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ORIGINAL ARTICLE

Patients with Adenocarcinoma of the Small Intestine with 9 or More Regional Lymph Nodes Retrieved Have a Higher Rate of Positive Lymph Nodes and Improved Survival

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Abstract
Purpose To assess the influence of regional lymph node (RLN) retrieval on stage migration of adenocarcinoma of the small intestine and survival.
Patients and Methods From the Surveillance, Epidemiology, and End Results database,1090 patients with nonmetastatic small bowel adenocarcinoma were identified in between 2004 and 2011. The impact of the number of RLNs removed on histopathological staging and oncological outcome was assessed utilizing Cox proportional hazard regression models with and without risk-adjustment, propensity score methods, and joinpoint regression analysis.
Results The rate of node-positive cancer increased steadily with the number of retrieved RLNs up to 9 RLNs, which suggests that a minimum of 9 (95 % CI 5.5–10.5) retrieved RLNs are needed for the detection of node-positive disease ($P<0.001$). From 657 of 1090 patients (60.3 %), 9 or more RLNs were retrieved. While in 2004 only in 46.0 % of all cases 9+ RLNs were retrieved, this rate increased to 69.3 % in 2011 ($P<0.001$). The multivariable analysis demonstrated that the retrieval of 9+ RLNs was associated with better overall (hazard ratio of death [HR]=0.67, 95 % CI 0.55–0.82, $P<0.001$) and cancer-specific survival (HR=0.77, 95 % CI 0.61–0.96, $P=0.022$). This finding was confirmed by a propensity score-adjusted analysis, which indicated increased overall (HR=0.67, 95 % CI 0.50–0.89, $P<0.001$) and cancer-specific survival (HR=0.67, 95 % CI 0.49–0.92, $P=0.013$) in patients with the retrieval of 9+ RLNs.
Conclusion To our knowledge, this is the first population-based propensity score-adjusted investigation in small bowel adenocarcinoma. A sufficient number of RLNs should be retrieved to achieve an optimal oncological outcome.

Keywords Small intestine · Survival · Lymph nodes · Adenocarcinoma

Introduction

Malignancies of the small intestine are rare. They account for 3 % of all gastrointestinal neoplasms and approximately 0.5 % of all cancers in the USA.[1,2] Histologically they can be subdivided into adenocarcinoma accounting for 25 to 40 % of small bowel neoplasms, carcinoids (approximately 40 %), lymphomas (approximately 16 %), and sarcomas (approximately 10 %).[3–5]

Most patients with small bowel adenocarcinoma present with locoregional disease; thus, the surgical resection of the primary and the investing mesentery with regional lymph nodes (RLNs) at risk for metastases is the recommended therapeutic strategy.[3,6] In the absence of distant metastases, the extent of the surgical resection and RLN metastases are the main predictors of oncological outcomes.[7–10] For a number of other malignancies (e.g., colorectal cancer), the number of retrieved lymph nodes is a well-recognized prognostic factor.[11–13] According to international guidelines, a minimum of 12 retrieved locoregional lymph nodes is a prerequisite for adequate histopathological staging in colorectal cancer patients.[14–16] The clinical decision-making about adjuvant chemotherapy is primarily based on the detection of metastases in regional lymph nodes. To ensure the optimal

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oncologic outcome subsequent to adjuvant therapy in colorectal cancer patients with regional lymph node metastasis, accurate staging is of utmost importance.[17] For small bowel adenocarcinoma, there is little evidence for the adequate number of resected regional lymph nodes required for an appropriate staging. Previous research suggested at least 8 RLNs; however, the study lacked a contemporary statistical methodology for multivariable adjustment of potential confounders.[10]

Therefore, the aim of this population-based analysis was to identify the minimum number of retrieved regional lymph nodes needed for optimal staging utilizing a joinpoint regression trend analysis and to assess the impact of lymph node retrieval on survival utilizing a multivariable and propensity score-matched adjustment for potential confounders.

Methods

Cohort Definition: Surveillance, Epidemiology, and End Results

Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute in the USA were the source of this population-based analysis.[18] SEER data were collected and reported using data items and codes as documented by the North American Association of Central Cancer Registries (NAACCR).[19] Primary cancer site and histology were coded according to criteria found in the third edition of the International Classification of Diseases for Oncology (ICD-O-3).[20] Patients with adenocarcinoma of the small intestine were identified by the ICD-O-3 site codes C170 to C179 and behavior code 3 (NAACCR Items 522 and 523). Patients diagnosed at autopsy or by death certificate, as well as patients with no histologically confirmed cancer, were excluded (NAACCR Items 490 and 2180). Patients with histological types other than adenocarcinoma (NAACCR Item 522), patients with a lifetime occurrence of another primary malignancy (NAACCR Item 380), patients without the oncological resection of the cancer (NAACCR Items 1290), patients who preoperatively received radiation (NAACCR Item 1360), and patients without retrieved regional lymph nodes (NAACCR Item 830) were excluded.

Statistical Analysis

Statistical analyses were performed using R statistical software (www.r-project.org). A two-sided P value <0.05 was considered statistically significant. Continuous data are expressed as the mean±standard deviation or the median (interquartile range, IQR). Chi-square tests and t-tests were used to compare proportions and continuous variables. In the regression analysis, all P values were computed by likelihood ratio tests. Wald-type confidence intervals were estimated.

To test for a significant correlation between the number of RLNs and the rate of node-positive carcinomas, Spearman's rho was applied. The rate of node-positive carcinomas was modeled by logistic regression, and Davies' test[21] were applied to test for breakpoints in the number of RLNs at which a significant change in the rate of node-positive carcinomas had occurred. Joinpoint regression analysis was applied to define the best fitting points for changes in the trend of the rate of node-positive carcinomas.[22] For sensitivity analysis, the relationship between the number of RLNs and the rate of node-positive carcinomas was finally assessed utilizing LOESS regression analysis.[23]

After comparing patients who received the retrieval of 1–8 versus 9+ RLNs utilizing a descriptive analysis, the factorized number of retrieved RLNs was assessed as a prognostic factor for overall and cancer-specific survival utilizing Kaplan-Meier and Cox regression analyses with and without risk adjustment for stage, location, grading, postoperative radiation, year of diagnosis, age, gender, ethnicity, and marital status (risk set). The univariable analysis of the impact of the number of retrieved RLNs was performed with stratification for tumor stage to minimize a possible stage migration effect (Will Rogers phenomenon).[24]The full model Cox regression was further elucidated by a backward variable selection procedure from the full model based on Akaike's information criterion. The proportional hazard assumption was tested utilizing scaled Schoenfeld residuals and by the inspection of hazard ratio (HR) plots.[25] Thereafter, predictors of the number of retrieved RLNs in the risk set were assessed utilizing multivariable logistic regression to assess the bias. Moreover, a propensity score analysis, a superior and more refined statistical method to adjust for potential baseline confounding variables, was performed.[26–28] The "MatchIt" and the "optmatch" R packages were used to perform a bipartite weighting propensity score analysis.[29,30] The distance measure was estimated by logistic regression using the risk set described above. Patients with 1–8 retrieved RLNs who did not have a counterpart regarding the distance measure among the patients with 9+ retrieved RLNs and vice versa were excluded. Afterwards, the baseline risk profiles of the matched patients were compared to assure that no major differences in baseline patient characteristics existed. Finally, the prognostic value of 1–8 versus 9+ retrieved RLNs for overall and cancer-specific survival was assessed utilizing a Cox regression analysis via the weights and strata obtained by the bipartite matching propensity score analysis with additional stratification for tumor stage.

Results

Patient Characteristics and Bias for Lymph Node Retrieval

Of 5368 patients diagnosed with adenocarcinoma of the small intestine between 2004 and 2011 in one of the regions covered

by SEER, 1090 were eligible for analysis (Fig. 1). The mean follow-up was 30.0±25.9 months, and the median follow-up was 22 months (IQR 9 to 47 months). At the end of the follow-up, 652 (59.8 %) patients were alive, 346 (31.7 %) patients had died from cancer and 92 (8.4 %) patients had died from causes other than cancer. The mean number of retrieved RLNs was 30.0±25.9 and the median was 11 (IQR 6 to 17). In 433 patients (39.7 %), 1 to 8 RLNs were retrieved, and in 657 patients (60.3 %), 9+ RLNs were retrieved. Table 1 depicts the patient characteristics of these two groups. Utilizing

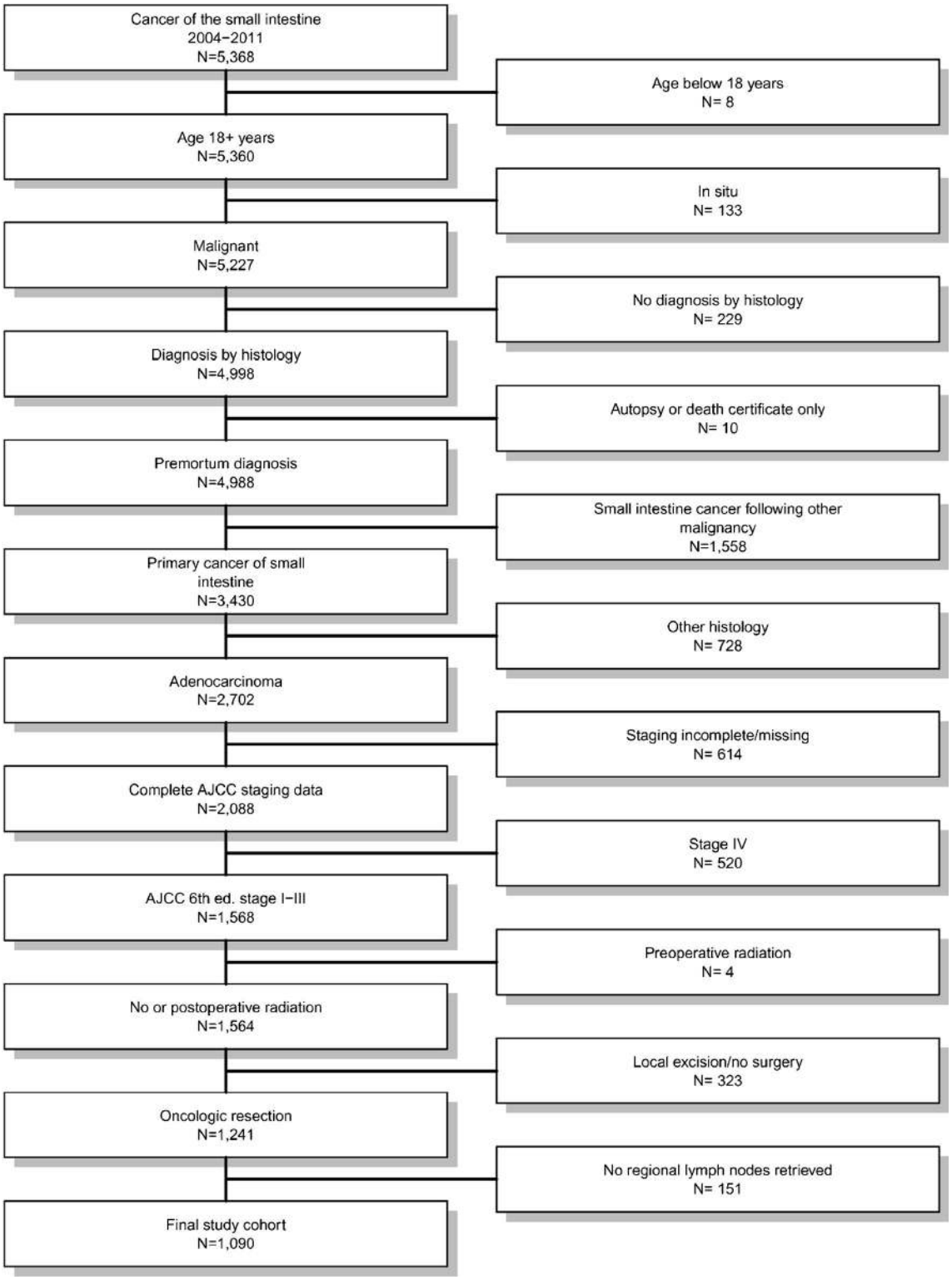

Fig. 1 Flow chart of patient cohort selection

Table 1 Patient characteristics and bias in the retrieval of regional lymph nodes

		Patient characteristics and univariable bias for the number of retrieved regional lymph nodes (RLNs)				Multivariable bias in logistic regression[a]	
		Total *N*=1090	1 to 8 RLN *N*=433	9+ RLN *N*=657	*p* value[b]	Odds ratio (95 % CI)	*p* value[c]
Stage	Stage I	117 (10.7 %)	47 (10.9 %)	70 (10.7 %)	<0.001	Reference	<0.001
	Stage II	412 (37.8 %)	206 (47.6 %)	206 (31.4 %)		0.61 (0.39–0.95)	
	Stage III	561 (51.5 %)	180 (41.6 %)	381 (58.0 %)		1.23 (0.79–1.92)	
Location	Duodenum	547 (50.2 %)	187 (43.2 %)	360 (54.8 %)	<0.001	Reference	<0.001
	Jejunum	218 (20.0 %)	111 (25.6 %)	107 (16.3 %)		0.51 (0.36–0.72)	
	Ileum	189 (17.3 %)	65 (15.0 %)	124 (18.9 %)		1.18 (0.82–1.72)	
	Other	136 (12.5 %)	70 (16.2 %)	66 (10.0 %)		0.56 (0.37–0.84)	
Grading	G1	104 (9.5 %)	52 (12.0 %)	52 (7.9 %)	0.005	Reference	0.007
	G2	556 (51.0 %)	215 (49.7 %)	341 (51.9 %)		1.57 (1.00–2.46)	
	G3/4	387 (35.5 %)	141 (32.6 %)	246 (37.4 %)		1.64 (1.02–2.63)	
	Unknown	43 (3.9 %)	25 (5.8 %)	18 (2.7 %)		0.59 (0.28–1.25)	
Radiation	None	985 (90.4 %)	400 (92.4 %)	585 (89.0 %)	0.068	Reference	0.447
	After surgery	105 (9.6 %)	33 (7.6 %)	72 (11.0 %)		1.20 (0.76–1.92)	
Year of Diagnosis	2004–2005	252 (23.1 %)	129 (29.8 %)	123 (18.7 %)	<0.001	Reference	<0.001
	2006–2008	405 (37.2 %)	160 (37.0 %)	245 (37.3 %)		1.62 (1.16–2.26)	
	2009–2011	433 (39.7 %)	144 (33.3 %)	289 (44.0 %)		2.17 (1.56–3.03)	
Age	<50	187 (17.2 %)	65 (15.0 %)	122 (18.6 %)	0.112	Reference	0.008
	50–64	386 (35.4 %)	146 (33.7 %)	240 (36.5 %)		0.71 (0.48–1.05)	
	65–79	392 (36.0 %)	163 (37.6 %)	229 (34.9 %)		0.55 (0.37–0.82)	
	80+	125 (11.5 %)	59 (13.6 %)	66 (10.0 %)		0.49 (0.29–0.81)	
Gender	Male	600 (55.0 %)	243 (56.1 %)	357 (54.3 %)	0.563	Reference	0.509
	Female	490 (45.0 %)	190 (43.9 %)	300 (45.7 %)		1.09 (0.84–1.43)	
Ethnicity	Caucasian	874 (80.2 %)	348 (80.4 %)	526 (80.1 %)	0.670	Reference	0.756
	African-American	158 (14.5 %)	65 (15.0 %)	93 (14.2 %)		0.88 (0.61–1.27)	
	Other/unknown	58 (5.3 %)	20 (4.6 %)	38 (5.8 %)		1.05 (0.59–1.94)	
Marital status	Married	662 (60.7 %)	261 (60.3 %)	401 (61.0 %)	0.274	Reference	0.545
	Single/widowed	295 (27.1 %)	126 (29.1 %)	169 (25.7 %)		0.89 (0.65–1.21)	
	Other/unknown	133 (12.2 %)	46 (10.6 %)	87 (13.2 %)		1.13 (0.75–1.72)	

N (%) and odds ratio (95 % confidence interval)

[a] Multivariable logistic regression (full model) for prediction of 9+ versus 1–8 retrieved RLNs

[b] Chi-square test

[c] Likelihood ratio test

multivariable logistic regression, a significant bias based on stage, location, grading, and year of diagnosis was consistently found.

Trend Analysis of Lymph Node Retrieval and N-stage

The rate of node-positive small bowel adenocarcinoma was 28.1 % in patients with 1 retrieved RLN. This rate increased to 57.9 % in patients with more than 25 RLNs (r=0.714, P<0.001). In a joinpoint regression analysis, one notable change in the trend between the number of retrieved RLNs and the rate of node-positive small bowel adenocarcinoma was identified at 8 RLNs (95 % CI 5.5 to 10.5 RLN, P<0.001) (Fig. 2). Between 1 and 8 RLNs, the rate of node-positive cancer per 1 RLN increased on average by 3.8 % and thereafter by 0.2 %. There was no evidence of additional relevant changes in the trend (P=0.917). A LOESS regression was performed as a sensitivity analysis and confirmed the joinpoint regression analysis (Fig. 2). The rate of patients with the retrieval of 9+ RLNs increased from 46.0 % in 2004 to 69.3 % in 2011 (P<0.001).

Lymph Node Retrieval as a Prognostic Factor for Survival

In univariable Cox regression analyses, the number of retrieved RLNs significantly correlated with the overall survival

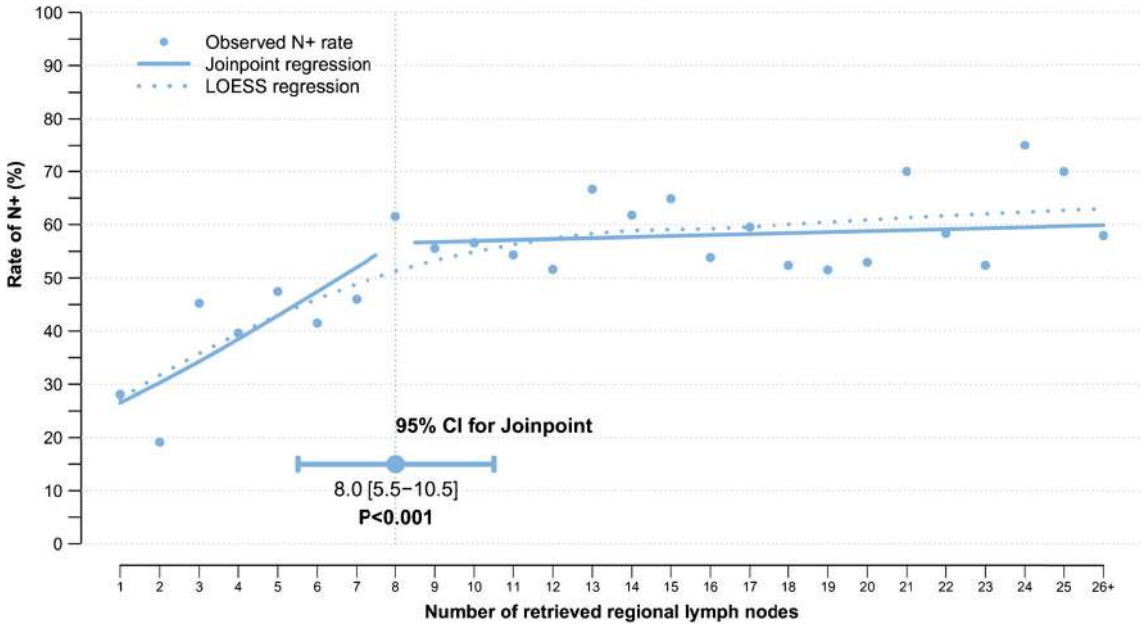

Fig. 2 Trend analysis of the number of retrieved lymph nodes and N-stage. This figure depicts the observed rate of node-positive adenocarcinoma of the small intestine for a given number of retrieved regional lymph nodes (RLNs). Also shown is the prediction curve from a joinpoint regression analysis. This analysis identified a significant change that occurred at 8 RLNs (95 % CI 5.5 to 10.5 RLN, $P<0.001$). In a sensitivity analysis, a LOESS regression line is shown supporting the findings of joinpoint regression analysis

($P<0.001$) but not with the cancer-specific survival ($P=0.085$) (Table 2). The 5-year overall and cancer-specific survival rates for patients with 1 to 8 retrieved RLNs were 38.5 % (95 % CI 33.4–44.3 %) and 52.8 % (95 % CI 48.2–57.8 %) compared to 52.8 % (95 % CI 48.2–57.8 %) and 60.4 % (95 % CI 55.9-65.4 %) in patients with 9+ RLNs (upper panels of Fig. 3). In full model multivariable analysis, the number of retrieved RLNs significantly affected the overall and also cancer-specific survival. Compared to patients with 1 to 8 retrieved RLNs, the risk of overall mortality in patients with 9+ retrieved RLNs was reduced by 33 % (hazard ratio: 0.67, 95 % CI 0.55 to 0.82, $P<0.001$), and the risk of cancer-specific mortality was reduced by 23 % (hazard ratio 0.77, 95 % CI 0. 61 to 0.96, $P<0.001$) in patients with 9+ retrieved RLNs (Table 2). A backward variable selection confirmed a significant association between the number of retrieved RLNs and overall and cancer-specific survival rates.

Adjusting for Patients' and Cancer Characteristics with Propensity Score Matching

To further corroborate the inconclusive findings of the adjusted and unadjusted Cox regression analyses (Table 2) and to adjust for the bias in patients and cancer characteristics between patients with different numbers of retrieved RLNs (Table 1), a propensity score analysis was performed to compare the survival rates in patients with 1–8 and 9+ retrieved RLNs. The unadjusted propensity score for patients with 1–8 retrieved RLNs was 0.550±0.143, compared to 0.635±0.132 in patients with 9+ retrieved RLNs ($P<0.001$), indicating a strong and clinically relevant bias between the two groups. Due to missing counterparts with a comparable propensity score, 2 patients with retrieval of 1–8 RLNs and 7 patients with retrieval of 9+ RLNs were excluded from the propensity score analysis. After the matching procedure, the propensity score was virtually the same in both groups (0.635±0.132 and 0.635±0.132, $P=0.997$), indicating successful bias elimination between the groups (Table 3). Utilizing a Cox regression analysis after the propensity score-matching procedure with additional stratification for tumor stage (Fig. 3, lower panels), the retrieval of 9+ RLNs was a significant positive predictor for overall (hazard ratio 0.67, 95 % CI 0.50 to 0.89, $P<0.001$) and cancer-specific (hazard ratio 0.67, 95 % CI 0.49 to 0.92, $P=0.013$) survival. The 5-year overall and cancer-specific survival rates for patients with 1 to 8 retrieved RLNs were 38.3 % (95 % CI 33.3–44.1 %) and 48.4 % (95 % CI 43.0–54.6 %) compared to 53.0 % (95 % CI 48.4–58.0 %) and 59.4 % (95 % CI 54.8–64.4 %) in patients with 9+ RLNs.

Discussion

To our knowledge, this is the first population-based analysis investigating the prognostic relevance of regional lymph node retrieval of small intestine adenocarcinoma to survival utilizing trend analysis and propensity score matching. The present investigation provides two main results. First, the rate of node-

Table 2 Prognostic factors for overall and cancer-specific mortality

		Overall survival				Cancer-specific survival			
		Univariable[a]		Cox regression, full model[b]		Univariable[a]		Cox regression, full model[b]	
		HR (95 % CI)	*p* value[c]	HR (95 % CI)	*p* value[c]	HR (95 % CI)	*p* value[c]	HR (95 % CI)	*p* value[c]
Retrieved regional lymph nodes[d]	1–8	Reference	<0.001	Reference	<0.001	Reference	0.085	Reference	0.022
	9+	0.72 (0.59–0.87)		0.67 (0.55–0.82)		0.83 (0.66–1.03)		0.77 (0.61–0.96)	
Stage	Stage I	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
	Stage II	1.77 (1.14–2.76)		1.75 (1.11–2.76)		3.52 (1.78–6.95)		3.58 (1.79–7.16)	
	Stage III	3.07 (2.01–4.70)		3.28 (2.11–5.09)		6.48 (3.33–12.6)		6.70 (3.40–13.2)	
Location	Duodenum	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
	Jejunum	0.49 (0.37–0.65)		0.50 (0.37–0.66)		0.45 (0.32–0.61)		0.45 (0.33–0.63)	
	Ileum	0.68 (0.52–0.89)		0.76 (0.58–1.01)		0.65 (0.48–0.89)		0.74 (0.54–1.02)	
	Other	0.88 (0.66–1.17)		0.96 (0.71–1.30)		0.76 (0.55–1.06)		0.84 (0.59–1.19)	
Grading	G1	Reference	0.006	Reference	0.076	Reference	0.004	Reference	0.205
	G2	1.34 (0.92–1.95)		1.13 (0.76–1.67)		1.46 (0.94–2.28)		1.12 (0.71–1.77)	
	G3/4	1.70 (1.16–2.49)		1.37 (0.93–2.04)		1.93 (1.23–3.03)		1.37 (0.86–2.16)	
	Unknown	0.99 (0.53–1.86)		0.81 (0.43–1.53)		1.09 (0.53–2.26)		0.90 (0.43–1.87)	
Radiation	None	Reference	0.389	Reference	0.883	Reference	0.064	Reference	0.567
	After surgery	1.14 (0.85–1.53)		1.02 (0.75–1.39)		1.35 (0.99–1.84)		1.10 (0.79–1.52)	
Year of diagnosis	2004–2005	Reference	0.686	Reference	0.516	Reference	0.703	Reference	0.728
	2006–2008	1.07 (0.86–1.34)		1.14 (0.91–1.42)		1.04 (0.81–1.33)		1.08 (0.84–1.39)	
	2009–2011	0.97 (0.74–1.28)		1.06 (0.80–1.40)		0.92 (0.68–1.26)		0.98 (0.72–1.35)	
Age	<50	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
	50–64	1.44 (1.02–2.03)		1.32 (0.93–1.88)		1.31 (0.90–1.89)		1.19 (0.82–1.73)	
	65–79	2.41 (1.73–3.36)		2.17 (1.55–3.04)		2.05 (1.44–2.92)		1.81 (1.27–2.60)	
	80+	4.30 (2.97–6.21)		4.27 (2.91–6.26)		3.30 (2.20–4.95)		3.42 (2.24–5.21)	
Gender	Male	Reference	0.651	Reference	0.053	Reference	0.607	Reference	0.129
	Female	0.96 (0.79–1.16)		0.82 (0.67–1.00)		0.95 (0.76–1.17)		0.84 (0.67–1.05)	
Ethnicity	Caucasian	Reference	0.795	Reference	0.750	Reference	0.929	Reference	0.974
	African-American	0.97 (0.74–1.27)		1.06 (0.80–1.40)		0.96 (0.71–1.30)		1.03 (0.75–1.42)	
	Other/unknown	1.14 (0.75–1.72)		1.17 (0.76–1.79)		1.06 (0.66–1.72)		1.03 (0.63–1.69)	
Marital status	Married	Reference	0.005	Reference	0.033	Reference	0.170	Reference	0.285
	Single/widowed	1.43 (1.16–1.76)		1.35 (1.08–1.69)		1.26 (0.99–1.61)		1.22 (0.94–1.58)	
	Other/unknown	1.08 (0.80–1.46)		1.19 (0.87–1.62)		1.06 (0.76–1.48)		1.16 (0.82–1.63)	

HR hazard ratios with 95 % confidence intervals

[a] Univariate Cox regression analysis

[b] Multivariable Cox regression analysis, full model

[c] Likelihood ratio test

[d] Univariable analysis with stratification for stage to minimize a stage migration effect

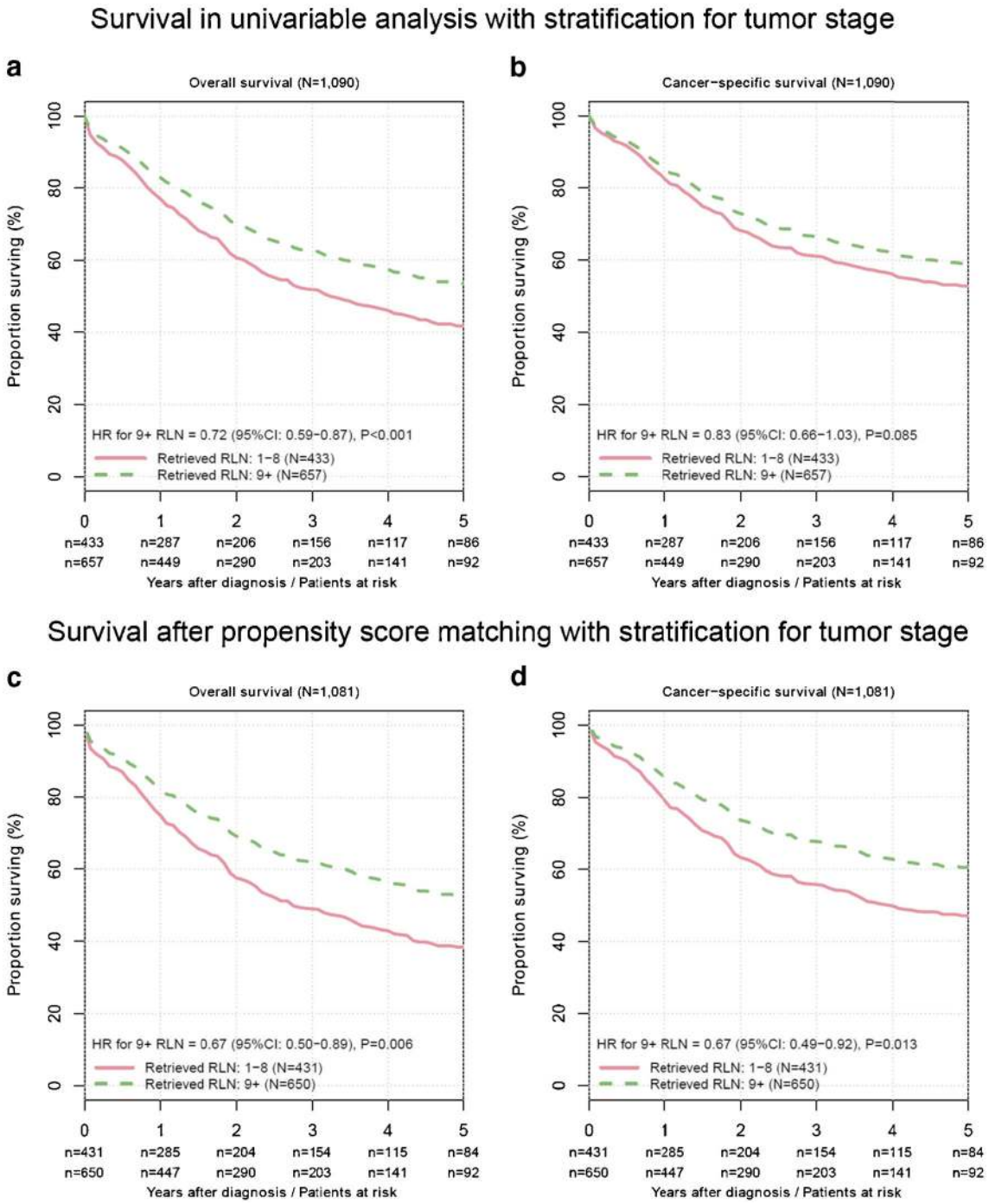

Fig. 3 Survival curves for overall and cancer-specific survival in unadjusted and propensity score-adjusted analyses. The two panels on the left side (**a**, **c**)show the overall survival and the two panels on the right side (**b**, **d**)depict cancer-specific survival. The number of patients at risk is given below each plot. The upper two panels(**a**, **b**) depict the unadjusted Kaplan-Meier curves for survival for patients with 1–8 and 9+ retrieved regional lymph nodes. The two panels in the lower part (**c**, **d**)display the survival in propensity score-adjusted analysis. *HR* hazard ratio for 9+ retrieved regional lymph nodes. *P* values were estimated with likelihood ratio tests

positive cancer steadily increased with the number of retrieved RLNs until 9 RLNs were retrieved, strongly suggesting that a sufficient number of RLNs is required for the detection of node positivity. Second, the retrieval of 9+ RLNs was associated with a statistically significant and clinically relevant advantage in overall and cancer-specific survival based on both multivariable Cox regression and propensity score-adjusted analyses.

Parsons et al.[31] demonstrated significant and stepwise guideline-recommended increases in lymph node evaluation for colorectal carcinomas over the past few years, particularly for high-risk patients. However, despite the recommendation in

Table 3 Bias after propensity score matching

		Univariable bias after propensity score matching		
		1 to 8 RLN *N*=431	9+ RLN *N*=650	*p* value[a]
Stage	Stage I	70 (10.8 %)	42.6 (9.9 %)	0.805
	Stage II	206 (31.7 %)	132.2 (30.7 %)	
	Stage III	374 (57.5 %)	256.1 (59.4 %)	
Location	Duodenum	356 (54.8 %)	250.7 (58.2 %)	0.651
	Jejunum	107 (16.5 %)	67.2 (15.6 %)	
	Ileum	121 (18.6 %)	69.1 (16.0 %)	
	Other	66 (10.2 %)	44 (10.2 %)	
Grading	G1	52 (8.0 %)	28 (6.5 %)	0.512
	G2	336 (51.7 %)	211.2 (49.0 %)	
	G3/4	244 (37.5 %)	177.6 (41.2 %)	
	Unknown	18 (2.8 %)	14.3 (3.3 %)	
Radiation	None	580 (89.2 %)	375.7 (87.2 %)	0.301
	After surgery	70 (10.8 %)	55.3 (12.8 %)	
Year of diagnosis	2004–2005	123 (18.9 %)	90.1 (20.9 %)	0.696
	2006–2008	245 (37.7 %)	162 (37.6 %)	
	2009–2011	282 (43.4 %)	178.9 (41.5 %)	
Age	<50	115 (17.7 %)	69.4 (16.1 %)	0.668
	50–64	240 (36.9 %)	159 (36.9 %)	
	65–79	229 (35.2 %)	164.9 (38.2 %)	
	80+	66 (10.2 %)	37.7 (8.7 %)	
Gender	Male	354 (54.5 %)	240.5 (55.8 %)	0.666
	Female	296 (45.5 %)	190.5 (44.2 %)	
Ethnicity	Caucasian	522 (80.3 %)	341.8 (79.3 %)	0.212
	African-American	92 (14.2 %)	54.2 (12.6 %)	
	Other/unknown	36 (5.5 %)	34.9 (8.1 %)	
Marital status	Married	398 (61.2 %)	276.3 (64.1 %)	0.578
	Single/widowed	167 (25.7 %)	99.3 (23.0 %)	
	Other/unknown	85 (13.1 %)	55.4 (12.9 %)	

N (%) (decimals for case number due to weighting)

[a] Weighted chi-square test

many guidelines, the rate of adequate lymph node evaluation, even in colorectal cancer patients, remains low.[31] Retrieval of a large number of RLNs reduces the risk of inappropriate staging in many tumor entities such as gastric cancer.[32,33] The number of retrieved RLNs is related to the quality of the surgery.[34] In colorectal cancer, the number of resected RLNs correlated significantly with surgical and hospital volume.[35,36] Miller et al.[36] demonstrated a significant rate of understaging in hospitals with low volumes compared to hospitals with medium or high volumes. For gastric cancer patients with node-negative disease diagnosed in routine histopathological examinations, micrometastases were detected by further pathological examinations in up to 32 % of the cases.[37] These associations are likely to exist in patients with small bowel adenocarcinoma.

Our findings show that in 60 % of the patients, 9 or more RLNs were retrieved, and this rate increased from 46 to 69 % during the study period. This increase could be explained by recent improvements in surgical therapy and by extrapolation from data of other cancers such as colorectal carcinoma, in which 12+ RLNs are recommended.

Focusing on patients with stage III small bowel adenocarcinoma, 28 % of patients with only 1 RLN removed were node-positive. With an increasing number of RLNs removed, the rate of lymph node-positive patients increased, reaching 50 % for patients with 9 and more RLNs retrieved. Thus, the lower the number of retrieved RLNs, the higher is the risk to miss a lymph node-positive patient and to incorrectly stage a patient as nodal negative. To avoid stage migration due to missing positive locoregional lymph nodes and to avoid underestimation of node-positive disease, the present data suggest that a sufficient number of RLNs have to be retrieved.

The significantly increased survival in patients with 9+ retrieved RLNs based on the multivariable and propensity score-matched analyses has various possible explanations. One explanation is the reduction of the tumor mass. In an extended lymph node dissection, micrometastasis and potential lymphovascular invasion will be removed; thus, the rate of recurrent disease may be less frequent.[32,37] Removal of a sufficient number of lymph nodes will result in more adequate histopathological staging, which in turn allows a better decision-making concerning the postoperative treatment. Node-negative histology can be seen as truly node-negative disease, and recurrent disease is less likely to occur. For high-risk patients with node-positive disease, the postoperative treatment can be evaluated.

Although a significant survival benefit in patients with small bowel adenocarcinoma who receive adjuvant chemotherapy has yet to be proven, it has been used increasingly in patients with node-positive disease.[3] Several recent studies demonstrated superior outcomes in patients with advanced and non-resectable small bowel cancer who are treated with chemotherapy, favoring fluoropyrimidine-based regimens.[38–40]

Assuming that adjuvant chemotherapy improves survival, understaging due to the retrieval of fewer than 9 RLNs will bar some patients from the benefits of adjuvant treatment.

Oncological resection of small bowel adenocarcinoma with sufficient lymph node dissection can be difficult due to anatomical circumstances. This might be an explanation for a low RLN retrieval. In some cases, the surgeon has to weigh the risk of an extended lymph node dissection against harm to the vascular supply of the remaining bowel and surrounding tissue, e.g., the superior mesenteric artery. In case the tumor is located close to important vessels, an option to retrieve sufficient lymph nodes would be to safely remove the tumor in a first step. As small bowel adenocarcinoma are rare and account for only 25 % to 40 % of all small bowel neoplasms, extended lymph node dissection might not be necessary in all cases of an incidental small bowel tumor. Thus, lymph node retrieval would only be performed after fast processing of pathological diagnosis confirmed the presence of an adenocarcinoma achieving oncological resection according to a two-staged procedure.

Overman et al.[10] proposed to retrieve at least 8 lymph nodes. However, this study did not utilize the joinpoint regression model to assess the number of lymph nodes needed to detect positive lymph nodes. Further, no statistical methodology with multivariable adjustment evaluated the impact on the oncological outcome. Even more importantly, the number of lymph nodes retrieved has increased considerably since 2005, the last time period examined by Overman et al.[10] Then, in 49 % of the surgeries, 9 or more RLNs were retrieved while in 2011 the rate had risen to 69 %. Our data indicated that with more than 9 RLNs removed, the rate of positive lymph nodes still increases but only minimally. Thus, we think that with 9 or more RLN removed, it is more likely to detect node-positive disease than with 8 or even less RLNs removed. With less than 9 RLNs removed, the risk of understaging the tumor increases considerably.

We would like to acknowledge the limitations of the present investigation. Most importantly, data on chemotherapy are lacking in the SEER database. To our knowledge, no data is currently available proving that after curative resection, nodal-positive patients benefit from adjuvant chemotherapy. After publication that chemotherapy improves survival in palliative situations, chemotherapy might have been applied more frequently in recent years.[40] This might have influenced the oncological outcome, especially when two cohorts from different time periods are compared. Furthermore, family history, comorbidities, performance status, and molecular data such as microsatellite instability are not available in the SEER database. To which extent these parameters may have influenced the analysis cannot be ascertained. Combining the findings of an increased rate of node-positive disease by removing a higher number of RLNs and a decreasing incidence of node-negative disease for the same quantity of RLNs, a potential bias due to the Will Rogers phenomenon[24] is very likely to exist in this study. Another potential bias might be based on the operating surgeon. When suspecting a malignant tumor because of the intraoperative aspect, the surgeon could more likely remove a higher number of RLNs.

Despite these limitations, the present investigation has various strengths. The population-based character of the SEER database leads to a high degree of generalizability. The large sample size of a rare disease is associated with a high degree of power. Additionally, the results of the multivariable analysis were confirmed by propensity score matching. The importance of matching the patients' characteristics is highlighted considering the different results of the plain univariable analysis versus the multivariable and propensity score-matching analyses.

In conclusion, extended lymph node dissection in small bowel adenocarcinoma increases the rate of node-positive disease, thus decreasing the rate of understaging, and leads to a statistically significant and clinically relevant increase in overall and cancer-specific survival.

Compliance with Ethical Standards

Source of Financial Support None

Conflict of Interest The authors declare that they have no competing interests.

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