A Population-Based, Descriptive Analysis of Malignant Intraductal Papillary Mucinous Neoplasms of the Pancreas

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Abstract

Background: **Intraductal papillary mucinous neoplasms (IPMN) are distinct precursor lesions that can progress to pancreatic adenocarcinoma; thus, it has been of particular interest to cancer prevention researchers. We set out to do a population-based analysis of malignant IPMNs compared with other pancreatic subtypes to better delineate its characteristics and explore implications for prevention and management.**

Methods: **We conducted a case-only analysis of California Cancer Registry data (2000-2007), including descriptive analysis of relevant clinical variables. Overall survival univariate analyses were conducted using the Kaplan-Meier method. Multivariate survival analyses were done using Cox proportional hazards ratios.**

Results: **Overall, 15,296 pancreatic cancer cases were identified, including incident cases of 10,186 adenocarcinomas, 880 mucinous tumors, 568 endocrine tumors, 3,619 carcinoma not otherwise specified tumors, and 43 malignant IPMNs. Thirty-three (80.5%) IPMN cases had localized disease at presentation, eight had regional disease (19.5%), and no IPMNs were identified with distant disease (two were unstaged). Five-year overall survival was better for malignant IPMN cases (65%) compared with pancreatic endocrine tumors (30%), mucinous tumors (5%), carcinoma not otherwise specified (2%), and adenocarcinoma cases (2%). Compared with adenocarcinoma cases, malignant IPMN cases (hazard ratio = 0.19; 95% CI, 0.10-0.35), endocrine tumors (hazard ratio = 0.28; 95% CI, 0.25-0.32), and mucinous tumors (hazard ratio = 0.84; 95% CI, 0.77-0.90) had higher overall survival in a multivariate survival analysis after adjustment for age, gender, stage, race, socioeconomic status, surgery, chemotherapy, and radiation therapy.**

Conclusions: **Pancreatic malignant IPMNs represent an uncommon pancreatic tumor subtype, uniquely characterized by early stage at presentation and better survival.** (Cancer Epidemiol Biomarkers Prev 2008; 17(10):2737–41)

Introduction

Pancreatic cancer was the 4th leading cause of cancer deaths in U.S. men and women during 1999 to 2003 (1). Overall survival for pancreatic cancer is poor, particularly in the setting of advanced or unresectable disease, and only 10% to 20% of patients with pancreatic cancer have potentially resectable tumors (2, 3). The estimated 5-year overall survival for advanced pancreatic cancer with current systemic therapy is <3% (4). Even with optimal therapy, median overall survival for advanced pancreatic cancer is estimated at just >6 months (5).

Survival for pancreatic cancer cases depends on the particular histologic subtype. Endocrine tumors have a significantly longer survival compared with adenocarcinoma or mucinous tumors (6). Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a subtype that was first described in 1982, classified by the WHO in 1996, and not included in the International Classification of Diseases for Oncology (ICDO) until the ICDO, 3rd edition in 2000. IPMN lesions range in a spectrum from hyperplasia to adenoma to borderline neoplasm to carcinoma (7, 8), representing another example of the well-described adenoma-carcinoma sequence (8-12). The clinical outcomes after diagnosis of malignant IPMN are poorly defined because of the relative rarity of this tumor type. Resected IPMN survival estimates range widely with 5-year survival, 36% for malignant disease compared with 88% for nonmalignant forms (13). Direct comparison of malignant IPMN cases to cases with pancreatic adenocarcnoma, mucinous tumors, or endocrine tumors has not been done.

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In this study, we did exploratory analyses of malignant IPMN cases to accurately delineate clinical characteristics of this distinct clinical entity, including distribution by gender, race, stage at presentation, socioeconomic status, treatment rendered, and survival. By comparing IPMN cases with the previously well-characterized histologic subtypes of pancreas cancer, our aim was to reveal the unique clinical characteristics of this uncommon malignancy that have relevance to prevention and management.

Materials and Methods

Study Population. We did a retrospective, case-only analysis of pancreatic cancer cases in the California Cancer Registry (CCR) database. The CCR is the largest contiguous-area, population-based cancer registry in the world, collecting >130,000 new cancer cases per year in California, as described elsewhere (6, 14). The state of California legally mandated cancer reporting in 1988; standardized data collection procedures and quality control procedures have been in place ever since (15, 16). The CCR is part of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program. Case reporting is estimated at 98% for the entire state of California, and follow-up completion rates exceed 95% (17, 18). Because of data completeness, timeliness, and accuracy, CCR has received the highest level of certification from the North American Association of Central Cancer Registries (19). Data were abstracted from medical and laboratory records by trained tumor registrars according to Cancer Reporting in California: Vol. 1, Abstracting and Coding Procedures for Hospitals (17). Tumor site and histology were coded according to criteria specified by the WHO in the ICDO (20). *In situ* and invasive tumors were identified using pancreatic cancer SEER primary site code (21100) and ICDO, 3rd edition, histology codes as follows: adenocarcinoma (8140, 8141, 8143, 8144, 8190, 8211, 8261, 8262, 8263, 8290, 8440, 8503, 8560, and 8570), mucinous tumors (8470, 8471, 8472, 8473, 8480, and 8481), endocrine (8150-8155, and 8246), carcinoma not otherwise specified (8010), as previously described (6), and malignant IPMN (that is, intraductal papillary-mucinous carcinoma, 8453). Data were obtained on 15,296 incident pancreatic cancer cases, including 53 consecutive malignant IPMN cases during 2000 to 2007 in the CCR with SEER summary staging or collaborative staging data and complete follow-up data available. Only 43 IPMN cases were analyzed because 10 were excluded based on having had previous incident cancers. Also excluded from the analyses were 2,048 (16.7%) of 12,234 adenocarcinomas, 197 (18.3%) of 1,077 mucinous tumors, 97 (14.6%) of 665 endocrine, and 738 (16.9%) of 4,357 carcinoma not otherwise specified. Recorded data included demographic information (age, gender, ethnicity), stage at presentation, histology, CCR region, socioeconomic status, and vital status. Socioeconomic status is denoted as a single index variable in CCR using statewide measures of education, income, and occupation from census data, as described previously (6, 21). The socioeconomic status variable used is a composite index based on principle component analysis of census block–level CCR data linked to census data assessing: education level, median household income, proportion below 200% poverty level, median house value, median rent, percentage of those employed, and percentage of those with blue-collar employment. Cases diagnosed before 1996 were linked to 1990 census data, and cases diagnosed after 1996 were linked to 2000 census data, as previously described (14). Quintiles for the socioeconomic status score were used for analysis, with socioeconomic status 1 and 5 denoting the lowest and highest socioeconomic status quintiles, respectively.

Treatment during the first course of therapy was ascertained using available data from CCR to determine whether cases underwent surgical resection (including the type of resection), radiation therapy, or chemotherapy. Cause of death was recorded according to the International Classification of Diseases criteria in effect at the time of death (22). Hospital registrars contacted cases annually, and CCR staff annually reviewed state death certificates to identify deceased registry cases. The last date of follow-up was either the date of death or the last date the case was contacted.

Statistical Analysis. The clinical characteristics, including age, gender, race, socioeconomic status quintile, treatment status, smoking status, and SEER summary stage, were analyzed with Pearson's χ^2 test or Fisher's exact test for categorical and dichotomous variables, and ANOVA with Tukey's post hoc test for comparison of continuous variables. Life tables and Kaplan-Meier curves were generated for cases with each histologic subtype of pancreatic cancer. Overall survival comparisons between groups were analyzed with the log-rank test. Multivariate survival analysis and analysis for effect modification were done using Cox proportional hazards ratios. All statistical analyses were conducted using SAS 9.1 statistical software (SAS Institute, Inc.). Statistical significance was assumed for a two-tailed P value <0.05.

Ethical Considerations. This research study involved analysis of existing data from the CCR database without subject intervention. No identifiers were linked to subjects. Therefore, the study was approved by the University of California, Irvine, institutional review board under the category ''exempt'' status (IRB 2006-5217).

Results

Demographic Characteristics. There were 15,296 incident cases of pancreatic cancer analyzed during 2000 to 2007, including adenocarcinomas (n = 10,186), carcinoma not otherwise specified tumors (n = 3,619), mucinous tumors (n = 880), endocrine tumors (n = 568), and IPMNs (n = 43). Table 1 displays demographic characteristics for the major pancreatic cancer histologic subtypes. There was an even distribution of adenocarcinomas and IPMNs among men and women, but a male predominance in endocrine tumors and a female predominance in carcinoma not otherwise specified and mucinous tumors were observed. A smaller proportion of IPMN cases were African-Americans. Thirty-three (80.5%) IPMN cases had localized disease at presentation, eight had regional disease (19.5%), and no IPMNs were identified with distant disease (two were unstaged). This was in contrast with a high proportion of distant disease observed among adenocarcinoma (41.9%), mucinous

Table 1. Demographic characteristics for pancreatic cancer cases by histologic subtype; incidence cases for 2000 to 2007

	Adenocarcinoma (n = 10,186)	Mucinous (n = 880)	Endocrine (n = 568)	IPMN (n = 43)	Carcinoma not otherwise specified (n = 3,619)
Gender					
Male	5,155 (50.6)	404 (45.9)	302 (53.2)	21 (48.8)	1,628 (45)
Female	5,031 (49.4)	476 (54.1)	266 (46.8)	22 (51.2)	1,991 (55)
Age (y)					
<50	733 (7.2)	76 (8.6)	155 (27.3)	3 (7)	137 (3.8)
50-59	1,813 (17.8)	171 (19.4)	147 (25.9)	8 (18.6)	339 (9.4)
60-69	2,631 (25.8)	218 (24.8)	125 (22)	5 (11.6)	571 (15.8)
70-79	3,199 (31.4)	270 (30.7)	99 (17.4)	16 (37.2)	1,022 (28.2)
80+	1,810 (17.8)	145 (16.5)	42 (7.4)	11 (25.6)	1,550 (42.8)
Ethnicity					
White	6,515 (64)	562 (63.9)	369 (65)	30 (69.8)	2,375 (65.6)
Black	773 (7.6)	78 (8.9)	44 (7.8)	2 (4.7)	322 (8.9)
Hispanic	1,797 (17.6)	151 (17.2)	86 (15.1)	1 (2.3)	550 (15.2)
Chinese	258 (2.5)	17 (1.9)	11 (1.9)	1 (2.3)	93 (2.6)
Non-Chinese Asian	784 (7.7)	67 (7.6)	52 (9.2)	8 (18.6)	258 (7.1)
Other	59 (0.6)	5 (0.6)	6 (1.1)	1 (2.3)	21 (0.6)
Stage					
Local*	1,489 (17.9)	137 (18.6)	142 (29.8)	33 (80.5)	531 (24.5)
Regional	3,357 (40.3)	240 (32.7)	126 (26.5)	8 (19.5)	629 (29.0)
Metastatic	3,472 (41.7)	358 (48.7)	208 (43.7)	0	1,011 (46.6)
Number missing	1868	155	92	2	1448
Surgery					
None	8,907 (87.4)	686 (78)	359 (63.2)	8 (18.6)	3,386 (93.6)
Pancreatectomy	1,219 (12)	185 (21)	198 (34.9)	34 (79.1)	65 (1.8)
Other surgery	45 (0.4)	9 (1)	9 (1.6)	1 (2.3)	13 (0.4)
Radiation					
No	8,697 (85.5)	751 (85.3)	525 (92.8)	41 (95.4)	3,314 (95.3)
Yes	1,475 (14.5)	129 (14.7)	41 (7.2)	2 (4.7)	163 (4.7)
Chemotherapy					
No	5,518 (54.2)	511 (58.1)	349 (61.4)	37 (86.1)	2,809 (77.6)
Yes	4,378 (43)	352 (40)	201 (35.4)	6 (14)	576 (15.9)
Socioeconomic status					
Lowest	1,470 (14.4)	129 (14.7)	67 (11.8)	3 (7)	594 (16.4)
2nd Lowest	1,853 (18.2)	167 (19)	89 (15.7)	5 (11.6)	734 (20.3)
Middle	2,157 (21.2)	157 (17.8)	115 (20.3)	8 (18.6)	782 (21.6)
High	2,279 (22.4)	201 (22.8)	121 (21.3)	10 (23.3)	773 (21.4)
Highest	2,427 (23.8)	226 (25.7)	176 (31)	17 (39.5)	736 (20.3)

*Includes *in situ* cases, as described in the text.

(48.7%), endocrine (43.7%), and carcinoma not otherwise specified (46.6%) cases. A greater proportion of malignant IPMN cases had *in situ* disease (16 or 37%) compared with adenocarcinoma (8 or 0.1%), mucinous (3 or 0.3%), endocrine (0), or carcinoma not otherwise specified (10 or 0.3%) cases. Of the 43 malignant IPMN cases analyzed, 34 (that is, 81.4%) received surgical resection, which was considerably greater than the proportion of cases receiving resection observed among adenocarcinoma (12.4%), mucinous (22.0%), endocrine (36.5%), and carcinoma not otherwise specified (2.2%) cases. Interestingly, 93.6% of carcinoma not otherwise specified cases did not have surgery, although 12% had localized disease. Most cases did not receive radiation therapy or chemotherapy. IPMN cases had the greatest proportion of cases from the highest socioeconomic status quintile.

Overall, 1.8% of cases refused surgery, 1.5% refused radiation treatment, and 3.7% refused chemotherapy. The proportion of cases refusing surgery (P = 0.27), radiation therapy (P = 0.66), and chemotherapy (P = 0.94) was similar across all ethnic groups analyzed in this study. Decreasing socioeconomic status quintile was associated with an increased likelihood of refusing treatment with surgery (P_{trend} < 0.0001), radiation therapy (P_{trend} = 0.03), or chemotherapy (P_{trend} = 0.0001).

Survival between Pancreatic Cancer Histologic Subtypes. Overall survival was substantially greater for IPMN cases compared with pancreatic adenocarcinoma, endocrine, mucinous, and carcinoma not otherwise specified tumors (Fig. 1). One-year and five-year survival rates were as follows: IPMNs (83%, 65%), endocrine tumors (68%, 30%), mucinous tumors (26%, 5%), adenocarcinoma (20%, 2%), carcinoma not otherwise specified cases (11%, 2%; P < 0.0001). Median overall survival for each of the pancreatic cancer histologic subtypes is as follows: IPMNs not yet reached, endocrine tumors (overall survival = 33 months; 95% CI, 24-39), mucinous tumors (overall survival = 6 months; 95% CI, 5-6), adenocarcinomas (overall survival = 4 months; 95% CI, 4-5), carcinoma not otherwise specified (overall survival = 2 months; 95% CI, NR). Compared with adenocarcinoma cases, IPMNs (hazard ratio = 0.19; 95% CI, 0.10-0.35; P < 0.0001), endocrine tumors (hazard ratio = 0.28; 95% CI, 0.25-0.32; P < 0.0001), and mucinous tumors (hazard ratio = 0.84; 95% CI, 0.77-0.90; P < 0.0001) had better overall survival in a multivariate survival analysis after adjustment for age, gender, stage, therapy, socioeconomic status, and race (Table 2). Carcinoma-NOS cases had an increased risk for death (hazard ratio = 1.07; 95% CI, 1.03-1.12; P = 0.0018) compared with

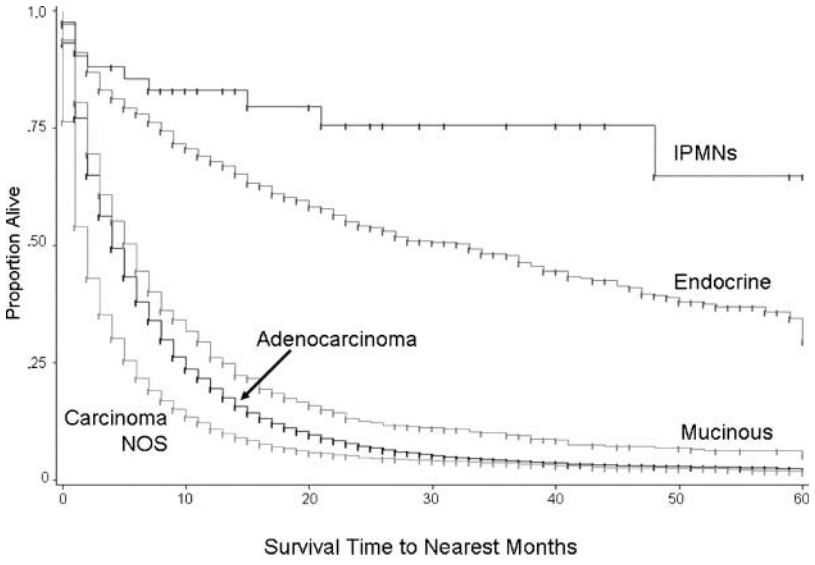

Figure 1. Five-year Kaplan-Meier survival curves for each of the investigated pancreatic histologic subtypes, showing better median overall survival for IPMNs ($n = 43$) compared with pancreatic endocrine ($n = 568$), mucinous ($n = 880$), adenocarcinoma ($n = 10,186$), and carcinoma not otherwise specified ($n = 3,619$) tumors ($P < 0.0001$).

adenocarcinoma cases in the above multivariate survival analysis.

Cause of Death Analysis. Overall, 13,252 (86.6%) of the 15,296 cases in this study died. Cause of death analysis revealed that 9,823 deaths were due to pancreatic cancer. Infection, unknown cause, and chronic obstructive pulmonary disease comprised most of the nonpancreatic cancer–related deaths.

Discussion

Although limited by small numbers, our descriptive analysis of malignant IPMN cases reveals several important findings about this rare condition. In congruence with previous surgical series showing 5-year survival to be between 36% and 60% (23), our data show that patients with malignant IPMN cases have significantly higher survival rates over each of the other major pancreatic cancer subtypes. Potential factors contributing to this include a large proportion of locoregional disease at diagnosis (100%) and a corresponding high rate of surgical resection (82%). This is also consistent with the previous observation of a lower prevalence of invasive malignancy in IPMN (43% for main duct IPMN and 15% for branch duct IPMN; ref. 23). Nevertheless, the higher survival clearly shows that the current treatment for malignant IPMN is more effective than for adenocarcinoma and thus warrants a more aggressive therapy of such patients. The high proportion of resected malignant IPMN cases observed in this study indicates that surgical management of malignant IPMN is routine in community practice.

Table 2. Multivariate survival analysis using Cox proportional hazards model; incidence cases for 2000 to 2007

Histologic subtype	HR (95% CI)
Adenocarcinoma	1.00 (reference)
Mucinous	0.84 (0.77-0.90)
Endocrine	0.28 (0.25-0.32)
IPMN	0.19 (0.10-0.35)
Carcinoma not otherwise specified	1.07 (1.03-1.12)

NOTE: Model adjusted for age at diagnosis, gender, ethnicity, stage, surgery, radiation, chemotherapy, and socioeconomic status.
Abbreviation: HR, hazard ratio.

As noted, 10 cases (18.9%) of IPMN were excluded from our analyses, and it is interesting to note that these cases were 2nd primaries. This finding was consistent across all subtypes as 16.7% of adenocarcinoma, 18.3% of mucinous, 14.6% of endocrine, and 16.9% of carcinoma not otherwise specified were also excluded because they were 2nd primaries. The superior survival of IPMN cases in our study compared with certain previous reports may reflect this exclusion. Although we did not find any association of these cases with previous pancreatic cancer, additional studies may help delineate risk factors. Because malignant IPMN was not coded in ICDO editions before ICDO, 3rd edition, in 2000, future epidemiologic studies in CCR and SEER will also likely yield more information about survival characteristics. It must be acknowledged that, because of the small sample size, we consider all such analyses related to malignant IPMNs in this study to be exploratory in nature.

This epidemiologic study shares limitations of other population based analyses, including the lack of independent histologic review of specimens, variable sources of reporting and diagnostic methods, and broad staging criteria used (that is, SEER summary staging instead of American Joint Committee on Cancer staging methods). The analysis of all possible confounding factors related to survival among pancreatic cancer cases cannot be done with such analyses; thus, important aspects affecting survival have not been accounted for, including access to health care, insurance coverage, and comorbid conditions.

Malignant IPMN represents a unique entity among pancreatic cancer cases, with better survival characteristics compared with each of the major pancreatic histologies. It is anticipated that more aggressive therapeutic and prevention efforts, including surveillance monitoring

and chemoprevention trials (24), will have an increasingly important role in the management of this unusual pancreatic neoplasm.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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