

## Stage migrationvsimmunology: the lymph node count story in colon cancer

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# Stage migration vs immunology: The lymph node count story in colon cancer

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## Abstract

Lymph node staging is of crucial importance for the therapy stratification and prognosis estimation in colon cancer. Beside the detection of metastases, the number of harvested lymph nodes itself has prognostic relevance in stage II/III cancers. A stage migration effect caused by missed lymph node metastases has

been postulated as most likely explanation for that. In order to avoid false negative node staging reporting of at least 12 lymph nodes is recommended. However, this threshold is met only in a minority of cases in daily practice. Due to quality initiatives the situation has improved in the past. This, however, had no influence on staging in several studies. While the numbers of evaluated lymph nodes increased continuously during the last decades the rate of node positive cases remained relatively constant. This fact together with other indications raised doubts that understaging is indeed the correct explanation for the prognostic impact of lymph node harvest. Several authors assume that immune response could play a major role in this context influencing both the lymph node detectability and the tumor's behavior. Further studies addressing this issue are need. Based on the findings the recommendations concerning minimal lymph node numbers and adjuvant chemotherapy should be reconsidered.

**Key words:** Colon cancer; Lymph node harvest; Stage migration; Understaging; Will Rogers; Immune response

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**Core tip:** The number of evaluated lymph nodes is prognostic in stage II and III colon cancers. Understaging due to inadequate lymph node harvest causing a stage migration effect is a widely accepted explanation for this. However, there is growing evidence that understaging plays only a minor role in this context. It seems much more likely that immune response has influence on the lymph nodes' detectability and is associated with outcome in colon cancer.

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## INTRODUCTION

Lymph node staging is still of crucial importance for the prognosis and the therapy stratification in colon cancer. The occurrence of lymph node metastases is associated with an adverse clinical course with an indication for adjuvant chemotherapy. In contrast, patients with stage I / II colon cancers show a considerable better outcome with a high rate of long-term survivors. Because only a small number of these patients benefit from adjuvant chemotherapy it is restricted to high risk situations like T4-stage or emergency resections<sup>[1,2]</sup>. In order to ensure high quality in staging colon cancer several national guidelines recommend the histopathological evaluation of at least 12 lymph nodes<sup>[3,4]</sup>. On the other hand it is well known that this recommendation is achieved only partially sometimes only in a minority of cases<sup>[5,6]</sup>. Low lymph node yields, however, are associated with an adverse outcome<sup>[7]</sup>. Cases with low lymph node harvests might be prone to the missing of positive lymph nodes and understaging. In contrast, high numbers of evaluated lymph nodes could prevent from understaging. Actually, high numbers of investigated lymph nodes are associated with favorable outcome in colon cancer. A stage migration effect also called Will Rogers phenomenon introduced by Feinstein *et al*<sup>[8]</sup> would take place resulting in improved survival curves both for stage II and III cancers. The elimination of false node negative cases within the collective of stage I / II cases and the shift of relatively early nodal positive cases into the correct stage III category is believed to cause such a phenomenon.

This prognostic impact of high lymph node yields prompted the demand of more intensive lymph node evaluations with up to 30 lymph nodes or even more<sup>[9-11]</sup>. Because insufficient lymph node harvest has been identified as an adverse prognostic factor adjuvant chemotherapy is recommended for patients with less than 12 identified lymph nodes regardless of the nodal status<sup>[1,2]</sup>.

However, the achievement of the 12 lymph node threshold is not only of prognostic and therapeutic relevance. It has also implications in terms of the quality measurement in surgical oncology. It is widely accepted that the identification of at least 12 lymph nodes is a good surrogate marker for an adequately performed surgical resection<sup>[12]</sup>. This is still the case today although it could be shown by several investigation that the number of elevated lymph nodes is not only influenced by the surgeon but by many other very different factors including the pathologist, the age of the patient and the molecular alterations

of the tumor<sup>[13,14]</sup>. The attempt to improve the quality of colon cancer therapy is very likely the reason for the increased rate of sufficiently staged cases in the past<sup>[9,15]</sup>. This development to an improved lymph node staging should influence the outcome statistics not only mathematically but also effectively because of a higher rate of correct stage adapted therapy. This would be a strong argument that understaging of cases with a poor lymph node yield is the reason for its prognostic impact. However, several authors express doubts that the Will Rogers phenomenon is really the correct explanation for this effect<sup>[16,17]</sup>. An alternative thesis is that immune response plays a major role in this context<sup>[16,18,19]</sup>. A strong immunologic reaction against the tumor could result in local lymph node hyperplasia with enlargement and enhanced lymph node detectability.

This review discusses the current literature in order to elucidate the biological nature of the prognostic impact of lymph node count in colon cancer.

For that a broad literature research within the MEDLINE Database was performed. The search terms included "lymph node" in combination with "colon" or "colorectal". Additionally previously published reviews<sup>[7,20,21]</sup> were screened for relevant references that might have been missed by the initial MEDLINE search. Because this review emphasizes on colon cancer articles that solely deal with rectal cancers were excluded. Articles in English and German language were considered for integration. In order to answer the question of this review articles providing information about the following topics were of particular interest: Factors influencing the lymph node harvest; Prognostic impact of lymph node harvest; Lymph node positivity rates; Upstaging from N0 to N+ after secondary lymph node dissection; Effect of advanced dissection techniques; Effect of improved lymph node recovery over time; Comparison of differently performing hospitals; Indications for the role of immune response.

## FACTORS INFLUENCING THE LYMPH NODE HARVEST

Analyzing the literature an increasing interest in identifying factors that influence the lymph node harvest is recognizable. It seems that a search is ongoing for the one who is to blame when the 12 lymph nodes rule could not be achieved and for answer of the question whether it is justified to demand this rule in all situations. Forty-four studies investigating such potential factors, published between 2003 and 2014, are included in this review. Before discussing these factors it might be worth to consider how many lymph nodes can be expected within a colonic specimen. Two studies reporting the results of entire submission of mesenteric tissue (ESMT). Brown *et al*<sup>[22]</sup> found about 90 lymph nodes per colonic specimen on average while Kim *et al*<sup>[23]</sup> detected about 43 lymph

**Table 1 Factors with influence on lymph node harvest in colorectal cancers**

Surgery	Pathology	Patient	Tumor	Other
Experience Volume	Experience Technique	Age Gender BMI	Location T-stage N-stage Lymph node size MSI	Specimen length Hospital status Year of operation

BMI: Body mass index; MSI: Microsatellite instability.

nodes in colorectal cancers. Anecdotally, the authors group found 360 lymph nodes in one specimen of a total colectomy using methylene blue assisted lymph node dissection (unpublished case). It is clear that the vast majority of these nodes are very tiny and barely visible. Nevertheless, these reports indicate that the theoretically achievable numbers are by far above the 12 recommended lymph nodes. The main different factor categories are given in Table 1 and discussed below.

### Surgery

The resection of the complete lymphatic basin is an essential part of the oncological adequate surgical therapy of colon cancer. As mentioned before the total number of evaluated lymph nodes is a well-established but also controversial debated marker for the surgery's quality. Many of the published studies show significant differences between individual surgeons and/or positive associations between, surgeon's experience/qualification and/or surgical volume and the number of harvested lymph nodes<sup>[13,24-30]</sup>. A few studies, however, found no influence of surgery related variables<sup>[31,32]</sup>. Open and laparoscopic technique were shown to be equal in terms of lymph node retrieval in two meta-analyses<sup>[33,34]</sup>.

### Pathology

The independent influence of the pathologist on lymph node retrieval is also reported in several studies<sup>[13,25,27,29,30,35,36]</sup>. Interestingly, an inverse association between qualification or level of training and number of identified lymph nodes is reported. Kuijpers *et al*<sup>[37]</sup> reported better results of pathology assistants compared to pathologists and Bamboat *et al*<sup>[35]</sup> showed that residents in their first year of training are more successful in dissecting lymph nodes than there more experienced colleagues. To pathologists these results are probably less surprising as the might be to others. Dissecting lymph nodes of a surgical specimen is certainly one of the most unpopular task in pathology. Diligence and lack of time play a major role in this context. Pathology assistance and young residents may have more time and patience to do a better job.

The usage of special techniques like fat clearance,

methylene blue technique or ESMT improves the lymph node yield effectively in comparison to the conventional manual technique<sup>[38]</sup>. The same two studies that did not find lymph node retrieval influenced by the surgeon also reported a lacking influence of pathology related factors on<sup>[31,32]</sup>. This, however, is probably more the result of homogenous performance levels of these specialties within these single centers.

### Patient

Patient related factors are unmodifiable and therefore different from the former discussed points. Patient's age is mentioned by many authors as an independent predictor for the lymph node count<sup>[19,28,39-47]</sup>. All these studies reported consistently an inverse association between higher age and lymph node harvest. To our knowledge there are no studies available that investigated the underlying reasons for that. One can speculate that surgical aggressiveness differ between different age groups. On the other hand increasing age could be accompanied by a diminishing immunologic response resulting in smaller lymph nodes.

The role of patient's gender is somewhat more controversial. Gender was identified only by a minority of studies as a lymph node yield influencing factor. Nevertheless, three of the four of these studies reported an association of female sex with higher lymph node count<sup>[19,41,48]</sup>. Only Horzic *et al*<sup>[49]</sup> found a higher lymph node count in males.

Whether the body mass index (BMI) plays a role or not remains unclear. There are studies that found a positive association between particular low BMI and lymph node harvest<sup>[31,50]</sup> others report an association between high BMI and poor harvest<sup>[13,32]</sup>. Explanations again are speculative and point in the same direction as in age. In several other studies, however, no effect was seen<sup>[25,51,52]</sup>.

### Tumor

Tumor associated factors are also unmodifiable. There is strong evidence from 15 studies<sup>[14,19,26,28,31,36,39,42-44,53-57]</sup> that right location of the tumor is associated with significant higher lymph node counts compared to left sided tumors. This might be related to anatomic differences between the different parts of the colon. A higher rate of microsatellite instability (MSI) positive cancers - which are mainly located in the right colon - could be another explanation at least in certain a part of cases.

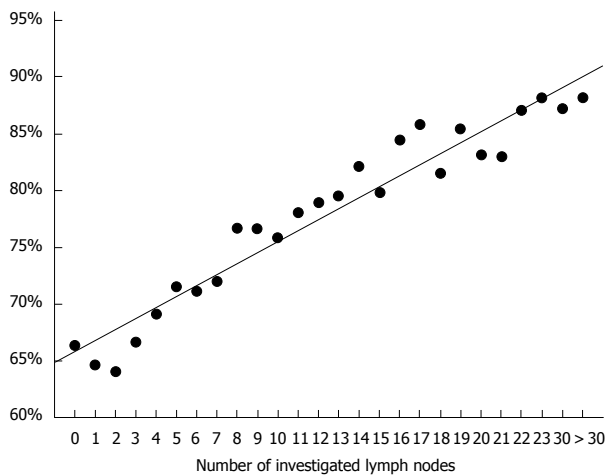
Like location, T-stage and/or tumor size were found to be predictive for the lymph node yield in colon cancer very often<sup>[13,31,36,41-43,46,49,55,56,58-60]</sup>. The immunogenicity of advanced tumors seems to be higher compared to low stages inducing a stronger reaction in lymph nodes. A more aggressive surgical treatment in advanced diseases is also thinkable.

Several authors report a positive correlation between lymph node number and the detection of lymph node metastases<sup>[41,44,56,61]</sup>. Nevertheless, it

**Table 2** Prognostic relevance of lymph node harvest in stage II colon cancers

First author	Year	n	Insuff.-rate	pT3/4	Prognostic	Endpoints	Cut off	Survival
Swanson	2003	35787	60%	100%	Yes	5yOS	No cut off	linear increase of 5yOS-rate
Law	2003	115	NA	100%	Yes	5yOS, 5yDFS	$\geq 7$	5yOS: < 7LN 69% vs > 6LN 89%
Bui	2006	453 <sup>1</sup>	NA	NA	Yes	OS	1-3 vs 10-36	HR = 0.6 (CI: 0.4-1.0), $P = 0.03$
Bilimoria	2008	142009	NA	59%	Yes	5yOS	$\geq 12$	HR = 0.75 (CI: 0.71-0.8), $P < 0.0001$
Maggard	2009	11263	NA	69%	Yes	5yOS	4 (T1) and 10 (T2)	T1: HR = 0.76 (CI: 0.641-0.902), $P = 0.002$ T2: 0.853 (CI: 0.776-0.937), $P = 0.001$
Stocchi	2011	901	NA	100%	Yes	OS, DFS, CsS	$\geq 12$	< 12 LN: HR = 1.93 (1.27-2.94), $P = 0.002$
Sato	2011	1476	56%	100%	Yes	5yOS	> 12	ACT: improved 5yOS for LNs $\leq 12$

<sup>1</sup>Sub-group of the study collection. NA: No available data; 5yOS: 5 years overall survival; 5yDFS: 5 years disease-free survival; OS: Overall survival; CsS: Cancer specific survival; ACT: Adjuvant chemotherapy; LN: Lymph node.



**Figure 1** Linear correlation between between 5-year overall survival rates and lymph node count in T3N0 colon cancers calculated on the data published by Swanson *et al*<sup>[77]</sup>.

seems questionable whether this means that a greater lymph node yield necessarily results in higher detection of metastases. The opposite linkage - the metastatic involvement induce a stronger lymph node reaction - is at least as plausible similar to advanced T-stages.

Lymph node size was recently reported as being associated with total lymph node count by the authors group, Märkl *et al*<sup>[62]</sup> and Sloothak *et al*<sup>[63]</sup>. MSI is also believed to interfere with the lymph node count. However, we found only four articles addressing this issue. Three authors report higher lymph node numbers in MSI positive cancers<sup>[14,53,64]</sup>. MacQuarrie *et al*<sup>[65]</sup> did not find such an association focusing on stage III cancers. Both factors lymph nodes size and MSI might indicate an immunologic association.

### Other factors

Other factors that influence lymph node yields are the specimen length, the status of the hospital and the year of diagnosis/operation. The latter will be discussed in detail in one of the following paragraphs. The specimen length is probably multifactorial influenced by the surgeon, the tumor and patient's individual anatomy. Several studies report this factor as lymph node count

influencing<sup>[19,26,29,47,55,56,60]</sup>.

A view studies investigated the impact of hospital status on lymph node count retrieval<sup>[60,66-68]</sup>. The results indicate that teaching and high volume centers are more successful in identifying a sufficient number of lymph nodes.

## PROGNOSTIC RELEVANCE OF LYMPH NODE COUNT IN COLON CANCER

We identified 49 studies published between 1998 and 2014 including total 625279 (range: 94-194459) that investigated the prognostic impact of lymph node count in colon and colorectal cancers, respectively. These studies show a very high heterogeneity in many respects. The study endpoint differ as cut offs, included locations and stages, case numbers and study designs do. Two nested cohort studies<sup>[69,70]</sup> and 10 register studies<sup>[45,71-79]</sup> were found. The other studies are mainly performed in single centers.

### Stage I /II colon cancers

All seven studies that were restricted to stage I /II colon cancers showed survival advantages with considerable risk reductions for the groups with higher lymph node counts (Table 2)<sup>[28,76,77,79-82]</sup> or increased risk for patients with low lymph node yields. Most authors used defined cut offs for their analyses. Swanson *et al*<sup>[77]</sup> however showed a linear increase of the 5 year overall survival rates with increasing numbers of evaluated lymph nodes (Figure 1). The work of Sato and coworkers<sup>[82]</sup> seems unique because of addressing the issue of adjuvant chemotherapy in patients with poor lymph node yield. The authors reported an improved outcome in the chemotherapy group.

### Stage I -III colon cancers

Twelve studies performed between 2002 and 2014 investigated colon cancers with and without lymph node metastases (stage I -III or stage III colon cancers exclusively) (Table 3)<sup>[44,45,54,69-71,73,74,78,83-85]</sup>. Both nested cohort studies<sup>[69,70]</sup> which are retrospective analyzes from two large multicenter studies belong to this group. All ten studies that included stage II cases



**Table 3** Prognostic relevance of lymph node harvest in stage II and III colon cancers

First author	Year	n	N+	Insuff rate	pT3/4	Endpoints	Cut off	Prognostic stage II	Prognostic stage III
Prandi <sup>1</sup>	2002	3491	48%	50 <sup>1</sup> %	n.m.	OS, PFS	8-12 (RR = 0.46) vs 13-17 (RR = 0.76) vs > 17 (RR = 0.79)	Yes	No
Le Voyer <sup>2</sup>	2003	3411	81%	NA	89%	CsS	N1: ≥ 12 vs > 10 vs > 40; N2: > 35; N0: ≥ 12 vs ≥ 12 vs > 20 and < 35	Yes	Yes
Jestin	2004	3735	31%	NA	NA	OS	≥ 12	Yes	/ <sup>3</sup>
Johnson	2006	20702	100%	NA	92%	5yCsS	< 4 neg LN vs > 12 neg LN	/	Yes
Kelder	2009	2281	32.4%	79%	79%	5yOS	< 6; 6-11; > 11	Yes	N
Tsikitis	2009	329	100%	49%	NA	CsS/DFS	> 12	/	N
Vather	2009	4309	NA	NA	NA	5yOS	4 LN wide steps	Yes	Yes
Dillman	2009	574	NA	NA	NA	OS	≥ 12	Yes	No
Shanmugam	2011	490	46.9%	24%	NA	5yCsS/CsS	≥ 20	Yes	Yes
Chang	2012	9644	41%	27.7%	80.2%	5yOS	≥ 12	Yes	Yes
Gleisner	2013	154208	34% <sup>4</sup>	NA	69.4%	OS	Linear risk reduction up to 25 LN in N- and up 10 LN in N+	Yes	Yes
Khan	2014	194459	NA	41%	NA	CsS	≥ 12 LN	Yes	Yes

<sup>1</sup>Intergroup Trial INT-0089; <sup>2</sup>INTAC-Trial; <sup>3</sup>Lymph node ratio is prognostic; <sup>4</sup>Mean out of two collectives. NA: No available data; 5yOS: 5 year overall survival; 5yDFS: 5 year disease-free survival; OS: Overall survival; CsS: Cancer specific survival; HR: Hazard rate; ACT: Adjuvant chemotherapy; LN: Lymph node; PFS: Progression-free survival; DFS: Disease-free survival; N-: Node negative; N+: Node positive.

**Table 4** Prognostic relevance of lymph node harvest in stage II colorectal cancers

First author	Year	n	Insuff rate	pT3/4	Prognostic	Endpoint	Cut off	Survival
Cserni	2002	8574	NA	100%	Yes	OS	No cut off	Continuously improved survival
Cianchi	2002	140	min 40% <sup>1</sup>	n.m.	Yes	5yOS	≥ 9	54.9% vs 79.9%, $P < 0.001$
Wong	2002	345	NA	NA	≥ 68	DFS	22.6 vs 11.3 <sup>2</sup>	40% vs 90% <sup>1</sup> , $P < 0.001$
Berberoglu	2004	301	53.5% <sup>1</sup>	69%	Yes	5yOS	≤ 10	RR = 2.8 (CI: 1.6-5.2), $P = 0.0008$
Yoshimatsu	2005	94	35%	100%	Yes	5yOS	≥ 9	66.7% vs 86.7%
Tsai	2007	180	NA	70%	Yes	OS	≥ 18	5yOS: 70 vs 98% <sup>1</sup> , $P = 0.015$
Norwood	2009	2449	NA	NA	Yes	OS	< 12	about 15% difference <sup>1</sup> , $P = 0.001$
Ishizuka	2010	205	min 36% <sup>1</sup>	100%	Yes	CsS	≤ 9 vs > 9	44.5 mo vs 66 mo, $P = 0.0042$
Nir	2010	117	28%	100%	No	5yOS, 5yDFS	≥ 12	No difference
La Torre	2012	204	16%	100%	Yes	5yDFS, 5yCsS, and 5yOS	> 12	5yOS 78.5% vs 53.1%, $P = 0.001$
Iachetta	2013	657	22%	100%	Yes	CsS/PFS	< 12 vs ≥ 20	HR = 0.49 (CI: 0.30-0.79), $P = 0.003$
Xingmao	2013	729	NA	100%	Yes	OS	> 12	88.7% vs 64.9%, $P = 0.000$

<sup>1</sup>Estimated based on Kaplan-Meier-curve; <sup>2</sup>Comparison of different cohorts. NA: No available data; 5yOS: 5 year overall survival; 5yDFS: 5 year disease-free survival; OS: Overall survival; CsS: Cancer specific survival; HR: Hazard rate; LN: Lymph node; PFS: Progression-free survival.

found favorable outcomes of the groups with higher lymph node counts. Again the chosen cut offs differed considerable. In 8 of 12 studies superior survival rates were found in stage III cancers also. One study showed an advantage for cases with low lymph node ratio (number metastatic lymph node divided by total lymph node number). Three groups including Kelder *et al*<sup>[44]</sup>, Prandi *et al*<sup>[70]</sup> and Tsikitis *et al*<sup>[85]</sup> however, found no significant association between lymph node harvest and outcome in stage III cancers.

### Stage I / II colorectal cancers

Twelve publication between 2002 and 2013 were restricted to stage I / II cases but included both colon and rectal cancers (Table 4)<sup>[47,72,86-95]</sup>. Despite the very different cut off points and endpoints, all except one paper reported favorable outcomes for the groups

with better lymph node harvests. Nir *et al*<sup>[91]</sup> were not able to show such an effect. This, however, might be the result of a relatively small sample number with only 117 cases. The authors reported at least a non-significant trend ( $P = 0.15$ ) towards better disease free survival in the group of ≥ 12 lymph nodes.

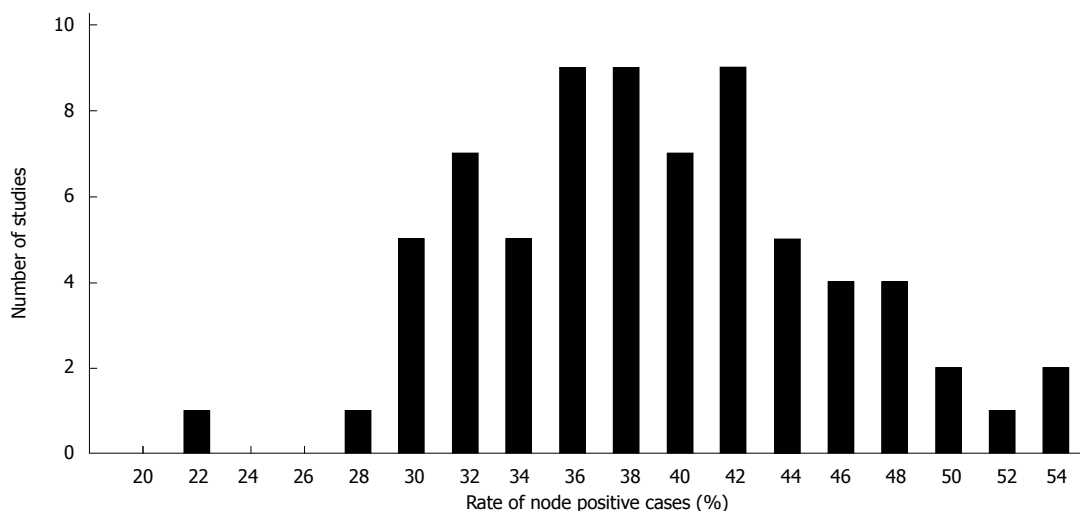
### Stage I - III colorectal cancers

Node negative and positive colorectal cancers were investigated in 17 studies between 1998 and 2014 (Table 5)<sup>[19,26,75,96-109]</sup>. Again all but one study reported better clinical courses for cases with higher lymph node counts in stage II cancers. The half of the studies, however, found no significant difference in stage III cancers. An explanation for this discrepancy to the findings in other constellations could be that fact locally advanced rectal cancers are usually treated

**Table 5 Prognostic relevance of lymph node harvest in stage II and III colorectal cancers**

First author	Year	n	N+	Insuff-rate	pT3/4	Endpoints	Cut off	Stage II	Stage III
Caplin	1998	377	NA	NA	NA	OS	> 6	Yes	No
Sarli	2005	1040	NA	NA	100%	5yOS	< 10	Yes	No
Wong	2005	2149 <sup>1</sup>	37%	NA	67%	OS	> 13	Yes	<sup>1</sup>
George	2006	3592	NA	79%	NA	5yOS	0-4; 5-10; > 10	Yes	Yes
Edler	2007	125	51%	87%	NA	OS	0-11 vs > 11	Yes	Yes <sup>1</sup>
Evans	2008	381	45.3%	47% <sup>1</sup>	82%	5yOS	≥ 9	Yes	<sup>2</sup>
Choi	2010	664	NA	NA	100%	DFS	> 20	Yes	No
Desolneux	2010	362	NA	NA	72.4%	OS	< 8 vs ≥ 8 and < 12 vs ≥ 12	Yes	No
Ogino	2010	716	38%	63% <sup>1</sup>	68.3%	CsS/OS	0-3 negative LN, 7-12 and > or = 13 negative LN	Yes	Yes
Fretwell	2010	351	48%	min 20%	95%	5yOS	≥ 9 (Dukes B); > 9 (Dukes C)	Yes	Yes
Wong	2011	8521	About 30%	32%	66%	CsS	medians: 4 vs 8 vs 10	Yes	No
Kotake	2011	16865	46%	24% <sup>1</sup>	100%	5yOS	< 10 vs > 27	Yes	Yes
Kritsanasakul	2012	533	43%	59.1%	82%	5yOS	≥ 12	Yes	<sup>1</sup>
Moro-Valdezate	2013	1166 <sup>2</sup>	39.7%	65% <sup>1</sup>	79.7%	5yOS/5yCsS	≥ 12	No	No
Zhang	2013	265	42.3%	75.1%	79.2%	OS	< 12	Yes	Yes
Onitilo	2013	1397	37%	26%	67%	OS	≥ 12	Yes	Yes
Duraker	2014	461	NA	51%	74%	CsS	≥ 12	Yes	No <sup>1</sup>

<sup>1</sup>Survival analysis only in the nodal negative sub group ( $n = 1348$ ); <sup>2</sup>Based on cases with available survival data ( $n = 359$ ). NA: No available data; 5yOS: 5 year overall survival; 5yDFS: 5 year disease-free survival; OS: Overall survival; CsS: Cancer specific survival; HR: Hazard rate; LN: Lymph node; PFS: Progression-free survival.

**Figure 2** Mean or median lymph node positivity reported in 71 studies.

by neoadjuvant radiochemotherapy which itself is associated with decreased lymph node yields<sup>[13]</sup>. Govindarajan *et al*<sup>[110]</sup> found that lymph node harvests beyond the 12 lymph node rule in neoadjuvantly treated rectal cancers were not associated with understaging or inferior survival.

## LYMPH NODE POSITIVITY RATES

For an estimation of the lymph node positivity rate that can be expected by conventional pathological examination technique 57 studies including about 750000 cases of colon and colorectal cancers were analyzed published between 1987 and 2015 [5,6,10,14,15,17,24,26,40-44,46,48,53,55,57,59,61,63,64,66,71,73,75,83,84,95,100,101,103-109,111-127].

The mean and median rates of lymph node positivity rate on the basis of the selected studies were 39%

and 38% (range: 28-53) (Figure 2). Based on patients the mean percentage of node positive cases was 37%. There was a significant correlation between the portion of pT3/4 cancers and the occurrence of lymph node metastases (Figure 3A). The rate of inadequately staged cancers, however, had no influence on the rate node positive cases (Figure 3B). The results of the five largest studies are given in Table 6.

## UPSTAGING AFTER RE-EVALUATION AND INFLUENCE OF ADVANCED TECHNIQUES

### *Influence of re-evaluation on staging*

Fourteen studies were identified that evaluated the effect of secondary or even tertiary lymph node

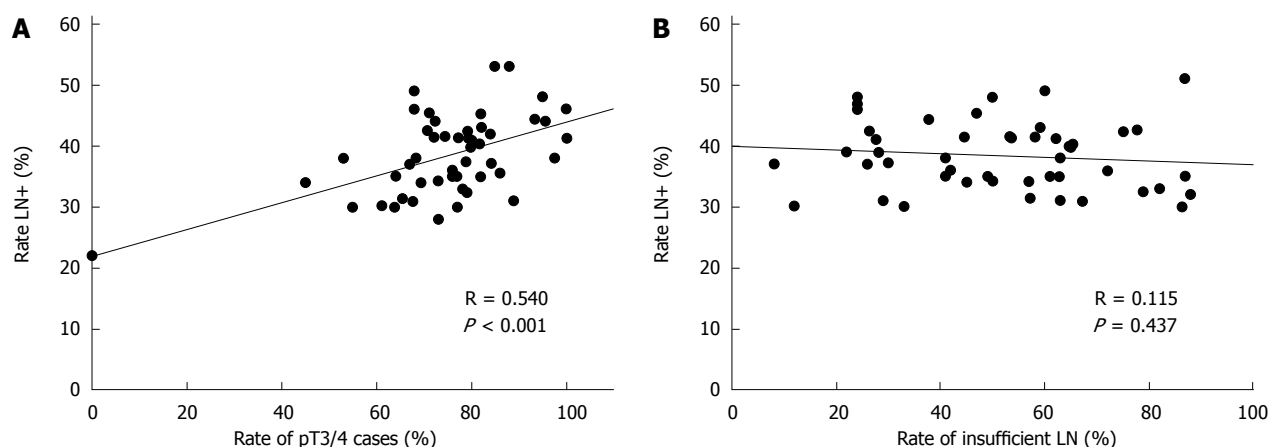


Figure 3 Association between the rate of pT3/4 cancers and the lymph node positivity rate in 51 studies (A) and rate of cases with inadequate lymph node harvest ( $< 12$  LN) and lymph node positivity (B).

Table 6 Lymph node positivity rates of the five largest studies

First author	Year	n	Register	N+ rate	Insuff rate	Rate T3/4
Gleisner	2013	154208	SEER	34%	NA	69.4%
Baxter	2010	110444	SEER	41%	53.6%	100%
Ricciardi	2006	106900	SEER	34%	57%	73%
Gonsalves	2011	19240	VACCR	30%	NA	61.1%
Chang	2012	9644	Taiwan Cancer Database	41%	27.7%	80.2%

SEER: Surveillance, Epidemiology and End Results cancer registry; VACCR: Veteran's Affairs Central Cancer Registry; NA: No available data.

dissection in colorectal cancer most often with aid of clearance techniques (Table 7)<sup>[22,23,48,128-137]</sup>. Only the authors study was restricted to colon cancers. All these studies are limited by relatively small case numbers ranging from 15 to 188. Nevertheless, nine studies report upstaging from N0 to N+ after re-evaluation of the specimens in up to 31%. All studies reporting relatively high upstaging rates between 5%-31%, however, show poor harvest results after the initial dissection step with mean numbers between 3 and 10 lymph nodes. In studies with adequate or high primary lymph node counts upstaging occurs almost exclusively in single cases.

#### Influence of advanced dissection techniques on staging

Eleven studies published between 1999 and 2015 which compared the result of advanced techniques like fat clearing or methylene blue injection with conventional manual dissection were selected to investigate the influence of these techniques on staging (Table 8)<sup>[16,138-147]</sup>. Only three of these studies<sup>[141,145,146]</sup> report significant higher node positivity rates in the study groups compared to the control groups. Despite acceptable or even excellent lymph node yields the rates of node involvement was considerable low in the control groups of these studies. The study groups showed results comparable to the values achieved by standard technique as shown in the section above. This indicates that the reported

differences might be caused more by the especially low metastatic rates in the control arms than by the effect of the advanced technique. A study performed by the authors group including more than 1300 cases revealed no differences regarding the local metastatic rate<sup>[16]</sup>.

## CHANGES OF LYMPH NODE HARVEST OVER TIME

Several studies report an improvement concerning the lymph node yields over time with increasing mean/median lymph node numbers per case and increasing rates of adequately staged cases. Twelve studies were identified investigating the development from the 50ies to present<sup>[9,15,17,95,119,120,126,148-151]</sup>. An increase in evaluated lymph nodes per case is shown in all these investigations. However, only three report an associated increase of the lymph node positivity rate. Analyzing data from 750 patients with pT3 colorectal cancers from the SEER database Goldstein *et al*<sup>[149]</sup> found an almost continuous increase concerning the mean lymph node count from 3.3 in the 1950ies to 19.4 in 1990ies. Reaching a mean count of 8.4 lymph nodes the metastases rate increased relatively abruptly from rates  $\leq 35\%$  to 38%-53%. A rate of 70% found in the latest investigation period is very likely a statistical outlier. In 2002 Goldstein published an analysis of an enlarged group from the SEER database



**Table 7 Upstaging rates after re-evaluation**

First author	Year	n	Mean LN before	Mean LN after	Upstaging NO/N+	Up-rate	Location	Technique	Comment
Scott	1989	103	6.2	12.4	Yes	8.6%	CR	Fat clearing	5yFU available
Haboubi	1992	41	6.7	58.2	Yes	28% <sup>1</sup>	CR	Fat clearing	Based on HE;
Cohen	1994	41	13	17	? <sup>1</sup>	<sup>1</sup>	CR	Xylene	higher up-staging with ICH <sup>1</sup>
Koren	1997	30	2.6	8.6	Yes	31%	CR	Fat clearing	Upstaging in 1 single case;
Brown	2005	15	20.8	89.6	Yes	<sup>1</sup>	CR	ESMT	primary N-stage (N0/1) not given;
Kim	2007	48	19.4	43	No	/	CR	ESMT	%tage N+ not given <sup>1</sup>
Richter	2007	188	n.m.	n.m.	Yes	min 4%	CR	Fat clearing	1 of 7; however unclear whether it was a
Vogel	2008	80	6.9	11.3	Yes	2%	CR	Fat clearing	LN metastasis or a deposit <sup>1</sup>
Märkl	2008	30	17	25	Yes	3%	C	Fat clearing	Initial insuff rate 59; after 9
Märkl	2008	30	35	40	No	/	C	Fat clearing	Primarily conventional technique
Fan	2010	115	9.1	14.2	Yes	5%-10% <sup>1</sup>	CR	Re-evaluation	Primarily methylen technique
Hernanz	2010	50	13.9	23.9	Yes	4% <sup>1</sup>	CR	Fat clearing	Insuff Rate 79%; Up Staging rate not
Chapman	2012	94	22.5	29	Yes	<sup>1</sup>	CR	Schwartz-clearing	exactly calculatable
Chen	2014	83	7.2	14.1	No	/	CR	Re-evaluation: partly Fat clearing	based on own calculation
Ma	2014	55	9.8	18.4	Yes <sup>1</sup>	<sup>1</sup>	CR	GEWF	1 single case upstaged <sup>1</sup>
									Upstaging in cases with primary
									insufficient LNY; 3 cases N0 to N+ <sup>1</sup>

<sup>1</sup>See comment in the same row. CR: Colorectal; C: Colon; ESMT: Entire submission of mesenteric tissue; GEWF: Glacial acetic acid, ethanol, distilled water, formaldehyde; LN: Lymph node.

**Table 8 Results of advanced pathological lymph node dissection techniques in colorectal cancers**

First author	Year	n	Mean/median LN-Conv	Mean/median LN-Spec	N+ Konv	N+ Spec	T3/4 Konv	T3/4 Spec	Technique	P value
Ratto	1999	801	11.4%	29.4%	30.2%	37.5%	76.9%	84.5%	Fixing Technique	< 0.05
Newell	2001	67	6.8%	10.2%	31%	46%	81%	85%	GEWF	NS
Kukreja	2009	701	12.8%	17.3%	36.9%	32.4%	65.8%	62.8%	Fat clearance	NS
Törnroos	2009	32	22%	61%	56.3%	37.5%	100%	100%	MB	NS
van Steenberg	2010	170	11%	14%	42%	41%	80%	79%	mesent. Patent Blue Injection	ND
Frasson	2012	473	20.6%	37.1%/47.6%	38.9%	48%	80.9%	72%	MB	NS
Jepsen	2012	428	24%	37%	9.4% <sup>1</sup>	26.7% <sup>1</sup>	82%	81%	MB	0.040
Märkl	2013	1332	13%	34%	37%	37%	65%	63%	MB	ND
Kir	2014	180	21.5%	24.5%	28%	47.9%	91.6%	84.9%	MB	0.006
Borowski	2014	100	15%	23%	34% <sup>1,2</sup>	40% <sup>1,2</sup>	NA	NA	MB	NS
Iversen	2015	120	9.5%	16.5%	44%	36%	81%	71%	GEWF	NS

<sup>1</sup>Subgroup of T1/2 cases; <sup>2</sup>Based on the number of % Dukes C cases. LN-Conv.: Lymph node harvest of conventional dissected cases; LN-Spec: Lymph node harvest of cases using advanced techniques; NA: No data available; GEWF: Glacial acetic acid, ethanol, distilled water, formaldehyde; MB: Methylene blue assisted lymph node dissection; NS: Not significant; ND: No difference.

including 2427 pT3 cases<sup>[9]</sup>. Again, the author found a similar association. Noteworthy, despite a temporary decrease of the lymph node yield in the 1980ies the trend of an increasing rate of lymph node metastases was not affected. Wong *et al*<sup>[95]</sup> investigated a cohort of total 345 patient between 1995 and 1999. They found an inverse association between increasing numbers of investigated lymph nodes and the percentage of node negative cases. However, similar mean lymph node numbers in 1995 and 1997 corresponded to considerable differing node negative rates of 65% and 55.4%, respectively. This indicates that random

changes could play a major role. All other studies including total about 250000 patients found no change in the rate of lymph node metastases over time although the lymph node yield could be improved significantly.

## COMPARISON OF DIFFERENTLY PERFORMING HOSPITALS

Hospitals belong to the factors that inhere with the lymph node harvest in colon cancers. Several investigations addressed this issue particular with

respect on its impact on the detection of lymph node metastases. Nine such studies published between 2004 and 2014 were identified<sup>[68,80,105,109,122,125,129,152,153]</sup>. Miller *et al*<sup>[152]</sup> evaluated the performance of low-, medium and high volume hospitals and found significant differences concerning the rate of poor lymph node harvest (< 7 lymph nodes) and lymph node positivity rates of 15.2% vs 35.6% and 42.6%, respectively between the low volume hospitals and the other hospital categories. Chen *et al*<sup>[129]</sup> analyzed two branches of the same institution and found significant differences with rates of inadequate staging in 20% vs 75% with corresponding lymph node positivity rates of 40.5% vs 30.6%. This was also associated with an increased long term survival. In contrast, all other seven studies, did not identify an association between the number of identified lymph nodes and the rate of stage III cancers on the hospital level. Despite the lacking impact on staging, an influence of lymph node count on survival could be shown. Wong *et al*<sup>[68]</sup> showed a favorable outcome for cases with  $\geq 12$  evaluated lymph nodes on the patients' level. Survival difference for N0 patients between differently performing hospital despite similar rates of lymph node positivity were reported by Wong *et al*<sup>[105]</sup>.

## INDICATIONS FOR THE ROLE OF IMMUNE RESPONSE

Facing limitations of the current explanation of the prognostic impact of lymph node count a possible link between immune response and the number of detected lymph nodes was proposed by a number of authors discussing their results or commenting other's papers<sup>[19,42,68,102,150,154]</sup>. These authors suggest changes of the lymph nodes - either enlargement or a diminishing - that alter its detectability. The associated differences in the number of identified number of lymph node would display a surrogate marker of the immune response against the tumor. The important role of the immune system for the patient's prognosis is unquestionably. For instance tumor infiltrating lymphocytes are associated with a favorable prognosis<sup>[155]</sup>. The same is true for crohn-like reactions in colon cancer<sup>[156]</sup>.

To the authors knowledge, however, there are only a few studies published that investigated a direct connection between parameters representing the extent of an immune response and the numbers of investigated lymph nodes. Recently, Kim *et al*<sup>[18]</sup> as well as George *et al*<sup>[102]</sup> found an association between tumor infiltration lymphocytes and the number of retrieved lymph nodes. In 1980 Pihl *et al*<sup>[157]</sup> described favorable outcomes in colorectal cancer cases with germinal center- or paracortical hyperplasia in Dukes B and C stages. Dworak<sup>[158]</sup> reported 1991 the incidence of germinal center- and paracortical hyperplasia in non-involved lymph nodes in rectal cancers. The

author, however, did not perform a survival analysis. An association between the occurrence of  $\geq 7$  lymph nodes larger than 5 mm with the total number of dissected lymph node and with favorable outcome was shown by the authors group<sup>[62]</sup>. As mentioned above microsatellite instability is found to be associated with lymph node harvest by a several authors<sup>[14,53,64]</sup>. Moreover, it is a well-known predictor for a favorable prognosis and immunologic factors are believed to be the reason for that<sup>[159]</sup>.

## CONCLUSION

Lymph node harvest has a substantial impact on the prognosis in colon cancer and has been proven in many investigations as could be shown in this review and also in a systematic review by Chang *et al*<sup>[7]</sup>.

The number of harvested lymph nodes in colon cancers is influenced by a number of modifiable and unmodifiable factors. The pathologist, surgeon and the hospital volume belong to the modifiable factors. Age, tumor stage, location and genetic alterations of the tumor are unchangeable. Stage migration also known as Will-Rogers-phenomenon is believed to be the result of understaging of stage I / II cases caused by poor lymph node retrieval. If this is true surgeons and/or pathologist would be to blame for it.

Depending on the used technique and the extent of the operation surgeons doubtless can influence the number of identifiable lymph nodes in colonic specimens. Therefore, it is to assume that more restricted excisions are prone to miss involved lymph nodes. To the author's knowledge, however, there is no evidence for that. On the other hand there are some arguments at least against a relevant frequency of its occurrence. Complete mesocolic excision has shown to be associated with reduced local recurrence and superior overall and disease-free survival in stage II and III cancers<sup>[160,161]</sup>. Nevertheless, despite improved lymph node yields the rates of nodal positive cases did not increase by this technique and seem therefore unrelated to the improved outcome results. Moreover, the reported rates of local recurrence after curatively intended resections are low which seem not compatible with a relevant rate of missed positive lymph during surgical excision<sup>[162]</sup>. Law *et al*<sup>[81]</sup> reported a higher incidence of recurrence in stage II colon cancers with inadequate lymph node harvest. Interestingly, this was caused by a higher rate of distant metastases. The rates of local recurrence did not differ between well and poorly lymph node harvested cases.

On the other hand it seems obvious that pathologist in deed have a big influence on the number of reported lymph nodes. This can be stated based on the author's experience in daily practice and many reports in the literature. The fact that pathology assistants and young residents do a better job than pathologist by spending more time and diligence<sup>[35,37]</sup> as well as the fact that the same surgeons achieve

different results when he is collaborating with different pathology department<sup>[67]</sup> are only two examples. If pathologist missed positive lymph nodes by inadequate dissection of the specimens in a significant number differences regarding the lymph node positivity rates should be determinable. However, the analysis of the data provided in the literature shows no association between the rate of inadequate lymph node yields and the rate of lymph node positivity (Figure 2). Upstaging occurs after reevaluation, however, this is mainly restricted to cases with poor lymph node harvests or single cases as shown above. Techniques to improve lymph node harvest are highly effective but not associated with higher rates of stage III cancers<sup>[38]</sup>. This is remarkable. However, pathologists seem to be highly effective in picking the relevant lymph nodes from the correct area. In an experimental model the authors group could show that there is 63% chance to detect the first lymph node metastases within the first five dissected lymph node. This increases to 86% when analyzing the first nine lymph nodes<sup>[163]</sup>. The work of Mainprize *et al*<sup>[164]</sup> point in the same direction.

These arguments raise doubts that understaging is actually a relevant problem in the management of colon cancer. The comparison of differently performing hospitals as well as the analysis of the continuously improved lymph node harvest results over time show in the vast majority of studies no association between the numbers of investigated lymph nodes and the rate of lymph node positivity.

Another point is that lymph node count was shown to be prognostic in stage III cancers at least in a part of studies. Stage migration in these cases is ruled out, naturally. Based on these arguments stage migration as reason for the well investigated prognostic impact can be excluded in the author's point of view. If at all stage migration effects seem to be restricted to the very poorly staged node negative cases. Such cases show a prognosis similar to stage III cancers. If false negative diagnoses would be the reason for that logically 100% of these cases actually had to be node positive, which seems very unlikely.

In concordance with other authors<sup>[19,42,68,102,150,154]</sup> one can state that a confounder which is related to the both lymph node harvest and to outcome has to be searched. It seems very likely that immune response is this confounder. A strong reaction can cause lymphatic hyperplasia with enlargement of lymph nodes and enhanced detectability. On the other hand an intensive immune reaction can prevent the patient from tumor progression. This hypothesis, however, is not proven yet. Nevertheless, there are indications pointing in this direction. Emerging evidence is provided by studies addressing the impact of lymph node reactions on survival as well as the prognostic relevance of lymph node size and tumor infiltrating lymphocytes<sup>[16,18,102,157,158]</sup>. Microsatellite instable tumors seem to be especially immunogenic associated with both high lymph node counts and reduce risk of

progression. They could, therefore, serve as model helping to understand what happens.

This is of high clinical relevance. The role of lymph node number as reliable quality marker becomes more and more questionable. More important a low lymph node count is currently accepted as a risk factor and often prompts the administration of adjuvant chemotherapy<sup>[165]</sup>. In many cases such poor lymph node harvests are probably not the result of poorly performing physicians but the expression of an impaired immune response. With growing success of quality initiatives these cases will escape from a possibly necessary adjuvant therapy by forcing the 12 lymph nodes. It is therefore of crucial importance to close the existing knowledge gaps and reconsider the concerned recommendations.

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