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Frequency and Determinants of Lymph Node Dissection for Node-Negative Cancers of the Biliary Tract

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Bachelor of Science

University of California Los Angeles

2011

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Abstract

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By Kristina W. Lai

Background: Adequate lymph node (LN) resection has been shown to be a significant predictor of survival among node-negative cancer patients. These considerations apply to cancers of the gallbladder and of the intra- and extra-hepatic bile ducts. The goals of the present study were 1) to assess the temporal changes in the proportion of node-negative biliary tract cancer cases that were evaluated using 1998 AJCC recommendations for LN resection; and 2) to investigate if the numbers of LN examined during surgery for the three cancers of interest were associated with year or place of diagnosis, patient demographic characteristics, and disease related factors.

Methods: We retrieved information on demographic characteristics, clinical features, and year of diagnosis for 3,093 eligible cases from the population-based Surveillance, Epidemiology and End Results database for the period from 2000 to 2012. Trends in number of LN examined were assessed using the annual percent change in proportion of cases with the number of lymph nodes examined for years 1992 through 2012. The change in trend was tested for statistical significance using a Monte Carlo Permutation method. Multivariable logistic regression models were used to examine factors associated with adherence to LN resection recommendations.

Results: The percentage of patients with at least 3 LN examined ranged from 34% to 57% in the period from 1992 to 2012. Trend analysis indicated a significant increase in the overall proportion of cases with AJCC recommended LN examination during the study period. The results were generally similar using an alternative cutoff of 10+ LN. There was a significant positive association between diagnosis after 2008 and 3 LN examined, with odds ratio (OR) of 1.49 and a 95% confidence interval (CI) from 1.28 to 1.73, and significant associations with older age and primary site.

Conclusion: Our results indicate that half of all reported patients do not receive adequate LN examination. Nevertheless the data indicate that the recommendations have led to a significant increase in proportion of patients receiving adequate staging care.

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BACKGROUND

Cancers of the gallbladder, and extrahepatic and intrahepatic bile ducts are relatively rare malignancies that affect different parts of the biliary tract. Each year, approximately 7,500 people are diagnosed with these cancers in the United States (1); of those, approximately 56% are gallbladder cancers (GBC), 40% are extrahepatic bile duct cancers (EHBDC), and 4% are intrahepatic bile duct cancers (IHBDC) (2). Both incidence and survival of these cancers in the US remain relatively low. GBC is diagnosed at a rate of approximately 1.13 cases per 100,000 person-years (1, 3) and 5-year survival is below 5% (3-5). Rates of EHBDC range from 0.7 to 2.5 cases per 100,000 person-years (2) and average 5-year survival estimates range from 30 to 40% (6-11). The reported IHBDC rates range from 0.6 to 1.0 cases per 100,000 person-years (12, 13) and 5-year survival ranges from 17% to 44% (14). Biliary tract cancers are difficult to detect and treatment options are typically limited to surgical removal of the primary tumor or more extended radical resection if the cancer has metastasized to nearby lymph nodes.

Common risk factors for GBC, EHBDC, and IHBDC include choledochal cysts older age, and obesity. Exposures to radiographic contrast materials such as thorotrast, dietary nitrosamines, and various industrial chemicals including dioxin, and polychlorinated biphenyls have also been examined as possible risk factors for these malignancies (13). Risk factors of EHBDC and IHBDC, specifically, include cholangitis, ulcerative colitis, biliary tract infection, viral hepatitis B and C, cirrhosis, and alcohol and cigarette use (13). Additionally, history of gallstones and calcification of the gallbladder wall have been shown to increase the risk of GBC (13).

GBCs are more common in women than men, and highest incidence is observed among Native Americans and Mexican Americans, likely correlating to the high prevalence of gallstones in these populations (2). Both EHBDC and IHBDC are 1.3 times more common in males, although rates in women appear to be increasing in recent years. Both of these malignancies are particularly common in American Indians and Alaska Natives (2.0-2.5 per 100,000 person-years) (13). By contrast, the rates in Whites and Blacks are only 0.7 and 1.11 per 100,000, respectively (2).

A known predictor of survival among patients diagnosed with biliary tract cancers is lymph node (LN) involvement (N-stage) (15-18). Previous research has also shown that among many node-negative cancers, 5-year survival is associated with the total number of lymph nodes examined (6-8, 10, 19-22). In 1998, the American Joint Committee on Cancer (AJCC) staging manual (fifth edition) recommended that at least three LN should be examined for adequate N-stage determination for EHBDC, GBC and IHBDC (23). Although 3 LN is an AJCC-recommended cutoff, some researchers have questioned the strength of evidence to support this recommendation (20) and at least two recent studies have shown that higher numbers of LN examined may provide greater survival benefits.

Schwarz et al. conducted an analysis of the Surveillance Epidemiology and End Results (SEER) data that included curative intent resections of LN for GBC, EHBDC, and IHBDC/ampullary cancers (19). Among node-negative patients in that study, those with 10 or more LN dissected had the highest median survival. The authors also noted an increasing trend in cumulative 5-year survival by number of LN examined. Based on these findings the authors recommended that for all biliary tract cancers, at least 10 lymph nodes should be resected.

In a more recent study, Ito et al. conducted a review of 257 EHBDC patients' pathology reports from one hospital (20). After controlling for clinical factors, they found that node negative patients with at least 11 LN examined had mean survival significantly greater than that of patients with less than 11 LN examined. Based on these findings Ito et al suggested that optimal dissection should include at least 11 LNs.

Previous research has shown that compliance with N-staging recommendations may be low, depending on various disease-, patient- and provider-related characteristics. A number of studies addressed this issue for other cancer sites (24-29); however, to our knowledge there are very limited population-based data (30, 31) on frequency and determinants of adherence to LN dissection recommendations for biliary tract cancers. With these knowledge gaps in mind, the goals of the present study were 1) to assess the temporal changes in the proportion of N-negative EHBDC, IHBDC, and GBC cases that were evaluated using 1998 AJCC recommendations; and 2) to investigate if the numbers of LN examined during surgery for the three cancers of interest were associated with year or place of diagnosis, patient demographic characteristics, and disease related factors.

METHODS

The current analysis was based on the SEER data for years 2000 through 2012 (32). Using International Classification of Disease-Oncology 3rd edition (ICD-O-3) primary site codes C22.1 (IHBDC), C23.9 (GBC), and C24.0 (EHBDC), we selected all patients newly diagnosed with these cancers of interest and reported to SEER during the study period. The analyses were restricted to node negative cases with at least one LN examined.

Multivariable Analysis

Total number of LN examined was divided into three categories: <3, 3-9 and ≥10, and the distributions of various patient and disease characteristics across these categories were calculated. Logistic regression models were then used to examine the association between year of diagnosis (before 2008 vs. 2008 or later) and adherence to recommendations for LN examination. 2008 was chosen as the cutpoint to correspond to the year following publication of research suggesting that 10 LN was a more appropriate guideline (19). Only cases diagnosed in the year 2000 or later are included in this analysis to account for all new SEER data registry sites becoming operational in that year. These models used two alternative cutoffs for the dependent variable: <3 vs 3+ LN and <9 vs. 10+ LN. The logistic regression models examined the association of interest after controlling for age (categorized as <60, 60-69, 70-79, and 80+ years), gender, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, Native American/Alaska Native), primary site (based on ICD codes), level of urbanization (metropolitan, urban, and rural) and U.S. region (West, Midwest, South, and Northeast). Each model was examined for interactions and collinearity (33). The results of multivariable analyses were expressed as adjusted odds ratios (OR) and the corresponding 95% confidence intervals (CI).

Trend Analysis

Trends in number of LN examined were assessed using annual proportion of cases with the AJCC recommended number of lymph nodes examined (3 or more) for years 1992 through 2012. To assess trends over time, we calculated the annual percent change (APC) for the study period by fitting a weighted least-squares regression line to the natural logarithm of the rates where the regressor variable was the calendar year (34). The change in trend was tested for statistical significance using a Monte Carlo Permutation method. We used three pre-specified models: one with no joinpoints, the second with one joinpoint and the third with two joinpoints. The same analyses were also conducted using the cutoff of 10+ LN as recommended in the Schwarz et al. (2007) publication.

The cut-point for statistical significance was a two-sided alpha error of 0.05 for all analyses. All analyses were conducted using SAS 9.4 statistical analysis software (Cary, NC) or Joinpoint Regression Program version 4.0.4 (available from NCI, Bethesda, MD).

RESULTS

A total of 392 cases of IHBDC (12.7%), 1,265 cases of EHBDC (40.9%), and 1,436 cases of GBC (46.4%) were reported to the SEER program from 2000 through 2012 (Table 1). The average age at diagnosis was 66.4 years and 46.4% of patients were male. The majority (63.4%) were non-Hispanic Whites; followed by 14.2% Hispanics; 12.3% Asian/Pacific Islanders; 9.0% non-Hispanic Blacks; and 1.1% Native American/Alaska Natives. The majority of cases were residents of metropolitan areas (89.4%), with the remaining 10.6% residing in urban or rural areas. Most cases were reported in the Western United States (54.5%), a region with the largest concentration of SEER sites. Overall, 47.7% (n = 1,476) of all cases had at least 3 LN examined during staging, but in only 15.2% (n=471) LN examinations included at least 10 LN.

Crude analysis showed a significant positive relationship between diagnosis after 2008 and AJCC recommended examination of at least 3 LN (OR= 1.36; 95% CI: 1.18, 1.57). In the multivariable model, this association remained of similar magnitude with an adjusted OR of 1.49 (95% CI: 1.28, 1.73). Patients who were 80 years of age or older were significantly less likely (OR=0.59; 95% CI: 0.45, 0.76) to have at least 3 LN examined compared to those under the age of 60 years. Primary site was also independently associated with adherence to AJCC recommendations. Compared to EHBDC cases, the OR (95% CI) estimates for IHBDC and GBC were 0.31 (0.24, 0.40) and 0.27 (0.23, 0.33), respectively (Table 2). No significant associations were observed for race/ethnicity, gender, level of urbanization, or geographic region.

In the model that used the cutoff of 10 LN to define the dependent variable there was a significant interaction between geographic region and year of diagnosis. Specifically the association with post-2008 year of diagnosis was different in the West than in other regions. For this reason, we created a variable that included four categories pre-2008 (West), post-2008 (West), pre-2008 (Other regions) and post-2008 (Other regions). Using pre-2008 (West) as the reference category, OR (95 CI) estimates for post-2008 (West), pre-2008 (Other regions) and post-2008 (Other regions) were 2.00 (1.50, 2.67), 1.57 (1.14, 2.15), and 1.97 (1.44, 2.70), respectively (Table 3). As in the model using a 3 LN cutoff, primary site was associated with examination of 10 or more LN. There was a significant association among Asian/Pacific Islanders (OR=1.45; 95% CI: 1.06, 1.98) but no other racial/ethnic group.

Trend analysis for both cutoffs showed significant increases from 1992 to 2012, with APC estimates for 3 LN and 10 LN of 1.71 and 4.37, respectively in the model with no joinpoints (Figures 1 and 2). Both models with one joinpoint suggested that the observed trend may have changed in 2010, but the change was not statistically significant. In the two joinpoint models, APC for the 3 LN cutoff changed from 0.44 for 1992-2001 to 3.29

for 2001-2008 and then began to decrease with a post-2008 APC of -0.51. For 10 or more LN, there was a significant change in APC in 1992-1994 vs. 1994-2010 (APC = -15.83 vs. 5.85) until 2010 when prevalence began to decrease (APC= -6.29).

DISCUSSION

Adequate lymph node resection has been shown to be a significant predictor of survival among node negative cancer patients. Survival analyses have found that at least 10-11 LN should be examined to have the greatest benefit in survival for patients with cancers of the and biliary tract (19, 20). This analysis builds on previous work by investigating population-level implementation and predictors of adequate N-staging that can offer the greatest benefit to patients. By assessing the temporal trends in LN resection and characteristics that may be associated with quality of LN examination, we highlight the high prevalence of inadequate staging and the great potential for improved practices.

Between 1992 and 2012, there were significant increases in the number of patients who received the AJCC recommended number of LN examined, with average annual percent change of +1.71. Compared to cases diagnosed between the years 2000 and 2007, cases diagnosed in 2008 or later were 50% more likely to have at least the AJCC recommended 3 LN examined, and were nearly twice as likely to have at least 10 LN examined. However, even among cases diagnosed after 2008 when the AJCC recommendation had been in place for 10 years and other published research suggested that greater survival was associated with greater numbers of LN examined, only about half of patients had 3 or more LN examined. Of those patients, 52.3% had 10 or more LN examined, making up only 17.8% of all reported cases diagnosed after 2007. Moreover the data for recent years appear indicate that the proportion of guideline-concordance with respect to LN dissection is starting to decrease, although this observations may reflect natural year-to-year variability rather than trend.

Our analysis indicates that patients with IHBDC and GBC are 70-85% less likely to have adequate N-staging compared to patients with EHBDC. This may be due to access to lymph nodes during surgery or later stage at diagnosis, which might increase risks during more extensive lymphadenectomy. Asian and Pacific Islander patients may be more likely to have adequate LN examinations because of high incidence of biliary tract cancers in this population resulting in greater focus on adequate staging.

The SEER Program expanded the number of registries in the Western region in order to increase coverage of minority populations (35). Accordingly, in our data over 87% of all cases among Asian/Pacific Islanders are reported in the Western region, with very few cases reported in the South and Northeast and no cases in the Midwest.

To our knowledge, only two studies have evaluated temporal trends in LN examination for GBC and no previous study has assessed these trends for EHBDC or IHBDC. In 2010, Mayo et al. used SEER-Medicare linked data to assess compliance with National Comprehensive Cancer Network (NCCN) guidelines for gallbladder adenocarcinomas. They included LN examination compliance as a covariate in a survival analysis with other surgical factors (30). In their data, less than 7% (205 out of 2955) of patients who underwent surgical resection from 1991-2005 had 3 or more LN examined. In multivariate analysis, they found that unmarried status, white race, male gender, and <3 LN examined were associated with worse survival. Consistent with trends found in our analysis, the authors also noted an increase in adequate lymphadenectomy during the study period (from 4.8% in 1991-1995 to 8.4% in 2003-2005). However, their analysis was restricted to patients covered by Medicare and diagnosed with gallbladder adenocarcinoma, who represent only about 35% of all gallbladder cases in SEER registries in that time period.

This positive association between at least 3 LN examined and increased year of resection (from 1988) was also found in another study of non-metastatic gallbladder adenocarcinoma (31). Of the cases in the SEER registry reported from 1988 to 2003, only 5.3% of patients had 3 or more LN examined. Adequate LN resection in that study was only associated with increased survival in stage T2 and T3 patients. No significant survival benefit was found in T1 patients, while T4 patients were excluded.

Although this is the first analysis of its kind in terms of including all biliary tract cancers, similar analyses have focused on quality of LN staging in gastric (36) and colon cancers (27, 28, 37-39). A study of LN examination and survival of gastric adenocarcinoma found that between 1998 and 2011, less than 40% of patients in the National Cancer Data Base received adequate LN staging according to AJCC guidelines (36). Furthermore, age (>76 years) was positively associated with inadequate LN examination, which is consistent with our results. Bilimoria et al. conducted a hospital level review of compliance with staging measures for colon cancers and found that 60% of hospitals surveyed were not compliant with LN examination guidelines (37).

To explore the factors that may influence adequacy of LN examination and staging of colorectal cancers, Gagliardi et al. conducted semi-structured interviews with providers and found that educational presentations played a major role in improving staging practices, as well as self-initiated changes by pathologists (38).

Parsons et al. studied hospital performance and likelihood of having a recommended number of LNs examined for colon cancer patients and found that urban location, prior performance, and membership in American College of Surgeon's Oncology Group were associated with better adherence to guideline recommended LN evaluations (27).

This population-based analysis is limited by the constraints of SEER data, particularly the lack of provider- and facility-level data that may also affect the quality of cancer staging. Specific patient characteristics that could serve as predictors of LN dissection, but are not available in the SEER data, include insurance status, education, and income. Patient comorbidities and contraindications to lymphadenectomy also remain unknown.

On the other hand, the large sample size enables SEER-based studies to examine rare cancers, allows sufficient power for detecting relatively moderate associations, and permits a variety of multivariable analyses. The population-based, as opposed to institution-based, identification of cases increases the generalizability of findings.

CONCLUSION

Although thorough lymph node assessment can provide significant survival benefits to patients with biliary tract cancers, we have found that half of all reported patients do not receive adequate N-staging. Nevertheless we see that the recommendations have led to a significant increase in proportion of patients receiving adequate staging care. The results of this analysis highlight the opportunities for more informed guidelines to influence providers and offer greater quality of care to patients.

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TABLES & FIGURES

Table 1. Patient characteristics by number of lymph nodes examined

Characteristic	<3 LN		3-9 LN		10+ LN		Total	
	n	%	n	%	n	%	n	%
Year of Diagnosis								
2000-2007	921	55.9%	514	31.2%	214	13.0%	1,649	53.3%
2008-2012	696	48.2%	491	34.0%	257	17.8%	1,444	46.7%
Age at Diagnosis								
<60 years	437	52.0%	283	33.7%	120	14.3%	840	27.2%
60-69 years	429	48.2%	297	33.4%	164	18.4%	890	28.8%
70-79 years	454	49.9%	317	34.9%	138	15.2%	909	29.4%
80+ years	297	65.4%	108	23.8%	49	10.8%	454	14.7%
Race/Ethnicity								
White, non-Hispanic	1,022	52.2%	648	33.1%	289	14.8%	1,959	63.4%
Black, non-Hispanic	145	52.3%	89	32.1%	43	15.5%	277	9.0%
Hispanic	240	54.5%	144	32.7%	56	12.7%	440	14.2%
Asian/Pacific Islander	191	50.3%	112	29.5%	77	20.3%	380	12.3%
American Indian/Alaska Native	17	51.5%	11	33.3%	5	15.2%	33	1.1%
Gender								
Female	913	55.1%	527	31.8%	217	13.1%	1,657	53.6%
Male	704	49.0%	478	33.3%	254	17.7%	1,436	46.4%
Primary Site								
C22.1 Intrahepatic Bile Duct	237	60.5%	133	33.9%	22	5.6%	392	12.7%
C23.9 Gallbladder	939	65.4%	389	27.1%	108	7.5%	1,436	46.4%
C24.0 Extrahepatic Bile Duct	441	34.9%	483	38.2%	341	27.0%	1,265	40.9%
Urbanicity								
Metro	1,431	51.9%	912	33.1%	413	15.0%	2,756	89.4%
Urban (adjacent to metro)	85	51.8%	49	29.9%	30	18.3%	164	5.3%
Rural (non-adjacent to metro)	97	59.5%	39	23.9%	27	16.6%	163	5.3%
U.S. Region								
Midwest	161	55.1%	87	29.8%	44	15.1%	292	9.4%
Northeast	265	50.0%	177	33.4%	88	16.6%	530	17.1%
South	295	50.4%	194	33.2%	96	16.4%	585	18.9%
West	896	53.1%	547	32.4%	243	14.4%	1,686	54.5%
Total	1,617	52.3%	1,005	32.5%	471	15.2%	3,093	100%

[a] U.S. region determined by location of SEER registries as of 2000: Midwest (Detroit metropolitan area, Iowa); Northeast (Connecticut, New Jersey); South (Atlanta metropolitan area, rural Georgia, Kentucky, Louisiana, Greater Georgia); and West (San Francisco-Oakland, San Jose-Monterey, Los Angeles, Hawaii, New Mexico, Seattle, Utah, Alaska Natives)

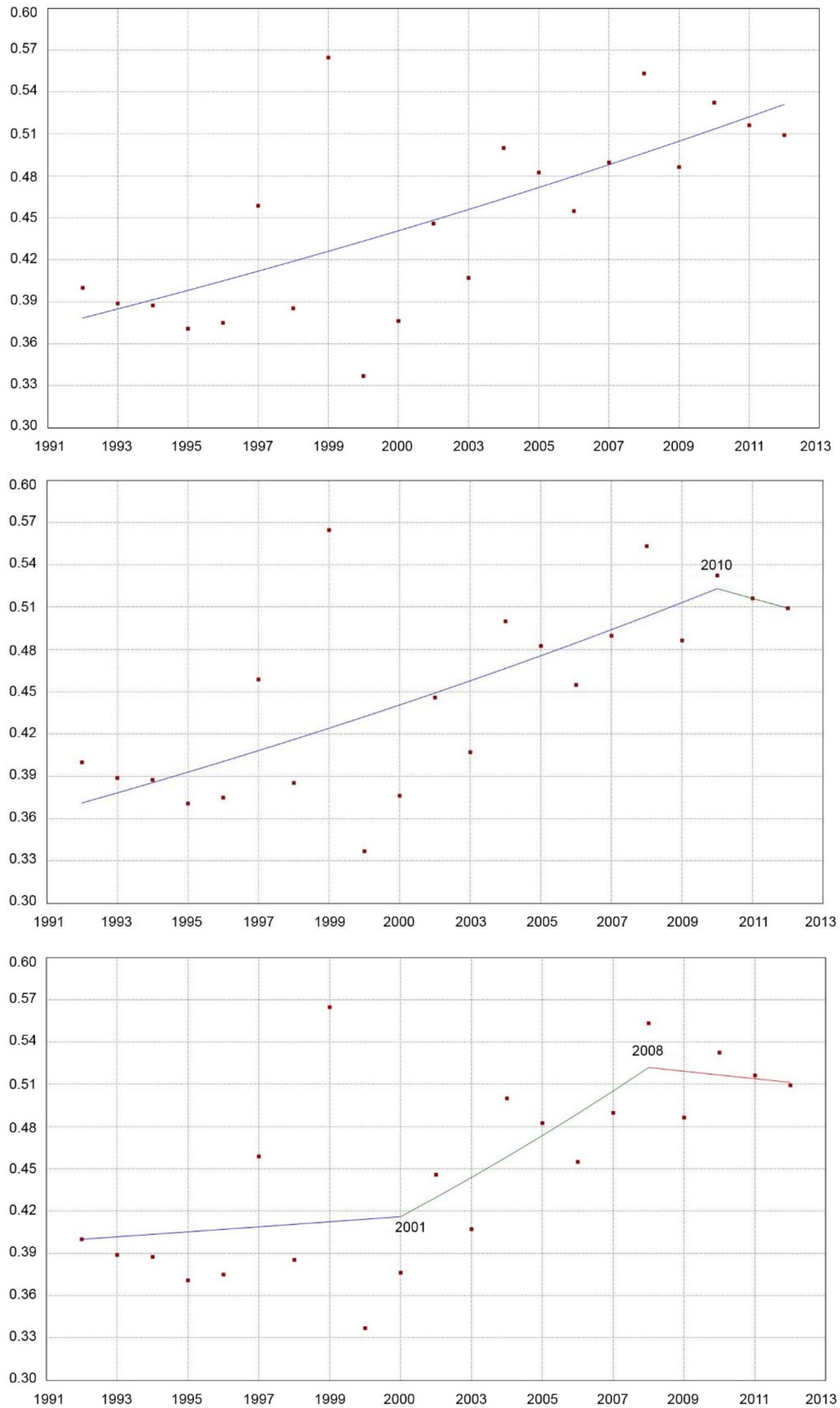
Table 2. Results of fully adjusted logistic regressions relating year of diagnosis and 3 lymph nodes examined

	OR	95% CI
Year of Diagnosis (ref = before 2008)		
Diagnosed after 2008	1.49	(1.28, 1.73)
Age (ref = <60 years)		
60-69 years	1.05	(0.86, 1.29)
70-79 years	1.02	(0.83, 1.25)
80+ years	0.59	(0.45, 0.76)
Race/Ethnicity (ref = White, non-Hispanic)		
Black, non-Hispanic	0.99	(0.75, 1.30)
Hispanic	1.04	(0.82, 1.31)
Asian/Pacific Islander	0.97	(0.76, 1.23)
American Indian/Alaska Native	1.06	(0.44, 2.55)
Gender (ref = female)		
Male	0.88	(0.76, 1.04)
Primary Site (ref = C24.0 EHBDC)		
C23.9 Gallbladder	0.27	(0.23, 0.33)
C22.1 Intrahepatic Bile Duct	0.31	(0.24, 0.40)
Urbanicity (ref = metro area)		
Urban	0.95	(0.67, 1.35)
Rural	0.78	(0.55, 1.10)
U.S. Region (ref = Northeast)		
Midwest	0.83	(0.61, 1.13)
South	0.96	(0.74, 1.25)
West	0.84	(0.68, 1.04)

Table 3. Results of fully adjusted logistic regressions relating year of diagnosis and at least 10 lymph nodes examined, accounting for interaction in the West region

	OR	95% CI
Year of Diagnosis by region (ref = pre-2008, West)		
Post-2008, West	2.00	(1.50, 2.67)
Pre-2008, non-West	1.57	(1.14, 2.15)
Post-2008, non-West	1.97	(1.44, 2.70)
Age (ref = <60 years)		
60-69 years	1.17	(0.89, 1.54)
70-79 years	0.95	(0.72, 1.26)
80+ years	0.74	(0.51, 1.08)
Race/Ethnicity (ref = White, non-Hispanic)		
Black, non-Hispanic	1.13	(0.78, 1.64)
Hispanic	1.11	(0.79, 1.56)
Asian/Pacific Islander	1.45	(1.06, 1.98)
American Indian/Alaska Native	1.80	(0.57, 5.71)
Gender (ref = female)		
Male	0.92	(0.74, 1.15)
Primary Site (ref = C24.0 EHBDC)		
C23.9 Gallbladder	0.22	(0.17, 0.28)
C22.1 Intrahepatic Bile Duct	0.15	(0.09, 0.23)
Urbanicity (ref = metro area)		
Urban	1.21	(0.78, 1.88)
Rural	1.24	(0.79, 1.95)

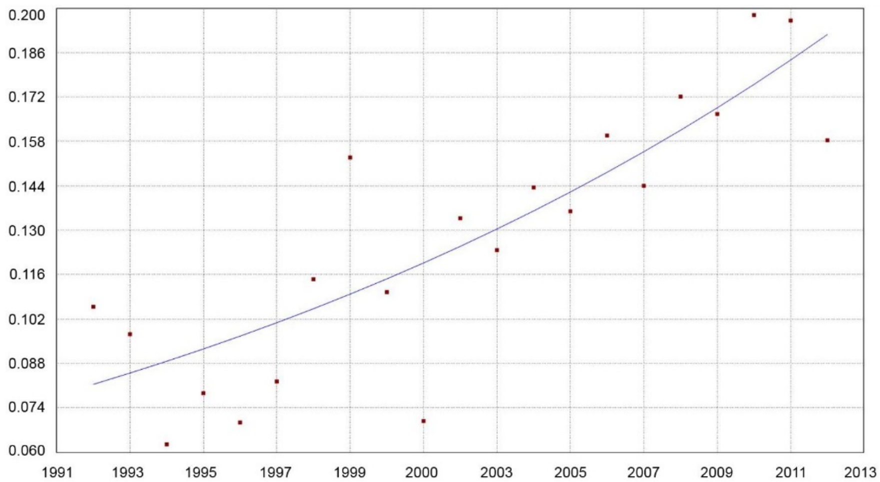
Figure 1a-c. Join points for annual percent change in proportion of cases with at least three lymph nodes examined, 1992 to 2012. a) No joinpoints (APC = 1.71†); b) One joinpoint (1992-2010: APC = 1.92†; 2010-2012: APC = -1.33); c) Two joinpoints (1992-2001: APC = 0.44†; 2001-2008: APC = 3.29; 2008-2012: APC = -0.51).



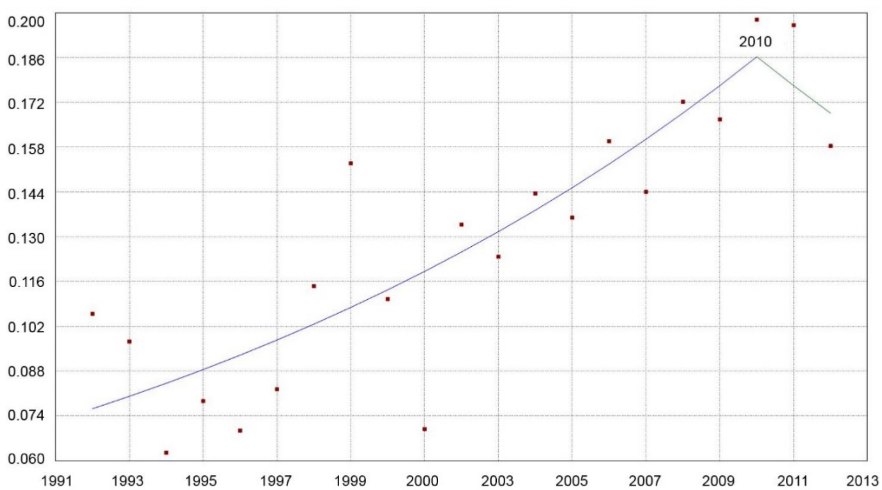
a) b) c)

†Statistically significant at alpha=0.05.

Figure 2a-c. Join points for annual percent change in proportion of cases with at least ten lymph nodes examined, 1992 to 2012. a) No joinpoints (APC = 4.37†); b) One joinpoint (1992-2010: APC = 5.09†; 2010-2012: APC = -4.86); c) Two joinpoints (1992-1994: APC = -15.83; 1994-2010: APC = 5.85†; 2010-2012: APC = -6.29).



a)



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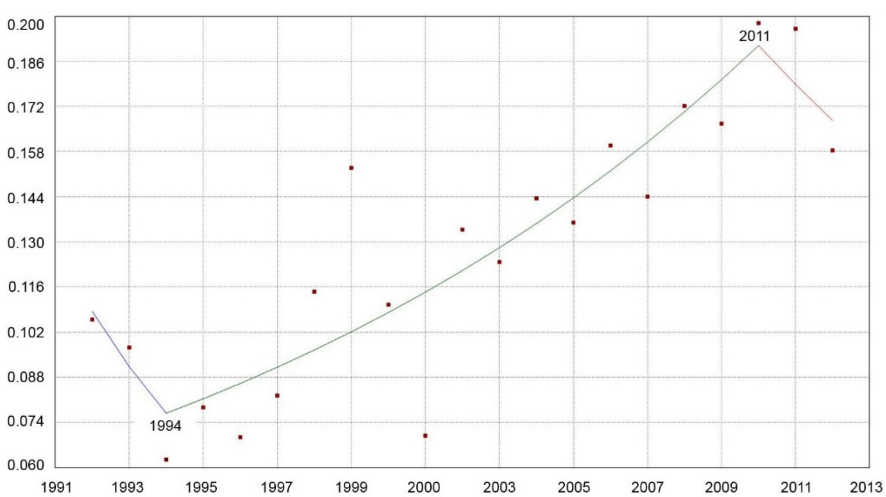

c)

†Statistically significant at alpha=0.05.