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2012 SSAT PLENARY PRESENTATION

Time Trends and Disparities in Lymphadenectomy for Gastrointestinal Cancer in the United States: A Population-Based Analysis of 326,243 Patients

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Abstract
Background The value of lymphadenectomy in most localized gastrointestinal (GI) malignancies is well established. Our objectives were to evaluate the time trends of lymphadenectomy in GI cancer and identify factors associated with inadequate lymphadenectomy in a large population-based sample.
Methods Using the National Cancer Institute's Surveillance Epidemiology and End Results Database (1998–2009), a total of 326,243 patients with surgically treated GI malignancy (esophagus, 13,165; stomach, 18,858; small bowel, 7,666; colon, 232,345; rectum, 42,338; pancreas, 12,141) were identified. Adequate lymphadenectomy was defined based on the National Cancer Center Network's recommendations as more than 15 esophagus, 15 stomach, 12 small bowel, 12 colon, 12 rectum, and 15 pancreas. The median number of lymph nodes removed and the prevalence of adequate and/or no lymphadenectomy for each cancer type were assessed and trended over the ten study years. Multivariate logistic regression was employed to identify factors predicting adequate lymphadenectomy.
Results The median number of excised nodes improved over the decade of study in all types of cancer: esophagus, from 7 to 13; stomach, 8–12; small bowel, 2–7; colon, 9–16; rectum, 8–13; and pancreas, 7–13. Furthermore, the percentage of patients with an adequate lymphadenectomy (49 % for all types) steadily increased, and those with zero nodes removed (6 % for all types) steadily decreased in all types of cancer, although both remained far from ideal. By 2009, the percentages of patients with adequate lymphadenectomy were 43 % for esophagus, 42 % for stomach, 35 % for small intestine, 77 % for colon, 61 % for rectum, and 42 % for pancreas. Men, patients >65 years old, or those undergoing surgical therapy earlier in the study period and living in areas with high poverty rates were significantly less likely to receive adequate lymphadenectomy (all $p<0.0001$).
Conclusions Lymph node retrieval during surgery for GI cancer remains inadequate in a large proportion of patients in the USA, although the median number of resected nodes increased over the last 10 years. Gender and socioeconomic disparities in receiving adequate lymphadenectomy were observed.

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Keywords Lymph node counts · Gastrointestinal carcinoma · Population based data · Disparities · Adequate lymph node dissection

Background

Surgical resection with en-bloc removal of the draining lymph nodes provides the best chance of cure for most localized gastrointestinal carcinomas.[1–3] Although the therapeutic effect of lymphadenectomy has been questioned, its value as a significant prognostic indicator and a major determinant for the need of adjuvant therapy is undisputed.[4–7] Data from population-based studies demonstrate a strong relationship between the number of removed lymph nodes during surgery and survival in several types of cancer,[8–10] and recent data suggest that the reason for the improved survival seems to be a better overall oncologic care and not the more accurate detection of node-positive disease.[11] Furthermore, in contrast to most other aspects of the complex oncologic therapy, lymph node count is easily measured and communicated, becoming one of the most focused on quality indicators and comparison tools of different health care providers in cancer care. Adherence to National Cancer Center Network (NCCN) guidelines defining adequate lymphadenectomy is relatively low; a large number of patients receive suboptimal lymph node dissection even in high-volume expert centers.[12] Variations in the quality of cancer care are well documented,[13–16] but population-based reports comparing the lymphadenectomy rates for different types of gastrointestinal cancer are scarce.[12]

The aims of this study were to assess the national rate of adequate lymphadenectomy during resection for potentially resectable gastrointestinal (GI) cancer in the USA in a population-based sample, determine time trends of lymphadenectomy in each studied cancer type, and identify sociodemographic and clinicopathologic variables associated with the failure of undergoing optimal lymphadenectomy.

Material and Methods

The Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute is the only comprehensive source of population-based cancer information in the USA.[17] From this database, all cases of primary invasive gastrointestinal adenocarcinomas (esophagus, stomach, small bowel, colon, rectum, and pancreas) that were diagnosed between 1998 and 2009 were identified using respective tumor site and histology codes. From these patients, we then selected cases that were not diagnosed at autopsy or from death certificate data and excluded all patients with metastatic disease and those who did not undergo surgical resection. The final study cohort comprised 332,480 patients with surgically resected non-metastatic adenocarcinoma of the esophagus, stomach, small and large bowels, and the pancreas. Information about the number of lymph nodes removed at resection, age at diagnosis, sex, race, county of residence, stage, and cancer-related survival was obtained from SEER. Race was dichotomized into "white" or "non-white." Because individual-level socioeconomic status (SES) data are not available in the SEER database, county of residence was linked with the United States Census data throughout the study period.[18] This variable was categorized into quartiles, with the fourth quartile as the poorest SES.

Definitions of Adequate Lymphadenectomy

Adequate lymphadenectomy was defined based on NCCN's recommendations as ≥15 lymph nodes (LNs) removed in esophageal, gastric, and pancreatic cancers and ≥12 LNs in colorectal cancer.[19] There are no recommendations regarding optimal lymphadenectomy for small bowel cancer. We have defined adequate lymph node dissection in this cancer type as at least 12 lymph nodes removed based on surgical and biological similarities to colorectal cancer.

Statistics

We calculated the rates of adequate lymphadenectomy among patients with GI cancer as well as the rates of adequate lymphadenectomy by cancer type and time of diagnosis.

Categorical variables were compared using χ^2 tests. Logistic regression was used to identify significant independent predictors of the lack of adequate lymph node dissection. The percentage of adequate lymphadenectomy and the rate of patients with zero lymph nodes removed according to the year of diagnosis were compared for temporal trends in the patterns of treatment of all cancer patients with the Cochran–Armitrage test. The level of statistical significance was set at $p<0.005$. All analyses were conducted using R 2.15.0.[20]

Results

Characteristics of the Study Population

We identified 332,480 patients with surgically resected non-metastatic adenocarcinoma of the esophagus, stomach, small and large bowels, and the pancreas. Patient characteristics in the population are shown in Table 1. The median age of the patients was 70 years. Patients with inadequate lymphadenectomy were significantly but not clinically relevantly older than those who underwent adequate surgical staging. Most patients were white (82 %). Most tumors (84 %) were located in the large bowel, followed by the stomach (6 %), and the esophagus and the pancreas (both 4 %).

Table 1 Characteristics of the study population

	Adequate LND	Inadequate LND
Age (years; median)	69	71
Male	79,979 (50)	90,251 (54)
Race		
White	130,174 (82)	137,240 (82)
Tumor site		
Esophagus	4,151 (32)	9,014 (68)
Stomach	6,092 (33)	12,496 (67)
Small bowel	1,871 (24)	5,795 (76)
Colon	125,534 (54)	106,811 (46)
Rectum	17,672 (42)	24,666 (58)
Pancreas	3,685 (30)	8,456 (70)
Poverty level (%)		
Q1	65,105 (49)	66,359 (51)
Q2	32,681 (51)	31,925 (49)
Q3	41,613 (47)	46,966 (53)
Q4	19,606 (47)	21,988 (53)

Data in parentheses are percentages

Lymphadenectomy Rates

The median number of removed lymph nodes improved over the study period in all types of cancer: esophagus, from 7 to 13; stomach, 8–12; small bowel, 2–7; colon, 9–16; rectum, 8–13; and pancreas, 7–13 (Table 2.). Forty-nine percent of the total population underwent adequate lymphadenectomy during surgical resection. Cancers of the colon (54 %) and the rectum (42 %) had higher rates than in gastric (33 %), esophageal (32 %), pancreatic (30 %), and small bowel (24 %) carcinomas. The rates of optimal lymphadenectomy were showing a constantly rising trend throughout the study period: by 2009, the percentages of patients with adequate lymphadenectomy were 43.1 % for esophagus, 41.6 % for stomach, 35.1 % for small intestine, 77.4 % for colon, 61.5 % for rectum, and 42.4 % for pancreas (Cochran–Armitage test: $P_{trend}<0.0001$ for all types; Fig. 1.) On multivariate analysis (Table 3.), the factors predicting adequate lymphadenectomy were female sex, patient age younger than 65 years, lower level of poverty, and undergoing cancer-related treatment in the latter part of the study period. Furthermore, when compared to colon cancer, all other studied cancer types were independently and significantly associated with inadequate lymph node dissection. The rate of patients with no lymph nodes removed during surgical resection remained fairly constant in gastric cancer (13 %) and decreased in all other localizations. A strikingly large proportion of patients with surgically resected small bowel adenocarcinoma underwent zero lymphadenectomy (30.4 %; Fig. 2).

Table 2 Median (interquartile range) of lymph nodes removed according to cancer type: 1998–2009

	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Colon	9 (5–15)	9 (5–15)	10 (5–15)	10 (6–16)	10 (6–16)	11 (6–17)	12 (7–18)	12 (7–18)	13 (8–19)	15 (10–21)	15 (11–21)	16 (12–22)
Esophagus	7 (3–13)	8 (3–15)	8 (3–14)	8 (3–14)	9 (4–15)	9 (4–16)	10 (5–17)	10 (5–17)	11 (5–18)	12 (6–19)	12 (7–19)	13 (6–20)
Pancreas	7 (3–12)	8 (4–12)	8 (4–14)	8 (4–13)	8 (4–13)	9 (4–14)	9 (4–14)	10 (5–16)	10 (5–16)	11 (6–18)	12 (7–19)	13 (7–20)
Rectum	8 (4–13)	7 (3–13)	7 (3–13)	8 (4–13)	8 (4–14)	8 (4–14)	9 (5–15)	10 (5–16)	11 (6–17)	12 (7–18)	13 (7–18)	13 (8–18)
Small Bowel	2 (0–8)	4 (0–9)	2 (0–9)	3 (0–9)	3 (0–9)	4 (0–11)	4 (0–10)	5 (0–11)	5 (0–12)	6 (0–13)	6 (0–14)	7 (0–15)
Stomach	8 (3–15)	8 (3–15)	8 (3–15)	9 (4–15)	8 (3–15)	9 (4–17)	9 (3–17)	10 (4–18)	11 (4–18)	11 (4–19)	11 (4–20)	12 (5–20)

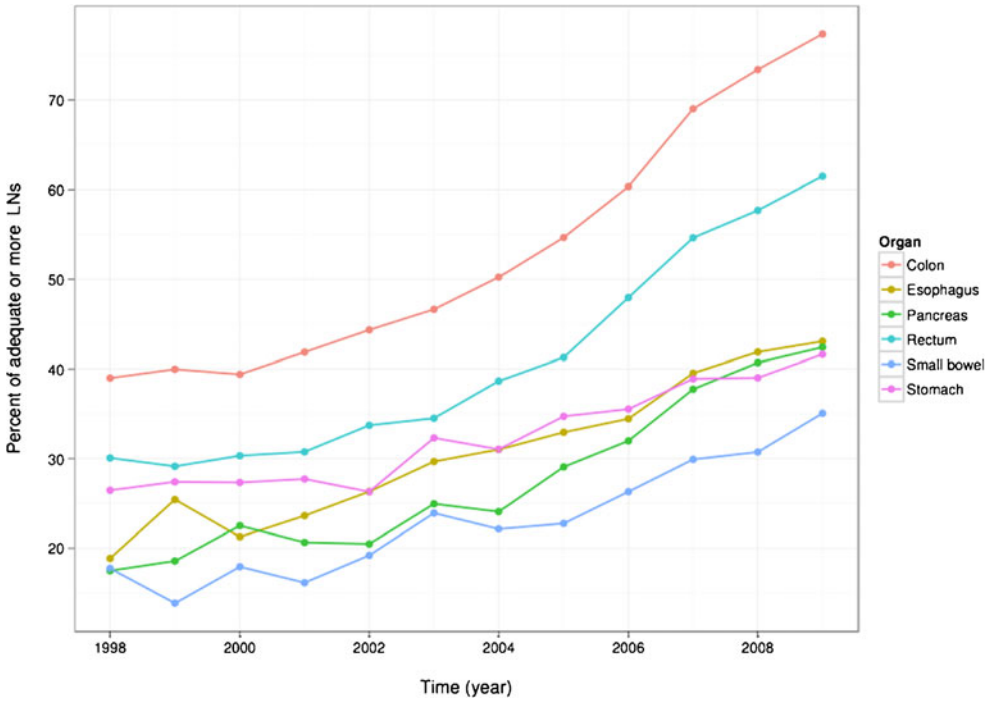

Fig. 1 Percentage of patients with adequate LND by cancer type between 1998 and 2009

Discussion

This population-based study demonstrates that the percentage of US patients undergoing adequate lymphadenectomy during surgery for potentially resectable malignant disease of the GI tract is low. Only 49 % of the total study population received adequate lymphadenectomy while undergoing surgery for cancer during the study period. Unsurprisingly, this proportion was highest in colorectal cancer in which lymph node count has been widely emphasized as an important quality control standard. The rates of adequate lymphadenectomy in patients with esophageal, gastric, small bowel, and pancreatic cancers are much lower.

Similarly, the median number of lymph nodes removed remained far from ideal even at the end of the study period in most cancer types, surpassing NCCN's minimum recommendations of only patients with colon and rectal carcinoma. Somewhat unexpectedly, 6 % of the total population had zero lymph node removed while undergoing resection for gastrointestinal cancer. Even if this could be partly attributable to the pathologic workup of the surgically resected specimen, the fact that over 10 % of US patients underwent gastrectomy for cancer with a D0 lymphadenectomy is especially alarming.

Our results are similar to other reports analyzing the lymphadenectomy rates on population-based data depending on the time frame studied. Bouvier et al. found that only

Table 3 Predictors of adequate LND by multivariate analysis

Reference	Level	β	OR	CI	p
Male	Female	0.11	1.116	1.1–1.132	0.0000
Non-white	White	−0.011	0.989	0.971–1.008	0.2643
45–65	<45	0.376	1.456	1.404–1.509	0.0000
	65–80	−0.208	0.813	0.799–0.827	0.0000
	>80	−0.272	0.762	0.746–0.777	0.0000
1998–2003	2004–2009	0.835	2.304	2.27–2.338	0.0000
Poverty Q1	Q2	−0.042	0.959	0.94–0.978	0.0000
	Q3	−0.178	0.837	0.822–0.852	0.0000
	Q4	−0.254	0.775	0.758–0.793	0.0000
Colon	Esophagus	−1.015	0.362	0.349–0.377	0.0000
	Pancreas	−1.175	0.309	0.297–0.322	0.0000
	Rectum	−0.563	0.569	0.557–0.582	0.0000
	Small bowel	−1.466	0.231	0.219–0.244	0.0000
	Stomach	−0.928	0.395	0.383–0.409	0.0000

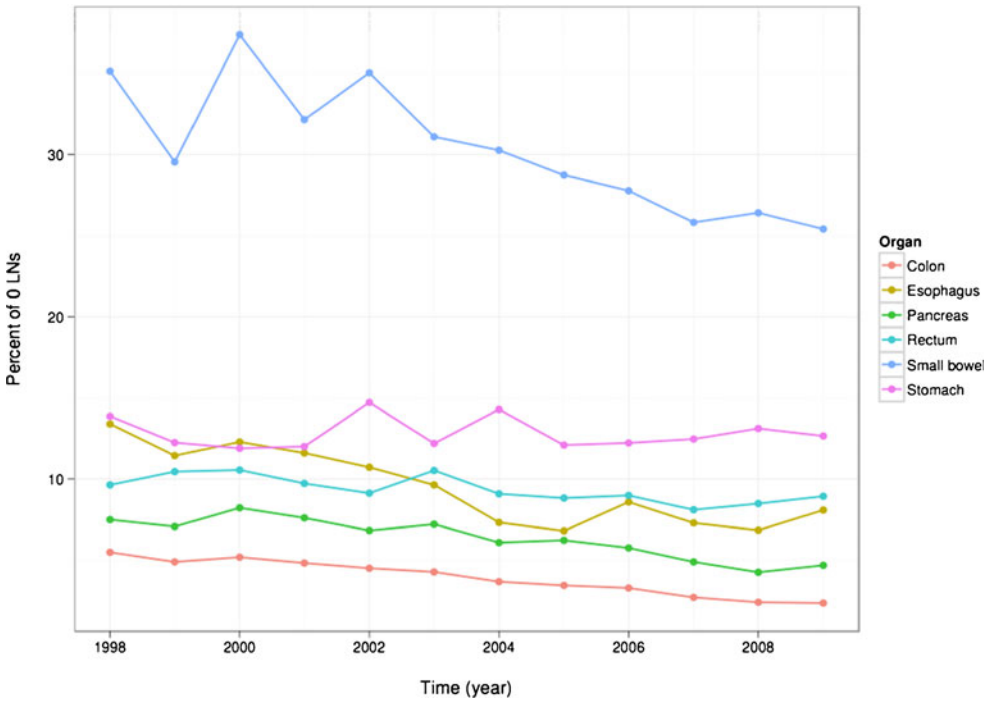

Fig. 2 Rates of zero lymph nodes removed during surgical resection according to type of cancer between 1998 and 2009

17 % of French patients with gastric cancer underwent adequate lymphadenectomy.[21] Bilimoria et al.[12] published lymphadenectomy rates in locoregional gastric and pancreatic cancers based on the National Cancer Data Base of the American College of Surgeons. They found that only 23.2 % of patients with gastric cancer and 16.4 % of patients with pancreatic cancer underwent adequate lymphadenectomy between 2003 and 2004 . Merkow and co-authors identified 13,995 patients with stage I–III esophageal cancer undergoing esophagectomy in 639 US hospitals. Adequate lymphadenectomy rates increased from 23.5 to 34.4 % during the study period, but only 45 centers (7.0 %) examined a median of at least 15 lymph nodes.[22] Similar results were found analyzing the SEER database in patients with gastric and pancreatic cancers.[8,23] Single-center studies report markedly superior rates[6,7]; for example, results of the Worldwide Oesophageal Cancer Collaboration (WECC) collecting data from high-volume expert centers around the world show 70 % optimal lymphadenectomy rates per WECC recommendations based on tumor stage (pTis/T0/T1≥10 LN; pT2≥20 LN; pT3/T4≥30 LN).[24] Japanese authors propagating extended lymph node dissection in cancer surgery report far superior lymph node sampling rates accordingly.[25–27]

Based on the results of our study, elderly patients are more likely to receive inadequate lymph node dissection during operative therapy for potentially resectable GI cancer. Older patients are more likely to succumb to postoperative complications, and comorbid diseases might limit long-term survival; therefore, a tailored approach weighing the risks and benefits of a more thorough lymph node dissection (LND) could be reasonable. On the other hand, considering that the average life expectancy for an 80-year-old is >8 years[28] and high-volume surgeons perform major oncologic resections with acceptable morbidity and mortality even in the very elderly,[29–32] therapeutic decisions influencing long-term survival based on chronologic age are not justified.

The association of socioeconomic deprivation with lower quality cancer care is well documented.[33–37] According to our data, patients living in areas with higher poverty rates were more likely to receive inadequate lymphadenectomy during surgical resection for GI adenocarcinoma than patients living in more prosperous counties. Interestingly, contrary to several previous reports describing racial disparities in cancer-related health care and adequate lymphadenectomy rates,[12,38–43] we have found that race was not associated with inadequate lymphadenectomy.

The reasons for the disparities in undergoing adequate lymphadenectomy observed in this study are unclear. Interestingly, our results suggest that undergoing surgical therapy for non-colorectal cancer is a much stronger predictor of inadequate lymphadenectomy than gender, race, or socioeconomic status. Esophageal or pancreatic resections are complex operations where lymph node dissection contributes substantially to the risk of procedure-related morbidity.[6,44,45] This added to the ongoing controversy about its role in influencing long-term survival could create nihilistic attitudes toward performing proper lymphadenectomy. Furthermore, achieving adequate lymphadenectomy requires special expertise as previous studies have demonstrated higher lymph node counts and better long-term survival in patients undergoing surgical therapy for cancer in designated centers.[12] Men, ethnic minorities, and patients of lower socioeconomic status are more

likely to be uninsured, therefore less likely to receive state-of-the-art treatment including adequate lymphadenectomy in a high-volume hospital.[46] Numerous other factors including patient and tumor characteristics and provider-level factors could also be responsible for the variance in nodal counts.[44,45]

Although a substantial proportion of patients were undergoing inadequate lymph node dissection during surgical treatment for esophageal, pancreatic, and gastric cancers even in 2009, both the median numbers of lymph nodes removed and the rates of adequate lymphadenectomy improved significantly throughout the study period. One of the probable reasons for this improvement is the inclusion of lymph node counts as a quality benchmark in national guidelines and third party recommendations starting in the early 1990s and gaining wider acceptance after 2000.[46–48] Improvements in lymph node yield could also be consequences of recent centralization in cancer surgery in the USA. According to results published by Stitzenberg and Meropol, [49] the likelihood of treatment at a low-volume hospital in 2007 was significantly less than in 1999 for cancers of the esophagus (OR=0.42, CI=0.34–0.53), pancreas (OR=0.40, CI=0.35–0.46), colon (OR=0.88, CI=0.85–0.91), and rectum (OR=0.83, CI=0.78–0.89). Bilimoria et al.[50] found that high-volume centers examine more lymph nodes for gastric and pancreatic cancer as low-volume centers and community hospitals. Similarly, an analysis by Senthil and colleagues[51] showed that patients undergoing colorectal resections at NCCN-associated cancer hospitals have a higher chance of receiving adequate lymphadenectomy than in a community hospital, even when controlling for the surgeon as a cofounding factor. The impact of various other factors on lymph node retrieval has been studied extensively in patients undergoing surgery for colorectal cancer. Several authors indicate that pathologist characteristics, including the use of special retrieval techniques, might be the most important factor determining lymph node counts. Wang and coworkers[52] retrospectively analyzed lymph node counts after the application of fat clearance method compared to the traditional technique in 237 colorectal resection specimens and found significantly improved lymph node yields. These results from the literature suggest that further centralization and increasing awareness of the importance of nodal evaluation through multidisciplinary initiatives can further improve this aspect of cancer care. On the other hand, Nathan et al.[45] showed that the majority of the variation (78 %) in 12 LN evaluations in patients with colorectal cancer is related to non-modifiable patient-specific factors. Other factors with a possible effect on lymph node yields include patient's age and BMI, surgeon speciality, undergoing palliative or emergent surgery, tumor size, pT stage, and neoadjuvant therapy.[53,54]

Despite the extensive population-based cancer data available for this analysis, there are some limitations to consider regarding the results of our study as well. First, despite being advocated by several practice organizations and consensus panels,[19,46–48] the definitions of adequate lymphadenectomy used in this study are not universally accepted.[10,55,56] Second, our analyses are limited to the available variables in the SEER database with no information regarding patient insurance status, comorbidities, body mass index, or (neo-)adjuvant chemotherapy. Furthermore, a possible misclassification of patient information must always be considered when using administrative claims data. Despite these limitations, using the SEER dataset analyzed for this study has several advantages: large, population-based database, rigorous quality control standards, and a patient follow-up rate of >95 %.[17] Therefore, it can be reasonably assumed that our conclusions are probably justified even with the limited dataset.

Conclusions

This is the first study to analyze population-based data on lymphadenectomy rates directly comparing patients with different types of gastrointestinal cancer. We have found that the rates of adequate lymphadenectomy for locoregional gastrointestinal carcinoma are improving over time, but remain far from ideal in a large proportion of US patients. The strongest predictor for inadequate lymph node dissection was undergoing surgical therapy for esophageal, gastric, small bowel, or pancreatic cancer. To a lesser extent, male gender, older age, and higher level of poverty were also associated with this underuse. Racial differences in survival after surgical therapy for gastrointestinal cancer are probably influenced by factors other than disparities in adequate lymph node dissection rates.

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Nothing to disclose.

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Discussant

Dr. Thomas A. Aloia (New York, NY): Time-Trends and Disparities in Lymphadenectomy for Gastrointestinal Cancer in the United States: A Population-Based Analysis of 342,792 Patients

In this study the authors present data regarding temporal trends in nodal recovery for several gastrointestinal cancers. The data source is the SEER database and the cohort is recent. The majority of procedures examined were colorectal resections. The analysis determined that although progress in appropriate nodal recovery has been made, large numbers of patients may still be subject to undersampling of regional lymph nodes at the time of primary GI tumor resection.

In an additional analysis, the authors note that demographic and socioeconomic factors were statistically associated with adequate node sampling. However, the absolute differences are very small and may not be clinically or socially relevant.

These data are timely. As improved surgical techniques and more effective systemic therapies emerge, the number of patients with metastatic disease who are eligible for attempts at curative resection is on the rise. As we have seen frequently with colorectal liver metastases, these attempts are often thwarted by inadequate oncologic surgery for the primary tumor.

In order to better understand these data and to learn the possible clinical impact of these data the following questions are posed:

1. Large numbers of patients are recorded in the analysis as having no lymph nodes removed. This calls into question either the dataset or the curative intent of the operation. How were missing data handled in your analysis? Were the patients coded as having no lymph nodes removed listed as 0 nodes recovered in the dataset or was the data missing?

2. You dismiss differences in node removal rates based on age as "not clinical significant" but the magnitude of difference for age was at least if not more than for socioeconomic status. Do you really think that the data show a clinically significant bias against nodal recovery based on socioeconomic status or is this simply a byproduct of small differences becoming statistically significant in a very large dataset?

3. Nodal recovery is certainly a team sport. Both surgeon and pathologist need to participate to obtain a proper record of nodal recovery. Your discussion does not include consideration of the role of the pathologist in this issue. Why focus only on the surgeon?

4. Is it possible that palliative primary tumor resections are included in these data and may account for some of the patients with apparent "inadequate" nodal recovery? Can you tell in SEER if the resections had a curative vs. palliative intent?

Closing Discussant

Dr. Attila Dubecz: Thank You for Your comments.

1. Patients classified as "unknown number of lymphnodes removed" were excluded from the study population.

2. Socioeconomic status is the most important factor driving cancer disparities in the United States. Therefore, the measured differences in our study are not only statistical significant but also theoretically plausible and do not contradict previous data. On the other hand, our data must be interpreted with caution since several other unknown factors, for example insurance status could have much larger influence on these disparities.

3. It is impossible to distinguish from the SEER Database whether the inadequacy of lymph node dissection is caused by suboptimal surgical resection, pathologic work-up or documentation. There are some data from our study that could point to an inadequate pathologic nodal recovery. For example, the measured improvements in lymph node dissection over time in patients undergoing small bowel resection cannot be explained with surgical factors alone since the technique of small bowel resection (and therefore the amount of mesentery removed) has not changed significantly over time. It can be therefore postulated, that these changes are mainly caused by superior pathologic work-up and/or documentation.

4. SEER does not collect data on the intent of surgery. It is therefore possible that a very small subset of patients in our study population with inadequate lymphadenectomy underwent palliative surgery (with limited lymph node dissection) only but as palliative or esophagectomy is very rare and pancreatectomy with palliative intent is practically non-existent, this number is probably negligible.