The emerging issue of ratio of metastatic to resected lymph-nodes in gastrointestinal cancers: An overview of literature

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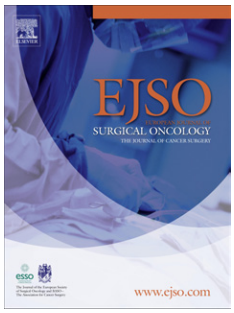

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The emerging issue of ratio of metastatic to resected lymph-nodes in gastrointestinal cancers: an overview of literature.

Lymph-node ratio in gastro-intestinal cancers

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Abstract

The prognosis of gastrointestinal epithelial malignancies is derived from TNM staging. The nodal status has the most importance. It guides the subsequent adjuvant therapies and gives the oncologist outstanding information about the biology of disease. Recently, a growing number of publications seem to be attributing importance to a ratio of positive to resected lymph nodes as a bad prognostic factor; particularly in gastro-oesophageal carcinomas, colorectal carcinomas and also pancreatic cancer. This particular value predicts the best significance in optimally (nodal) staged carcinomas, with less accurate, but probably equally meaningful information in not adequately resected tumours. Lymph node ratio maintains its value even after neo-adjuvant therapy, a factor known to be able to reduce lymph nodes' retrieval. The lymph node ratio is most accurate when more specialised pathologists in adequate volume cancer centres perform treatment and harvest of the lymph nodes. To date, no unconventional radiological tool is better able to perform standard armamentarium in correctly defining (preoperatively) patient carriers of massive nodal extension. The accurate definition of nodal staging is crucial for the potential down-staging benefit of neo-adjuvant chemo(radio)therapy on lymph node ratio. In conclusion, lymph node ratio stands out as an independent prognostic factor in adequately (nodal)-staged gastrointestinal epithelial malignancies and could be useful as a stratification factor in future randomised controlled trials.

Keywords

Lymph-nodes, ratio, surgeon, pathologist, prognosis, gastro-intestinal carcinomas

1.Introduction

The decision to perform a comprehensive lymphadenectomy as part of regional control of a malignancy or, alternatively, the highly accurate sentinel lymphadenectomy for staging purposes, has major implications: the information gained from lymph node pathologic examination is crucial not only for the estimation of prognosis, but also for the determination of the need for adjuvant systemic therapy.

Primary treatment of carcinoma of the esophagus and cardia relies on surgical resection. The characteristics of esophageal cancer (EC) that are associated with improved survival rate are known. Most studies suggest that only 2 factors (metastasis to lymph nodes [LNs] and tumour penetration of the esophageal wall) have a significant and independent influence on prognosis. Although current staging systems fail to take the number of LNs into account, most studies also show that patients having five or fewer LN metastases have a better outcome (1).

Gastric cancer (GC) is a serious health problem, as it is usually at an advanced stage at diagnosis. At diagnosis, approximately 50% of patients have GC that extends beyond the locoregional confines. Nearly 70% to 80% of resected GC specimens have metastases in the regional LNs. Thus, it is common to encounter patients with advanced GC at presentation. Poor performance status (ECOG 2 or more), liver metastases, peritoneal metastases, and alkaline phosphatase level of 100 U/L or more are the poor prognostic factors in patients with locally advanced and metastatic esophagogastric cancer (2-5). Surgical resection of pancreatic carcinoma (PC) is the only potentially curative technique for managing this disease. Negative margin status (R0 resection), tumour DNA content, tumour size and absence of LN metastases are the strongest prognostic indicators for long-term patient survival (6-8).

Resection of colorectal carcinoma (CRC) is based on standard anatomic regions according to the regional lymphatic drainage and blood supply. An adequate lymphadenectomy should remove all draining lymphatics at risk of metastatic involvement.

The Cancer Staging Handbook of the American Joint Committee on Cancer recommends that at least 12 LNs draining the primary cancer should be excised and examined to ensure proper staging and provide adequate surgical clearance (9-16).

Recent articles have called attention to the ratio of positive to resected lymph-nodes in gastrointestinal malignancies as a negative prognostic factor. The ratio of these 2 values (number positive/number total), the designated LN ratio (LNR), may improve differentiation between prognostic groupings by taking into account the extent of metastatic disease (number of positive nodes), as well as the adequacy of lymphadenectomy and its pathologic analysis (total number of nodes recovered and identified in the surgical specimen). Lymph node ratio has been found to be a powerful predictor of survival rate in patients with CRC and GC (see related chapters) and its use as a discriminatory tool for staging patients with PC has recently been investigated.

We report the results of published papers (both retrospective and prospective) in which information on the prognostic significance of LNR is reported within the context of a multivariate analysis. Articles were collected using PubMed: only those regarding EC-GC, CRC and PC were selected. Other non-digestive neoplasms were not considered for this review.

2. Esophageal cancer

The ratio of metastatic to total LNs (the LNR) has been shown to be a prognostic factor in EC (even independently of size of metastasis), but the value of LNR that is most predictive of patient survival rate is up for debate (see Table 1). It appears from the data that the more LNs examined, the lower the prognostic value of LNR. However if an insufficient

number of nodes is examined, the LNR ceases to be useful as a prognostic tool (17-27, 28-31; 114-116).

Other authors confirmed that the cut-off value of LNR that has prognostic significance is much lower when LNs are resected. Lymph node ratio value is a reliable parameter in adequately staged EC.

3. Gastric cancer

Nodal status is one of the most important independent predictors of GC patient survival. The current AJCC/UICC staging manual suggests that at least 15 LNs should be examined in order to achieve adequate predictive ability (32). One significant problem with the current staging system is stage migration (33). If an inadequate number of LNs is assessed, a patient may be inappropriately considered ‘‘node negative’’ and therefore classified as a lower stage, with a worse survival than those patients who were classified as node negative through a standard LN assessment. Studies have shown that the proportion of node positive tumours changes most significantly when fewer than 10 LNs are examined (33,35), but stage migration continues when even greater numbers of LNs are examined (34,36). A proposed new staging modality and emerging prognostic tool is LNR.

In 1998, Kim (37) first stated that with regard to the status of LN metastasis, the ratio of involved to resected LNs had a more accurate and comprehensive prognostic value than only the number of involved or resected LNs. Clinical and pathologic characteristics were analyzed in 10,783 consecutive patients who underwent surgery for GC at the Department of Surgery, Seoul National University Hospital, from 1970 to 1996. Finally, in recent years, various authors have reported evidence supporting LNR as a good and independent prognostic factor (38-70; 72; 106; 117-123). See table 2 for details.

In conclusion, LNR appears to be a useful tool for the staging of patients with advanced GC, as it enables more homogeneous patient classification and better definition of their prognoses than pathological nodal status. However, the value of LNR should be confirmed in prospective randomized trials. It is meaningful especially in radically resected GCs or in patients in whom at least 15 LNs were removed during surgery. In these cases it has prognostic value independently of the number of nodal metastases. Probably the more the negative nodes, the better the prediction of survival in patients with a low LNR (71). Some authors argue that LNR is not strictly related to the number of nodes retrieved and this may potentially decrease the stage migration phenomenon.

4. Pancreatic cancer

While the *Fifth Edition* of the AJCC staging system used the N1 suffixes a and b to discriminate between single and multiple positive regional LNs, no such distinction has been made in the most recent edition. Nonetheless, both the number of metastatic regional LNs and the total number of LNs evaluated in the surgical specimen may have prognostic significance in PC. A recent study by Tomlinson et al. (73) evaluated data from the Surveillance, Epidemiology, and End Results (SEER) program to identify 3505 patients who had undergone pancreatico-duodenectomy for adenocarcinoma of the pancreas from 1988 to 2002. The primary outcome of this study was the number of LNs required for accurate staging of node-negative (pN0) PC after pancreatico-duodenectomy. Univariate and multivariate analyses were performed on this data set, which included 1,150 patients who were pN0 and 584 patients with a single positive node (pN1a). The number of LNs examined ranged from 1 to 54 (median 7 LNs). The univariate analysis demonstrated that the pN0 cohort, >15 examined LNs resulted in the most significant survival difference, with Kaplan–Meier survival curves demonstrating a median survival difference of 8 months ($p<0.001$). As stated previously, a recently introduced concept in the evaluation of several

malignancies has been the concept of LNR as a prognostic indicator in node positive disease (74-81; 124). See table 3 for details of published studies

Although LNR appears to provide prognostic information in all PC patients its prognostic value remains proportional to the adequacy of surgery in terms of nodal staging. In this case it is an independent prognostic factor for outcome in pN1 patients and may be a stronger independent prognostic indicator than the absolute number of affected lymph nodes in patients with resected PC (82).

5. Colorectal cancer

5.1 Colon cancer trials

Nodes are essential for accurate staging in CRC. Data from a populationbased study showed that LN recovery was significantly lower in hospitals with low patient volumes (83). However, LN recovery has consistently been at less than recommended levels in many institutions, with only 37% of CRC resection cases without neo-adjuvant therapy reporting recovery of at least 12 LNs in the Surveillance Epidemiology and End Results database (National Cancer Institute, Bethesda, Md) from 1988 to 2001 (84).

Current recommendations to examine at least 12 to 15 LNs are based on an amalgamation of data (the AJCC 6th edition recommends examination of 7–14 LNs), with the article by Scott and Grace (85) often cited as the source of the recommendation of 12 LNs after fat clearance of the mesorectum. Increased retrieval and evaluation of LNs does not improve detection of stage III CRC or identify more patients with positive nodes, according to research published in Archives of Surgery (86). To determine the impact of a multidisciplinary institutional initiative on LN sampling and staging, the authors compared the number of sampled LNs per CRC case and the associated staging before and after implementing new pathology sampling guidelines. The initiative was started in late 2004, with the intention of increasing the number of LNs removed during CRC resections. The

authors found that LN counts increased from a mean of 12.8 to 17.3, with 53.0% of patients in the early period (n = 553) and 71.6% in the late period (n = 148) having had at least 12 LNs examined. The proportion of patients with stage III disease was unchanged, despite the improvement in LN sampling (36.9% for the early period and 32.4% for the late period; P =0.31). Among patients who had positive LNs, the distribution of N1 and N2 disease remained unchanged (50.5% had N1 and 49.5% had N2 disease in the early period, and 54.2% had N1 and 45.8% had N2 disease in the late period; P = .54) Could LNR be a better prognostic index than the total number of nodes retrieved in stage III disease? Recent TNM (AJCC) staging version (seventh edition) also re-statified node positive (stage III) patients according to the number of positive lymphnodes (pN1a,b; pN2a, b) reinforcing the value of such information as prognostic factor. Could LNR calculated into each sub-stage (IIIA, IIIB and IIIC) add an independent variable to better identify high vs very high risk patients?. Some recent studies explored this possibility obtaining interesting results. Hong and colleagues (132) found infact that 7th AJCC stage IIIB and stage IIIC patients are heterogeneous groups with respect to DFS, when stratified by LNR (< or > 1.638), and suggest that an LNR-based algorithm be devised for incorporation into the 7th AJCC staging system.

The large majority of collected and reviewed studies represents a population of node positive (stage III) or mixed (stage II and III) colon cancer patients. In all but one trial (89), the prognostic value of the LNR (other than pathological nodal involvement) was assessed in the presence of possible confounding covariates by Cox multivariate regression. This information, that we report in table 4 where available, is of a paramount importance because would confirm that LNR is now considered to be an independent prognostic variable that has greater meaning than, and is superior to, the TNM-AJCC classification with regard to disease substaging in stage III disease.

Various authors have recently reported data highlighting the prognostic role of LHR, with almost identical levels of significance in colon carcinoma and are reported in table 4 (87-91; 93-105; 114; 125-129; 131).

In summary, the results of these studies demonstrate that in patients with (stage III) colon carcinomas, the LNR provides superior and independent prognostic stratification compared to the number of positive nodes. Future prospective studies are needed to validate and define the LNR cutoff that allows optimal separation of subgroups of node-positive patients, and to verify whether the LNR could be used to personalize adjuvant therapy. A ratio of about 20% has the most significance in the majority of publications. These figures were recently confirmed by Celen et al. with a systematic review and metanalysis of 16 studies involving > 30,000 stage III colorectal cancer patients that confirmed the independent prognostic role of LNR (113).

5.2 Rectal cancer trials

Locally extended rectal cancer has to be treated with (neo)adjuvant chemoradiotherapy. It is known that after neo-adjuvant therapy, the retrieval of nodes results as lower than th retrieval number before any treatment. This is particularly true for breast cancer, but als data has been published regarding gastrointestinal cancers. Does LNR portend the same prognostic value even in radiotherapy-exposed patients? Does rectal cancer differ in colon cancer according to LNR significance?

Peng and Stocchi papers confirms the independent prognostic attribute of LNR for DFS and OS in surgically resected only rectal cancers (92,127). Priolli (98), although evaluated upper rectal cancer only (n=81/113 with distal left colon disease), in which fewer lymph nodes are generally resected than in colon cancer, was able to demonstrate that the LNR was an independent and significant variable with regard to determining the survival of patients with colorectal cancer (p=0.009), in agreement with the literature. Pescaud and

Kim confirmed this data in 2 trials exploring adjuvant or neoadjuvant chemoradiotherapy in a population of stage III rectal cancer (94,99). In Qiu study (125), when the analysis was limited to 406 patients with rectal cancer (65% of total), the LNR staging is an important statistically significant prognostic factor in disease-free survival and local recurrence.

Edler showed that patients with rectal cancer treated with preoperative radiotherapy had a lower number of lymph nodes analyzed compared with non-radiated ($p<0.001$) (128) but the independent prognostic value of LNR was obvious in both colon ($p<0.0001$) and rectal cancer ($p=0.0003$). In patients with rectal cancer analysed by Wong (126), the LNR was a significant prognostic factor for 5-year disease free survival ($p=0.008$) while the relation to overall survival showed a trend towards statistical significance ($p=0.058$). Subgroup analysis of patients with rectal cancer who underwent neoadjuvant chemo-radiation did not show any significance of prognostic value of 5 year overall ($p=0.453$) or 5 year DFS ($p=0.51$) in relation to LNR. In Moug and colleagues paper (96) only pLNR was an independent predictor of OS in both colon and rectal cancers (HR 13.40, 95% CI 3.64–49.10, $P<0.001$ for last result). The result maintained its significance in multivariate analysis even in inadequate node retrival (20% of rectal cancer patients have undergoine neoadjuvant radiotherapy (96). Rosenberg (93) presented similar results derived from a mixed population of colorectal patients (n=1263/3026 rectal cancers; only 11% received preoperative radiation). Multivariate survival analysis identified both the LNR and the pN category, the number of resected lymph nodes, the patient's age, the tumor location (colon vs. rectum), the pT category, the pM status, the radicality status, the tumor grade, and the year of operation as independent prognostic factors.

Mekenkamp (107), in a total of 1227 patients selected from a multicenter prospective randomised trial investigating the value of neo-adjuvant radiotherapy (median number of examined LNs in all patients was 7.0), observed that the number of retrieved LNs in patients with node metastasis was significantly higher than in node negative patients and

in particular after neo-adjuvant radiotherapy fewer LNs were retrieved (6.9 vs. 8.5; P<0.0001). Sermier form Switzerland (108) published data indicating that: 1) radiation therapy affects the yield of LN retrieval in abdominoperineal resection specimen; 2) this impact is time-dependent (time by the end of treatment to the date of surgery). In contrast, Brazilian authors (109) observed that absence of LNs retrieved from the resected specimen is associated with favourable pathologic features (ypT and perineural invasion status) and good DFS rates. In this setting, absence of retrieved LNs may reflect improved response to neo-adjuvant chemo-radiation therapy rather than inappropriate or suboptimal oncologic origin. Rullier form France (110) concluded that although long course preoperative chemo-radiotherapy decreases the mean number of LNs retrieved by 24%, and the mean number of positive LNs by 48%, survival was not influenced by the number of LNs retrieved in irradiated rectal specimen (495 patients underwent rectal excision for cancer; 332 of whom received long course preoperative radiotherapy). German authors (111,112) stated that after neo-adjuvant radio-chemotherapy both the total LN yield (12.9 vs. 21.4, $p < 0.0001$) and the number of tumour-positive LNs (1.0 vs. 2.3, $p = 0.014$) were significantly lower than after primary surgery of rectal cancer followed by adjuvant radio-chemotherapy. The reduced total LN yield in neo-adjuvantly treated patients had no prognostic impact, with OS of patients with 12 or more LNs; the same as that of patients with less than 12 LNs. The overall survival of neo-adjuvantly treated patients was significantly influenced by the number of tumour-positive LNs with 5-year-survival rates of 88, 63, and 39% for 0, 1-3, and more than 3 positive LNs ($p < 0.0001$). This study reaffirmed that number of nodal metastasis influenced the outcome but not the number of LNs retrieved. Finally Kang (131) analysed a total of 75 patients diagnosed as node-positive after undergoing preop-CRT followed by curative resection. He discovered that LNR is an independent prognostic factor after preoperative-chemoradiotherapy for rectal cancer. LNR showed better prognosis stratification than the ypN stage. Therefore, LNR

should be considered, according to this analysis, as an additional prognostic factor in node-positive rectal cancer after preoperative-chemoradiotherapy.

In conclusion, node metastasis remains a poor prognostic factor in rectal cancer with or without neo-adjuvant therapy. Lymph-node ratio probably maintains the same prognostic information even after down-staging, despite the lower retrieval of nodes after chemo(radio) therapy. The real biological equivalence of a ypLNR with respect to a pLNR in cases not submitted to neo-adjuvant treatment is uncertain. Down-staged ypN0 (with ypLNR 0) carcinomas are probably not the same as pN0 (pLNR 0) ones in terms of immediate outcome.

6. Conclusions

The achievement of an optimal node ratio probably is the result of various components: the biology of the disease, the ability of the surgeon to perform an adequate lymphadenectomy and the ability of the pathologist to perform a suitable node retrieval and provide the LNR information.

6.1 potential advantages of obtaining a LNR information

What should the role of LNR be in clinical practice now?

We believe it may be important in improving TNM staging (a pN1 staged disease with LNR less than 0.01 obviously differs from pN1 disease with LNR 0.1!) LNR could also be useful in stratifying patients for inclusion in large studies that compare different active (adjuvant?) treatments. At the moment, from a practical point of view, our intuition tells us that LNR might be useful to define the prognosis of a patient who could potentially benefit from adjuvant therapy, especially in cases where the added value of treatment is still unknown and LNR is minimal (< 0.1 for example). Our intuition also suggests that the value of LNR can take on different biological meaning in EC/GC, PC and CRC. In particular, the effect of

preoperative treatment (namely neoadjuvant chemoradiation) seems to influence the latter setting.

Finally, despite consistent and clear findings across all presented studies, showing that LNR is a strong prognostic index of various outcomes, cut-off values vary across studies. Thus, the value of LNR is reduced by the issue of which cut-off values should be used.

6.2 existing pitfalls in LNR information

From our point of view some questions have not been answered yet.

1. is there a LNR cut off level below which this index has real prognostic meaning?

2. can we identify these patients preoperatively with reasonable certainty?

3-is there a value above which the patient undoubtedly benefits from adjuvant therapy?

4-is there a limit beyond which we can identify a patient with such a poor prognosis that it is comparable with advanced disease? in this case may the patient be treated according to the guidelines for metastatic settings?

5.can we avoid an unnecessary surgical procedure (overtreatment!) in cases with such a good or poor prognosis that surgical demolition would not offer any benefit in terms of survival (extended lymph-node dissection)?

We believe all these questions must be answered within a randomized trial that compares different treatments in a homogeneous population of patients (surgery + post or preoperative systemic treatment, or different surgical procedures). Despite these shortcomings, the emerging significance of the LNR seems sound.

In conclusion, it is an independent prognostic factor in adequately (nodal)-staged gastrointestinal and pancreatic (epithelial) malignancies. It may also be useful as a stratification factor in future randomised controlled trials. The information it provides enables the oncologist to select appropriate post-operative treatment and to define the prognosis and the stage of the disease better. More effective treatment modalities are

needed to potentially down-stage and eradicate node tumour bulk, at least down to a level at which LNR is not detrimental to survival.

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Table 1: Lymph Node Ratio (LNR) as a Predictor of Survival in oesophageal cancer

Author	N°pts	LNR	Median nodes examined	p for survival
Hagen (23)	100	> 0.10	48 (mean)	P< 0.001
Eloubeidi (26)	10441	>0.10	NR	HR 1.63 (95%CI: 1.25–2.11) P=0.0013)
Tachibana (29)	85	>0.10	40 (mean)	HR=3.366 (95% CI: 1.092–10.37)P=0.0345
Schwarz (22)	5620	0.01–019	8 (mean)	P<0.0001
Roder (27)	186	>0.20	34 (mean)	P<0.001
Bollschweiler (17)	135	>0.20	28 (mean)	P<0.01
Wijnhoven (25)	292	>0.20	11 (mean)	HR 2.39 (95% CI: 1.51–3.76) P<0.001
Greenstein (18)		>0.20	11 (mean)	P<0.001
Wilson (20)	173	> 0	NR	P=0153 (Vs LNR 0) for 5 year survival (34 vs 15%)
Mariette (21)	536	> 0.2	19.6 (mean)	22 Vs 54% 5 year survival Vs LNR < 0.2 (p< 0.001)
Rizk (28)	336	> 0.3	NR	P < 0.0001
van Sandick (24)	115	>0.30	12 (mean)	HR 5.6 (95% CI: 3.0–11.4) (P<0.0001)
Hsu (30)	488	> 0.2 vs < 0.2	22 (mean)	For patients with LNR 0-0.2 or >0.2, the 3-year survival rate was 28.7% and 9.8%, respectively (p < 0.001). However, survival rate differences were more evident when total LNs resected was more than 15.
Kelty (115)	224	0-0.19; 0.2-0.4; 0.4-0.6; > 0.6	17 (mean)	The ratio of nodes affected to the total number resected showed a significant decrease in survival as the percentage of positive nodes increased (p<0.001).
Smit (116)	212	>0.2 vs < 0.2	10 (mean)	pT stage LNR ratio greater than 0.2 were independent prognostic factors for survival and recurrences.

HR: hazard ratio; GEJ; gastroesophageal junction; NR: not reported

Table 2: Lymph Node Ratio as a Predictor of Survival in gastric cancer

Author	N°pts	LNR	Median nodes examined	P for survival
Kim (37)	10783	0, <0.1,<0.3, <0.5, > 0.5	NR (56% pN+)	RR: 2.0576 in multivariate analysis; p=0.0076
Siewert (38)	1654	0 vs >0.2	35.3 (mean)	RR 2.8 p< 0.0001(even for pts with < 15 LNs resected)
Tagakane (39)	360	0, 0.01-0.09, 0.1-0.24, >0.25	55 (mean)	p=0.0042 for 0 vs >0.25
Inoue (40)	1019	0, 0.25-0.5, > 0.5	32 (mean)	RR 2.769: >0.5 vs 0 (p<0.0001)
Hyung (41)	833 (T3N1/N2 only)	0.05 vs 0.05-0.1 vs 0.1-0.15 vs > 0.15 for T3N1 <0.15 vs 0.15-0.25 vs 0.25-0.35 vs > 0.35 for T3N2	41.4 (mean)	P=0.0026 e p=0.0057 for T3N1 and T3N2
Bando (42)	650	0 vs 0-0.1 vs 0.1-0.25 vs > 0.25	47 (N1/N2) (mean)	P<0.001 for LNR as independent prognostic over number and location of LNs metastasis
Nitti (43)	277	0 vs 0.01-0.1 vs 0.11-0.25 vs > 0.25	27	At multivariate analysis, the N ratio was the best single independent prognostic factor (p =.000).
Kunisaki (44)	758	0 vs <0.1 vs >0.1 <0.2 vs >0.2	46.9 (mean)	Survival in those with a metastatic lymph node ratio less than 0.1 was significantly better than in those with a higher metastatic lymph node ratio.
Rodriguez Santiago (45)	183	0 vs < 0.4 vs 0.4-0.8 vs >0.8	25.8 (mean)	P< 0.00001 for survival
Cheong (46)	156 (pN+)	> vs < 0.07	36.2 (mean)	The 5-year survival rate of patients with an N ratio <0.07 was 94.0%; this was significantly higher than the rate (72.6%) for those with a ratio >0.07 (P <0 .0001; log-rank test).
Marchet (47)	1853	0 vs 0.01-0.09 vs 0.1-0.25 vs > 0.25 (N ratio 1,2,3)	(32.9 and 11 for group 1 and 2: > and < 15 LNs resected)	At multivariate analysis, the NR (but not N stage) was retained as an independent prognostic factor both in group 1 and group 2 (HR for N ratio 1, N ratio 2, and N ratio 3 = 1.67, 2.96, and 6.59, and 1.56, 2.68, and 4.28,
Kulig (48)	738	> 0.4 vs < 0.4	8 (mean) (all indaquately staged pts)	Compared with node negative pts, the HR for an LNR of 0.1-0.4 per cent was 1.85 ($P <$ 0·001), increasing to 2.93 ($P <$ 0·001) when the LNR exceeded 0.4.
Persiani (49)	219	0 –0.15 vs 0.16-0.4 vs > 0.4	27 (mean)	Both of the LNR and TNM classifications significantly stratified patients outcomes (p< 0.0001), but the LNR system identified prognostic subgroups more homogeneous than the TNM system.
Kim (50)	529	> 0.6 for N2 and 0.3-0.6 for N3	61.4 (mean)	Stage migration can be adjusted by the LNR based on the survival rate.
Sun (51)	2159	0 vs 0.01-0.2 vs 0.2-0.5 vs > 0.5	19.88 (mean)	The rN stage has more potential advantages in minimizing stage migration phenomenon for patients with insufficient number or level of LNs retrieved.
Asoglu (52)	264	0–0.1 vs 0.11-0.25 vs > 0.25	27 (mean) (59% D2 dissection)	The 5-year survival % stratified by LNR was 81% vs 49% vs 25%
Wang (53)	513	0 vs 0.01-0.3 vs 0.3-0.5 vs > 0.5	15.5 (mean)	HR 5.2 for ratio > 0.5 (p<0.001)
Xu (54)	906	0 vs 0.01-0.09 vs 0.1-0.25 vs > 0.25	6 and 20 (≤ 15 and > 15 LNs examined)	By multivariate analysis, only the N ratio classification was retained as an independent prognostic factor in both group 1 and 2 compared with the N stage system.
Yu (55)	217	0 vs 0-0.3 vs 0.3-0.6 vs >0.6	≥ 15 LNs resected	The 2-year survival rate decreased as ratio increased: 98.1% for ratio 0; 79.1% for ratio 0-0.3; 52.2% for ratio 0.3-0.6; and 30.1% for MLRO0.6.
Van der Schoot (57)	NA	NA	NR	NA
Persiani (58)	247	0 vs < 0.2 vs > 0.2	30 (mean)	In terms of survival, there were statistically significant differences between pts with a different NR stage but included in the same pn stage (for n1 patients, NR1 versus NR2 with p < 0.0001; for n2 patients, NR1 versus NR2 with p = 0.002) and pN stage (for N1 patients, NR1 versus NR2 with p = 0.014).
Ozguc (60)	306	0 vs 0.01-0.2 vs 0.2-0.4 vs >0.4	30.1 (mean)	LNR < 0.2 vs > 0.4 (p=0.042 and p=0.013 for 5 year survival

Mariette (61)	536	≤ 0.2 vs > 0.2	19.6 (mean)	Based on multivariate analysis the only independent factors of poor prognosis were the number of LNM+>4 (OR = 1.9, P = 0.008), and a LNR >0.2 (OR = 1.6, p = 0.014).
Celen (65)	164	0.01-0.1 vs > 0.1	27 (mean)	When pN1, pN2 and pN3 categories of the AJCC/UICC classification were subdivided into the ratio groups of 1-10% and >10%, the survival rate of ratio group 1–10% was better than ratio group >10% (p=0.0001 for > 0.1 vs ≤0.1.
Saito (63,67)	777	0-0.05 vs 0.05-0.1 vs 0.1-0.2 vs 0.2-0.3	46.9 (mean)	Multivariate analysis indicated that the n ratio was an independent prognostic indicator, as was the level of lymph node metastasis, depth of invasion, age and blood vessel invasion, but not the number of lymph node metastases. Moreover, the LNR was an independent prognostic factor in N1, N2, and N3 patients defined by the JCGC (p<0.0001 for N1/2/3)
Liu (64)	224	0 vs 0-0.4 vs 0.4-0.8 vs > 0.8	(range 15-75)	The 5-year survival rates were 78%, 61%, 25%, 0% in cases with a metastastic node ratio of 0%, > 0% but < 40%, 40–80%, > 80%, respectively (*P* < 0.001).
Kunisaki (59)	166 (pN+)	0 vs 0-0.15 vs 0.15-0.3 vs > 0.3	27 vs 33 (mean) (in D1 and D2 resection)	The metastatic LNR showed less stage migration and homogenous stratification.
Huang (56)	236	< 0.1 vs 0.2 vs 0.3 vs >0.3	23	A linear correlation between MLR and the 5-year survival was statistically significant based on the multiple linear regression (P < 0.001)
Kwon (68)	401	0.01-0.15 vs 0.15-0.3 vs >0.31	35.6 (mean)	Among 3 variables (LNR, pN1/N2, n° positiveLNs, the ratio of the number of metastatic LNs to the total number of dissected LNs was the most meaningful prognostic factor.
Fukuda (69)	186	0 vs 0.01-0.19 vs ≥ 0.2	33.7 (mean)	Multivariate analyses revealed that of the three factors used to stage lymph node involvement (UICC, JGCA, LNR), LNR was the most significant prognostic factor.
Sianesi (70)	282	0-0.1 vs 0.11-0.25 vs > 0.25	23 (mean)	there was no difference between NR0 and NR1 patients but NR1 survived longer than NR >1 (p<0.02)
Bilici (72)	111	0 vs 0-0.09 vs 0.10.25 vs > 0.25	27	Both UICC/AJCC pN stage and LNR (HR 0.33 p=0.03) were detected as prognostic factor by multivariate analysis, as was perineural invasion
Wang (117)	1343	0 vs 0.01-0.3 vs 0.31-0.6 vs 0.61-1	55% < 15 LN retrieved	In univariate, multivariate and stratified analyses, the LNR staging showed superiority to the 7th edition pN staging.
Kim (118)	153	Not available	NR	Multivariate analysis confirmed the impact of the LNR and T stage on overall survival and disease-free survival
Wang (119)	980	0-0.25 vs 0.26-0-5 vs 0.51-0.75 vs 0.76-1	52% > 15 LN retrieved	LNR prognostic factor for survival on multivariate analysis (p=0.022; HR 1.164)
Zhao (120)	171	0-0.1 vs 0.1-0.3 vs > 0.3	NR	LNR prognostic factor for survival on multivariate analysis (p=0.001; relative risk 1.924)
Pedrazzani (106)	526	0 vs 0-0.25 vs > 0.25	5 (mean)	LNR retained significance in multivariate analysis: pN ratio1 e 2 vs pN0 (HR 1.27 and 2.44)
Huang (121)	634	0 vs 0.01-0.2 vs 0.21-0.5 vs > 0.5	23 (mean)	Cox regression analysis showed that depth of invasion, pN and LNR category were the independent predictors of survival (P< 0.05).
Sianesi (122)	282	Not available	NR	LNR was an independent prognostic factor at Cox regression
Deng (123)	196	0.01-0.09 vs 0.1-0.25 vs > 0.25	20.6 (mean)	LNR was more appropriate to evaluate OS of lymph node-positive patients than number of metastatic LNs by using the case-control matched fashion (HR 1.936; p<0.001)
Coimbra (130)	165	0 vs 0.01-0.09 vs 0.1-0.25 vs > 0.25	35 (mean)	In the multivariate analysis, the interaction between N-category and N-ratio was an independent prognostic factor.

NR: not reported; Pts: patients; HR: hazard ratio; LNR: lymphnode ratio;

Table 3: Lymph Node Ratio (LNR) as a Predictor of Survival in pancreatic cancer

Author/year	N°pts	Median nodes examined	LNR	p
Berger/2004 (74)	128	17	0 vs 0-0.15 vs > 0.15	When LNR was examined as a continuous variable, it had a borderline impact on OS (P = 0.068). Examination of LNR by 3 groups showed an impact on OS (P = 0.037) and DFS (P = 0.013).
Sierzega/2006 (75)	96	17	> 0.2	If the analysis was limited to node-positive patients, lymph node ratio of more than 20% (HR, 1.364; 95% CI, 1.116-2.599), moderate or poor tumor differentiation (HR, 3.393; 95% CI, 1.041-11.061), and positive resection margins (HR, 9.400; 95% CI, 2.235-39.536) significantly correlated with a poorer survival.
Pawlik/2007 (76)	905	15/18 (N0/N1)	0 vs 0-0.2 vs 0.2-0.4 vs > 0.4	As the LNR increased, median overall survival decreased (LNR = 0.25 3 months; LNR > 0 to 0.2, 21.7 months; LNR > 0.2 to 0.4, 15.3 months; LNR > 0.4, 12.2 months; P = .001). After adjusting for other factors associated with survival, LNR remained an independent predictor of OS (p < .001).
Slidell/2008 (78)	4005	7	0 vs 0-0.2 vs 0.2-0.4 vs > 0.4	For N1 patients, LNR was one of the most powerful factors associated with survival (LNR > 0-0.2, 15 months; LNR > 0.2-0.4, 12 months; LNR > 0.4, 10 months) (P < .001).
Smith/2008 (77)	109	17	Continuos covariate (105 pts analysed)	Preoperative CA19-9 levels (p = 0.030) and LNR (HR 3.75; p = 0.042) emerged as independent predictors of survival on multivariate analysis.
Riediger/2009 (79)	204	16	$\geq$ 0.2 vs $\geq$ 0.3	In multivariate analysis, a LNR $\geq$ 0.2 (p < 0.02; relative risk RR 1.6), LNR $\geq$ 0.3 (p < 0.001; RR 2.2), positive margins (p < 0.02; RR 1.7), and poor differentiation (p < 0.03; RR 1.5) were independent factors predicting a poorer outcome.
Massucco (81)	59	28 (mean)	$\geq$ 0.1	Positive LNs, LNR, and node level were all significant predictors of survival (P < 0.015)
Bhatti (82)	84	9	0 vs 0-0.199 vs 0.2-0.299 and > 0.3	LNR at both levels [>/=0.2 (p = 0.05; HR 1.8) and LNR of >/=0.3 (p = 0.01; HR 2.7)] were independent predictors of a poor outcome
Showalter (124)	445	NR	Not available	Increased LNR was associated with worse OS (HR = 1.01, p < 0.0001) and DFS (HR = 1.006, p = 0.002)

HR: hazard ratio; NR not reported

Table 4: Lymph Node Ratio (LNR) as a Predictor of Survival in colorectal cancer (surgically only patients)

Author/year (ref)	N°total pts/ stage III pts/ rectal	Median nodes examined	LNR	Data analysis/ prognostic significance
Berger/2005 (87)	3411 / 2763 / 0	13 (mean)	0-0.05 vs 0.05-0.19 vs 0.20-0.39 vs 0.4-1	MV (cox) Significant predictor of OS, DFS, CSS when ≥ 10 nodes examined
Lee/2007 (88)	201 / 201 / 0	17	0- 0.11 vs 0.12-0.24 vs 0.25-0.92	MV (cox) Significant predictor of DFS
Schumacher/2007 (89)	232 / 74 / 0	17	0.08 for all pts	UV (log rank) Significantly associated with DFS but not OS
Wang/2008 (90)	24477 /24477 / 0	60.7% of pts ≥ 10 LNs examined	1/14 vs 0.25 vs 0.5	MV (cox) Significant predictor of OS (RR 3.5 p< 0,0001)
Derwinger/2008 (91)	265 / 265 / 0	11(mean)	0-0.125 vs 0.126-0.266 vs 0.267-0.45 vs 0.45-1	MV (cox) Significant predictor of DFS (p<0,0002)
Peng/2008 (92)	318 /318 / 318	12 (mean)	< 0.14 vs 0.14-0.49 vs > 0.5	MV (cox) Significant predictor of LR, DFS, and OS
Rosenberg/2008 (93)	3026 / 1328 / 1263	16	0.17 vs 0.41 vs 0.69	MV (cox) Significant predictor of CSS in colon and rectum
Peschaud/2008 (94)	307 / 127 / 307	22 (mean)	0 vs 0.07-0.2 vs > 0.2	MV (cox) Significant predictor of OS and DFS
Park/2009 (95)	318 / 318 / 0	24 (mean)	< 0.059 vs 0.059-0.23 vs >0.23	MV (cox) Significant predictor of DFS (p<0,001)
Moug/2009 (96)	295 / 115 / 100	10 (mean)	< 0.05 vs 0.05-0.19 vs 0.2-0.39 vs 0.4-1	MV (cox) Significant predictor of OS in colon and rectal cancer
Chin/2009 (97)	624 / 624 / 0	490/624 > 12 LNs harvested	≤ 0.4 vs 0.4-0.7 vs > 0.7	MV (cox) Significant predictor of DFS
Priolli/2009 (98)	113 / 113 / 50	22.77 (mean)	0 vs < 0.2 vs > 0.2	MV (cox) Significant predictor of OS (p=0,003)
Kim/2009 (99)	232 / 232 / 232	17	< 0.1 vs < 0.2 vs < 0.4 vs > 0.4	MV (cox) Significant predictor of OS and DFS
Vaccaro/2009 (100)	362 / 362 / 0	20	0-0.06 vs 0.06-0.12 vs 0.12-0.25 vs > 0.25	MV (cox) Significant predictor of OS, DFS, and CSS
Ainsworth/2009 (102)	56 / 56 / 19	12	> 0.25	MV (cox) Significant predictor of OS, and DFS
Galizia/2009 (103)	145 / 145 / 0	16.8 (mean)	< or > 0.1818	MV (cox) Significant predictor of DSS and DFS
Ng/2009 (101)	2636 / 2636 / 0	10.4 (N0), 11 (N1) and 14.6 (N2) (mean)	<0.19, 0.20-0.39, 0.40-0.59, 0.60-0.79, and 0.80-1.0	MV (cox) Significant predictor of OS
Huh/2010 (105)	514 /514 / 279	14	<0,09 vs 0,09-0,18 vs 0.18-0,34 vs ≥ 0,34	MV (cox) Significant predictor of OS, DFS
Rosemberg/2010 (104)	17309/ 7654 / NR	16.8 (mean)	0 vs 0.01-0.17 vs 0.18-0.41 vs 0.42-0.69 vs > 0.7	MV (cox) Independent prognostic factor of survival
Qiu/2011 (125)	626 / 626 / 406	10	0-0,1 vs 0,11-0,25 vs 0,251-0,5 vs >0,5	MV (cox) Significant predictor of DFS, and LR
Wong/2010 (126)	533 / 533 / 179	11	≤0,125 vs 0,125≤0,263 vs 0,263≤0,5 vs >0,5	MV (cox) Significant predictor of OS, and DFS
Stocchi/2001 (127)	673 / 454 / 673	NR	<0,25 vs 0,25-0,5 vs 0,51-0,75 vs >0,75	MV (cox) Significant predictor of LR and OS
Edler/2007 (128)	1025 / 527 / 298	5 (mean)	<0,20 vs 0,20-0,49 vs 0,50-0,69 vs 0,7-1	MV (cox) Significant predictor
Vather/2009 (129)	4309 /2364 / 0	11(mean)	0,10	MV (cox) Significant predictor of OS
De Ridder/2006 (114)	26181 / 26181 / 0	10	0,4	MV (cox) Strong independent risk factor (p<0,0001)

Hong/2011 (132)	130/130/0	28	0.1638	MV $_{(cox)}$ Prognostic factor of 3-yr DFS

CSS: CRC specific survival; LR: local recurrence; OS: overall survival; DFS: disease-free survival; HR: hazard ratio; DSS: disease specific survival; pNR: pathologic node ratio; MV multivariate; UV: univariate; NR: not reported