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Histological classification of liver and intrahepatic bile duct cancers in SEER registries

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Abstract

Clear definitions of histological groups are essential for studies of liver and intrahepatic bile duct cancers. Thus, we developed a classification system based on abstracted information on histologies of liver and intrahepatic bile duct cancers diagnosed during 1978–2007 within all Surveillance, Epidemiology, and End Results (SEER) registries. Of 61,990 reported primary liver and intrahepatic bile duct cancers, 108 distinct ICD-O histology codes were identified. During the five recent years of diagnosis, 2003–2007, the leading histological groups were hepatocellular carcinoma (75%) and cholangiocarcinoma (12%). The remaining categories were other specified (3%) and poorly specified carcinomas (3%), hepatoblastomas (1%), sarcomas (1%), embryonal sarcomas (0.1%), other specified malignancies (0.05%), and poorly specified malignancies (5%). During 2003–2007, only 68% of diagnoses were microscopically confirmed. Factors contributing to incomplete histological classification may include reluctance to obtain diagnostic specimens from late stage cases and administration of therapy in lieu of histological confirmation after positive diagnostic imaging.

Conclusion—The proposed histological classification in this report may facilitate studies of primary liver cancers. This is of value because the inconsistent characterization of some cancers, particularly cholangiocarcinomas, may affect interpretation of incidence trends. Incomplete histological characterization of hepatocellular carcinomas was noted in this report. It is likely to be explained by guidelines affirming the use of non-invasive diagnostic and treatment procedures for this cancer.

Keywords

Hepatocellular carcinoma; cholangiocarcinoma; microscopic confirmation; trends

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Introduction

Defining histological groups of cancers is essential for surveillance and clinical research. For the first several years of the Surveillance, Epidemiology, and End Result (SEER) program, the Manual of Tumor Nomenclature and Coding (MONTAC) 1968 edition was used to code anatomic site and histologic type.[1] The morphology code consisted of three digits, with a 4th digit designating the degree of malignancy or behavior. SEER started using the International Classification of Diseases for Oncology (ICD-O), published in 1976 for cases diagnosed during 1977.[2] The morphology coding was expanded to four digits, with many new codes added and the 5th digit was used to designate the behavior. As an example, the MONTAC code 8163 was expanded to two codes, cholangiocarcinoma (8160) and bile duct cystadenocarcinoma (8161). The 1990 revision, ICD-O-2,[3] added a code for Klatskin tumor (8162/3) with a site of C22.1=intrahepatic bile duct suggested. In 2000, ICD-O-3 added the site C24.0=extrahepatic bile duct as a site for Klatskin tumor.[4] Each edition attempted to include new nomenclature appearing in the contemporary World Health Organization Classification of Tumours series, or WHO “Blue Books”. [5,6] Changes in these and other classifications[7,8] reflect advances in understanding of liver and intrahepatic bile duct cancer histologies. The changing classifications could introduce bias if cases are assigned to different histological groups based on when they were diagnosed. For example MONTAC code 8163 (above) includes cancers in two histological groups, cholangiocarcinoma and other specified carcinoma. In an effort to address this issue, we restricted histologic type-specific analyses to the 30 years covered by ICD-O, 1978–2007, with additional analyses restricted to even more recent time periods.

Liver and intrahepatic bile duct cancers are completely characterized when site of origin and histology are known. However, this detail is often unavailable. Thus, a high proportion of cholangiocarcinomas are coded to liver rather than intrahepatic bile duct. These cancers are therefore classified as cholangiocarcinomas without consideration of site of origin. Protocols from the College of American Pathologists specify clinical information that could improve diagnostic completeness when examining surgical specimens from patients with cancers of these sites.[9,10]

Several factors can impede characterization of liver and intrahepatic bile duct cancers. Some histological terms for primary cancers of these sites are general, [1–4] and case definitions for histological groups can vary between classification systems.[5–8] Complete characterization requires pathology review of a primary resection or clinical findings, images[11] and pathology reports. Patients with advanced stage cancer may not have tissue collected.[12] Electronic record review[13] and greater diagnostic imaging technology[14] may also affect tissue collection. With the increasing incidence of hepatocellular carcinoma in the United States[15] and current guidelines affirming diagnosis based on imaging only and the use of ablative therapy under specified circumstances[16] may affect the percentage of hepatocellular carcinoma cases that are histologically confirmed. Furthermore, inconsistent definitions of anatomic location and histologies may impede analysis of epidemiological trends for intrahepatic cholangiocarcinomas.[17] Taken together, these factors could affect interpretation of liver and intrahepatic cancer surveillance data. This report presents proposed histological groups for cancers of the liver and intrahepatic bile duct diagnosed within SEER registries

from 1978 through 2007 based on abstracted data on histology and site of origin. Our goal was to define histological groups and changes in histologic confirmation to facilitate cancer surveillance and epidemiologic studies.

Methods

Data

Primary cancers of the liver (ICD-O topography code=C22.0) and intrahepatic bile duct (ICD-O topography code=C22.1) were included in this analysis.[2–4] Cases were diagnosed among persons residing within the National Cancer Institute's SEER Program (SEER-17) registry areas during 1978–2007. A total of 61,990 incident cases met the site criteria. The SEER-9 registries (Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, San Francisco Bay Area, Utah, Seattle-Puget Sound and Atlanta) contributed cases as of 1978, with the implementation of ICD-O. Cases from San Jose-Monterey, Los Angeles, Alaskan Native and Rural Georgia registries were included as of 1992. In Greater California, Kentucky, Louisiana, and New Jersey registries, cases were included starting in 2000. Registries collected case data under state mandated rules for reportable diseases. Incidence data were de-identified prior to submission to the SEER Program.

Abstracted Data

Histologies of reported liver and intrahepatic bile duct cancers were abstracted by cancer registrars, usually from pathology reports. A liver pathologist (DK), a certified cancer registrar (LD), and epidemiologists with expertise in liver and intrahepatic bile duct cancer etiology (KM), surveillance (SA), and cancer classification (SD) analyzed data regarding reported sites and histologies with the interest of validating the histological classification. One interest was to identify histologies that should be classified as cholangiocarcinomas because inconsistent designation of this group of cancers may impede analysis and interpretation of surveillance trends.[16] Through a process including literature review and consultation, a proposed classification was developed for liver and intrahepatic bile duct cancers.

Histological Groups

Hepatocellular carcinomas were defined by ICD-O morphology codes 8170 through 8175. Cholangiocarcinomas included the most common histology within this group (i.e. ICD-O-3 topography code 8160: Cholangiocarcinoma) and 12 other histologies deemed to be primary adenocarcinomas or squamous cell carcinomas arising from the intrahepatic bile duct epithelium. Other and poorly defined carcinomas were defined based on the specificity of the ICD-O code. Sarcomas were classified as hemangiosarcomas, hemangioendotheliomas and other sarcomas. Hepatoblastomas and embryonal sarcoma were each considered to be unique histological groups. Other specified malignancies that were rarely diagnosed within the SEER registries included germ cell cancers, carcinosarcomas and malignant melanomas. Approximately 5% of cancers were grouped as poorly specified malignancies. As in "Cancer Incidence in Five Continents",[7] information on the primary cancer site, liver (topography code C22.0) versus intrahepatic bile duct (topography code C22.1) did not affect the assignment of histological groups (see discussion).

The resulting classification reflected the logic of the 2010 WHO Classification of Tumours.[5,6] Our approach to classification was also similar to "Cancer Incidence on Five Continents" [7] however we classified 17 spindle cell carcinomas (ICD-O, 8032) and six pseudosarcomatous carcinomas (ICD-O, 8033) as cholangiocarcinomas, as likely variants of poorly differentiated adenocarcinoma rather than unspecified carcinomas. Eighteen cancers were reassigned from cholangiocarcinoma to other specified carcinoma [bile duct cystadenocarcinoma (ICD-O, 8161) and cystadenocarcinoma, not otherwise specified or NOS, (ICD-O-3, 8440)], as a biologically distinct set of cancers. The 35 cases with the histologic diagnosis of infiltrating duct carcinomas (ICD-O-3, 8500) were grouped with other specified carcinomas. Papillary carcinoma of the liver was classified as a poorly specified carcinoma.

Histological Confirmation

The proposed classification system for liver and intrahepatic bile duct cancers was used to assess the frequency distribution and diagnostic confirmation of these cancers in the five most recent diagnosis years, 2003 to 2007.

Results

Frequencies

Of 61,990 primary liver and intrahepatic bile duct cancers diagnosed within the SEER 17 registries, 57,987 (94%) were classified as carcinomas (Table 1). Hepatocellular carcinomas (n=44,120) were diagnosed more often than all other histologic groups combined and the next most frequent group of tumors, cholangiocarcinomas (n=9,048), were reported more often than the remaining histologic groups, combined. Only three other histologic groups accounted for more than 2,000 cases, two carcinomas: other specified carcinomas (n=2,044) and poorly specified carcinomas (n= 2,775) and poorly specified malignancy (n=2,878). Hepatoblastoma was the only other histology reported more than 500 times (n=527). In the class "sarcoma," 500 cases were reported, including 190 hemangiosarcomas. Less than 100 tumors were reported in each of two classes: embryonal sarcomas and other specified malignancies. Two extrahepatic histologies were reported: Klatskin tumor (n=691) and hepatoid adenocarcinoma (n=9), data not shown.

Histological classification

Cancers were assigned into broad histological categories that reflect prior criteria.[5,6] Broad histological classes were carcinomas, hepatoblastomas, sarcomas, embryonal sarcomas, other specified malignancies, and poorly specified malignancies (Table 2). Three of these five classes were divided into more detailed histological groups. For example, carcinomas included hepatocellular carcinomas, cholangiocarcinomas, other specified carcinomas, and poorly specified carcinomas. Sarcomas included hemangiosarcomas, hemangioendotheliomas, and other sarcomas. Other specified malignancies included germ cell cancers, melanomas, and carcinosarcomas.

Histological confirmation

In the SEER 17 registries during the five most recent diagnosis years, 2003 to 2007, 68% of liver and intrahepatic bile duct cancers were microscopically confirmed (Table 3). Microscopic confirmation rates were higher than the overall rate for specific histological categories with the exception of hepatocellular carcinoma, the only specified histology for which less than 70% of cases had microscopic confirmation. In contrast, less than half of poorly specified carcinomas (43%) and poorly specified malignancies (9%) were histologically confirmed.

Discussion

The present report is based on the 30 year experience in SEER registries and included 61,990 cases of liver and intrahepatic bile duct cancer. In diagnosis years 2003–2007, 93% of liver and intrahepatic bile duct cancers were carcinomas. The most frequent morphologic type was hepatocellular carcinoma (75%), followed by cholangiocarcinoma (12%).

Defining ICD-O histologies that correspond with cholangiocarcinomas in order to facilitate analysis and interpretation of incidence trends for this group of cancers was a primary study objective because inconsistent designation of this group of cancers may impede analysis and interpretation of surveillance trends.[17] These cancers are primary carcinomas of the epithelium of the intrahepatic bile duct. Most were classified as cholangiocarcinomas (ICD-O=8160) followed by adenocarcinomas, NOS; however, squamous cell carcinomas infrequently arise within this site and were here classified as cholangiocarcinomas. Thus, in this report, with a few exceptions that involved fewer than 20 cases each, our classifications were consistent with those presented in “Cancer Incidence in Five Continents”.[7] Based on tumor biology, spindle cell and pseudosarcomatous carcinomas were grouped as cholangiocarcinomas rather than unspecified carcinomas while bile duct and other cystadenocarcinomas were grouped as other specified carcinomas rather than cholangiocarcinomas. Infiltrating duct carcinomas, which are elsewhere considered to be cholangiocarcinomas, [7] were classified as other specified carcinomas. Although there was agreement between classification systems on the leading cholangiocarcinoma histologies surveillance data could be affected by inclusion or exclusion of less common histologies.[5–8] Furthermore trend analyses that fail to account for shifts in histological classification over time could be biased. For example, before 1978, cystadenocarcinoma and bile duct adenocarcinoma were classified as one cancer-type[1] but are now classified as “cholangiocarcinoma” and “other specified carcinoma”, respectively.[2–7]

In this report, “liver” rather than “intrahepatic bile duct” was specified as the primary site of 38% of cholangiocarcinomas. As in the WHO “Blue Books” [5,6] we classified these histologies as cholangiocarcinomas without respect to primary site. Since the two anatomic sites are intertwined, when a primary site is not recorded, cholangiocarcinomas are often coded to the primary site of liver. We suggest that cholangiocarcinomas arising in one of these two sites be assigned to the site of intrahepatic bile duct. In the present study, two extrahepatic histologies were classified as intrahepatic histologies. [7] These histologies were Klatskin tumors (n=691) and hepatoid adenocarcinoma (n=9). Pathologists and tumor registrars are encouraged to designate these histologies to an extrahepatic site of origin.

Furthermore, when the International Classification of Diseases for Oncology is updated, we recommend that Extrahepatic Bile Duct (C24.0) alone be suggested as the primary site for Klatskin tumors (17) without inclusion of Intrahepatic Bile Duct (C22.1). Liver is not, at present, a suggested site for hepatoid adenocarcinoma in ICD-O.[1–3]

Approximately one third of cancers in this report were not histologically confirmed. In addition, 9% of cases in SEER 17 registries during five recent diagnosis years were diagnosed with either poorly specified carcinomas or other poorly specified malignancies. Complete histological classification is preferred to provide users of cancer surveillance data with optimal information on incidence rates and trends, prognosis, and demographic disparities. Several factors may contribute to incomplete histological characterization. First, histological terms for liver and intrahepatic bile duct cancers range from very specific terms such as hepatocellular carcinoma to more general terms such as adenocarcinoma, not otherwise specified.[2–4] Complete characterization depends on pathology review of an intact untreated, resected, primary tumor or review of clinical findings, images and pathology reports. Poor prognoses associated with advanced stage liver cancer may dissuade practitioners from collecting diagnostic specimens.[12] The increasing incidence of hepatocellular carcinoma in the United States, [15] as well as clinical guidelines affirming the use of non-invasive imaging for diagnosis and ablative therapy for treatment[16] of hepatocellular could contribute to unconfirmed hepatocellular carcinoma diagnoses.

Conclusion

We propose a more defined histological classification system to facilitate studies of liver and intrahepatic cancers.

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Abbreviations

SEER	Surveillance, Epidemiology and End Results
ICD-O	International Classification of Diseases for Oncology
WHO	World Health Organization
NOS	Not otherwise specified

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Table 1

Reported liver and intrahepatic cancer cases, by site, SEER 17, 1978–2007*

	Histological classification (ICD-O)	Liver	IHBD†	Total
Class:	Carcinoma	51,504	6,483	57,987
Group:	Hepatocellular carcinoma	44,080	40	44,120
Group:	Cholangiocarcinoma	3,483	5,565	9,048
Group:	Other specified carcinoma	1,322	722	2,044
Group:	Poorly specified carcinoma	2,619	156	2,775
Class:	Hepatoblastoma	527	0	527
Class:	Sarcoma	~	~	500
Group:	Hemangiosarcoma	~	~	190
Group:	Hemangioendothelioma	77	0	77
Group:	Other sarcoma	~	~	233
Class:	Embryonal sarcoma	65	0	65
Class:	Other specified malignancy	~	~	33
Group:	Germ cell tumor	~	~	12
Group:	Carcinosarcoma, NOS	~	~	20
Group:	Malignant melanoma, NOS	~	~	~
Class:	Poorly specified malignancy	2,719	159	2,878
All liver and intrahepatic cancer cases combined		55,344	6,646	61,990

*International Classification of Diseases for Oncology

†IHBD: Intrahepatic Bile Duct

Source: Incidence-SEER 17, Nov 2009 File, Katrina/Rita Population Adjustment, 1973–2007 varying

~Data were suppressed when site specific or total counts included less than 12 cases. Zero counts were allowed.

Table 2

Proposed histological classification of liver and intrahepatic bile duct cancers, SEER 17, 1978– 2007

Class	Group	ICD-O Morphology Code
Carcinoma	Hepatocellular carcinoma	8170–8175
	Cholangiocarcinoma	8032, 8033, 8070, 8071, 8140, 8141, 8160, 8260, 8480, 8481, 8490, 8560
	Other specified carcinoma	8012, 8013, 8041, 8142, 8124, 8161, 8162, 8180, 8190, 8211, 8240, 8246, 8249, 8255, 8290, 8310, 8323, 8337, 8440, 8450, 8453, 8470, 8471, 8500, 8503, 8510, 8521, 8550, 8574, 8576
	Poorly specified carcinoma	8010, 8020, 8021, 8022, 8031, 8046, 8050
Hepatoblastoma		8970
Sarcoma	Hemangiosarcoma	9120
	Hemangioendothelioma	9130, 9133
	Other Sarcoma	8800–8805, 8810, 8815, 8830, 8850, 8852, 8890, 8891, 8894–8896, 8900, 8910, 8920, 8935, 8936, 8940, 8963, 8990, 9040, 9041, 9124, 9150, 9180, 9220, 9260, 9364, 9473, 9500, 9540, 9560
Embryonal sarcoma		8991
Other specified malignancy	Germ cell tumor	9064, 9070, 9071, 9080, 9100
	Melanoma, carcinosarcoma	8720, 8980
Poorly specified malignancy		8000–8004

Database: Incidence - SEER 17 Registries, Nov 2009 Submission, Katrina/Rita Population Adjustment (1973–2007 varying).

Table 3

Classification of liver and intrahepatic bile duct cancers by histological confirmation, SEER 17, 2003–2007

		All Cases			Microscopically Confirmed		Unconfirmed Cases	
Class	**Group**	**No.**	**Percent %**	**Confirmed**	**No.**	**Percent**	**No.**	**Percent**
All Liver and IHBD Cancers[†]		26,130	100%	68%	17,773	100%	8357	100%
Carcinoma		24,367	93%	71%	17,273	97%	7094	85%
	Hepatocellular carcinoma	19,669	75%	69%	13,613	77%	6056	72%
	Cholangiocarcinoma	3,092	12%	86%	2,650	15%	442	5%
	ICC: Site, IHBD	1,848	7%	80%	1,486	8%	362	4%
	ICC: Site, Liver	1,244	5%	94%	1,164	7%	80	1%
	Other specified carcinoma	740	3%	86%	637	4%	103	1%
	Poorly specified carcinoma	866	3%	43%	373	2%	493	6%
Hepatoblastoma		185	1%	97%	179	1%	6	0%
Sarcoma		162	1%	96%	155	1%	7	0%
	Hemangiosarcoma	58	0%	97%	56	0%	2	0%
	Hemangioendothelioma	35	0%	94%	33	0%	2	0%
	Other Sarcoma	69	0%	96%	66	0%	3	0%
Embryonal sarcoma		31	0%	100%	31	0%	0	0%
Other specified malignancies		12	0%	100%	12	0%	0	0%
Poorly specified malignancies		1,373	5%	9%	123	1%	1250	15%

[†]IHBD: Intrahepatic Bile Duct

Database: Incidence - SEER 17 Registries, Nov 2009 Submission, Katrina/Rita Population Adjustment (1990–2007 varying)