancreas, Ampulla and Extrahepatic Bile Ducts: Influence of Patient Demographics, Disease Characteristics and Geographic Factors

By Silu Liu

BACKGROUND: Despite shared anatomic location and similar surgical treatment, cancers of the periampullary region, which includes head of pancreas, ampulla, and extrahepatic bile ducts, have important differences with respect to histologic features, patient demographics, clinical manifestation and survival. The purpose of this analysis was to assess which patient-, disease- and treatment-related characteristics may act as determinants of survival among patients newly diagnosed with periampullary tumors.

METHODS: Patients with resectable adenocarcinoma of the head of pancreas, ampulla, and extrahepatic bile ducts who were reported to the US National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program, from 2004 to 2012, were categorized by primary tumor site, surgery status, sex, marital status, race, age, grade, AJCC stage, tumor size, and residency. Post-diagnosis survival was examined using Cox regression models with results expressed as hazard ratios (HR) along with the corresponding 95% confidence intervals (95% CI).

RESULTS: A total of 10,383 eligible patients were identified in the SEER data. Surgery receipt was consistently associated with better prognosis for all three tumors with adjusted HRs (95% CI) of 0.41 (0.34 - 0.50), 0.21 (0.16 - 0.27), 0.35 (0.33 - 0.38) for extrahepatic bile ducts, ampulla and head of pancreas, respectively. Greater age and advanced grade were consistently associated with a significant worse prognosis for all three sites. Among patients in the surgical group, ampullary cancers were associated with better prognosis (HR, 0.56; 95% CI, 0.49 - 0.66) compared to cancers of the pancreatic head. Other significant predictors for worse prognosis in the surgically treated groups included male gender, black race, older age, greater tumor size, and more advanced tumor grade.

CONCLUSIONS: Our study identified substantial heterogeneity of factors that affect prognosis of patients diagnosed with tumors of the periampullary region. Additional research evaluating the roles of the interval between diagnosis and surgery, resection margins, preoperative laboratory values, perioperative complications, provider characteristics and individual patient-level lifestyle and socioeconomic factors is warranted.

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BACKGROUND

Cancers of the head of pancreas, ampulla, and extrahepatic bile ducts originate from organs that share a common anatomic location, which includes the ampulla of Vater and the periampullary region. The ampulla of Vater is a complex structure formed by three components: the ampulla (common channel), the common bile duct (CBD) and the pancreatic duct, which adjoin the papilla of Vater together with the duodenum [1, 2]. The term ampullary carcinoma should be distinguished from periampullary carcinoma, which is commonly referred to a group of neoplasms arising from heterogeneous structures including the head of pancreas, the distal common bile duct (CBD) and the duodenum [3].

Cancer of the pancreatic head represents 75% of all malignant tumors of the pancreas, which are the fourth most common cause of death from cancer in the United States [4, 5]. It is estimated that in 2015 alone, nearly 50,000 new pancreatic cancer cases were diagnosed and more than 40,000 patients died from this disease [5]. The prognosis for carcinoma of the pancreas is poor. The five-year survival is less than 5% overall and only 15% - 20% even for patients who underwent tumor resection [6].

Primary ampullary carcinoma is defined as a malignancy originating in the enterocoele or the wall of the intra-ampullary component of the common bile and/or pancreatic duct, or at the papilla of Vater, or the duodenal surface of the papilla [1]. Based on the 1973-2005 data, the overall incidence of ampullary cancer is 0.49 per 100,000. This represents 6-8% and 0.2-0.5% of tumors in the pancreatic head region and all gastrointestinal malignancies, respectively [7]. There are two main histological subtypes of this carcinoma, intestinal and pancreatobiliary with the former characterized by lower probability of lymph node metastasis, less perineural invasion, lower risk of recurrence and better long-term survival after resection [8]. The overall five-year survival across both types varies between 4% and 45% depending on stage at presentation [9].

Approximately 90% of cholangiocarcinomas are extrahepatic bile duct cancers. The incidence of extrahepatic bile duct carcinoma is reported to be 1.2 per 100,000 and 0.8 per 100,000 for males and females, respectively [10]. For patients undergoing curative resection followed by adjuvant chemoradiotherapy, five-year survival for distal extrahepatic carcinoma varies from 9% to 50% depending on the pathologic stage, number of lymph nodes and perineural invasion [11, 12].

In the addition to common anatomic location, the three tumors of the ampulla and periampullary region share similar surgical treatment which typically involves pancreaticoduodenectomy, also known as Whipple procedure [13]. The classic Whipple procedure, which was developed specifically for pancreatic cancers, is defined as removal of the head of the pancreas, distal bile duct, gallbladder, duodenum, first few centimeters of the jejunum and about 50% of the distal stomach [14]. In recent years, however, the term "pancreaticoduodenectomy" has been used to describe a variety modifications, which may include total pancreatectomy, regional pancreatectomy, portal vein resection, and extended lymphadenectomy [15].

Due to the shared anatomic location and similar surgical treatment, the adenocarcinomas of the head of pancreas, ampulla, and extrahepatic bile ducts are sometimes viewed as a single group. Despite the similarities, however, these tumors have important differences with respect to histologic features, patient demographics, clinical manifestation and survival [3, 7].

This heterogeneity of resectable ampullary and periampullary adenocarcinomas prompted the current analysis, which uses national cancer surveillance data to examine the differences and similarities of prognostic factors across the three tumor types. The specific aim of this paper is to assess how disease stage, tumor size, extent of lymph node involvement, and primary site may act as determinants of survival among patients who underwent pancreaticoduodenecotomy. Although in some cases duodenal carcinomas may also be considered as periampullary tumors, cancers of the duodenum are included in this category only if they are located within the duodenal-facing surface of the ampullary protrusion [1]. Unfortunately, the precise location of the duodenal tumors is not reported in the national cancer surveillance data, and for this reason carcinomas of the duodenum are not included in this study. The association between clinical characteristics and postoperative prognosis will be examined while controlling for patient demographic residential factors.

MATERIALS AND METHODS

The data for the present analysis were obtained from the US National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program [16]. Selection of cases was based on the primary disease site using codes from the International Classification of Diseases for Oncology, third edition (ICD-O-3). Inclusion criteria for this study were: 1) primary sites of carcinomas in extrahepatic bile ducts, ampulla, or head of pancreas (ICD-O-3 codes C24.0, C24.1 and C25.0); 2) years of diagnosis 2004 - 2012; 3) one primary carcinomas only (sequence number 0); 4) histologic type of adenocarcinoma (ICD-O-3 codes 8140 – 8389); 5) malignant behavior; and 6) patients in a research database.

As 90% of eligible patients were Whites or African Americans, the dataset was limited to these two race groups. In addition, since the primary purpose for this study was to assess survival among patients treated with or without pancreaticoduodenecotomy patients with localized disease were considered for analyses. Thus the additional inclusion criterion was the American Joint Commission on Cancer (AJCC) 6th edition stages I and II.

The main predictor variable of interest was Whipple or Whipple-like surgery (Yes vs. No). For patients with carcinomas in extrahepatic bile ducts or in ampulla, the Whipple-like procedure includes radical surgery with "debulking", and partial or total removal of the primary site with a resection in continuity with other organs. For patients with carcinomas in head of pancreas, the surgery of interest includes local or partial pancreatectomy and duodenectomy (with or without distal/partial gastrectomy), pancreatectomy or total pancreatectomy (with or without subtotal gastrectomy or duodenectomy), and extended pancreatoduodenectomy. Patients with no surgery of primary site were defined as the “no surgery” group. [16] The covariates included sex (male vs. female), marital status (married/ other partner, single, separated/ divorced, or widowed), race (White vs. Black), age (<70 vs. ≥70 years old), grade (I-II, III-IV or unknown), tumor size (<2 cm, ≥2 cm or unknown), AJCC stage (I vs. II), and residency (metropolitan vs. non-metropolitan).

Survival time was defined as the interval from the date of diagnosis to the recorded date of death or end of follow up (60 months from diagnosis or December 31, 2012, whichever came first).

Distributions of patient demographics, disease characteristics and residency variables were compared across three cancer sites. Median overall survival (the post diagnosis interval during which half of the patients are still alive) and observed survival (the proportion of patients surviving beyond a given time interval) were analyzed according to surgery category for different primary cancer sites. Kaplan-Meier methods with corresponding log-rank tests for statistical significance were used to examine unadjusted overall survival. Multivariable Cox proportional hazard models were used to evaluate the association between survival and surgery for each cancer site, while adjusting for possible confounders including patient demographics, disease characteristics and residency. Results of the Cox models were expressed as adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Proportional hazard (PH) assumptions were assessed using log-log survival curves for all independent variables in the model. If the PH assumption was not satisfied, a Cox model stratified by the variable which violates the assumption was used. Interaction between the main exposure variable of interest (surgery) and each covariate was evaluated using trunk test and backward elimination methods [17]. In the presence of interactions, restricted models were used to determine whether the HRs differences were appreciably different across strata.

All statistical tests in this study are based on a two-sided significance level of 0.05. All analyses were performed using SAS statistical software (SAS 9.4, SAS Institute, Cary, NC).

RESULTS

A total of 10,383 patients with primary adenocarcinomas of extrahepatic bile ducts, ampulla and head of pancreas were identified in the 18 SEER registries from 2004 to 2012. As shown in Table 1, most cases originated in the head of pancreas (78%) and nearly 90% of the patients were from metropolitan areas. Extrahepatic bile duct cancer patients were less likely to undergo Whipple-like procedures (28%) compared to patients diagnosed with pancreatic or ampullary. Nearly half of the patients were 70 years of age or older. Black patients constituted 9% of cases for both extrahepatic bile duct and ampullary cancer, 12% for carcinomas originating in the head of pancreas. The majority of pancreatic carcinoma patients had AJCC Stage II disease (83%) or tumor size greater than 2 cm (85%). The corresponding proportions for cancers of the ampulla and extrahepatic bile ducts ranged from 33% to 52%. (Table 1)

The unadjusted Kaplan-Meier survival curves illustrated that the overall survival of patients differed significantly by tumor site and by surgery receipt. As shown in Figures 1a – 1c, patients with Whipple or Whipple-like surgeries had better overall survival for all the three cancer sites ($p < 0.0001$ for all log-rank tests). In the no-surgery group, median overall survival across all three cancer sites was less than 10 months. In contrast, median overall survival estimates for surgically treated patients were 22 months for extrahepatic bile duct cancer, 49 months for ampullary cancer, and 19 months for the carcinomas of the pancreatic head (Supplementary Table 1). Among all surgically treated patients, ampullary cancer had the best overall survival (83% and 47% at 1- and 5-years after diagnosis, respectively); the corresponding 1- and 5-year survival estimates for the other two cancers ranged from 67% to 69% and from 19% to 25%, respectively. (Figure 2a, Supplemental Table 1)

In the multivariable Cox models evaluating the association between surgery and disease-specific survival, all independent variables except AJCC stage, satisfied the PH assumptions for all the three tumor sites. For this reason Cox proportional hazards models were stratified by AJCC stage. A statistically significant interaction term ($p<0.05$) for surgery and sex was found in the analysis of ampullary cancers. Similarly, interactions between surgery and marital status, and between surgery and AJCC stage were found in model evaluating cancer of the head of pancreas. However, after comparing the HRs across different categories of covariates, no meaningful differences were observed (Supplemental Table 2). For this reason we used models without interactions.

As demonstrated in Table 2, surgery receipt was associated with better prognosis across all sites with multivariable adjusted HR (95% CI) estimates of 0.41 (0.34, 0.50) cancers of extrahepatic bile ducts,); 0.21 (0.16, 0.27) for ampullary cancers and 0.35 (0.33, 0.38) for carcinomas of the head of pancreas. Married patients and the Black patients experience better prognosis for cancers of the extrahepatic bile ducts and head of pancreas, but not for ampullary cancers. For all three sites, patients aged 70 years and older had consistently higher mortality than those with of younger age. Higher grade was associated with significantly worse prognosis in three analyses; however greater tumor size was associated with greater mortality for cancers of the extrahepatic biliary duct and head pancreas but not for ampullary carcinomas. Patients residing in metropolitan areas had significantly lower mortality for cancer of the head of pancreas, but not for extrahepatic bile duct or ampullary cancers. (Table 2)

In the evaluation of association between tumor site and survival among patients with Whipple or Whipple-like surgeries, Cox proportional hazards model stratified by

AJCC stage, tumor size and residency because the data for these variables did not satisfy the PH assumption. As demonstrated in Table 3, compared with patients with tumors of head of pancreas, ampullary patients experienced better prognosis with adjusted HR estimate of 0.56 (95% CI: 0.49, 0.65). Survival among surgically treated patients of extrahepatic bile duct cancers was similar to that of pancreatic cancer patients. White patients, patients with greater age and advanced grade had significantly higher mortality. (Table 3)

Table 4 presents the results of an alternative Cox model that excluded patients with unknown tumor size. After exclusion of this category of patients (N=176) the PH assumption for tumor size was no longer violated, and for this reason the model was only stratified on AJCC stage and residency Patients with greater tumor size were found to have significantly worse prognosis with HR (95% CI) estimate of 1.29 (1.15, 1.45). Other findings in Table 4 were similar to the results of the original model. (Table 3)

DISCUSSION

Primary findings in this study indicate that surgery receipt, younger age, and lower grade tumors may be associated with better prognosis for patients with carcinomas of extrahepatic bile ducts, ampulla and head of pancreas. Among patients who underwent Whipple surgeries, those diagnosed with ampullary cancer may experience better prognosis compared to patients treated for tumors of the other two sites. White patients, patients of more advanced age, those with tumors of more advanced grade and larger size had significantly higher mortality.

Our findings are consistent with previous studies which indicate a good prognosis for patients who underwent Whipple or Whipple-like surgeries [15]. The effectiveness of this surgery was in doubt because of the disappointing postoperative mortality, but it remains the only potentially curative therapy for periampulary carcinomas [14, 15].

Our observation that primary tumor site is associated among surgically treated patients is consistent with earlier reports. In one previous study reviewing the pathology, complications and outcomes for 650 consecutive pancreaticoduodenectomies, consistently better prognosis was found for ampullary tumors. Unlike our study results, 5-year survival for pancreatic tumors in that study was better than that for bile duct tumors [18]. In another earlier study of patients undergoing pancreaticoduodenectomy between 1980 and 2002, those with pancreatic tumors had the worst 5-year survival, while in contrast to our findings, patients with bile duct cancers had better 5-year survival than those with ampullary tumors [19].

One possible explanation for this inconsistency is that the three studies covered different periods. Our study concentrates on patients diagnosed most recently (between

2004 and 2012), while the data from the other two studies were collected in the 1990s [18] or in the 20 year interval between 1980 and 2002 [19]. Another possible explanation for the disagreement is the differences in the three study populations. Both previous studies were single institution based and the 1990s study, was limited to periampullary adenocarcinomas.

Advanced grade and stage, greater tumor size and age, were also identified as important predictors of worse prognosis in other studies [18-23]. However, in our study, AJCC stage violated the PH assumption, for this reason, it was included in the proportional hazards model as a stratified variable. A recent review regarding pathologic staging of ampulla-pancreatobiary tract tumors indicated that staging for periampullary tumors using current AJCC/TNM staging system lacks reproducibility and clinical relevance [24]. The association between TNM staging and survival for periampullary tumors needs further studies based on new proposals and staging system with proper revision.

To our knowledge, this is the first population-based study to investigate the association between surgery and disease-specific survival, as well as the association between primary tumor site and survival, in surgically treated patients with ampullary and periampullary cancers. An important advantage of this study is the use of population-based SEER data. As noted previously, the large sample size of SEER-based studies allow studying rare cancers, provide sufficient power to detect relatively moderate associations, and enables a variety of multivariable analyses. Population-based identification of patients adds external validity and allows more generalized conclusions. In addition, patients registered in SEER are under active follow-up, which increases accuracy of survival analyses [25, 26].

Despite the advantages of using population-based data, there are several inherent limitations of the SEER data. For example, information on the precise location of the duodenal tumors was not available from SEER data, and for this reason, carcinomas of the duodenum, some of which may originate in the periampullary region were excluded from the analyses. Another limitation for this study refers to the potential immortal time bias that may have affected the observed association between surgery and survival. For the surgical group, patients have to survive until the surgery. That is to say, during the period of follow-up between diagnosis and surgery, death cannot occur. In contrast, patients in nonsurgical group do not have a minimum survival requirement, and as a result, their follow up does not include the "immortal" period. If the interval between diagnosis and surgery is substantial this may have resulted in a spurious survival advantage observed in the surgical group [27]. One way to address this bias is to perform time-dependent analysis [28, 29]. But this is not feasible in our study since information of exact date of surgery is not available in SEER. On the other hand the results of the analyses by cancer site are less likely to be affected by immortal time bias because all patients in those analyses received surgery. Other limitations of the SEER data include lack of information on resection margins, preoperative laboratory values, perioperative complications and other socioeconomic factors that may affect patients' survival [18, 19].

CONCLUSIONS AND FUTURE DIRECTIONS

Our study identified a number of demographic factors, disease characteristics and geographic variables that may affect survival of patients diagnosed with tumors of the extrahepatic bile ducts, ampulla, or head of pancreas. Despite the shared anatomic location and similar surgical treatment, heterogeneity of survival for resectable ampullary and periampullary adenocarcinomas also exist, with a significantly better prognosis for tumors in ampulla. Additional research evaluating the roles of the interval between diagnosis and surgery, resection margins, preoperative laboratory values, perioperative complications, provider characteristics and individual patient-level lifestyle and socioeconomic factors is warranted.

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TABLES

Table 1. Patient demographics, disease characteristics and residency by primary site: Surveillance, Epidemiology, and End Results (SEER) program (2004 – 2012).

Variable	**Level**	**Extrahepatic Bile Ducts (N=1412) N (%)**	**Ampulla (N=854) N (%)**	**Head of Pancreas (N=8117) N (%)**
Sex	Female	663 (47.0)	362 (42.4)	4,132 (50.9)
	Male	749(53.0)	492 (57.6)	3,985 (49.1)
Marital Status	Married/Partner	775 (54.9)	502 (58.8)	4,664 (57.5)
	Single, Separated/divorced	310 (22.0)	206 (24.1)	1,944 (23.9)
	Widowed	327 (23.2)	146 (17.1)	1,509 (18.6)
Race	White	1281 (90.7)	781 (91.5)	7,115 (87.7)
	Black	131 (9.3)	73 (8.5)	1,002 (12.3)
Age	<70	580 (41.1)	427 (50.0)	4,235 (52.2)
	>=70	832 (58.9)	427 (50.0)	3,882 (47.8)
Grade	I,II	372 (26.4)	502 (58.8)	2,606 (32.1)
	III,IV	212 (15.0)	222 (26.0)	1,738 (21.4)
	Unknown	828 (58.6)	130 (15.2)	3,773 (46.5)
AJCC Stage	I	703 (49.8)	407 (47.7)	1,424 (17.5)
	II	709 (50.2)	447 (52.3)	6,693 (82.5)
Tumor size	<2 cm	250 (17.7)	294 (34.4)	629 (7.8)
	>=2 cm	469 (33.2)	389 (45.6)	6,901 (85.0)
	Unknown	693 (49.1)	171 (20.0)	587 (7.2)
Vital Status	Alive	280 (19.8)	407 (47.7)	1,885 (23.2)
	Dead	1,132 (80.2)	447 (52.3)	6,232 (76.8)
Surgery	No surgery	1,014 (71.8)	258 (30.2)	4,709 (58.0)
	Potential Whipple	398 (28.2)	596 (69.8)	3,408 (42.0)
Residency	Non-metropolitan	180 (12.8)	91 (10.7)	1,000 (12.3)
	Metropolitan	1,232 (87.3)	763 (89.3)	7,117 (87.7)

Table 2. Adjusted Cox proportional hazards model evaluating the association between surgery and disease-specific survival in patients with carcinomas in extrahepatic bile ducts, ampulla, and head of pancreas: Surveillance, Epidemiology, and End Results (SEER) program (2004 – 2012).

Variable	Level	Extrahepatic Bile Ducts N=1412 HR (95%CI)	Ampulla N=854 HR (95%CI)	Head of Pancreas N=8117 HR (95%CI)
Surgery	No Surgery	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Potential Whipple	0.41 (0.34, 0.50)	0.21 (0.16, 0.27)	0.35 (0.33, 0.38)
Sex	Female	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Male	1.05 (0.92, 1.19)	0.82 (0.67, 0.99)	1.06 (1.01, 1.12)
Marital Status	Married/Partner	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Single, Separated/divorced	1.26 (1.08, 1.47)	1.18 (0.93, 1.49)	1.15 (1.08, 1.22)
	Widowed	1.13 (0.96, 1.32)	0.88 (0.68, 1.15)	1.26 (1.17, 1.35)
Race	White	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Black	1.05 (0.86, 1.30)	1.27 (0.92, 1.75)	1.11 (1.03, 1.20)
Age	<70	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥70	1.39 (1.22, 1.59)	1.73 (1.39, 2.15)	1.38 (1.31, 1.46)
Grade	I,II	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	III,IV	1.34 (1.10, 1.64)	1.34 (1.07, 1.67)	1.36 (1.27, 1.46)
	Unknown	1.22 (1.03, 1.45)	0.92 (0.70, 1.21)	1.05 (0.98, 1.13)
Tumor size	<2 cm	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	≥ cm	1.21 (1.01, 1.46)	1.17 (0.93, 1.48)	1.32 (1.19, 1.46)
	Unknown	1.43 (1.19, 1.70)	1.08 (0.81, 1.45)	1.38 (1.21, 1.58)
Residency	Non-metropolitan	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Metropolitan	0.92 (0.77, 1.10)	0.97 (0.70, 1.32)	0.89 (0.82, 0.95)

Table 3. Adjusted Cox proportional hazards model evaluating the association between tumor site and survival in patients with Whipple or Whipple-like surgery: Surveillance, Epidemiology, and End Results (SEER) program (2004 – 2012).

Variable	Level	N (%)	HR (95% CI)
Tumor Site	Head of Pancreas	3408 (77.4)	1.00 (Ref)
	Extrahepatic Bile Duct	398 (9.0)	0.98 (0.85, 1.12)
	Ampulla	596 (13.5)	0.56 (0.49, 0.65)
Sex	Female	2065 (46.9)	1.00 (Ref)
	Male	2337 (53.1)	1.08 (1.00, 1.17)
Marital Status	Married/Partner	2815 (63.9)	1.00 (Ref)
	Single, Separated/divorced	1025 (23.3)	1.10 (1.00, 1.21)
	Widowed	562 (12.8)	1.11 (0.98, 1.25)
Race	White	3941 (89.5)	1.00 (Ref)
	Black	461 (10.5)	1.18 (1.04, 1.34)
Age	<70	2822 (64.1)	1.00 (Ref)
	≥70	1580 (35.9)	1.35 (1.25, 1.47)
Grade	I,II	2529 (57.5)	1.00 (Ref)
	III,IV	1526 (34.7)	1.38 (1.28, 1.50)
	Unknown	347 (7.9)	0.91 (0.78, 1.06)

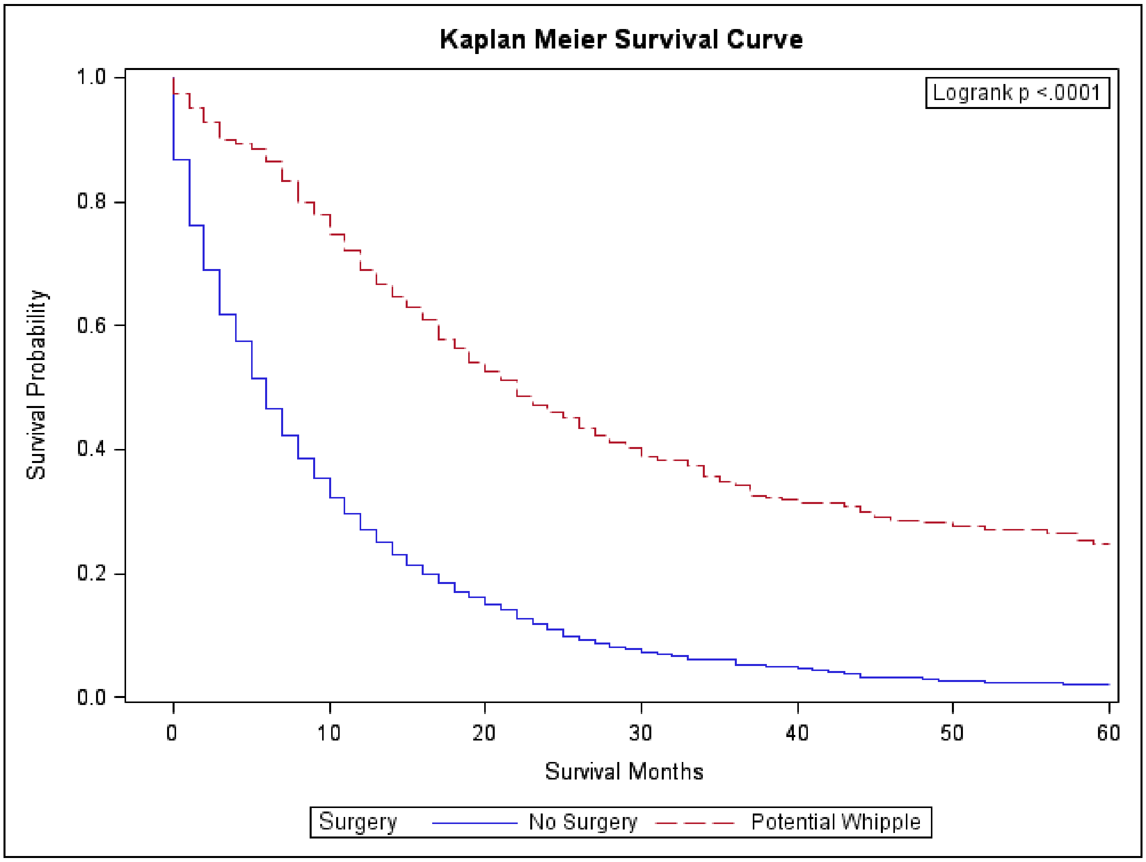
Table 4. Adjusted Cox proportional hazards model evaluating the association between tumor site and survival in patients with Whipple or Whipple-like surgery after excluding unknown tumor size: Surveillance, Epidemiology, and End Results (SEER) program (2004 – 2012).

Variable	Level	N (%)	HR (95% CI)
Tumor Site	Head of Pancreas	3343 (79.1)	1.00 (Ref)
	Extrahepatic Bile Duct	327 (7.7)	0.95 (0.82, 1.11)
	Ampulla	556 (13.2)	0.57 (0.49, 0.66)
Sex	Female	1993 (47.2)	1.00 (Ref)
	Male	2233 (52.8)	1.10 (1.01, 1.19)
Marital Status	Married/Partner	2699 (63.9)	1.00 (Ref)
	Single, Separated/divorced	988 (23.4)	1.10 (0.99, 1.21)
	Widowed	539 (12.7)	1.11 (0.98, 1.25)
Race	White	3777 (89.4)	1.00 (Ref)
	Black	449 (10.6)	1.22 (1.07, 1.38)
Age	<70	1999 (42.5)	1.00 (Ref)
	≥70	2707 (57.5)	1.36 (1.26, 1.48)
Grade	I,II	699 (14.9)	1.00 (Ref)
	III,IV	499 (10.6)	1.41 (1.30, 1.53)
	Unknown	3508 (74.5)	0.91 (0.77, 1.07)
Tumor size	<2 cm	411 (8.7)	1.00 (Ref)
	≥2 cm	4295 (91.3)	1.29 (1.15, 1.45)

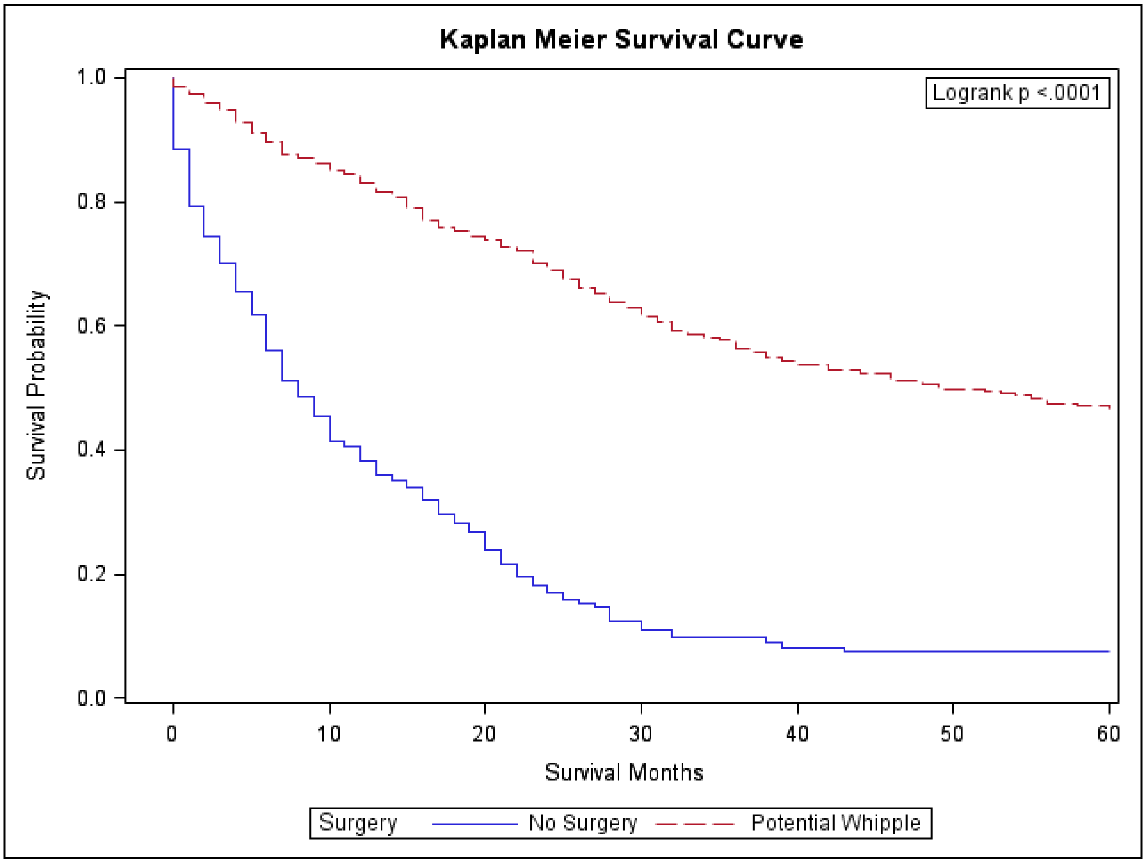
FIGURES

Figure 1. Kaplan-Meier survival curves by surgery receipt among patients with carcinoma of extrahepatic bile ducts (a), ampulla (b), head of pancreas (c) .

(a) Extrahepatic Bile Ducts



(b) Ampulla



Kaplan Meier Survival Curve
Logrank p <.0001
1.0
0.8
0.6
0.4
0.2
0.0
Survival Probability
0
10
20
30
40
50
60
Survival Months
Surgery
No Surgery
Potential Whipple

(c) Head of Pancreas

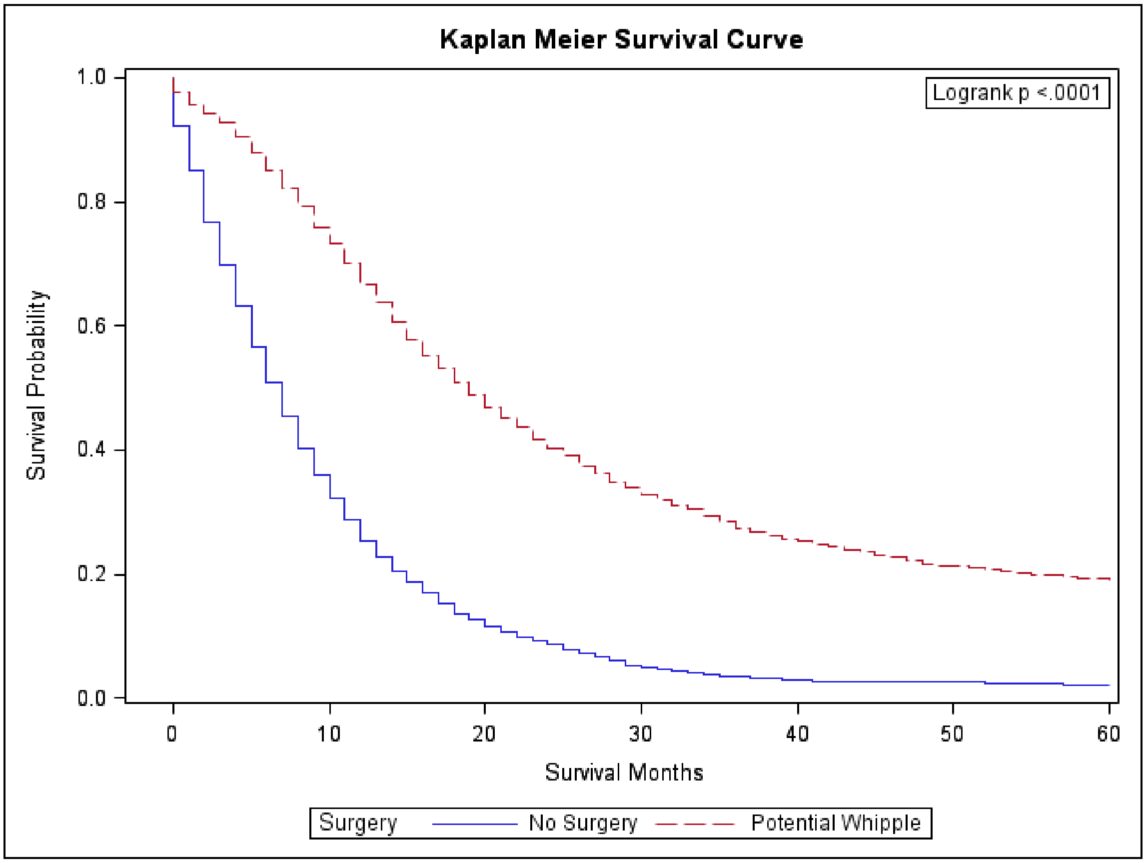
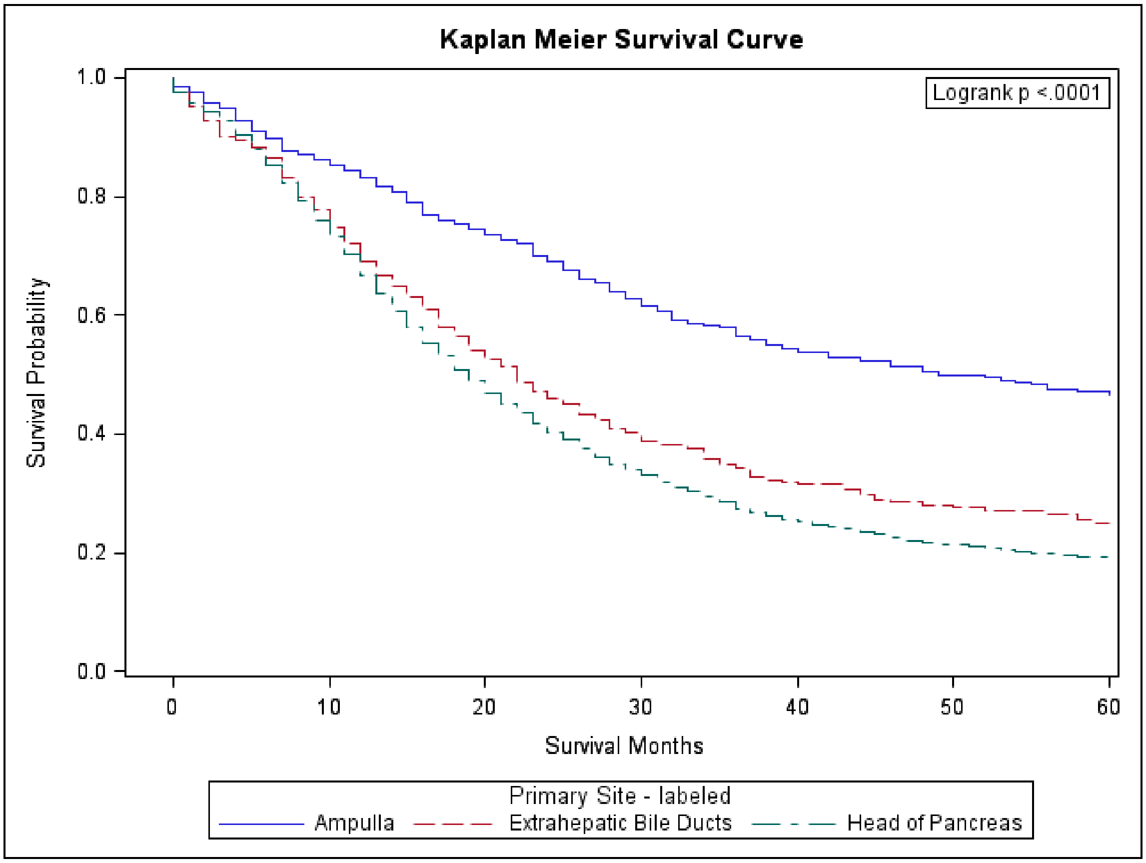
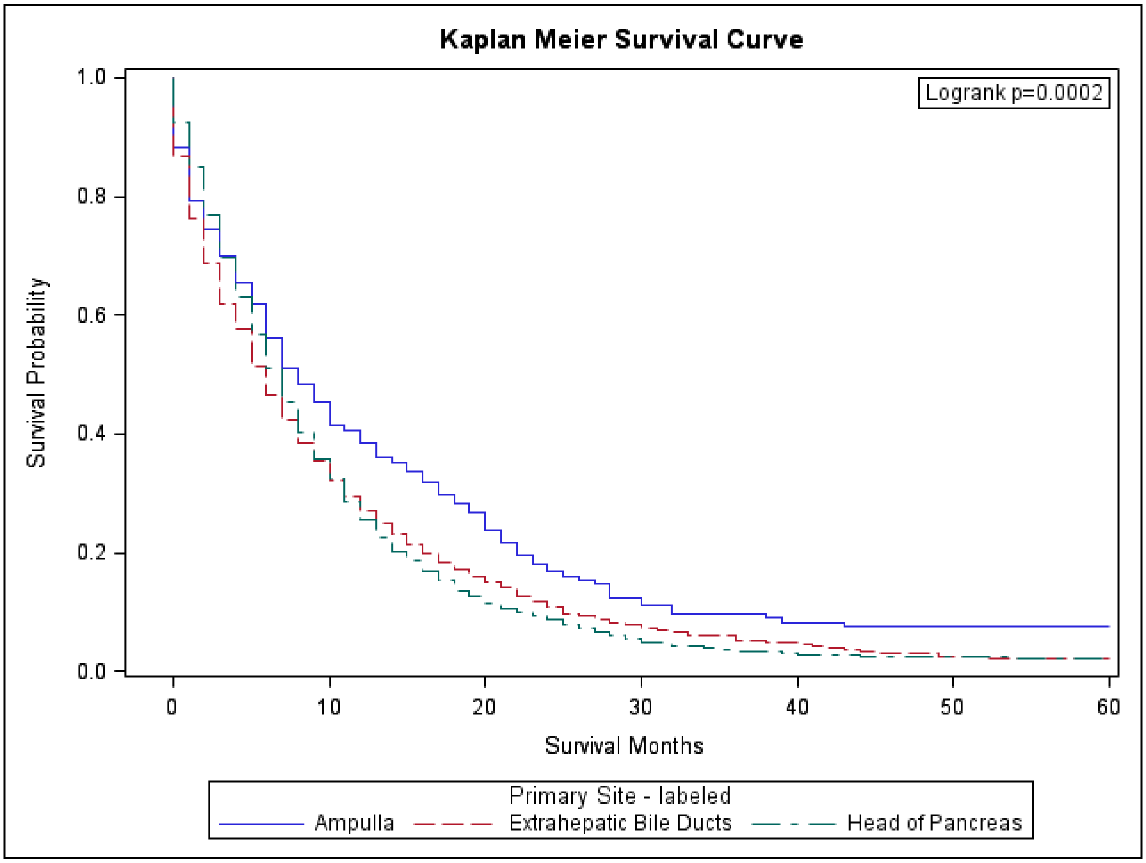


Figure 2. Kaplan-Meier survival curves by cancer site among surgical (a) and non-surgical (b) patients.

(a) Surgical



(b) Non-surgical



APPENDICES

Supplemental Table 1. Median survival, one-year survival and five-year survival by surgery status for three primary tumor sites.

Primary Site	No Surgery			Potential Whipple		
	Median Survival (95%CI)	1-year Survival (95% CI)	5-year Survival (95% CI)	Median Survival (95%CI)	1-year Survival (95% CI)	5-year Survival (95% CI)
Ampulla	8 (6, 10)	38.4% (32.2%, 44.5%)	7.4% (4.1%, 12.1%)	49 (39, NA)	83.0% (79.6%, 85.9%)	46.7% (41.6%, 51.6%)
Extrahepatic Bile Ducts	6 (5, 6)	27.0% (24.1%, 29.8%)	2.1% (1.1%, 3.5%)	22 (19, 26)	68.9% (63.9%, 73.4%)	24.8% (19.8%, 30.1%)
Head of Pancreas	7 (6, 7)	25.4% (24.1%, 26.8%)	2.1% (1.6%, 2.8%)	19 (18, 20)	66.7% (65.0%, 68.3%)	19.1% (17.4%, 20.8%)

Supplemental Table 2. Hazard ratios for surgery according to different levels of the covariate that showed statistically significant ($p<0.05$) interactions.

Primary Site	Variable	Restricted Level	HR (95%CI)
Ampulla	Sex	Female	0.12 (0.08-0.19)
		Male	0.19 (0.12-0.28)
Head of Pancreas	Marital Status	Married/Partner	0.27 (0.23-0.33)
		Single, Separated/divorced	0.24 (0.20-0.29)
		Widowed	0.23 (0.18-0.28)
	AJCC Stage	I	0.27 (0.23-0.33)
		II	0.39 (0.36-0.43)