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ORIGINAL ARTICLE

Are 12 Nodes Needed to Accurately Stage T1 and T2 Colon Cancers?

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Abstract Evaluation of 12 lymph nodes has been mandated to prevent colon cancer understaging. Given that the probability of node metastases is largely associated with T-stage, are <12 nodes substandard for T1 and T2 lesions? We evaluated if survival for T1 and T2 tumors varies by nodes examined. In SEER, 61,237 patients undergoing colon cancer resection were identified. For each T-stage, 5-year survival rates were compared for node-negative cancers by using stepwise node cut-point comparisons (4 nodes, <4, etc.). Survival impact was determined by log-rank test and hazard regression. For T1 tumors, 4 nodes had 24% lower hazard of death compared to <4. For T2 tumors, 10 nodes had the biggest survival impact, 15% lower hazard of death. In conclusion, the number of nodes to stage T1 and T2 lesions may be <12.

Keywords Colon cancer · Lymph nodes · Outcomes · T-stage · Quality measure

Introduction

One of the most important prognostic factors for patients diagnosed with colon cancer is the presence of lymph node metastases. Decisions to give adjuvant chemotherapy are based primarily on the status of lymph node involvement. Chemotherapy improves survival by approximately 30% for patients with node-positive disease [1, 2]. Patients in whom the extent of node evaluation is questioned, i.e., few nodes examined, may potentially have positive nodes that were either not resected or not identified in the specimen. It is conceivable that patients may be incorrectly staged as node negative. Due to these issues, the adequacy of lymph node evaluation has been proposed as a measure of quality.

There is ongoing debate over the number of lymph nodes that should be examined for adequate staging of colon cancer. In 1990 the American Association of Pathologists first proposed that 12 lymph nodes should be evaluated to adequately stage colon cancer patients. The selection of 12 lymph nodes was based primarily on data showing that 8% of patients were understaged when fewer nodes were evaluated [3, 4]. Recent updates by the National Cancer Institute published (Guidelines 2000 for Colon and Rectal Cancer Surgery), American Joint Commission on Cancer (AJCC), and the Union Against Cancer also recommend that 12 nodes should be examined, which is based mainly on data collected from T3 and T4 tumors [5–8]. Beyond consensus statements, other large published studies, using retrospective or prospective data, report a wide range of recommended minimum number of nodes, including 6, 8, 10, 12, and 17 [9–15]. Other authors have stated that there should be no minimum cutoff and have proposed instead that "as many nodes as possible should be evaluated" [16, 17]. This variation in recommendations begs the question, is 12 lymph nodes the correct number for T1 and T2 lesions?

The impact of the depth of tumor invasion, i.e., T-stage, on the number of nodes needed for adequate staging also needs further investigation. Early tumors may not require as many lymph nodes as more advanced cancers to obtain an adequate sample size of lymph nodes for accurate

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staging. Advanced T-stage has a strong correlation with the likelihood of having positive disease in the lymph nodes. Approximately 8–12% of T1 tumors and 14% of T2 tumors have node-positive disease [18–20]. While the majority of colon cancers are diagnosed with T3 tumors, T1 and T2 tumors comprise a considerable fraction of the patients (approximately 25%) [5, 20].

We hypothesized that the number of nodes to sufficiently stage T1 and T2 colon cancers will be less than 12 nodes. Through the use of a large population-based database, the specific aims of this paper are twofold: to determine the minimum number of lymph nodes required to adequately stage early colon cancer, and to evaluate if this number differs for T1 and T2 disease.

Methods

All patients diagnosed with colon cancer (adenocarcinoma) in the Surveillance, Epidemiology, and End Results (SEER) national cancer registry from 1993 to 2001 were evaluated ($n = 61{,}237$). SEER collects patient records from multiple sites across the USA and is regarded as a model population-based tumor registry. This national program includes 13 regional registries, which comprises approximately 14% of the population. The database was designed to reflect the overall characteristics of the USA, including the spectrum of racial/ethnic groups, geographic locations, and types of cities and states [21].

"Colon" location was defined by the "primary site" code 241 in SEER. In situ tumors were excluded. Tumors were further limited by specific histologies as defined by individual International Classification of Diseases for Oncology, 3rd edition codes for adenocarcinomas (8010, 8140–8145, 8210–8211, 8220–8221, 8260–8263), carcinoma undifferentiated (8020–8022), solid carcinoma (8230–8231), and mucinous adenocarcinomas (8470, 8480, 8481).

Patient Demographics, Tumor Characteristics, and Treatment for Node-Negative Patients

Tumor stage was coded using the AJCC 6th edition staging system based on the TNM stage organization. T-stage was defined as follows: T1 tumors invade the submucosa, T2 tumors invade muscularis propria, T3 tumors invade through the muscularis propria into the subserosa or non-peritonealized pericolic or perirectal tissue, and T4 tumors invade other organs, structures, or perforate the visceral peritoneum [7].

The analysis for node-negative patients was limited to T1 ($n = 3{,}505$) and T2 tumors ($n = 7{,}758$). We limited our analysis to patients who underwent "cancer-directed surgery." Patients who underwent bypass procedures (i.e., nonresective) were excluded, as were those with metastatic disease. Demographic information was recorded for each patient (grouped as T1 and T2 tumors) including: age, gender, race/ethnicity (White, Black, Hispanic, Asian, American Indian/Alaska, and other), and year of diagnosis. Tumor characteristics reported for each patient included: T-stage (T1 and T2), tumor grade, tumor location, and number of lymph nodes.

Tumor grade was categorized as well differentiated (grade I), moderately differentiated (grade II), poorly differentiated (grade III), undifferentiated (grade IV), or unknown. Tumor location was classified as follows: cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, and large intestine not otherwise specified (NOS). Number of lymph nodes examined is reported as the median value.

Number of Nodes Examined

Histograms demonstrating the distribution of number of nodes examined for node-negative patients (T1 and T2) were generated. Node-negative patients were defined as individuals who had one or more nodes examined, with no evidence of metastasis.

Survival and Regression Analyses

Kaplan–Meier survival curves were constructed to determine observed 5-year survival for patients with node-negative disease. "Observed survival" included survival from any cause of death. Survival analysis was completed for each T-stage (T1 and T2), comparing number of nodes examined for a series of lymph node cut points ($\geq$2 nodes examined versus <2 nodes, $\geq$3 versus <3, $\geq$4 versus <4, …to… $\geq$22 versus <22). Absolute difference in 5-year survival for each cut point and 95% confidence interval (CI) were determined. The log-rank test was used to determine statistical significance between survival curves. The number of nodes needed to reach greatest statistical significance was selected by identifying the cut point where the chi-square statistic was maximized.

Multivariate Cox proportional hazard regression modeling was utilized to further analyze the number of nodes for optimal survival of T1 and T2 node-negative patients. We began by determining the 5-year survival rate for each T-stage in node-negative cancers by separating the number of lymph nodes examined into three groups: <5, 5–11, and >12. After reviewing these results, individual regressions were then completed for each lymph node cut point. Covariates included in the analysis were: age, sex, race/ethnicity, tumor grade, tumor location, and number nodes examined by cut point (as a dichotomous variable). The minimum cut point for the number of lymph nodes examined

was determined by identifying where the statistically significant difference was the greatest (i.e., the lowest number of nodes with the highest statistical significance based on *P*-value). Statistical analyses were completed using STATA version 9.0 (Statacorp, College Station, Texas). *P*-values less than 0.01 were considered statistically significant.

Distribution and Incidence by T-Stage for All Colon Cancer Patients

The distribution (percentage) by T-stage (T1, T2, T3, and T4) of all colon cancer patients (both node negative and node positive) was established by each year of diagnosis (1992–2002 data available for incidence rate determination). To determine the incidence rate, the number of colon cancer cases reported in the SEER database (numerator) as defined by the registry sites was divided by the total number of people in those geographic areas as reported by the Census Bureau (denominator). Additionally, the incidence rates were calculated for the individual T-stages. Overall incidence rates were then age-adjusted to the standard 2000 population.

To evaluate the change in incidence from 1992 to 2002, the percentage change (PC) and estimated annual percentage change (APC), as determined by weighted least squares, were calculated. These calculations were performed within SEER*Stat 4.0^{TM} (Information Management Services, Inc, Silver Spring, Maryland).

Results

Patient Demographics

From 1993 to 2001, 61,237 patients with colon cancer who had undergone cancer-directed surgery and did not have evidence of stage IV disease were reported in SEER. By T-stage, 10% of T1 tumors, 17% of T2 tumors, 40% of T3, and 49% of T4 were node positive. Of these patients, 39,167 (63%) did not have evidence of lymph node involvement with metastases (i.e., node-negative disease). For node-negative patients, nearly one-third had T1 or T2 tumors: 9% T1, 20% T2, 60% T3, and 11% T4.

T1 and T2 node-negative patients had an average age of 71–72 years (Table 1). Slightly more than one-half of patients were female. Approximately 80% of patients were White, 8% were Black, 5% were Hispanic, and 5% were Asian.

Tumor Characteristics

Tumor grade varied notably between the T-stages; grade I accounted for 23.0% of T1 tumors as compared with 12.1% for T2 tumors (Table 1). Tumor location was similar across T1 and T2 tumors, with slightly fewer cecal tumors for T1 tumors, and fewer sigmoid lesions for T2 tumors. The majority of tumors were located in the sigmoid colon (28–32%), cecal (24–29%), and ascending colon (18–20%). T1 tumors had lower median numbers of nodes examined (7 nodes), as compared with T2 (9 nodes) (Figs. 1 and 2).

Table 1 Demographics and tumor characteristics by T-stage for node-negative colon cancer patients

Variable	T1 (n = 3,505)	T2 (n = 7,758)
Age (years)	71.3	72.5
Sex		
Male	49.9%	47.5%
Female	50.1%	52.5%
Race		
White	79.2%	79.6%
Black	8.6%	8.5%
Hispanic	4.6%	4.7%
Asian	5.7%	5.3%
American Indian/Alaska	0.4%	0.5%
Other	1.5%	1.4%
Grade		
I	23.0%	12.1%
II	61.3%	74.7%
III	6.5%	10.6%
IV	0.1%	0.2%
Unknown	9.1%	2.4%
Tumor location		
Cecum	24.2%	29.4%
Ascending colon	21.1%	18.7%
Hepatic flexure	5.6%	5.9%
Transverse colon	8.5%	9.1%
Descending colon	4.9%	5.0%
Splenic flexure	2.5%	3.2%
Sigmoid colon	32.6%	28.1%
Large intestine, NOS	0.6%	0.6%
Median number of nodes examined	7	9

Survival Outcomes: Comparing Number of Nodes Examined by Cut Points

The overall observed 5-year Kaplan–Meier survival rates for node-negative tumors by T-stage were: 73% T1 tumors and 71% T2. Five-year survival rates were determined for each T-stage, while grouping the number of lymph nodes examined as follows: <5, 5–11, and >12. The 5-year survival increased with greater numbers of nodes examined; for example, the T1 survival rate was 70%, when <5 nodes were examined and 76% when >12 nodes were examined. This minimal difference is contrasted by the results for T4

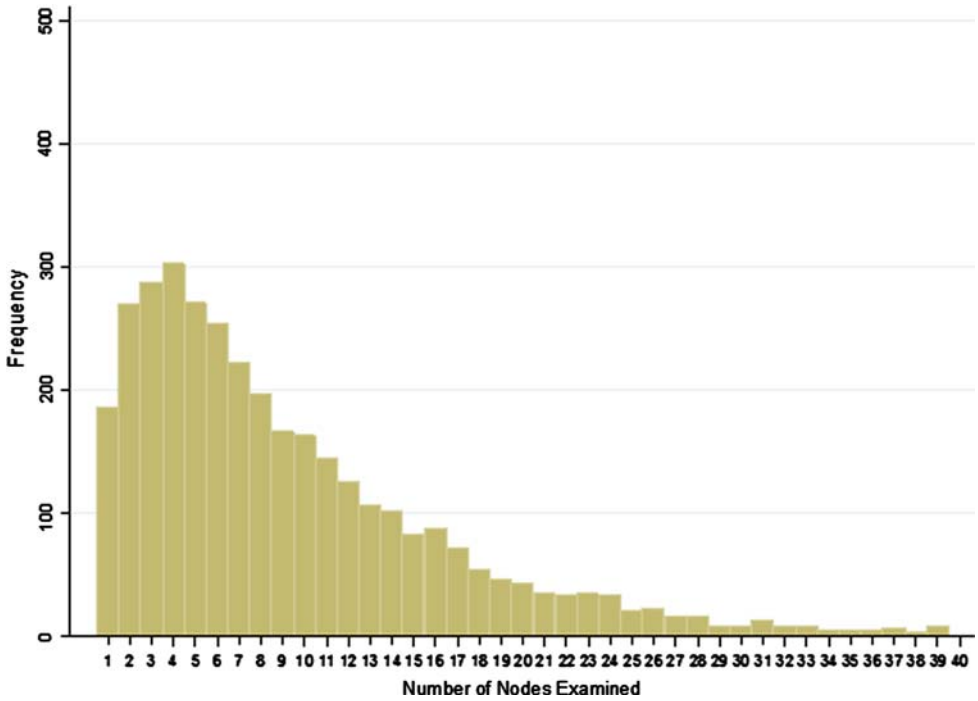

Fig. 1 Histogram of the number of nodes examined for T1 node-negative patients

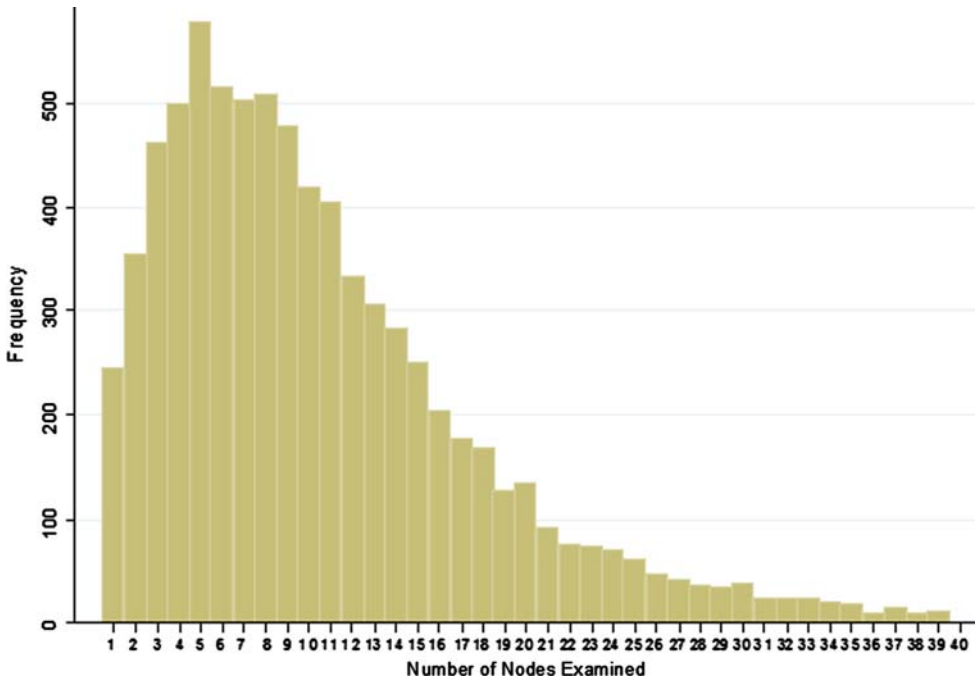

Fig. 2 Histogram of the number of nodes examined for T2 node-negative patients

tumors, which had 43% survival with <5 nodes and 60% when >12 nodes were examined. These results led us to further study what might be the optimal number of lymph nodes to harvest in colon cancer in order to maximize survival.

For T1 tumors, there was a statistically significant difference in survival at the cut point of 4 nodes, with better survival noted for patients with ≥4 nodes examined, as compared with those with <4 nodes examined; for example, T1 patients with ≥4 nodes had a 5-year survival of 74.1% as compared with 68.9% for <4 nodes (absolute difference of 5.2%, $P = 0.008$). In comparison, T1 patients with ≥5 nodes examined had a 5-year survival of 75.1% as compared with 68.3% for <5 nodes (absolute difference of 6.8%, $P = 0.005$). Examination of greater than 6 nodes (versus <6, ≥7 nodes versus <7, …. ≥22 versus <22) did not show a statistically significant improvement in survival. Thus, it appears that the majority of survival benefit for T1

tumors, as contributed by number of nodes examined, occurs at the cut points of ≥4 nodes and ≥5 nodes.

For T2 tumors, there was a statistically significant difference in survival noted at the cut point of 4 nodes (better survival for patients with ≥4 nodes examined versus <4). However, with stepwise increase in the number of nodes examined (≥5, ≥6, etc.), the survival difference was greater. The lowest number of nodes for which the *P*-value was maximized occurred at the cut point of 9 nodes ($P < 0.0001$). Also of note, the maximum chi-square value ($\chi^2 = 32.1$) occurred at the cut point of 13 nodes. Specifically, T2 patients with ≥13 nodes had a 5-year survival of 75.4% as compared with 68.9% for <13 nodes (absolute difference of 6.5%, $P = 0.001$).

Hazard Regression Models for Cutoff Points of Nodes Evaluated

Individual Cox proportional hazard regression models were performed for T1 tumors by applying the various node cut points (controlling for age, sex, race/ethnicity, tumor grade, and tumor location). In this adjusted model, patients with T1 tumors who had ≥4 nodes examined had an associated 24% lower hazard of death as compared with <4 nodes (hazard ratio [HR] = 0.760, confidence interval {CI} [0.641 to 0.902], $P = 0.002$) and 21% lower hazard of death for ≥5 nodes (HR = 0.794, CI [0.679–0.928], $P = 0.004$) (Table 2). As such, based on the univariate and multivariate analysis, it appears that the cut point of ≥4 nodes examined is the minimum number of nodes for which a significant survival benefit is observed.

For T2 tumors, regression analysis identified a wider range of cut point nodes examined with a statistically significant ($P < 0.01$) improvement in survival, with a range of ≥10 to ≥16 nodes. Of note, the univariate analysis found that the midpoint, i.e., cut point of 13 nodes, had the greatest significance. In the adjusted regression, the cut point of ≥10 nodes (versus 10 nodes) examined had a 15% lower hazard of death (HR = 0.853, CI [0.776–0.937], $P = 0.001$) and for ≥16 nodes examined (versus <16) there was a 16% lower hazard of death (HR = 0.848, CI [0.750–0.959], $P = 0.009$) (Table 3). In turn, based on the adjusted multivariate regression analysis, it appears that the minimum number of nodes needed for a significant survival benefit is the cut point of ≥10 nodes.

Table 2 Cox hazard regression models for T1 node-negative colon cancers by number of nodes examined*

Cut point (no. of nodes)	Hazard ratio	$P > \chi^2$	95% confidence interval
≥4 (ref. <4)	0.760	0.002	0.641–0.902
≥5 (ref. <5)	0.794	0.004	0.679–0.928

* Showing cut points where $P < 0.01$

Table 3 Cox hazard regression models for T2 node-negative colon cancers by number of nodes examined*

Cut point (no. of nodes)	Hazard ratio	$P > \chi^2$	95% confidence interval
≥10 (ref <10)	0.853	0.001	0.776–0.937
≥11 (ref. <11)	0.848	0.001	0.770–0.934
≥12 (ref. <12)	0.855	0.002	0.773–0.945
≥13 (ref. <13)	0.831	0.001	0.748–0.923
≥14 (ref. <14)	0.855	0.006	0.766–0.955
≥15 (ref. <15)	0.842	0.004	0.749–0.945
≥16 (ref. <16)	0.848	0.009	0.750–0.959

* Showing cut points where $P < 0.01$

Kaplan–Meier Survival Curves

Five-year survival curves were generated for the minimum value cut points determined by univariate and multivariate regression, i.e., the cut point of ≥4 nodes for T1 and ≥10 nodes for T2. Five-year survival curves were generated for ≥4 nodes examined as compared with <4 nodes, 74.1% versus 68.9%, respectively ($P = 0.008$) (Fig. 3). The cut point of ≥4 nodes examined was selected as it was the lowest number of nodes needed to achieve a significant statistically difference in survival, based on both the univariate survival comparison and the multivariate adjusted hazard regression model.

Five-year survival rates for T2 tumors with ≥10 nodes examined, as compared with <10 nodes were 74.1% versus 68.9%, respectively, $P = 0.008$ (Fig. 4). The cut point of ≥10 nodes examined was selected as it was the lowest number of nodes needed to achieve a statistically significant difference in survival, based on the multivariate adjusted hazard regression model.

Colon Cancer Incidence Rates by T-Stage

The overall incidence of colon cancer was 40.0 per 100,000 individuals in the year 1992 (age-adjusted), as determined from the population-based data, which decreased to 34.5 by the year 2002. This decrease translates into −13.0% percent change (PC) with –1.07% annual percent change (APC) ($P < 0.05$). The incidence of T1 tumors increased from 2.223 cases (per 100,000) in 1992 to 2.716 cases in 2002 (+22.2% PC, +3.4% APC, $P < 0.05$), as did the incidence of T2 tumors: 3.746 cases in 1992 to 3.967 cases in 2002 (+5.9% PC, +1.2 APC, $P < 0.05$). In contrast, the incidence of T3 and T4 tumors decreased over the same time period: T3 tumors decreased from 15.981 cases in 1992 to 14.203 cases in 2002 (−11.1% PC, −0.6% APC,

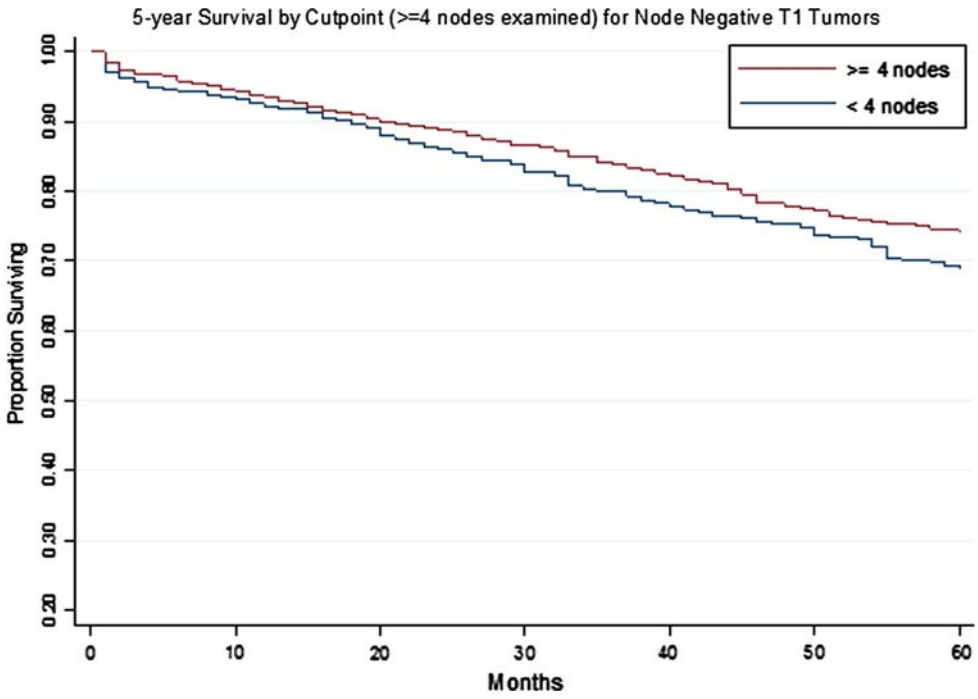

Fig. 3 Kaplan–Meier survival curves for T1 tumors

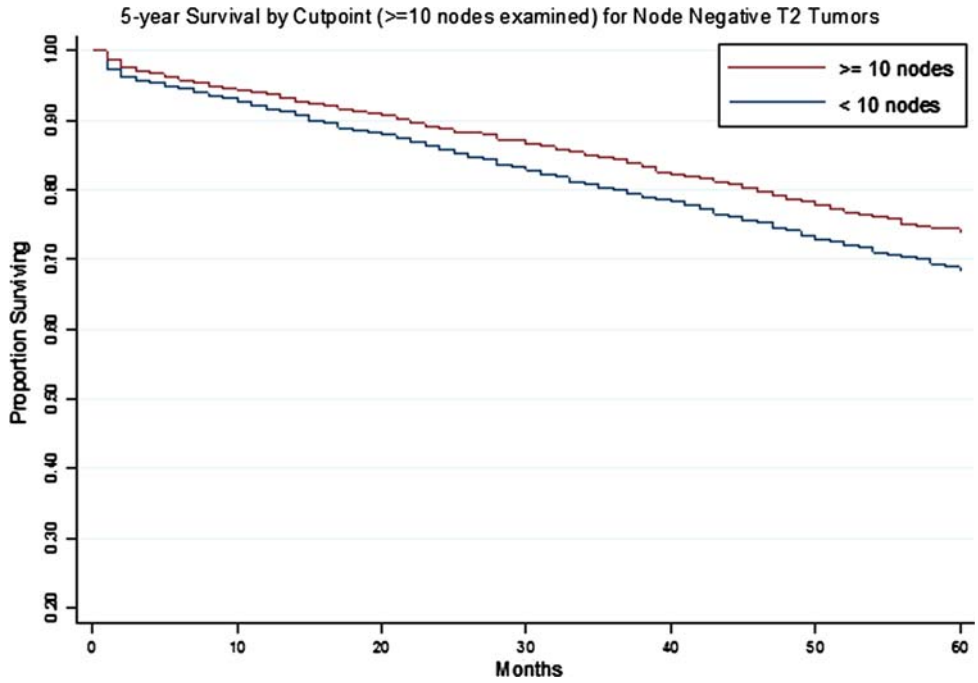

Fig. 4 Kaplan–Meier survival curves for T2 tumors

$P < 0.05$) and T4 tumors decreased from 0.970 cases in 1992 to 0.670 cases in 2002 (−30.9% PC, −3.5% APC, $P < 0.05$) (Figs. 4 and 5).

Discussion

Our data demonstrate that the examination of 10 lymph nodes is adequate for T2 colon cancer, and ≥4 lymph nodes is appropriate for staging T1 colon cancer. Although T1 tumors represent a small proportion of tumors at this point in time, their incidence is rising and may continue to increase with widespread screening practices. Our data suggest that the number of nodes required for confident staging of T1 tumors falls in the 4–5 node range. The lower end of the range (≥4 nodes) should be considered the minimum number of nodes needed to adequately stage the majority of patients. Ideally, a "cancer operation" involving high ligation of

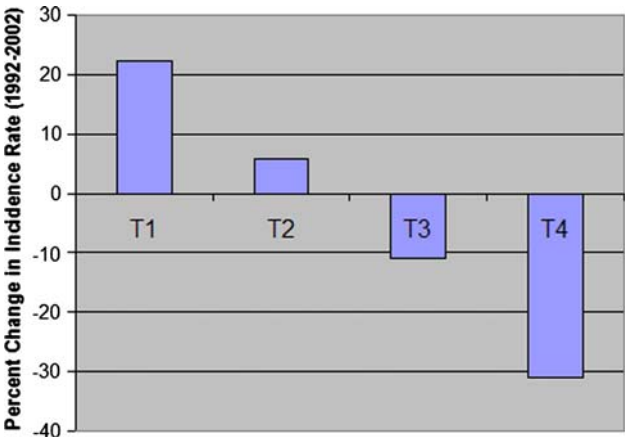

Fig. 5 Change in incidence rates for all colon cancer patients (1992–2002) by T-stage

major feeding and drainage vessels and adequate resection of proximal and distal margins should be performed for all patients with colon cancer, regardless of T-stage. Additionally, all the lymph nodes in the specimen should be examined for presence of metastatic disease, given that the number of lymph nodes evaluated has been shown to be associated with increased survival [22].

The examination of 12 lymph nodes for adequate staging of colon cancer is being strongly considered as a quality or pay-for-performance measure. When considering the number of nodes examined as a quality measure, not only the impact of T-stage, but also the minimum versus the optimal number of lymph nodes should be factored into assessing the confidence of staging.

The observed difference in survival noted for node-negative patients as a function of number of nodes examined likely is related to understaging. In general, T1 and T2 colon cancer patients who are determined to be node negative, regardless of number of nodes examined, will not be given adjuvant chemotherapy. As such, those patients in whom inadequate nodes are examined may in fact be truly node positive and understaged. However, as the likelihood of having node-positive disease is less in T1 and T2 lesions, the added benefit of examining greater numbers of nodes lessens. In other words, increasing the number of nodes past a certain point, i.e., the cut point, will not offer a survival benefit to the majority of patients.

Although previous studies have addressed the influence of T-stage on the required number of nodes examined, these studies have had limitations [20, 23]. For example, Leibl exclusively investigated sigmoid and rectal tumors, and Rasheed et al. studied only rectal tumors [20, 24]. Alternatively, others have combined T1 and T2 tumors in the analysis [23–27].

The adequacy of lymph nodes recovered following colon cancer resection is dependent not only on the extent of the surgical resection, but also on the pathologic recovery of nodes from the specimen. From the surgical perspective, the amount of mesentery resected for a "cancer operation," will presumably impact the available number of nodes for examination. From the pathologic standpoint, the method of fat clearance and attention to the identification of all nodes in the specimen act to determine the number of lymph nodes microscopically examined for metastases [4]. Measures of quality aimed at assessing adequacy of lymph node involvement will rate both of these influences—extent of resection and pathologic identification of nodes.

Given that there is no reliable method of preoperatively staging colon cancer patients, we do not recommend that the results of this study guide the extent of resection. However, our findings can be utilized as institutional measures to evaluate the overall quality of the involved surgeons and pathologists. For example, using our results, if a patient is found to have T1 disease and only five lymph nodes are identified and examined, this patient may not be understaged. In the past, the above patient may have been considered to be understaged and may have received chemotherapy as a precaution. By defining $\geq$4 lymph nodes as having survival benefit, we can save this patient from the morbidity associated with unnecessary chemotherapy.

Our study has several limitations. First, while the SEER database allows for longitudinal examination of population-based cancer data, it lacks comprehensive data such as the use of computed tomography findings, presence of pre-existing comorbidities, and receipt of adjuvant chemotherapy. We have assumed that patients with T1 or T2 tumors did not receive adjuvant chemotherapy, which, if incorrect, could have led to bias in survival rates. Additionally, this study did not analyze other outcomes, such as recurrence, and there may have been coding inaccuracies. Its strengths, however, include the ability to capture a large, population-based subset of patients that include a range of geographic regions and hospital settings to offer a perspective of cancer resection across the country.

Our work demonstrates a strong relationship between survival and the number of lymph nodes examined for node-negative patients. T-stage plays an important role in determining the minimum number of nodes required for confidence in the staging process. A "cancer operation" should be performed routinely for all colon cancer patients, but T1 tumors who have less than 12 nodes resected (specifically, 4–11 nodes for T1) should not be considered understaged, assuming reasonable attempts to identify as many nodes as possible in the specimen have been made. As a combined measure of both surgical and pathological quality, the minimum number of lymph nodes examined appears to be associated with T-stage.

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