D3 Lymphadenectomy in Colon Cancer
Where Does the Evidence Stand?

Julio Garcia-Aguilar, MD, PhD
New York, NY

Disclosures

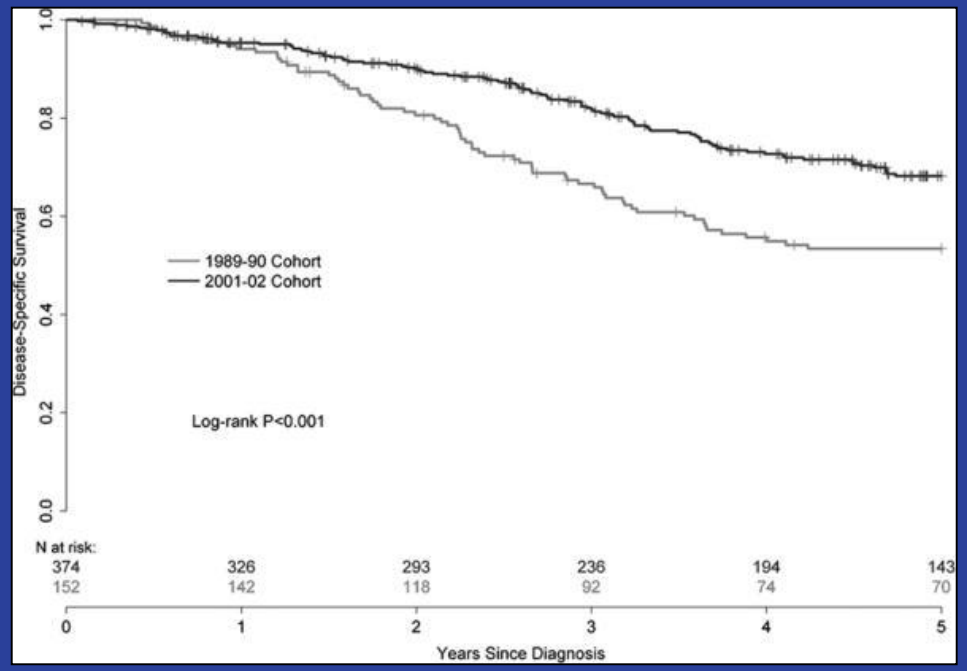
Honorarium and Stock Owner Intuitive Surgical

Surgical Technique Matters!!

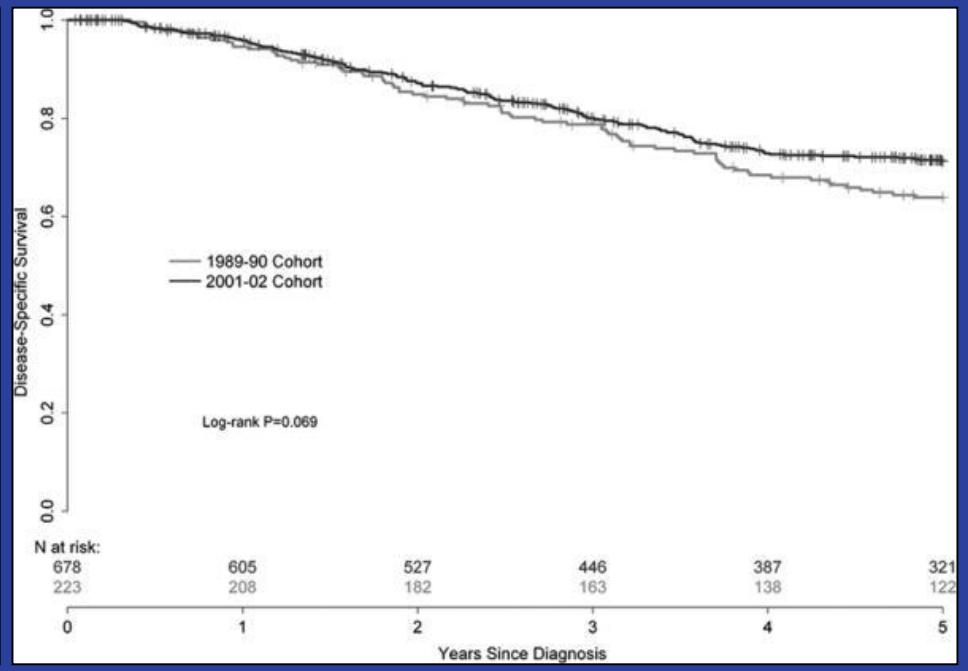
Do We Really Have a Problem with Surgery for Colon Cancer?

Outcomes Have Improved for Rectal Cancer not as Much for Colon Cancer

Rectal Cancer



Colon Cancer



Renouf et al, Am J of Clin Oncol 2013; 36(6):558-564.

Recurrence in Colon Cancer

- 30% of patients having curative resection for colon cancer
- Up to 19% are locoregional only
- Many misdiagnosed as peritoneal disease
- Rate depends on the stage
- Diagnosed approx. 18 months after surgery
- Usually in advanced tumors at diagnosis
- Many cases attributed to inadequate surgery

Complete Mesocolic Excision (CME) and Central Vascular Ligation (CVL)

1. Dissection in the embryological plane between the colonic mesentery and the parietal retroperitoneal fascia, ensuring complete removal of the mesentery
2. Resection of an adequate length of bowel to remove involved pericolic nodes
3. Central vascular tie to completely remove all apical nodes along main feeding vessels (smv) (D3)

Hohenberger et al, Colorectal Dis 2009
West et al, J Clin Onc 2009
Sondenaa et al, Int J Colorectal Dis 2014

Problem #1: Resection Margin in Colon Cancer

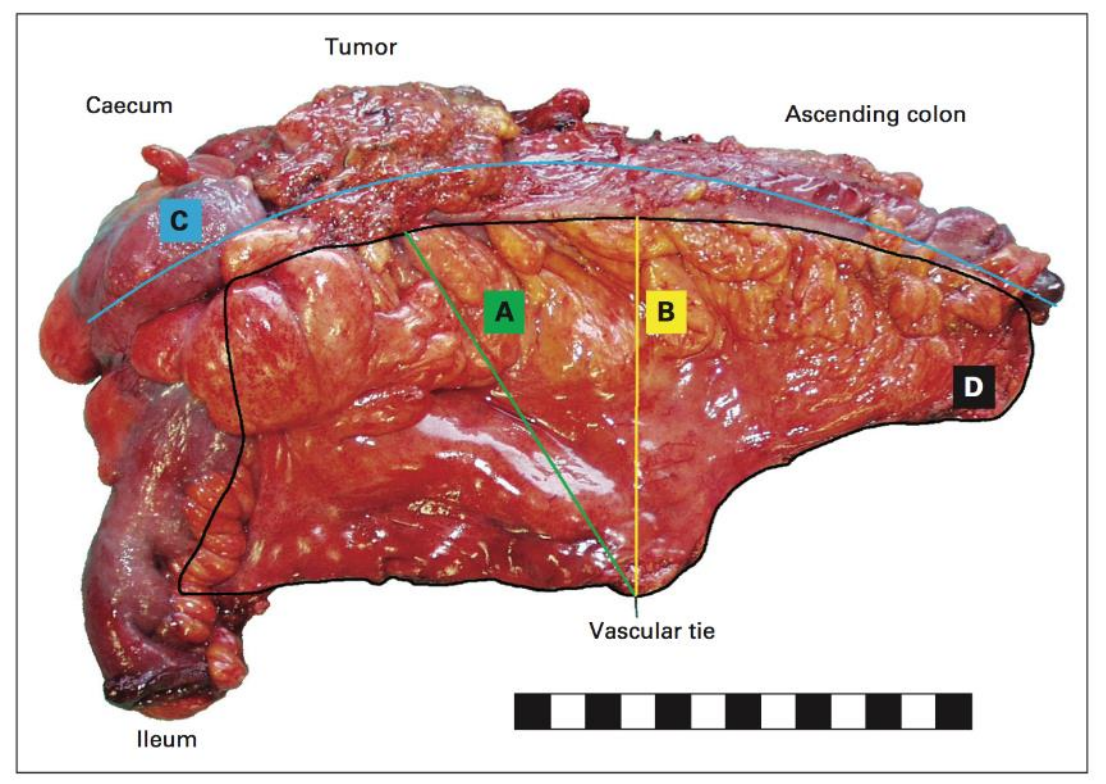
- pT1 4.5%
- pT2 6.3%
- pT3 10.9%
- pT4 25.8%

Healy et al, Ann Surg 2020; 262:891-8

- Stage II 9%
- Stage III 12%

Goffredo et al, J Surg Oncol 2020; 121:538-46

Pathology Grading of Colon Cancer Resection



- Plane of dissection
  - Muscularis
  - Intramesocolic
  - Mesocolic
- Tissue morphometry
  - Length of the specimen
  - Tissue area
  - Distance of the vascular tie to the bowel wall
  - Distance of the vascular tie to the tumor

West et al. Lancet Oncology 2008, 9 :857-65.

Pathology Grading of Colon Cancer Resection Association with Survival

- 399 patients with resection for colon cancer
- Only 39% had surgery in the mesocolic plane
- Intact mesocolic plane versus intra-mesocolic plane:
  - 15% improvement in survival for all patients
  - 27% improvement in survival for patients with stage III

West et al. Lancet Oncology 2008, 9 :857-65.

Lymph Node Drainage in Colon Cancer: Summary

- Longitudinal spread in the pericolic nodes can occur up to 10 cm
- Central spread increases from D1 to D3
- D3 nodal involvement occurs in 5% -10% to of cases
- Skip metastasis (D2 and/or D3 without D1) occurs in up to 22% of patients with stage III colon cancer
- Unusual patterns of spread – subpyloric and gastroepiploic nodes – occur in up to 4% of patients with locally advanced ascending or transverse colon cancer
- Aberrant nodes outside the tumor related D1-D3 area are considered M1 disease

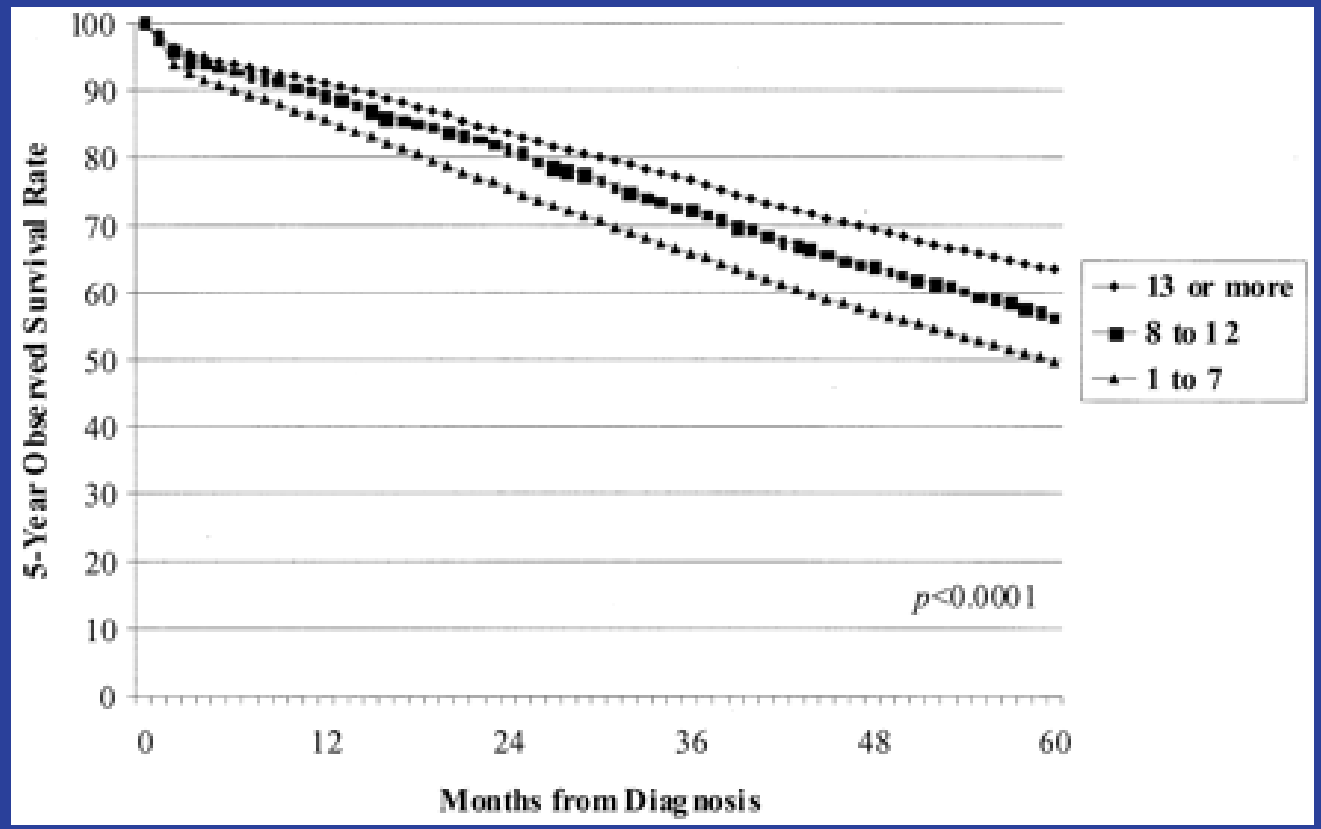
Yamamoto et al, Ann Surg 2017

Problem #2: Number of Lymph Nodes often Insufficient

Open/Laparoscopic	COST	COLOR	CLASICC	Leung	ALCCAS
Patients	863	1248	794 (413 colon)	403	594
Operative Time (min)	95/150 p<0.001	115/145 p<0.001	135/185	189/144 p<0.001	107/158 p=<0.001
Blood Loss	NR	175/100 p<0.001	NR	238/169 p=0.06	100/100 p=0.17
Length of Incision (cm)	18/6 p<0.001	NR	22.8/7	NR	20.6/8 p<0.001
Conversion %	21%	17%	25%	23%	14%
LN removed (mean/median)	12/12 (median)	10/10 (median)	13.5/12 (mean)	12/11 (mean)	13/13 (mean)
Overall Morbidity (%)	20/21 p=0.64	20/21 p=0.88	26/26 p=n/s	22/19 p=n/s	45/38 p=0.062
Length of Stay (days)	6/5 p<0.001	9.3/8.2 p<0.001	10/8	8.7/8.2 p<0.001	10.6/9.5 p0.068
5Y -DFS	68/69 p=0.94	68/66 p=0.7	64/58 p=0.399	78/75 p=0.45	71/73 p=0.7
5Y-OS	75/76 p=0.93	74/74 p=0.45	63/56 p=0.253	8076 p=0.61	76/77 p=0.64

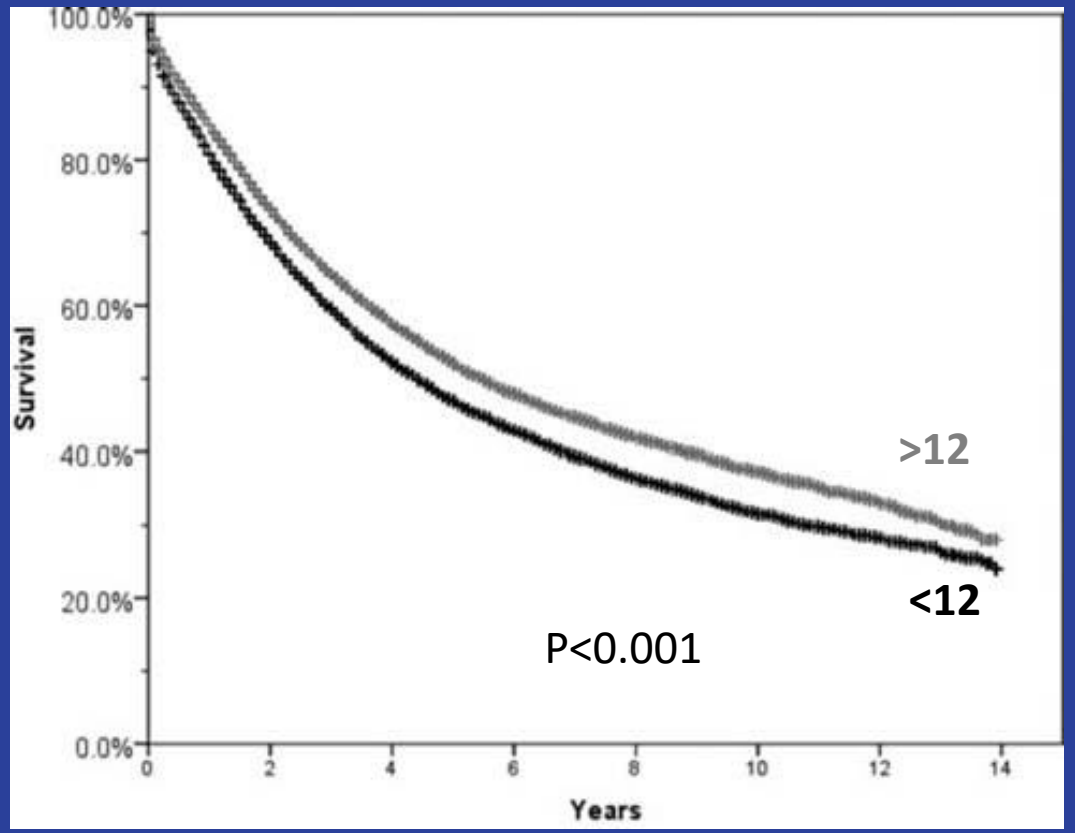
Survival Improves with Increasing Number of Lymph Nodes

Stage II



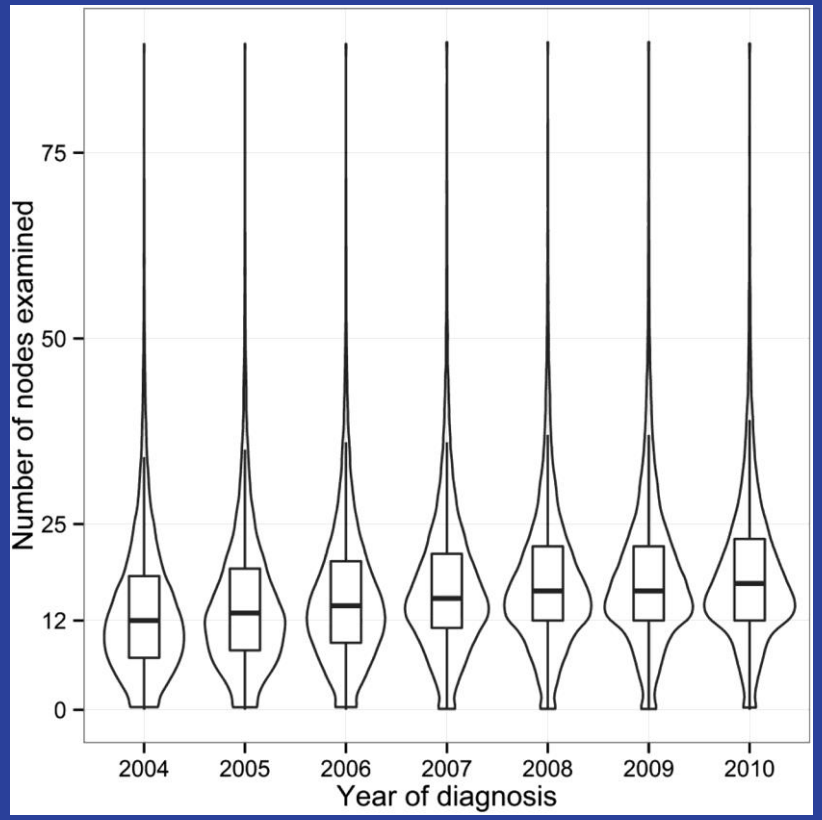
Baxter et al, Ann Surg Oncol 2003;10:65-71

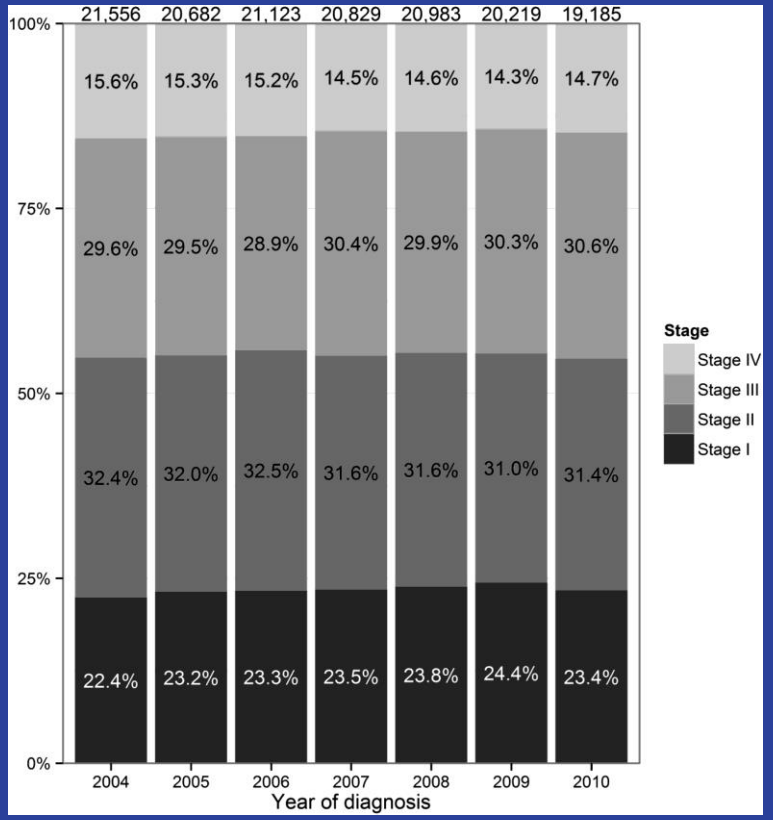
Stage III



Chen S et al, Ann Surg 2011, 253(1):82-87.

Increasing Number of Nodes Did Not Change Staging but Improved Survival





Improvement in survival with each node retrieved which was independent of stage, tumor site, patient age, year of diagnosis

Budde et al, J Am Coll Surg 2014; 2018:1004-1011

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Additional Facts About Lymph Nodes

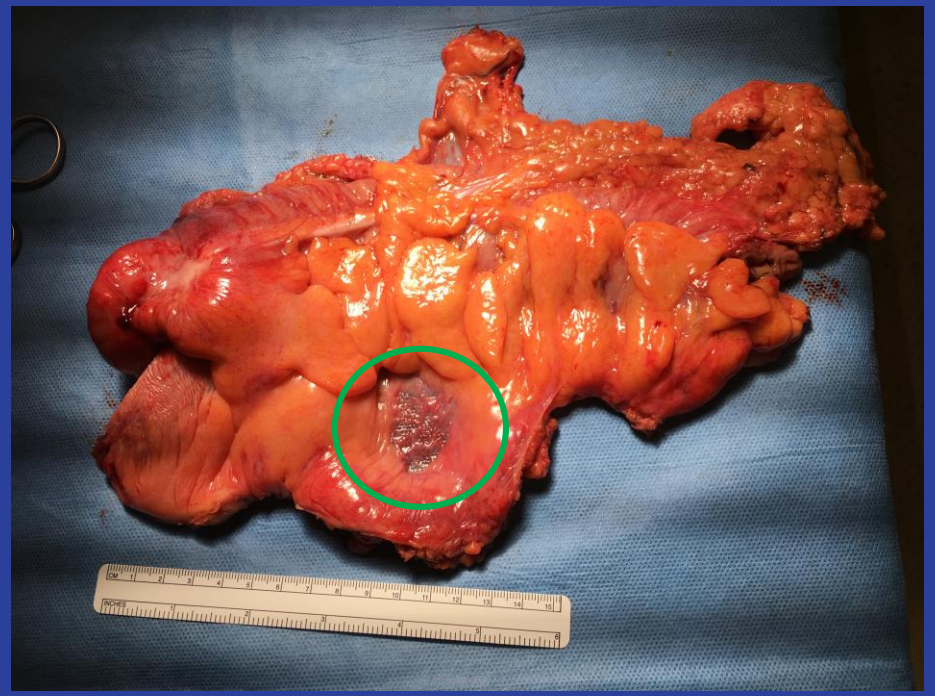
- Central location of positive nodes is a prognostic factor independent of stage III – 60% vs. 85%

  Kanemitsu et al, DCR 2013;56:815-24

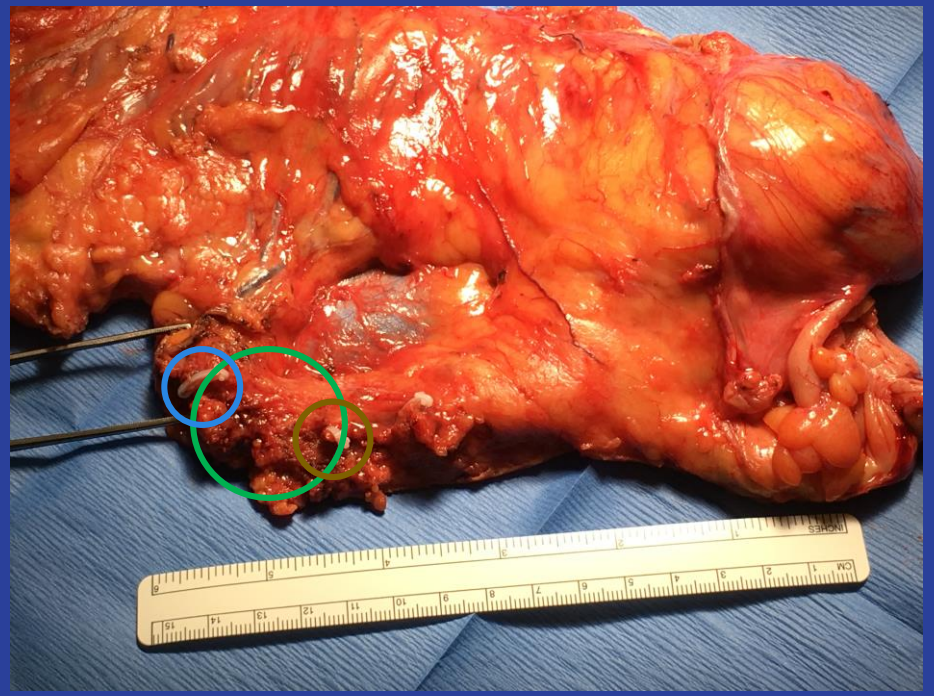
- D3 (compared to D2) dissection associated with improvement in survival (HR 0.827 [95% CI 0.96-0.90]) in patients with involved central lymph nodes

  Kotake et al, Int J Colorectal Dis 2014;29:847-52

CME and CVL Right Colectomy: Pathological Quality Control



Peritoneal window corresponding to the area overlaying the 3rd portion of the duodenum



Ileocolic vessels

Middle colic vessels

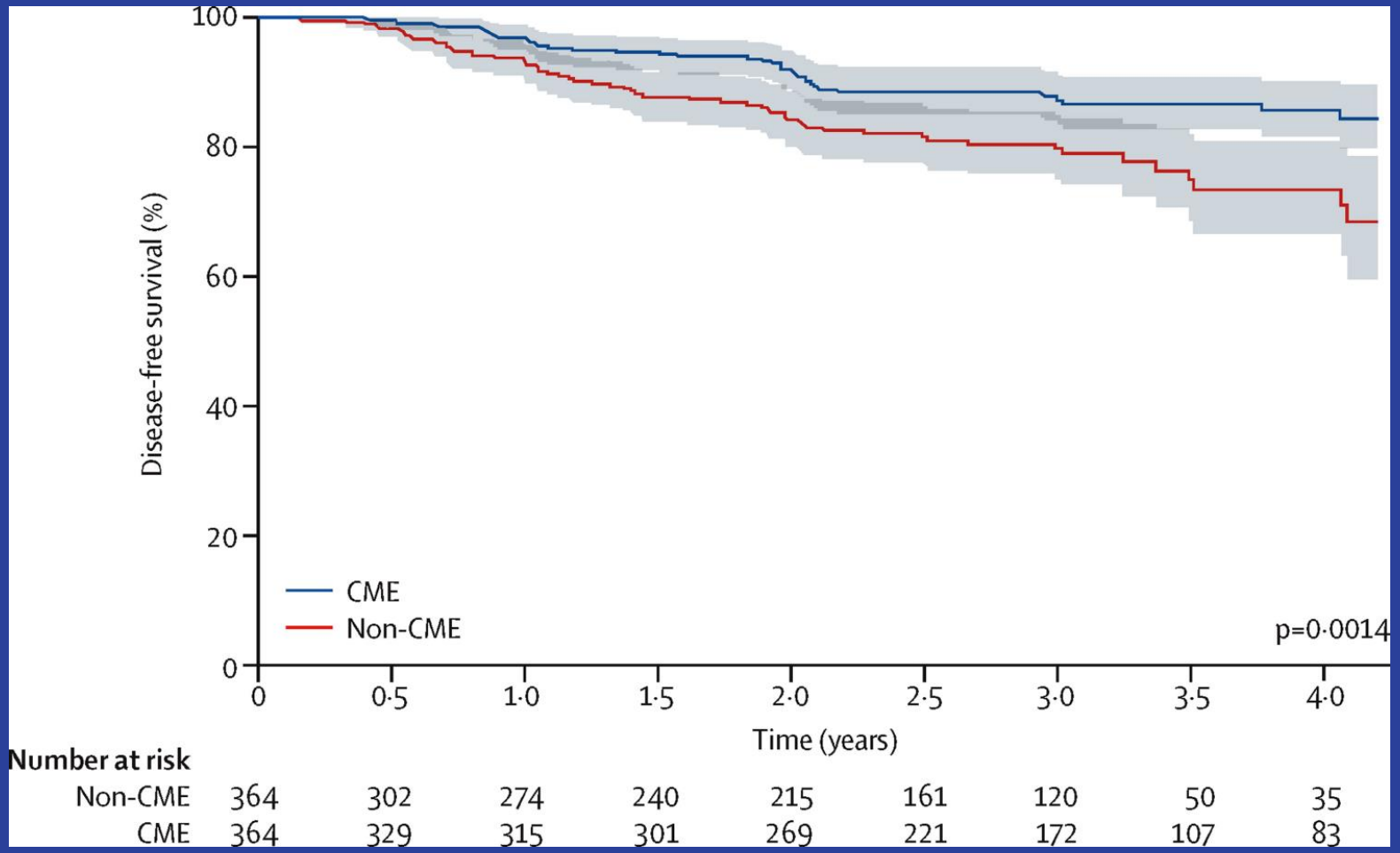
D3 lymph nodes

CME vs. Conventional Surgery
Danish Population Study 2008-2011

- Stage I–III colon cancer surgery in Denmark
  - Danish Colorectal Cancer Group Database for 1.75 million inhabitants of the Capital Region of Denmark
- CME group (Hillerod Hospital)
- Conventional group (Copenhagen University Hospitals)
- Exclusion criteria
  - Stage IV disease, metachronous colorectal cancer, rectal cancer, tumor of the appendix, or R2 resections

Bertelsen et al. Lancet Oncol 2015; 16: 161–68

CME vs. Conventional Surgery Disease-Free Survival



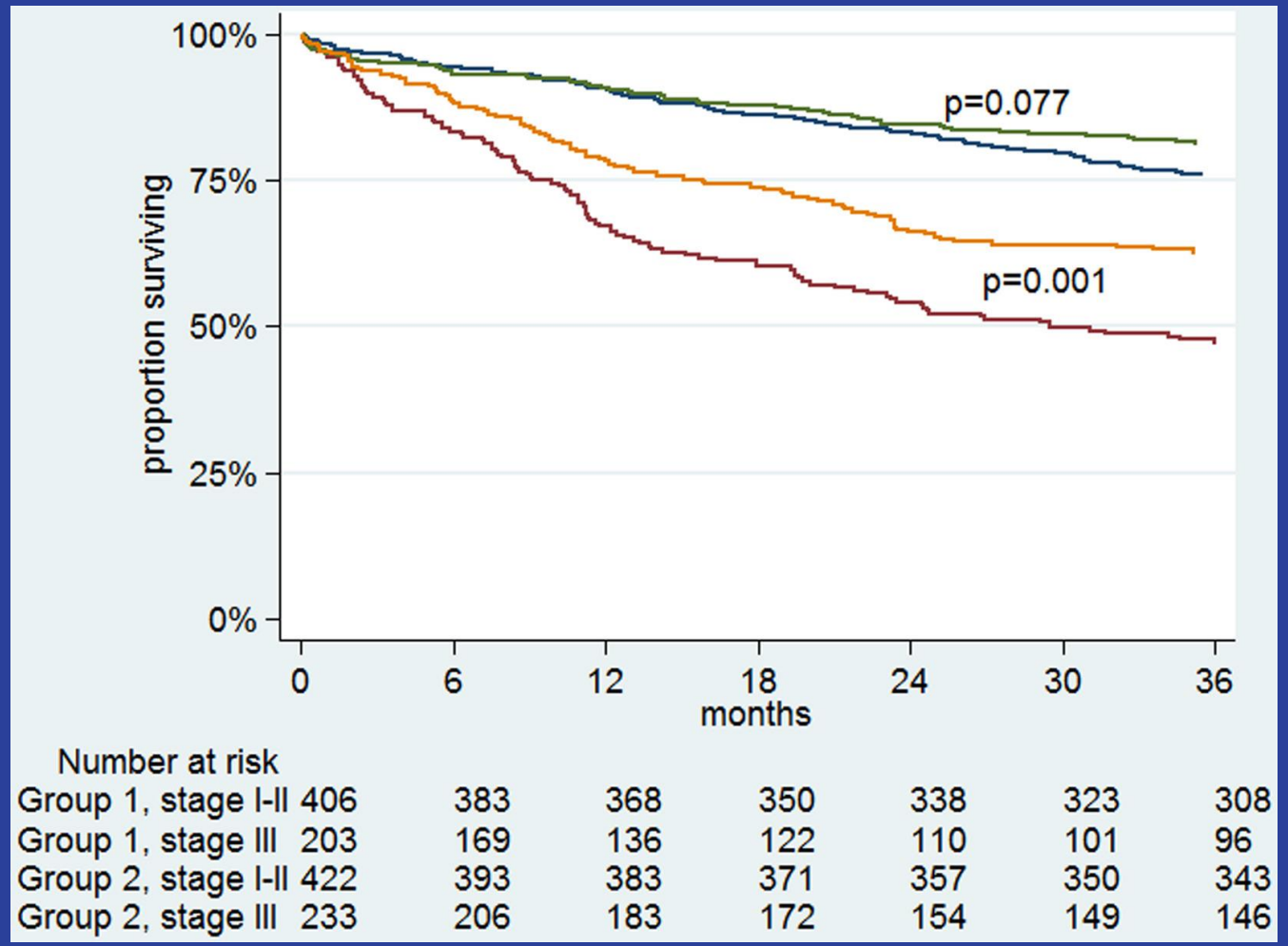
Bertelsen et al, Lancet Oncol 2015

CME vs. Conventional Surgery: Morbidity

	CME (*n* = 529)	'Conventional' resection (*n* = 1701)	*P*
Postoperative complications (total)	**30·6**	**28·5**	**0·351**
Surgical complications	**20·8**	**19·3**	**0·491**
Anastomotic leakage	**8·5**	**7·1**	**0·327**
Respiratory failure	8·1	3·4	< 0·001
Injury to superior mesenteric vein	1·7	0·2	< 0·001

Bertelsen et al, Br J Surg. 2016 Apr;103(5):581-9

Educational Project on Colon Cancer Management in the County of Stockholm – A Population-Based Cohort Study



Stage I-II 2006-8
Stage I-II 2001-3

Stage III 2006-8
Stage III 2001-3

Stockholm Colon Cancer Project

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Bernhoff et al, EJSO 2015; 41,:1479-1484

CME for Right-Sided Colon Cancer Does Not Increase Severe Short-Term Postoperative Adverse Events

	Exposure	Odds ratio	95% CI	*P* value
Postoperative death or reoperation	No CME surgery	1.00 (ref)		
	CME surgery	0.75	0.50–1.13	0.17
Reoperation	No CME surgery	1.00 (ref)		
	CME surgery	0.80	0.51–1.27	0.34
Death	No CME surgery	1.00 (ref)		
	CME surgery	0.58	0.22–1.48	0.25

Bernhoff et al, Colorectal Disease 2017; 20,:383–390

CME for Right-Sided Colon Cancer Does Not Increase Severe Short-Term Postoperative Adverse Events

	Exposure	Odds ratio	95% CI	*P* value
Postoperative death or reoperation	No CME surgery	1.00 (ref)		
	CME surgery in first third of study period	1.48	0.55–3.99	0.43
	CME surgery in second third of study period	0.82	0.46–1.46	0.51
	CME surgery in third third of study period	0.51	0.26–1.01	0.05
Postoperative death or reoperation	No CME surgery	1.00 (ref)		
	CME surgery in hospital with < 100 participants	0.97	0.54–1.72	0.91
	CME surgery in hospital with > 100 participants	0.61	0.35–1.06	

Bernhoff et al, Colorectal Disease 2017; 20,:383–390

Morbidity after CME-CVL

	RELARC *		COLD		Di Buono		Planellas		CoME	
	D3 (495)	D2 (500)	D3 (53)	D2 (39)	CME (67)	No-CME (65)	D3 (46)	D2 (47)	D3 (135)	D2 (116)
Overall postoperative complications	20%	22%	47%	48%	37%	37%	13%	11%	26%	31%
III-V complications	1%	3%	12%	7%	18%	20%	2%	2%	10.4%	14.6%

Xu et al, Lancet Oncol 2021;22:391-401
Karachun et al, Br J Surg 2020;107:499-508
Di Buono et al, Ann Surg 2021;274:57-62
Planellas et al, Ann Surg 2022;275:271-280
Degiuli et al, Ann Surg Oncol 2024, 31:1671-1680

Vascular Injuries

- Laceration or break of blood vessel supplying the right colon
- Vascular injuries more common in the D3 group (3% vs 1%; p=0.045)
- Blood loss was similar in both groups
- Conversion rate was similar in both groups (3% vs 1%, p=017)
- Only one conversion in each group was attributed to vascular injury

Xu et al, Lancet Oncol 2021;22:391-401

Oncologic Outcomes: Prospective Data

Original Reports | Gastrointestinal Cancer

Check for updates

Extent of Lymphadenectomy for Surgical Management of Right-Sided Colon Cancer: The Randomized Phase III RELARC Trial

Junyang Lu, MD[1]; Jiadi Xing, MD[2]; Lu Zang, MD[3]; Chenghai Zhang, MD[2]; Lai Xu, MD[1]; Guannan Zhang, MD[1]; Zirui He, MD[3]; Yueming Sun, MD[4]; Yifei Feng, MD[4]; Xiaohui Du, MD[5]; Shidong Hu, MD[5]; Pan Chi, MD[6]; Ying Huang, MD[6]; Ziqiang Wang, MD[7,8]; Ming Zhong, MD[9]; Aiwen Wu, MD[10]; Anlong Zhu, MD[11]; Fei Li, MD[12]; Jianmin Xu, MD[13]; Liang Kang, MD[14]; Jian Suo, MD[15]; Haijun Deng, MD[16]; Yingjiang Ye, MD[17]; Kefeng Ding, MD[18]; Tao Xu, MD[19]; Yuelun Zhang, PhD[20]; Zhongtao Zhang, MD[21]; Minhua Zheng, MD[3]; Xiangqian Su, MD[22]; and Yi Xiao, MD[1]; on behalf of the RELARC study group

DOI https://doi.org/10.1200/JCO.24.00393

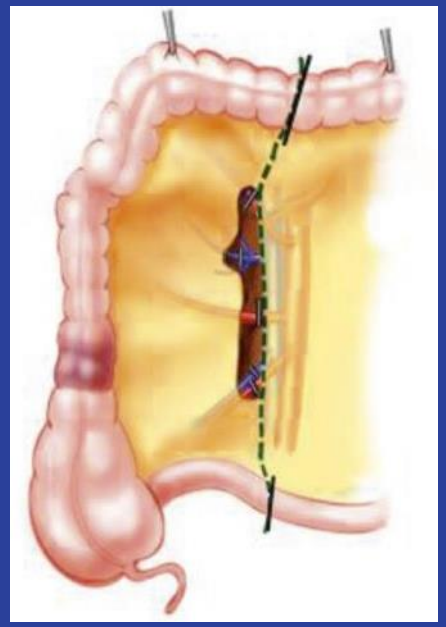
Lu et al, JCO.24.00393

RELARC Trial: Patients

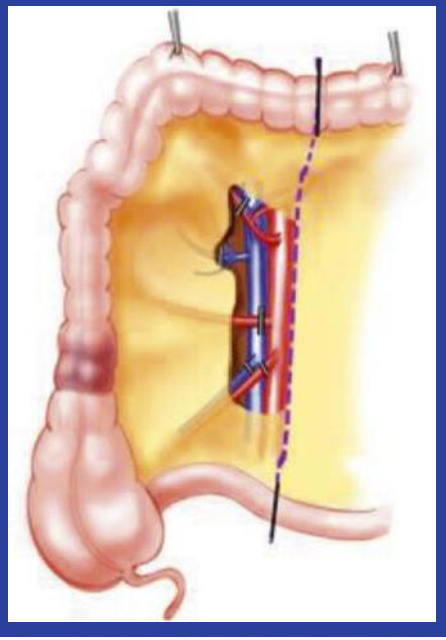
- Inclusion:
  - Colon cancer from cecum to the proximal 1/3 of transverse
  - T2—T4a N any or T any N+ by CT or surgical exploration
  - 18 to 75 years of age
- Exclusion
  - Enlarged D3 lymph nodes
  - Distant metastasis

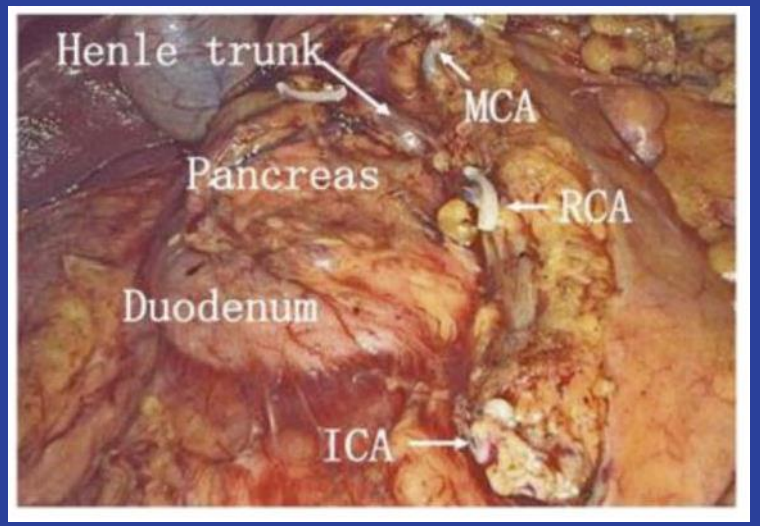
Lu et al, JCO.24.00393

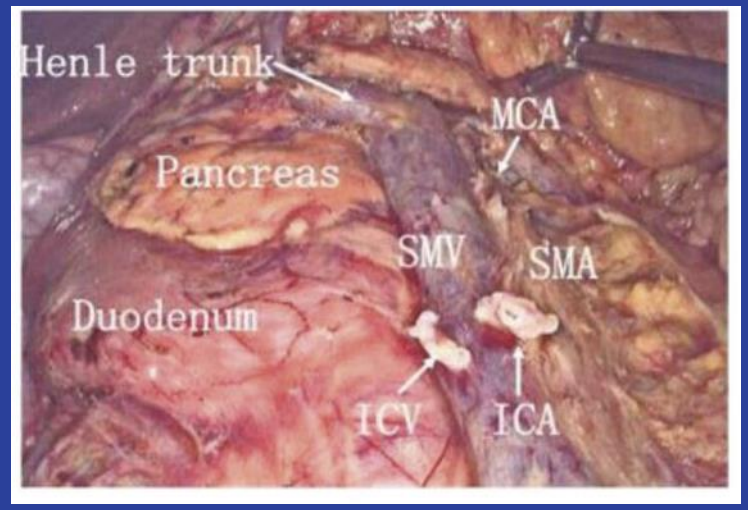
RELARC Trial: Interventions



CME D2 vs. CME D3







Lu et al, JCO.24.00393

Statistical consideration

- Superiority trial
- DFS primary endpoint
- Sample size calculation based on previous studies
- Accrual January 1, 2016 to December 26, 2019
- 17 hospital
- Skilled surgeons: required to have performed over 100 colon cancer operations a year for 2 consecutive years and to be proficient with laparoscopic CME
- Quality of surgery evaluated by photography

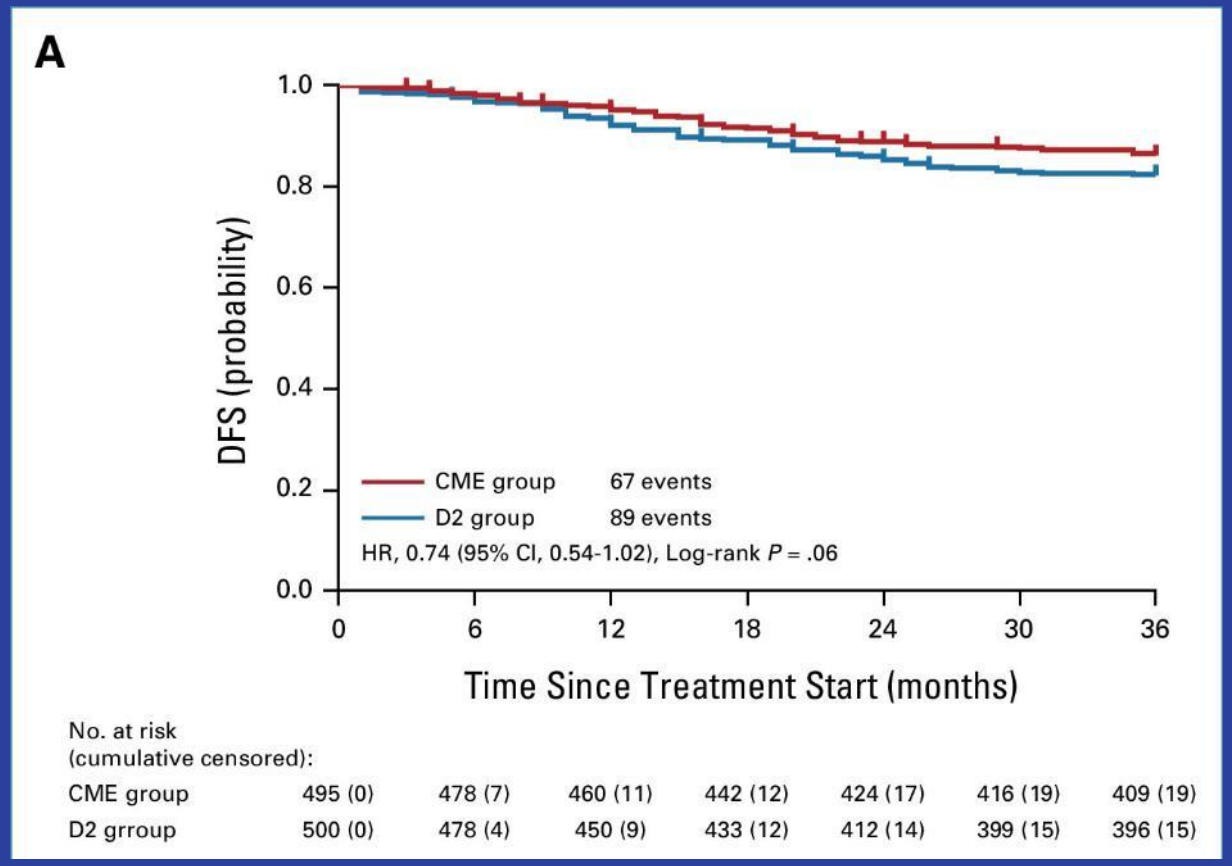
Lu et al, JCO.24.00393

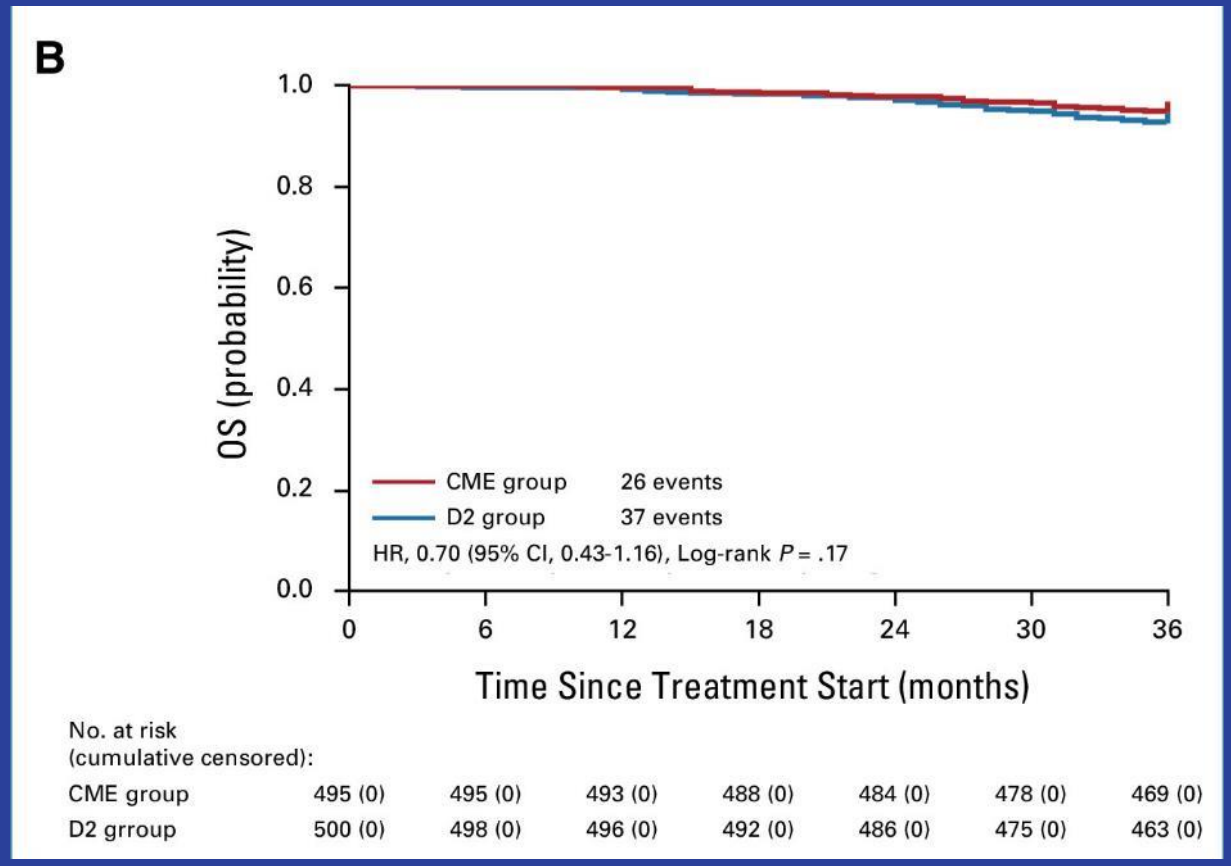
Results:

- ✓ 1072 patients accrued; 77 excluded (25 enlarged central nodes)
- ✓ 995 included in the primary analysis
- ✓ Pathology Stage:
  - I 10%
  - II 54%
  - III 36%
- ✓ Central lymph nodes involved (CME only) 13 (3%)
- ✓ dMMR 19%

Lu et al, JCO.24.00393

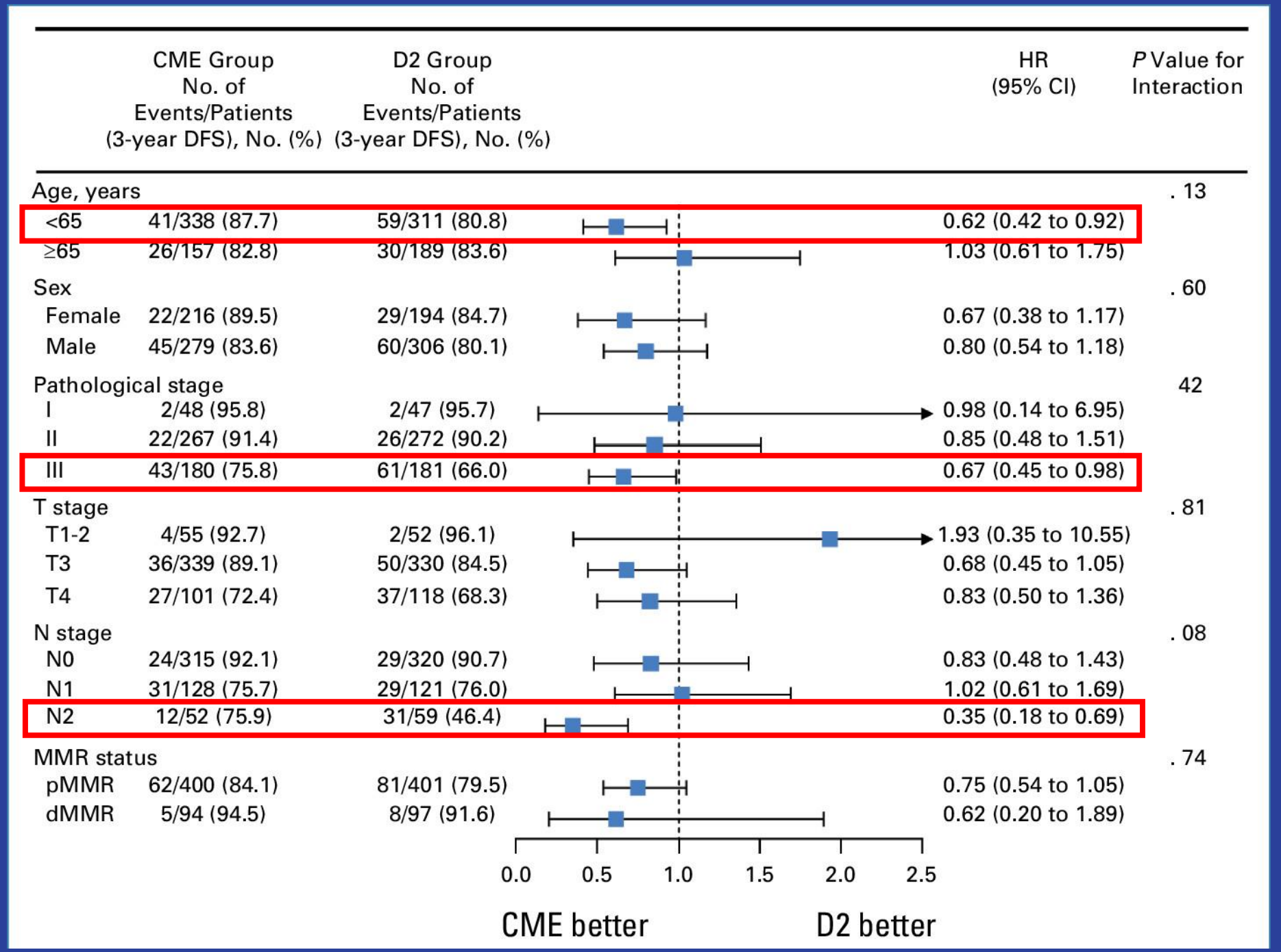
Results:





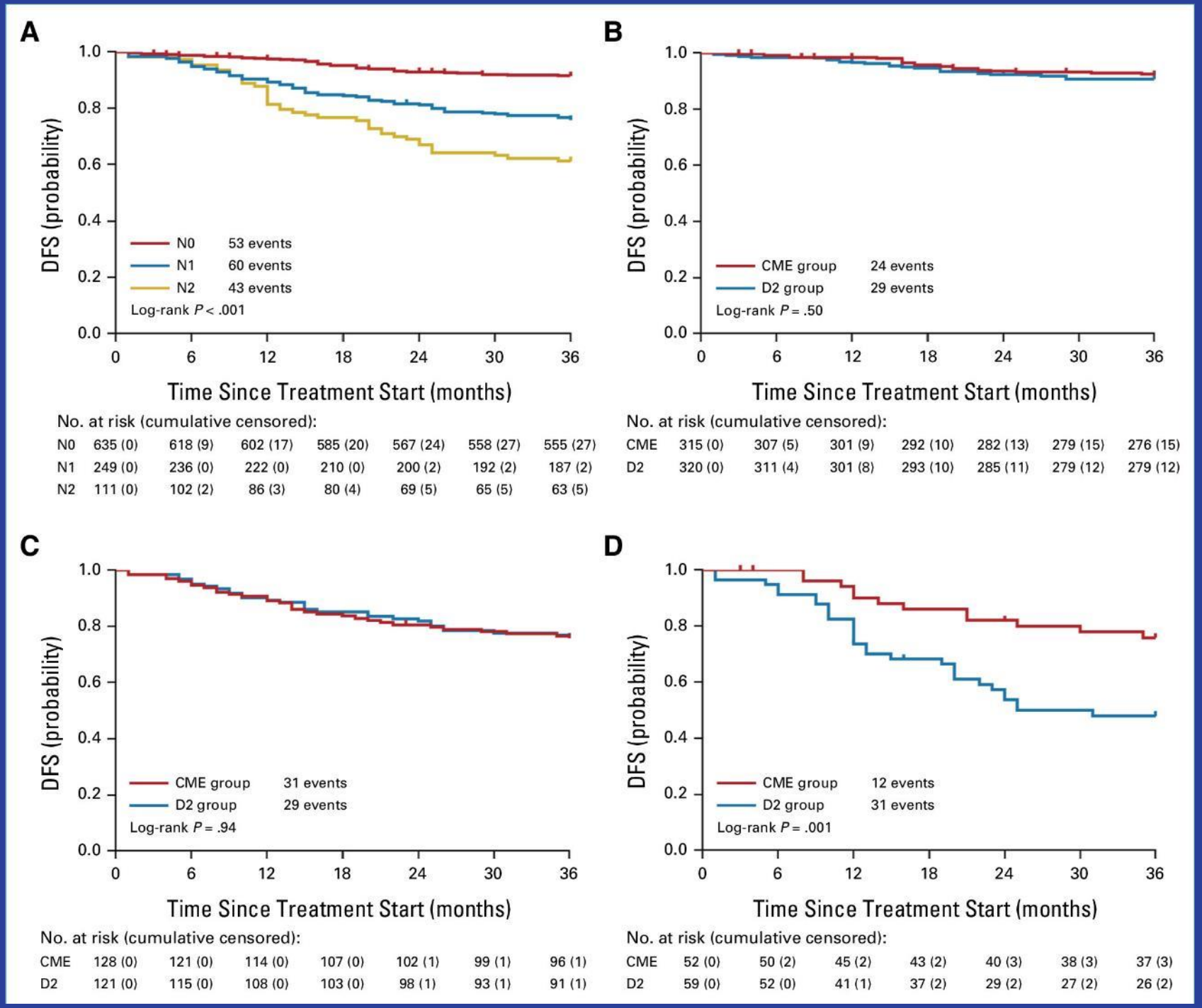
Lu et al, JCO.24.00393

Subgroup Analysis



Lu et al, JCO.24.00393

DFS by nodal classification



Lu et al, JCO.24.00393

Summary of the RELARC trial

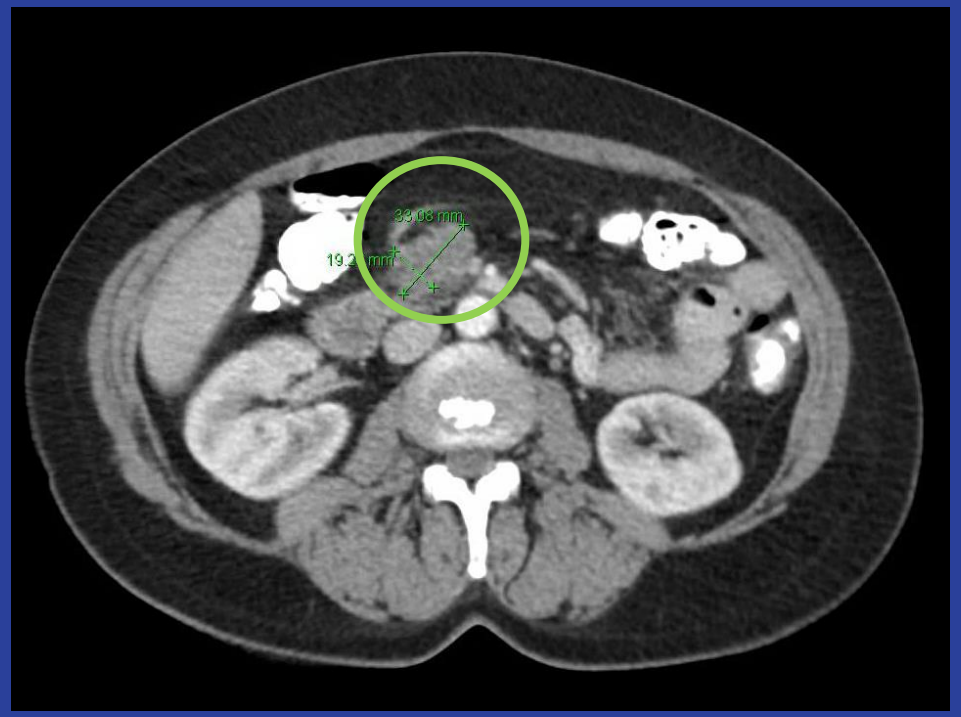
- Expert surgeons
- Comparing best D2 with D3 dissection in patients without enlarged central lymph nodes
- Mostly node negative patients; 19% dMMR
- A tend toward better survival in D3 group without increase in morbidity (study underpowered?)
- D3 superior to D2 in stage III disease (particularly N2 tumors)

A recent case

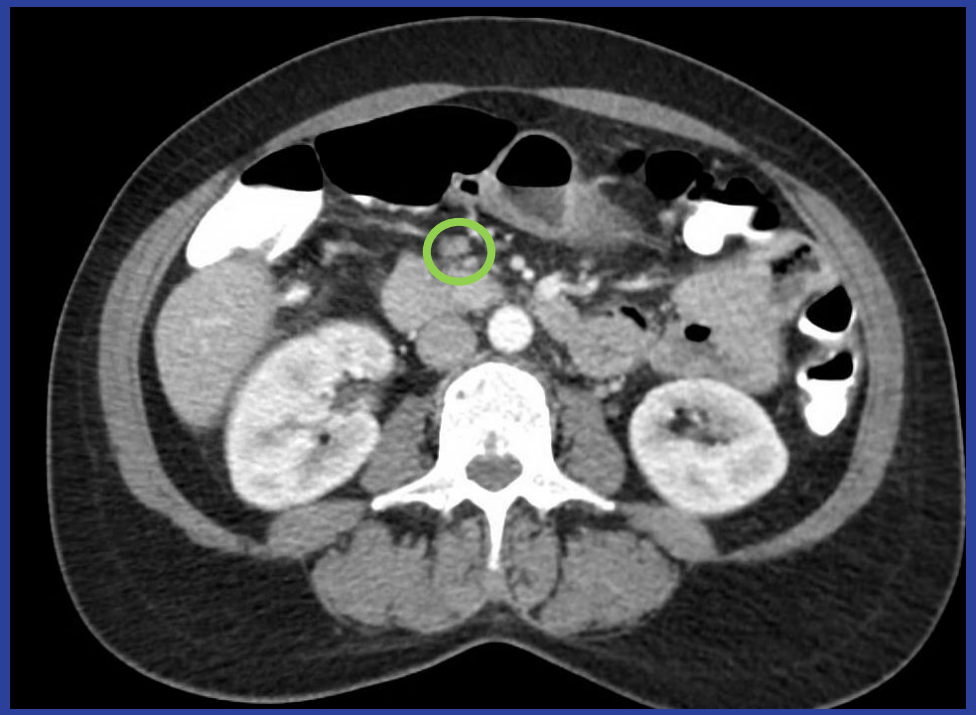
- 39 y/o female
- Ascending colon cancer diagnosed 10/2021
- CT: circumferential mass in the ascending colon, no distant mets
- Laparoscopic right hemicolectomy
- Stage IIIB
- FOLFOX between 11/2021 and 5/2023
- Since end of 2022 raising CEA, +ctDNA
- Early 2023 new mesenteric lesion in CT and PET

This is not biology; this is inadequate surgery

2 years after R Colectomy
(2023)



Baseline 2021



Salvage mesenteric lymphadenectomy

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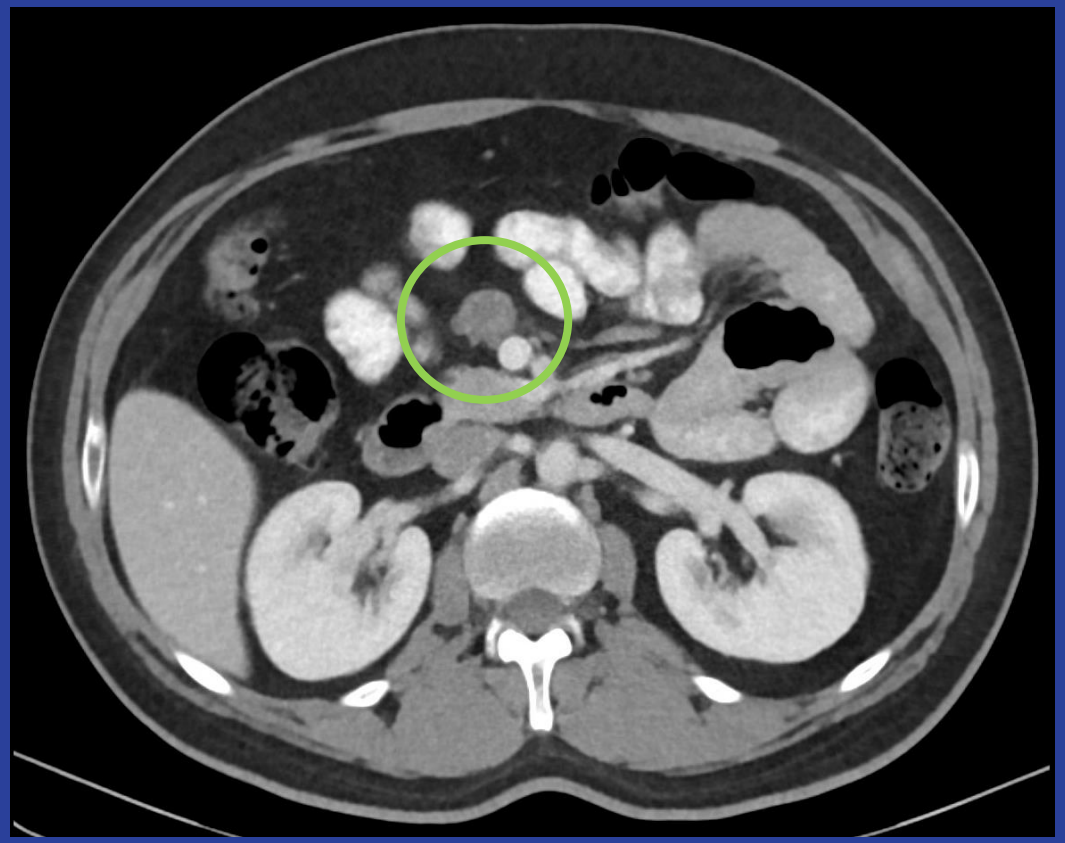
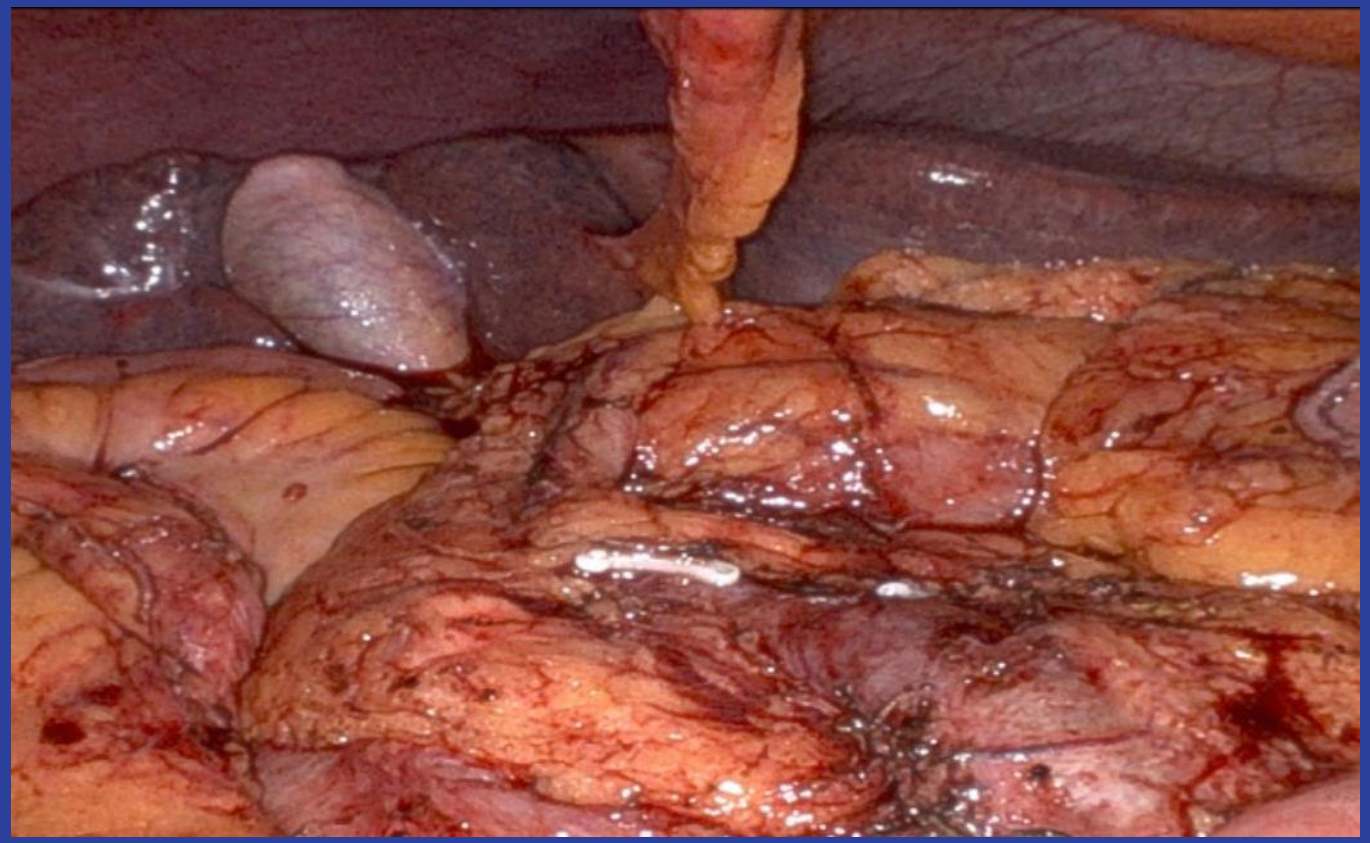
A case with enlarged central nodes even after neoadjuvant chemotherapy





Problems with the “selective approach” to CME-CVL

- Imaging not accurate enough for the locoregional staging of colon cancer
- Surgeons will have difficulty achieving competency with a procedure performed infrequently

Diagnostic Accuracy of CT for Local Staging of Colon Cancer: A Systematic Review

Parameter	Sensitivity % (95% CI)	Specificity % (95% CI)
T1-2 vs. T3-T4	90 % (83-95%	69% (63-75%)
T1-T3ab vs T3cd-T4	77% (66-85%)	70 (53-83%
N0 vs N+	71% (59-81%)	67% (46-83%)

Results affected by

- Slice thickness - <5 mm slices
- CT techniques – MDCT

Nerad et al, AJR, 2016;207:984-995

Summary:

- CME and CVL is an embryological-based anatomical procedure
- Routine CVL (D3 dissection) may not provide an oncologic advantage all colon cancer patients
- It may be helpful in patients with advanced disease
- No higher morbidity if standardized after proper training

Many Thanks