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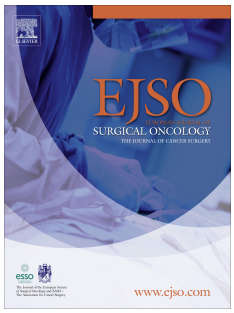

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Metastatic lymph node ratio in stage III rectal cancer; prognostic significance in addition to the 7th edition of the TNM classification.

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ABSTRACT

Aims: Optimal staging in rectal cancer is indispensable for the decision on further treatment and estimation of prognosis. This study assesses the prognostic capacity of the metastatic lymph node ratio (LNR) in addition to the new TNM classification.

Methods: LNR was determined, in stage III patients from the Dutch TME trial. Six year median follow up data from the trial database were used to analyse the relation of LNR to overall survival (OS) and local recurrence (LR). The relation of LNR to lymph node yield was assessed and appropriate cut off values of LNR for clinical use were determined.

Results: 605 patients were analyzed. 278 underwent preoperative radiotherapy. 82 patients developed a local recurrence and 289 distant metastases. LNR was an independent risk factor for OS, hazard ratio (HR) 2.10 (95%CI 1.35-3.27) (in addition to age >= 65 years, involved circumferential resection margin (CRM) and new TNM stage) and LR, HR 2.25 (95%CI 1.02-4.56) (in addition to pre operative radiotherapy and involved CRM). LNR is predictive of OS and LR from a lymph node yield of more than one and more than five respectively. A LNR value of 0.60 offers the best cut off to identify high risk patients (5 years OS was 61 vs. 32%, HR 2.45 (95% CI 1.96-3.08) and 5-years LR rate 12.6 versus 16.3%, HR 1.65 (95% CI 1.03-2.64)).

Conclusions: LNR is an independent risk factor for OS and LR in addition to the 7th edition of the TNM classification. It can aid in predicting prognosis and identifying patients that should be considered for adjuvant treatment.

Key words: lymph node ratio; rectal cancer; prognosis, lymph node yield, cut off values

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INTRODUCTION

Rectal cancer still poses many challenges to oncologists. Major advantages in surgical technique with complete removal of the mesorectum under vision have led to a significant drop in local failure and improvement of overall survival (1;2). Also the use of (neo-) adjuvant therapy has contributed to improved prognosis with a tendency towards pre- in stead of postoperative radiation (3-5).

Using TME surgery and pre-operative radiotherapy the problem of local recurrence seems to be contained (5.6% at five years (6)). However, as in colon cancer, distant recurrences are still a matter of concern and occur in 25-30% of patients at five years (6). Adjuvant chemotherapy can possibly aid, but there is still no strong evidence that its benefits in rectal cancer are comparable to those in colon cancer patients (7-10). Although there are some studies that show a minor benefit of adjuvant chemotherapy in rectal cancer patients (11-13) a recent European consensus conference failed to reach consensus on its use (14).

Optimal patient stratification is important to identify patients who will most likely benefit from adjuvant therapy. In this manner, overall morbidity from cytotoxic regimens will be reduced and health care costs are cut down by targeted delivery of expensive chemotherapeutic drugs.

Currently, the UICC/AJCC TNM staging system(15;16) is considered the most robust tool for prediction of prognosis and for decisions on the delivery of adjuvant treatment. However, some criticism is raised towards the validity of this system(17) and the usefulness of other tools such as nomograms is being explored (18).

In addition to the UICC / AJCC TNM stage(15), the metastatic lymph node ratio (i.e. the ratio of metastatic to retrieved lymph nodes) was found to be an important independent prognostic factor in various malignancies (19-22). Also in colon cancer some studies show a strong association of metastatic lymph node ratio (LNR) with disease recurrence and survival (23-26). In rectal cancer the evidence is still limited.

If the LNR can be considered as a prognostic factor it may also have the advantage to be less dependent on the number of retrieved lymph nodes than N stage. Especially in rectal cancer adequate retrieval of lymph nodes may be troublesome as it is dependent on many factors such as age over 60, obesity, female sex, small tumour size and localisation, poor differentiation grade, the absence of a lymphoid reaction and neo-adjuvant therapy (27-29).

Some questions remain unanswered. To what extend can the LNR be considered a reliable prognostic indicator? What is the effect of lymph node yield is on the predictive capacity of LNR? Which LNR cut off values have the best discriminative power? Most importantly, very recently the UICC / AJCC TNM system was updated (16) and T stage and N stage were further specified to improve its prognostic capacity. More emphasis is made to the number of retrieved malignant lymph nodes. Considering the inherent correlation between LNR and the number of positive lymph nodes it is not clear whether LNR remains an independent predictor prognosis in addition to this 7th edition of the TNM classification.

The aim of this study is to assess the prognostic capacity of the metastatic lymph node ratio in stage III rectal cancer in addition to the 7th edition of the TNM classification and to identify high risk patients.

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PATIENTS and METHODS

From the database of the Dutch TME-trial, a prospective multicentre randomized trial investigating the value of neo-adjuvant short term radiotherapy applying 5x5 Gy, all UICC / AJCC stage III patients were selected for this study. Inclusion and exclusion criteria for the TME-trial have been published previously by Kapiteijn et al. (30;31). Tumours had to be below the level of S1/S2 with the inferior tumour margin being 15 centimetres or less from the anal verge as measured during withdrawal of a flexible coloscope.

Surgery was performed between 1996 and 1999. Patients that died in the postoperative phase and patients that did not have adenocarcinoma on definitive pathological examination were excluded. The total number of retrieved lymph nodes and the number of metastatic lymph nodes were recorded and the metastatic lymph node ratio (LNR) was calculated. This was defined as the number of metastatic lymph nodes divided by that of retrieved lymph nodes. Classic prognostic data were available from the Dutch TME-trial records.

Follow up was registered within the Dutch TME-trial. For the purpose of this study outcome data with a median follow up of 6 years were used (earlier reported by Peeters et al.(6)).

Statistics

Overall survival (OS) was calculated from surgery to all cause mortality or end of follow up (censoring). Local recurrence time (LR) was defined from surgery to the

time of evidence of tumour within the pelvic or perineal area, or death (censoring) or end of follow up (censoring).

Univariate and multivariate analyses (of all univariate relations with $p <= 0.1$) were performed using a Cox regression analysis. Since the objective of the multivariate analysis was to assess the independent prognostic value of LNR, first a multivariate model was constructed using forward selection with the selected ($p < 0.1$ at univariate analysis) covariates. To this model, LNR was then added.

For all Cox regression analyses, hazard ratios were calculated including 95 % confidence intervals (95% CI).

Furthermore LNR was stratified on quartiles and again survival analyses were conducted using Cox regression analyses. Overall survival probabilities were estimated using the Kaplan-Meier method, while for LR the cumulative incidence was estimated accounting for death as competing risk (32).

To determine the best cut off values for LNR, the p-value from a log-rank test comparing LNR < cut off with LNR >= cut off were calculated for every possible cut off value. The smallest p-value was identified indicating the most significant cut off. It is known that such a minimum p-value approach yields biased p-values(33). Adjusted p-values suggested in that paper, were calculated (based on leaving out the smallest and largest cut off points.

Finally the minimal number of retrieved lymph nodes needed for a reliable LNR was evaluated using a Cox model with number of retrieved lymph nodes (log-

transformed), LNR and their interaction. From the estimated coefficients and covariance matrix of this model, for each number of retrieved lymph nodes, the implied hazard ratios and 95% confidence intervals were determined.

For all tests statistical significance was stated as two tailed $p < 0.05$.

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RESULTS

Six hundred five patients were included in the present analysis. There was a complete registration of lymph node harvest and survival data for all patients. For two patients information on local recurrence was unknown.

Patients had an average age of 63 years (range 26-92). Preoperative radiotherapy was given to 278 patients. Baseline characteristics are shown in table I.

The median number of retrieved lymph nodes was 9 (range 1-47). The median number of malignant lymph nodes was 2 (range 1-40).

During the follow up period 306 patients had a recurrence, 82 had a local recurrence and 289 developed distant metastases. Sixty three patients developed both local and distant recurrences. Three hundred twenty eight patients died during follow up. Two hundred sixty patients died of disease recurrence. Median follow up time for patients still alive at the end of study (n=277) was 6 years (range 1-9 years).

Univariate Cox regression analyses incorporating baseline characteristics showed that LNR, pN-stage, tumour-stage, number of malignant lymph nodes and involved circumferential resection margin (CRM) were significantly correlated to overall survival (OS) and local recurrence (LR). Age of 65 or more years, pT-stage and retrieved lymph nodes < 12 were significantly related to OS, but not to LR. Pre operative radiotherapy significantly decreased LR, but not OS. A test for interaction showed no interaction between LNR and radiotherapy in relation to OS and LR (p=0.94, p=0.50 respectively).

Multivariate analysis is shown in table II. When LNR was added, it was found to be an independent risk factor for OS and LR (hazard ratio 2.10 (95% CI 1.35-3.35 and 2.25 (95% CI 1.02-4.96) respectively).

Influence of lymph node yield

The Cox model used to determine the influence of the number of retrieved lymph nodes on the predictive capacity of LNR showed that LNR is predictive of OS from a lymph node yield of more than one node (figure 2A.). For a significant prediction on LR the lymph node yield should be more than five nodes (figure 2B.).

Cut off values

To determine cut off values for LNR further analyses were performed. First LNR was stratified on quartiles (LNR 0-0.17, 0.17- 0.33, 0.33-0.60, 0.60-1).
Univariate and multivariate analyses were repeated for LNR quartiles. LNR-quartile groups were independent risk factors for OS ($p<0.04$), but not for LR ($p=0.62$).
Kaplan-Meier curves for OS according to quartiles are shown in figure 1. Kaplan-Meier curves for stage I and stage II patients (from TME trial records) are added.

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Stage II patients did not have different outcomes from the lowest LNR quartile group (HR 1.15 (95% CI 0.85-1.55).

Figures 2C and D show the p-values of the log-rank test comparing low (LNR < cut off) and high (LNR >= cut off) LNR according to all cut off values in the data. Only patients with a sufficient lymph node yield (>1 and >5 respectively) were entered into this model. For OS the lowest p-value indicating the best cut off was found for LNR=0.60. The adjusted minimum p-value found was $2.3*10^{-13}$. For LR p-values were not so small. Here no distinct cut off value could be identified (figure 2d); the adjusted minimum p-value found was 0.34.

When patients were stratified on LNR < 0.60 and >=0.60, 5-years OS was 61 vs. 32%, HR 2.45 (95% CI 1.96-3.08) and 5-years LR rate 12.6 versus 16.3%, HR 1.65 (95% CI 1.03-2.64). Kaplan-Meier and cumulative incidence curves are shown in figure 3.

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DISCUSSION

The present study investigated the predictive capacity of metastatic lymph node ratio (LNR) in stage III rectal cancer. LNR was, in addition to the updated (7th) edition of the UICC/ AJCC TNM staging, an independent prognostic factor for LR and OS. Furthermore we determined the minimum number of retrieved lymph nodes required to ensure that LNR is a prognostic factor (two for prediction of OS and six for prediction of LR rate). Finally a cut off value of 0.60 was calculated for which LNR is most discriminating.

For rectal cancer the prognostic significance of the metastatic LNR was earlier addressed in four studies (34-37). All these studies determined the predictive capacity of LNR in addition to the previous (6th edition) TNM classification. In comparison to the present (7th edition) TNM classification the earlier classification contained less detailed information on the number of malignant nodes and thus less prognostic information. This could mean these studies found a larger effect of LNR than they would have in addition to the updated TNM classification. The present study shows that even with the 7th edition of the TNM classification, LNR can still improve patient stratification.

Influence of lymph node yield

The use of preoperative radiotherapy may alter the prognostic impact of clinical parameters among which the LNR. Only in the study by Moug et al. (37) neo-adjuvant radiotherapy was taken into account and then only in 21 patients. Neo-

adjuvant therapy diminishes the number of retrieved lymph nodes (27-29;38). The influence of lymph node yield on the predictive capacity of LNR has been a matter of debate. It is argued that the poor prognosis in patients with a high LNR might be attributed to an inadequate LN dissection (39). After all, if the denominator (the number of retrieved lymph nodes) is smaller the LNR will be higher and an inadequate LN dissection itself is associated with poor survival (40). However Derwinger et al. (41) found that in colorectal cancer at least part of this association is due to stage migration. Interestingly this is exactly where LNR can be useful. Reports on gastric cancer (19;42) show, that LNR-based staging can halve the incidence of stage migration.

In this study inadequate lymphadenectomy as defined by the UICC and AJCC as the retrieval of less than 12 lymph nodes was not independently related to OS and LR. Furthermore there was no interaction between LNR and the retrieval of less than 12 or 12 and more lymph nodes in relation to OS and LR (p=0.41 and p=0.84).

For a more specific answer to the question whether lymph node yield affects the predictive capacity of LNR, the present study tried to quantify this effect for every lymph node harvested.

LNR showed to be predictive for OS for a lymph node yield of more than one (figure 2A). This means it is a reliable predictor for OS in the vast majority of patients (594 out of 605 patients in this study). For a significant prediction on LR more than five lymph nodes need to be retrieved (figure 2B), which was the case in 474 of 605 patients.

As expected the number of retrieved lymph nodes was lower in patients that received preoperative radiotherapy compared to the other patients (median 8 and 11 respectively, p<0.01). As a consequence the LNR was higher (median 0.39 and 0.29, p<0.01). However, this had no effect on the predictive capacity of the LNR. A test for interaction showed no interaction between LNR and radiotherapy in relation to OS and LR (p=0.94, p=0.50 respectively).

Cut off values

Previous studies have stratified patients according to LNR in different ways. Methods to determine the cut off varied and different cut off values are used. Stocchi et al. (34) stratified by the percentage of positive nodes (0-25%, 25-50%, 50-75%, 75-100%).

Most studies, including the other studies in rectal cancer (35-37), stratified on quartiles. After stratifying in quartiles, overall the LNR lost its value for predicting LR. Only the highest quartile remained strongly associated with LR. All quartiles were prognostic for OS.

Interestingly stage II patients did not have a different prognosis from patients in the lowest quartile group (0-0.16). This is probably due to inadequate staging for stage II patients. When stage II patients were subdivided to adequacy of lymph node yield (<12 versus >=12), adequately sampled stage II patients (>=12 lymph nodes retrieved) had a better prognosis than stage III patients (p=0.04; data not shown). However, inadequately sampled patients (<12 lymph nodes retrieved)

had no different survival than stage III patients in the lower two quartile groups (p=0.82 and p=0.13 respectively; data not shown).

The actuarial overall survival data in the lowest 3 quartiles (0-0.60) are comparable, while there is an apparent difference with the highest quartile (0.60-1) (figure 1).

These findings do not match the results of Peng et al.(35), Kim et al.(36) and Moug et al.(37) They all found that only OS in the middle quartiles was comparable and Peng suggested combining them for stratification. These different findings could be based on differences in distribution of quartiles. In this study cut off values between quartiles seem to be somewhat higher than in the previous studies. This could be the effect of preoperative radiotherapy (278 of 605 patients) resulting in a higher LNR as outlined above. In patients that did not receive preoperative radiotherapy quartile distribution was 0-0.14; 0.14-0.29; 0.29-0.50; 0.50-1, in accordance with Peng's data. Kaplan Meier curves for these patients also match the previous studies (not shown). However it should be stressed again that neo-adjuvant radiotherapy has proven its value and it is the standard of care in the Netherlands and many Northern European countries. Therefore the distribution of quartiles in the present study is probably more applicable to patients treated in these countries.

Figures 2C and D show the p-values of the log-rank test comparing low (LNR < cut off) and high (LNR >= cut off) LNR according to all cut off values in the data. In search of the cut off value with the best discriminative power for OS we found the LNR value of 0.60 (figure 2c). For LR rate no discriminating cut off value was

found (figure 2d). The cut off value of 0.60 produces absolute differences for 5-years OS and LR (figures 3A and B). Using one cut off is very practical for modifying existing staging practices. Applying it in addition to the TNM classification (7th edition) it can modify patient stratification to more accurately reflect the impact on prognosis (figure 3C).

Possible limitations

A possible limitation of this study could be the fact we used data from a trial that was designed to study the effect of preoperative short course radiotherapy and did not have LNR as a covariate or outcome measure. However, this multicentre study with contributions of more than 80 hospitals reflects common practice among radiation oncologists, surgeons and pathologists throughout the Netherlands. Furthermore the data were gathered under extensive quality control within the framework of the TME trial (30). Therefore, we believe that this study provides useful information that may improve rectal cancer treatment.

Clinical relevance

Although we have shown that LNR is a powerful tool to predict a patients prognosis, we believe that it is still too premature to consider all high risk patients (LNR>0.6) suitable candidates for adjuvant chemotherapy. Nevertheless, future trails could focus on this patient subset to test (new) effective drugs. In these

patients their impact will most likely be larger than in low risk patients (LNR<0.6) Also, an accurate estimation of prognosis is increasingly considered important by both doctors and patients. Moreover, it could guide (the intensity of) follow up. Decisions on possible surgical interventions after initial treatment such as stoma reversal and incisional hernia repair could be based upon accurate information on patient's prognosis. Patients with poor prognosis and co-morbidity will preferably not undergo any surgery anymore whereas healthy and low risk patients will.

Conclusions

Accurate staging in rectal cancer is indispensable for a balanced clinical decision on further treatment and an accurate estimation of prognosis. This study shows that in addition to the 7th edition of the UICCC / AJCC TNM classification the metastatic lymph node ratio (LNR) is an independent prognostic factor for overall survival and local recurrence in stage III rectal cancer. LNR is a reliable measure for OS from a lymph node yield of more than one node. For adequate prediction of LR more than five nodes need to be retrieved. Stratification of patients is possible by dividing them in quartiles, but the LNR value with the best discriminating power is 0.60. This cut off value can improve TNM staging per stage and identify high risk patients.

Conflict of Interest: The authors state that they have no conflict of interest.

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Table I. Baseline characteristics of patients from dataset (605 stage III rectal cancer patients)

variable	characteristics	number
Age, years	< 65	312
	>= 65	293
sex	Male	370
	Female	235
Preoperative Radio Therapy	PRT+	278
	PRT-	327
Largest tumour diameter	< 5 cm	370
	>= 5 cm	221
	missing	14
pT stage	<=T2	115
	T3	458
	T4a	17
	T4b	12
pN	N1a	190
	N1b	185
	N2a	116
	N2b	114
Tumour stage	III A (T1-2/N1, T1/N2a)	85
	III B (T3-4a/N1, T2-3/N2a, T1-2/N2b)	405
	III C (T4a/N2a, T3-4/N2b, T4b/N1-2)	115
Involved CRM	No	427
	Yes	175
	missing	3
Retrieved lymph nodes	< 12	378
	>=12	227
Adjuvant treatment	Chemotherapy	99
	Radiotherapy*	53
	Chemo radiation*	14

The pT stage, pN stage and tumour stage were defined according to the 7th edition of the UICC / AJCC TNM staging. CRM, circumferential resection margin

** Patients receiving adjuvant radiotherapy/ chemo radiation had an involved CRM according to the pathology report (Marijnen et al. reported on this group (43)).*

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Table II. Multivariate Cox regression analysis for OS and LR

		Overall Survival		Local Recurrence	
variable	**characteristics**	**HR (95%CI)**	**P-value**	**HR (95%CI)**	**P-value**
Age, years	>= 65	1.77 (1.41-2.22)	<0.01	n.a.	
Preoperative Radio Therapy	PRT+	n.a.		0.43 (0.27-0.70)	<0.01
pT stage	T<=2		0.15	n.a.	
	T3			n.a.	
	T4a			n.a.	
	T4b			n.a.	
pN	N1a		0.82		0.86
	N1b				
	N2a				
	N2b				
Tumour stage	III A		<0.01		0.55
	III B	1.78 (1.18-2.67)			
	III C	2.88 (1.73-4.78)			
Involved CRM	Yes	1.52 (1.20-1.93)	<0.01	2.30 (1.46-3.62)	<0.01
Retrieved lymph nodes	< 12		0.86	n.a.	
Malignant lymph nodes		1.02	0.08		0.71
LNR		2.10 (1.35-3.27)	<0.01	2.25 (1.02-4.96)	0.04

Covariates with trend-significance (p<0.10) in univariate analysis were entered in multivariate analysis. HR, hazard ratio; CI, confidence interval; CRM, circumferential resection margin; n.a., variables not selected for multivariate analyses because they were not trend significant in univariate analysis.

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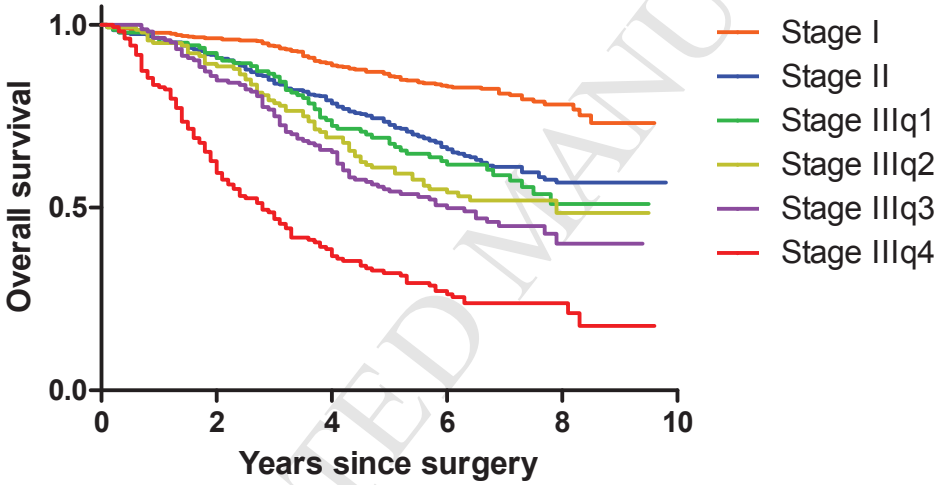
Figure 1
Dekker et al.



Numbers at risk

Stage I	491	473	416	287	64	0
Stage II	472	431	363	222	65	0
Stage IIIq1	161	145	110	67	19	0
Stage IIIq2	123	110	82	51	10	0
Stage IIIq3	163	140	105	61	12	0
Stage IIIq4	158	96	58	33	9	0

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Figure 2
Dekker et al.

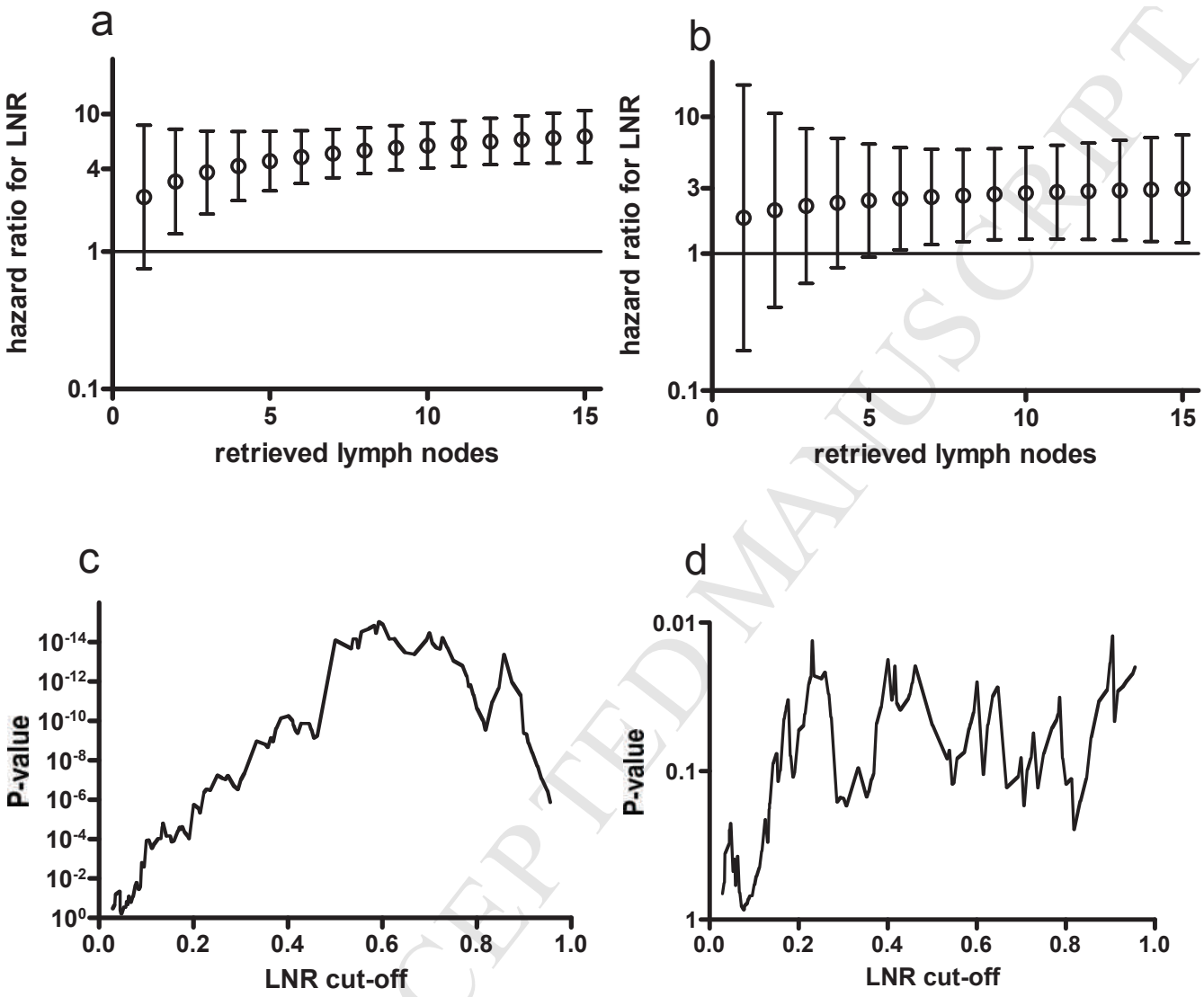

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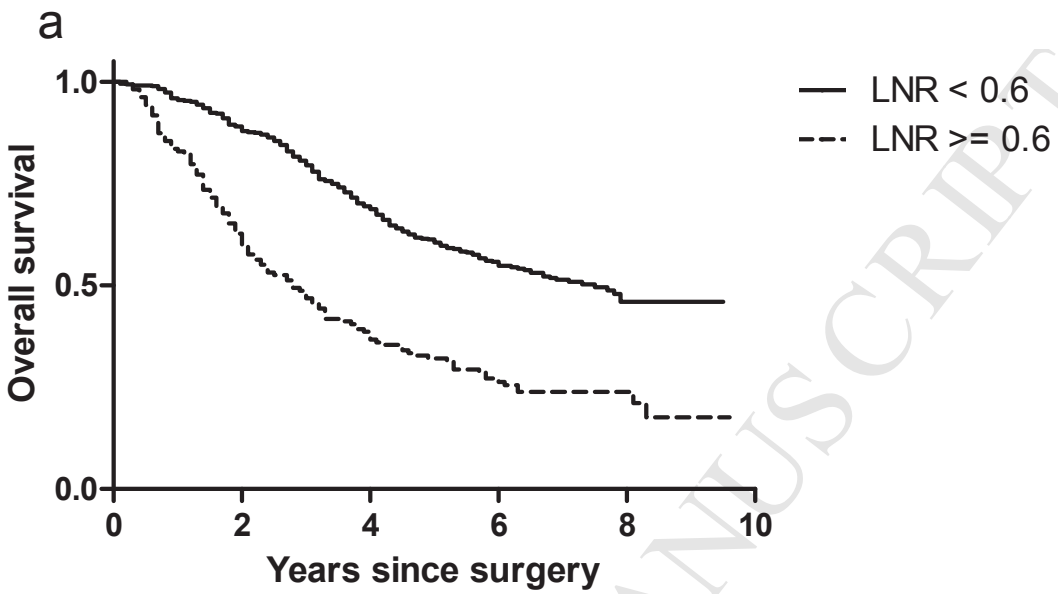
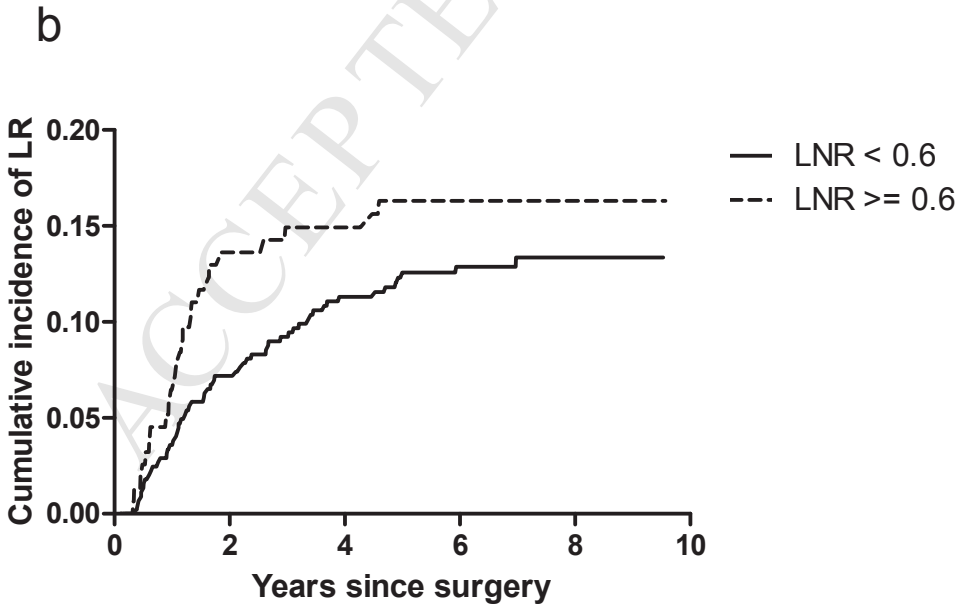
Figure 3
Dekker et al.

A.



Numbers at risk						
LNR < 0.6	447	395	297	179	41	0
LNR >= 0.6	158	96	58	33	9	0

B.



Numbers at risk						
LNR < 0.6	446	372	278	171	40	0
LNR >= 0.6	157	89	57	32	7	0

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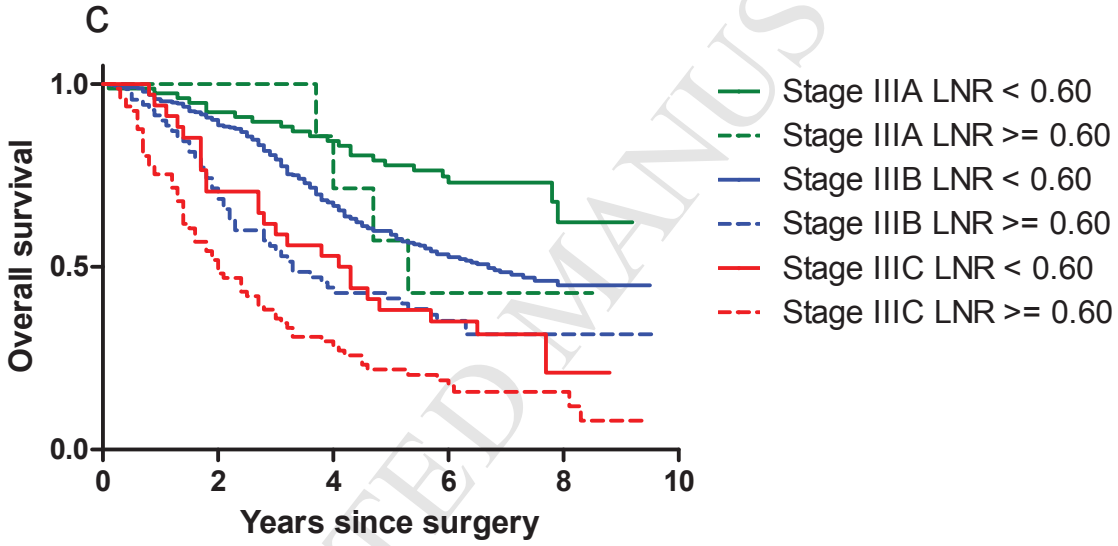
Figure 3
Dekker et al.

C.



Numbers at risk

Stage IIIA LNR < 0.60	78	71	64	41	10	0
Stage IIIA LNR >= 0.60	7	7	5	2	1	0
Stage IIIB LNR < 0.60	335	300	215	127	30	0
Stage IIIB LNR >= 0.60	70	49	30	20	4	0
Stage IIIC LNR < 0.60	34	24	18	11	1	0
Stage IIIC LNR >= 0.60	81	40	23	11	4	0

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