



## Extended Lymphadenectomy For Colonic Cancer

*Des Winter*



ST VINCENT'S UNIVERSITY HOSPITAL  
DUBLIN, IRELAND



Are we all talking about the same operation and staging ?

Does lymph node staging matter beyond positive / negative ?

Is it finding positive nodes or overall count that is important?

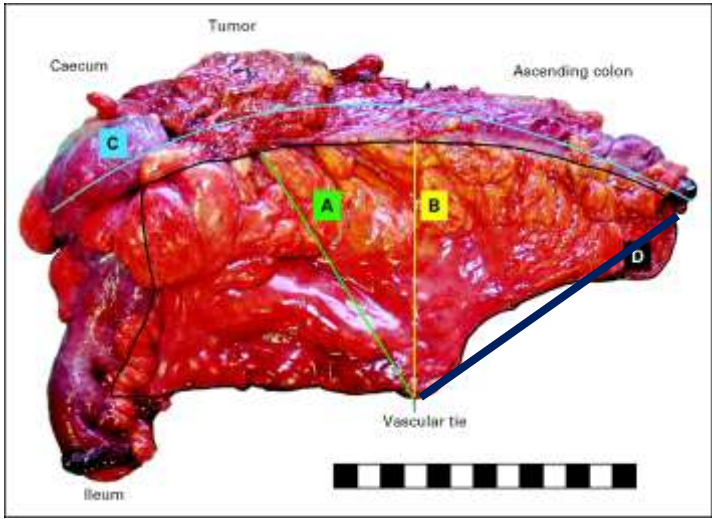
Does finding a lot of nodes improve survival because of upstaging / chemo?

What else does it mean ?

What does extended mean ? Horizontal or vertical ?

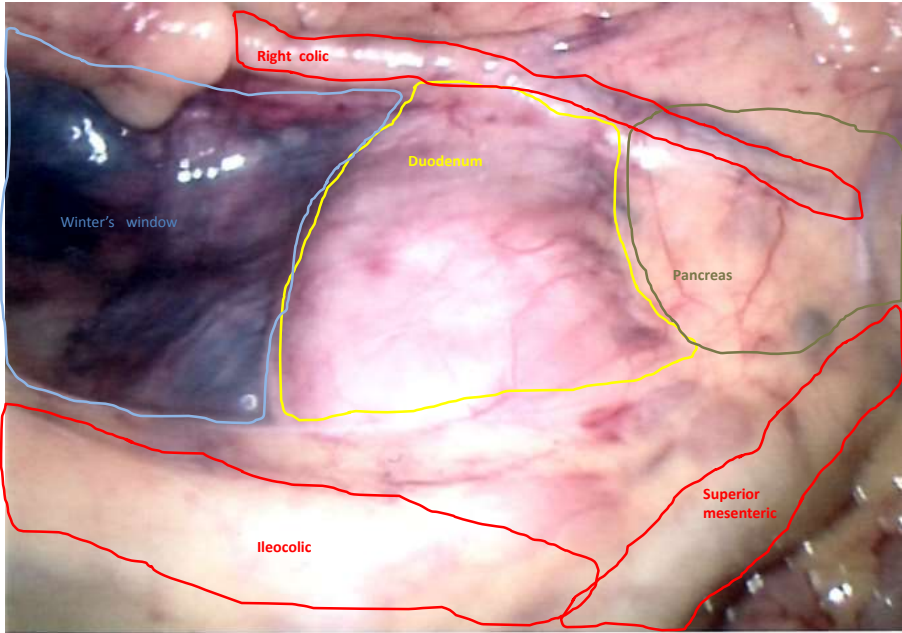
Have we accepted poorly standardised surgery *and* pathology for too long?

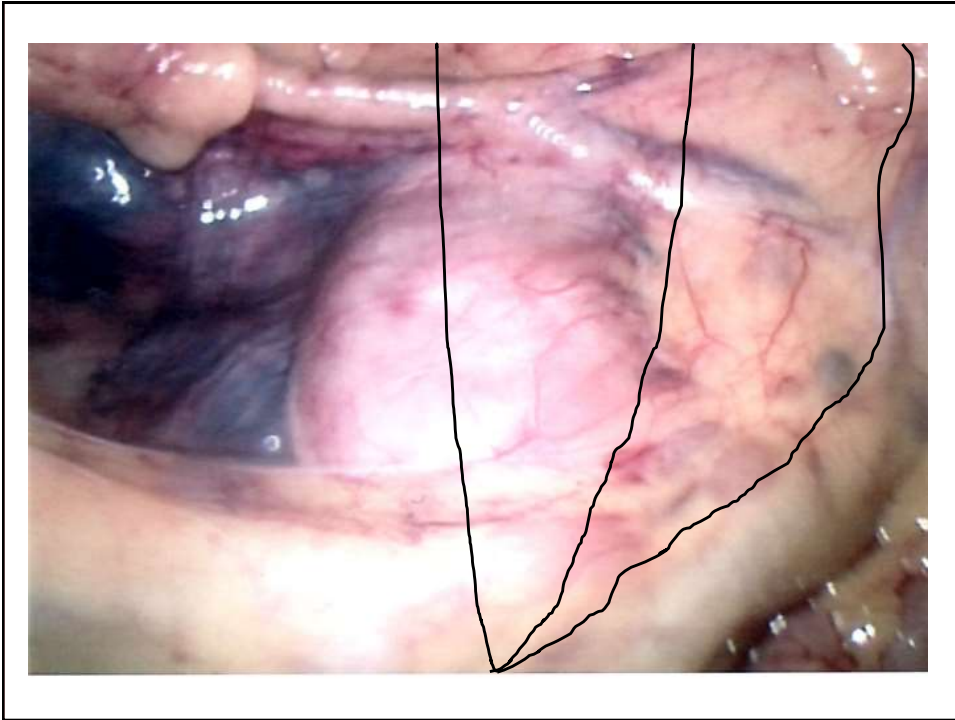
(A) distance from the tumour and (B) closest bowel wall to the high vascular tie (C) length of the large bowel and (D) area of mesentery.



JOURNAL OF CLINICAL ONCOLOGY

West N P et al. JCO 2010;28:272-278





	Erlangen 1978-2002		Dublin 2005-2009	
	<u>n</u>	<u>%</u>	<u>n</u>	<u>%</u>
Total	1329 (55 p.a.)		573 (115 p.a.)	
T1	125	9	27	5
T2	1909	13	68	12
T3	906	63	286	50
T4	217	15	191	33
N1/2	545	38	239	42
N0	893	62	333	58
V1	315	22	263	46
V0	1114	78	306	53
Vx	9	1	4	1
Elective	1219	91	476	83
Emergency	110	9	97	17

Hohenberger et al Colorectal Dis 2009; 11(4): 354-364

Erlangen 1978-2002		Dublin 2005-2009	
	<u>n</u>	<u>%</u>	
Total	1329 (55 p.a)		573 (115 p.a.)
T1	125	9	27
T2			
T3	906	63	286
T4	217	15	191
N1/2			
N0			
V1	315	22	263
V0	1114	78	306
Vx			
Elective	1219	91	476
Emergency	110	9	97

Hohenberger et al Colorectal Dis 2009; 11(4): 354-364

Erlangen 1978-2002		Dublin 2005-2009	
	<u>n</u>	<u>%</u>	
Total	1329 (55 p.a)		573 (115 p.a.)
T1			
T2			
T3			
T4			
N1/2	545	38	239
N0	893	62	333
V1			
V0			
Vx			
Elective			
Emergency			

Universal constant *HW*

Hohenberger et al Colorectal Dis 2009; 11(4): 354-364



## Lymph Node Evaluation and Survival After Curative Resection of Colon Cancer: Systematic Review

**Background** Adequate lymph node evaluation for cancer involvement is important for prognosis and treatment of patients with colon cancer. The number of lymph nodes evaluated may be a measure of quality in colon cancer care and appears to be inadequate in most patients treated for colon cancer. We performed a systematic review of the evidence for the association between lymph node evaluation and oncologic outcomes in patients with colon cancer.

**Methods** Medline, Scopus, Cochrane, and the National Guidelines Clearinghouse databases were searched from January 1, 1990, through June 30, 2006, for studies in which survival data as a function of number of lymph nodes evaluated were available. These studies were evaluated for methodologic quality, design, and data source. A total of 61 371 patients were included.

**Results** Seventeen studies from nine countries were eligible for systematic review, including two secondary analyses of multicenter randomized trials of adjuvant chemotherapy for colon cancer, five population-based observational studies, and 10 single-institution retrospective cohort studies. Despite heterogeneity in methodology and differences in threshold numbers of lymph nodes evaluated (range = 6 – 40 lymph nodes), 16 of 17 studies reported that increased survival of patients with stage II colon cancer was associated with increased numbers of lymph nodes evaluated. Four of six studies with data from stage III patients also reported a positive association with survival among patients with stage III colon cancer.

**Conclusions** The number of lymph nodes evaluated after surgical resection was positively associated with survival of patients with stage II and stage III colon cancer. These results support consideration of the number of lymph nodes evaluated as a measure of the quality of colon cancer care.

Chang G et al. J Natl Cancer Inst 2007;99: 433 – 41



## Lymph Node Evaluation and Survival After Curative Resection of Colon Cancer: Systematic Review

**Table 3 . Five-year overall survival from population-based cohort studies of stage II cancer**

Source, y	No. of patients	No. of lymph nodes	Overall survival %	HR or RR (95% CI)	P
NCDB, 2003	35 787	1 – 7	49.8	1.0 (referent) †	<.001 ‡
		8 – 12	56.2	0.81 (0.77 to 0.84)	
		≥ 13	63.4	0.68 (0.65 to 0.71)	
Kentucky Cancer Registry, 2004	2437	1-12	56		<.001 ‡
		>12	63		
Uppsala/Orebro Registry, 2005	3735	1 – 11	~ 65		<.001 ‡
		>11	~ 75		
Ontario Registry, 2006	1000	1 – 3		1.0 (referent) §	
		4 – 6		0.9 (0.6 to 1.3)	.59
		7 – 9		0.9 (0.6 to 1.3)	.53
		10 – 36		0.6 (0.4 to 1.0)	.03
SEER registry, 2002	8574	Each additional lymph node		0.98 (0.97 to 0.98)	<.001

Chang G et al. J Natl Cancer Inst 2007;99: 433 – 41

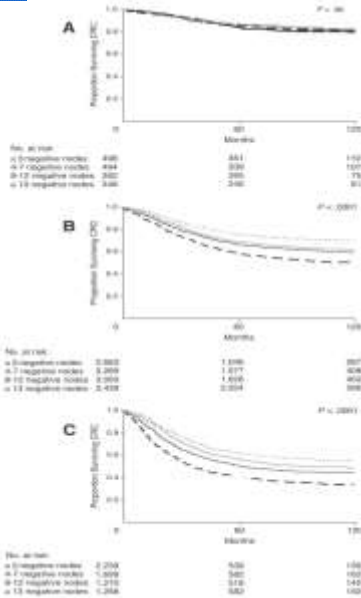
**Increasing Negative Lymph Node Count Is Independently Associated With Improved Long-Term Survival in Stage IIIB and IIIC Colon Cancer**

Stage III colon cancer between 1988 - 1997 from the Surveillance, Epidemiology and End Results cancer registry. A proportional hazards model with 20,702 patients

**Table 3. Disease-Specific Survival for Stage III Colon Cancer Stratified by No. of Positive Lymph Nodes**

No. of Positive Lymph Nodes	Cumulative 5-Year Survival (%)	Stage IIIA	Stage IIIB	Stage IIIC
1		87.3	69.1	—
2		83.1	63.2	—
3		77.3	57.0	—
4		—	—	55.7
5		—	—	50.5
6-7		—	—	45.6
>7		—	—	34.3

Johnson PM, Porter GA, Ricciardi R, Baxter NN. *J Clin Oncol* 2006 24:3570-3575.



Johnson PM, Porter GA, Ricciardi R, Baxter NN. *J Clin Oncol* 24:3570-3575.

International survival differences ( $\Delta S$ )  $\propto$  Patient variables - age / gender / comorbidity  
 type of presentation  
 Tumour characteristics - stage  
 LVI  
 immunological profile  
 molecular markers  
 No. negative nodes examined (? removed)

$\Delta S \propto \frac{\text{Nodal positivity (Stage + LVI + Markers)}}{\text{No. Negative nodes}}$

$\Delta S \propto \frac{HW (\text{Tumour profile})}{\text{No. Negative nodes}}$

$\Delta S \propto \frac{1}{\text{No. Negative nodes}}$

Universal constant  $HW (-1)$

JOURNAL OF CLINICAL ONCOLOGY

**Increasing Negative Lymph Node Count Is Independently Associated With Improved Long-Term Survival in Stage IIIB and IIIC Colon Cancer**

Stage III colon cancer between 1988 - 1997 from the Surveillance, Epidemiology and End Results cancer registry.  
 A proportional hazards model with 20,702 patients

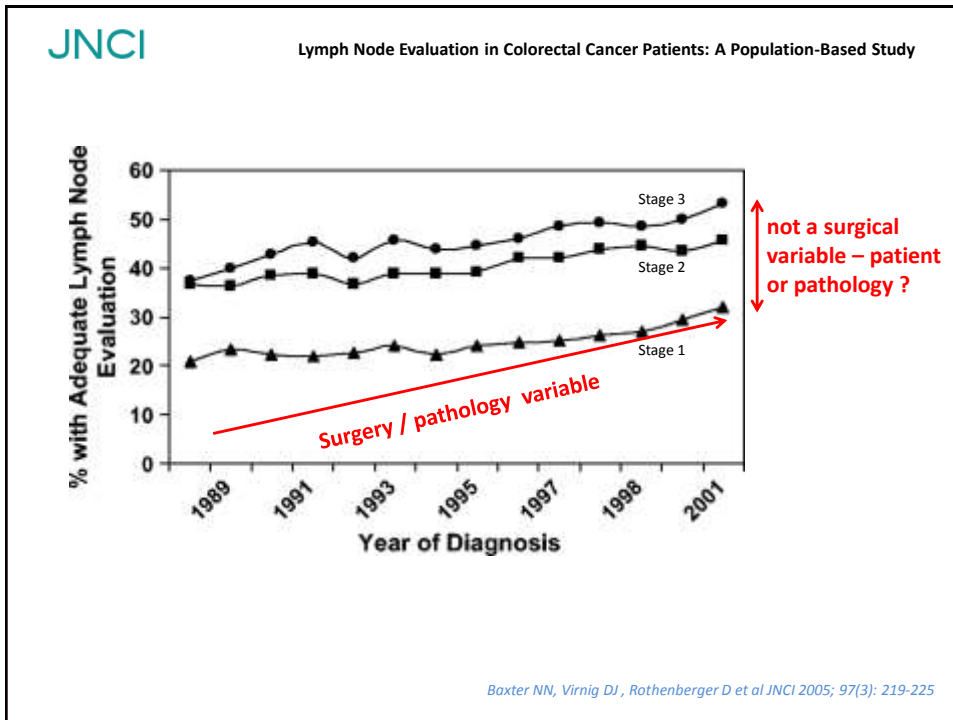
**Table 2. Disease-Specific Survival for Stage III Colon Cancer Stratified by the No. of Negative Lymph Nodes**

No. of Negative Lymph Nodes	Cumulative 5-Year Survival (%)	Stage IIIA	Stage IIIB	Stage IIIC
<4		85.5	54.7	35.5
4-7		83.2	63.3	46.5
8-12		86.0	65.8	52.6
>12		86.0	72.6	58.1

↑ Surgery +  
 Pathology  
 + Host  
 variables

← Tumour – host variable →

Johnson PM, Porter GA, Ricciardi R, Baxter NN. *J Clin Oncol* 2006 24:3570-3575.



JNCI

Lymph Node Evaluation in Colorectal Cancer Patients: A Population-Based Study

Table 4. Multivariable analysis of factors influencing adequate lymph node evaluation in patients with colorectal cancer

Characteristic	OR	95% CI
Patient age		
≤ 50	1	Referent
51 – 60	0.68	0.64 to 0.72
61 – 70	0.55	0.52 to 0.58
≥ 71	0.45	0.44 to 0.47
Patient sex		
Male	1	Referent
Female	1.05	1.02 to 1.08
Anatomic site of tumor		
Right colon	1	Referent
Left colon	0.45	0.44 to 0.47
Rectum	0.52	0.50 to 0.54
Patient race/ethnicity		
White	1	Referent
Nonwhite	1.00	0.96 to 1.04
Tumor stage		
I	1	Referent
II	1.86	1.80 to 1.93
III	2.27	2.18 to 2.35
Tumor grade		
Well or moderately differentiated	1	Referent
Poorly differentiated	1.11	1.07 to 1.15

Patient And Pathology variables

Baxter NN, Virnig DJ, Rothenberger D et al JNCI 2005; 97(3): 219-225



Are we all talking on (about) the same stage ?

Does lymph node staging matter beyond positive / negative ?

Is it finding positive nodes or overall count that is important?

Does finding a lot of nodes improve survival because of upstaging / chemo?

What else does it mean ?

What does extended mean ? Horizontal or vertical ?

Have we accepted poorly standardised surgery *and* pathology for too long?

### More up-staging ?

With the power of ~100000 patients

The odds of finding positive nodes increases with more lymph nodes examined  
-but not much beyond 7-12 nodes

Cancer survival has improved and more lymph nodes are being examined

The rate of nodal positivity is static - no upstaging has occurred (HW)

Goldstein NS. Lymph node recoveries from 2427 pT3 colorectal resection specimens spanning 45 years: recommendations for a minimum number of recovered lymph nodes based on predictive probabilities. *Am J Surg Pathol.* 2002; 26(2): 179-189.

Bui L et al. Lymph node counts, rates of positive lymph nodes, and patient survival for colon cancer surgery in Ontario, Canada: a population-based study. *J Surg Oncol* 2006; 93(6): 439-445.

Baxter NN et al. An evaluation of the relationship between lymph node number and staging in pT3 colon cancer using population-based data. *Dis Colon Rectum* 2010; 53(1): 65-70.

Parsons HM et al. Association between lymph node evaluation for colon cancer and nodal positivity over the past 20 years. *JAMA.* 2011; 306(10): 1089-1097.

### Better staging and use of chemotherapy ?

Better survival for both node-negative and -positive patients with higher negative node recovery (irrespective of chemotherapy)

Patient factors are important - younger patients (and perhaps females) do better

INTACC (Italy) 3248 Stage II / III patients - all received 5 FU therapy

INT089 (USA) 3557 Stage II / III patients - all received 5 FU therapy

Joseph N et al. *Ann Surg Oncol* 2003; 10(3): 213-218

Le Voyer TE et al. *J Clin Oncol* 2003; 21: 2912-2919

Prandi M et al. *Ann Surg* 2002; 4:458-463

### Simple arithmetic or a linear equation or a complex number ?

Increasingly extensive lymphadenectomy (left colon) may not improve survival.  
(Standardised surgery is quality enough?)

Rouffet F et al. French Association for Surgical Research. Curative resection for left colonic carcinoma: hemicolectomy vs segmental colectomy: a prospective, controlled, multicenter trial. *Dis Colon Rectum*. 1994; 37(7): 651-659.

Higher nodal counts (right and left colon) by hospital not associated with improved survival.  
(Not simply down to the process of care. Are patient factors more important?)

Wong SL et al. Hospital lymph node examination rates and survival after resection for colon cancer. *JAMA*. 2007; 298(18): 2149-2154.

## What about the tumour and the interaction with the patient ?

Patients with a stronger immune response and larger nodes have better survival irrespective of whether node-positive or not

Microsatellite instability confers a good prognosis

The life and work of the late Jeremy Jass.

Pages F et al. Effector memory T cells, early metastasis, and survival in colorectal cancer. *N Engl J Med*. 2005; 353(25): 2654-2666.

George S et al. Wessex Colorectal Cancer Audit Working Group. Will Rogers Revisited: prospective observational study of survival of 3592 patients with colorectal cancer according to number of nodes examined by pathologists. *Br J Cancer* 2006; 95(7): 841-847.

Are we all talking on (about) the same stage ?

Does lymph node staging matter beyond positive / negative ?

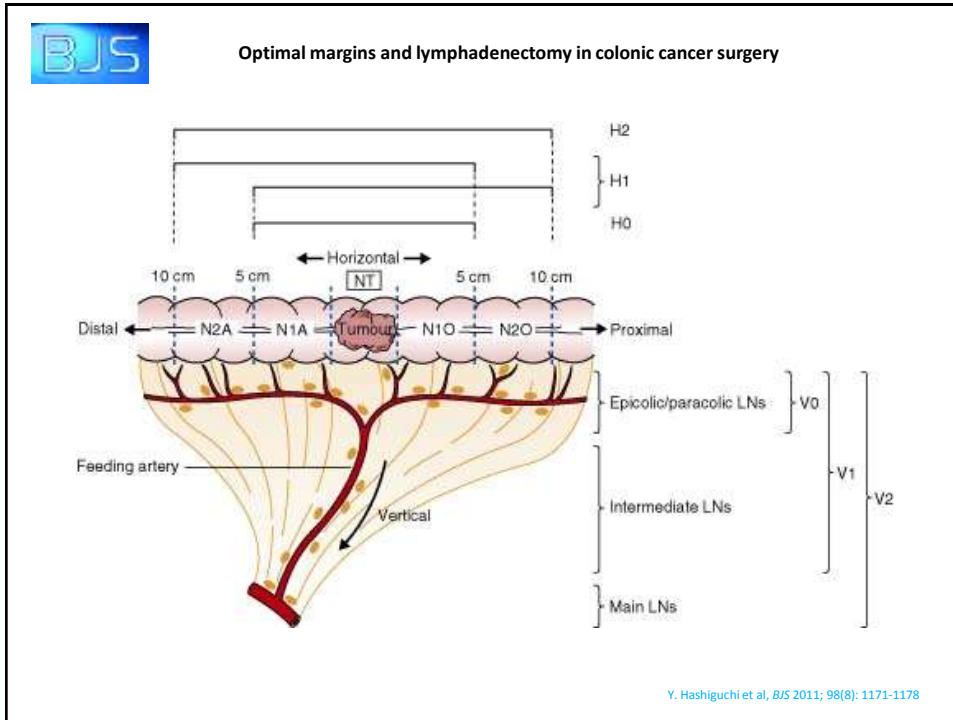
Is it finding positive nodes or overall count that is important?

Does finding a lot of nodes improve survival because of upstaging / chemo?

What else does it mean ?

What does extended mean ? Horizontal or vertical ?

Have we accepted poorly standardised surgery *and* pathology for too long?



**Table 1. Characteristics of patients, node status, and prognosis with respect to surgical resection**

Type of surgical resection	HV0 (n = 31)	HOV1 (n = 33)	H1V1 (n = 43)	H2V1 (n = 185)	HOV2 (n = 49)	H1V2 (n = 75)	H2V2 (n = 498)	Total (n = 914)	P <sup>a</sup>
Mean age (years)	71.1	69.6	61.9	66.1	61.4	62.3	61.5 <sup>§</sup>	63.2	0.001 <sup>‡</sup>
Sex ratio (M:F)	20:11	21:12	26:17	104:81	30:19	37:38	262:236	500:414	0.468
Tumour location									
Right colon	10 (32)	8 (24)	12 (28)	72 (38.9)	14 (29)	26 (35)	161 (32.3)	303 (33.2)	0.121
Left colon	15 (48)	19 (58)	25 (58)	90 (48.6)	20 (41)	29 (39)	234 (47.0)	432 (47.3)	
Rectosigmoid	6 (19)	6 (18)	6 (14)	23 (12.4)	15 (31)	20 (27)	103 (20.7)	179 (19.6)	
Tumour depth									
T2	5 (16)	3 (9)	8 (19)	23 (12.4)	6 (12)	10 (13)	57 (11.4)	112 (12.3)	0.940
T3	19 (61)	20 (61)	27 (63)	117 (63.2)	31 (63)	47 (63)	337 (67.7)	598 (65.4)	
T4	7 (23)	10 (30)	8 (19)	45 (24.3)	12 (24)	18 (24)	104 (20.9)	204 (22.3)	
No. of LNs examined									
Mean	6.9 <sup>‡</sup>	13.2	14.7	17.0	17.8	23.2 <sup>‡</sup>	23.9 <sup>‡</sup>	20.7	< 0.001 <sup>‡</sup>
≤ 12	4 (13) <sup>‡</sup>	18 (55)	24 (56)	136 (73.5)	34 (69)	66 (87) <sup>‡</sup>	433 (86.9) <sup>‡</sup>	714 (78.1)	< 0.001
No. of LNs involved									
Mean	0.4	1.5	1.3	1.2	1.1	1.6	1.4	1.3	0.380 <sup>‡</sup>
Patients with involved LNs	10 (32)	17 (52)	23 (53)	81 (43.8)	22 (45)	32 (43)	236 (47.4)	421 (46.1)	0.564
5-year overall survival (%)	64 <sup>‡</sup>	75	76	75.3	81	85	79.5	78.4	0.032 <sup>‡</sup>

Table 2. Univariable and multivariable Cox proportional hazards analyses of factors influencing overall survival

	n	Univariable Crude HR	P	Multivariable Adjusted HR	P
Age	914	1.03 (1.02, 1.04)	< 0.001	1.03 (1.02, 1.04)	< 0.001
Sex					
M	500	1.00		1.00	
F	414	0.73 (0.57, 0.94)	0.015	0.66 (0.51, 0.85)	0.001
LN dissection					
Vertical					
V0	31	1.00		1.00	
V1	261	0.49 (0.29, 0.84)	0.010	0.52 (0.30, 0.90)	0.020
V2	622	0.44 (0.26, 0.73)	0.002	0.54 (0.32, 0.92)	0.024
Horizontal					
H0	96	1.00			
H1	128	0.87 (0.54, 1.42)	0.592		
H2	690	0.78 (0.53, 1.15)	0.211		
Tumour depth					
T2	112	1.00		1.00	
T3	598	1.78 (1.03, 3.09)	0.039	1.48 (0.85, 2.57)	0.169
T4	204	4.13 (2.36, 7.24)	< 0.001	3.15 (1.78, 5.57)	< 0.001
Node status					
Negative	493	1.00		1.00	
Positive	421	2.71 (2.09, 3.52)	< 0.001	2.67 (2.05, 3.49)	< 0.001
Tumour grade					
Well differentiated	356	1.00			
Moderately differentiated	500	1.10 (0.85, 1.43)	0.468		
Poorly differentiated	22	1.36 (0.63, 2.92)	0.438		
Mucinous/signet ring cell	34	1.16 (0.61, 2.23)	0.649		
Tumour location					
Right colon	303	1.00			
Left colon	432	0.87 (0.66, 1.15)	0.331		
Rectosigmoid	179	0.95 (0.67, 1.35)	0.791		
Tumour size (cm)					
< 5	564	1.00			
≥ 5	350	0.93 (0.72, 1.20)	0.582		

## Conclusions

Lymph node positivity has changed little (*HW* constant) while nodal counts are rising

Higher lymph node counts are associated with: better prognosis independent of chemotherapy

tumour-host interactions that confer better prognosis

Internationally *standardised* surgical planes with: vertical node clearance make sense

extended horizontal nodal extension do not

Internationally *standardised* pathological techniques and reporting are needed