Adjuvant Chemotherapy for Stage II colon Cancer: for which patients?

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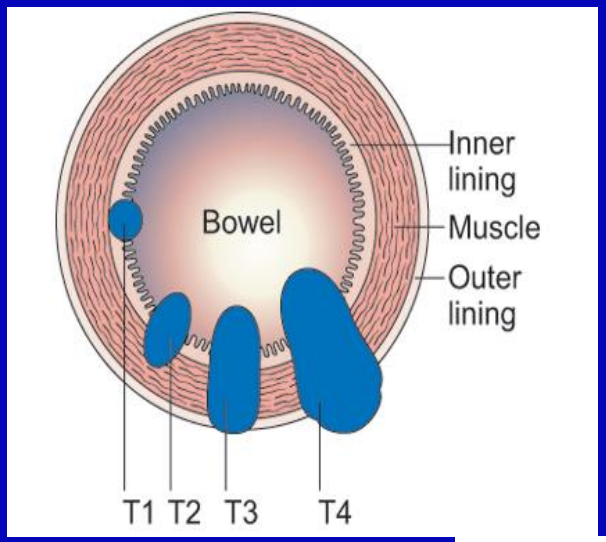
Adjuvant Chemotherapy of colon cancers

- Adjuvant chemotherapy is a concept with proven efficacy in several human solid tumors including colon cancer.
- Most of the data were generated in the past 20 years
- Adjuvant chemotherapy benefits to a very limited number of patients, most of them are cured after surgery and numerous patients are over-treated.
- The Risk/benefit ratio has to be considered .
- This is particularly tru in stage II colon cancer

Recommended references:
Early colon cancer ESMO Guidelines Annals of Oncology 24 Suppl 6 2013
ESMO Consensus Guidelines for CRC Annals of Oncology 23; 2479 2012

Adjuvant Chemotherapy for Stage II colon Cancer: for which patients?

- What defines a stage II colon cancer?
- Risk factors and outcome of stage II colon cancer
- Adjuvant chemotherapy results from trials
- Could biomarkers help?
- Proposed algorithm



TNM staging system AJCC/UICC 7th edition 2010 Stage II Colon Cancer

T

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*: intraepithelial or invasion of lamina propria[a]
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through the muscularis propria into the pericolorectal tissues
T4a	Tumour penetrates into the surface of the visceral peritoneum[b]
T4b	Tumour directly invades or is adherent to other organs or structures[b,c]

TNM staging system AJCC/UICC 7th edition 2010
Stage II Colon Cancer: N stage

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in two to three regional lymph nodes
N1c	Tumour satellite deposits in subsierose or in non peritonealised tissues
N2	Metastases in ≥4 regional lymph nodes (a: 4–6, b: ≥7)
Distant metastases (M)	
M0	No distant metastases
M1	Distant metastases
M1a	Metastases confined to one organ or site (for example liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

TNM staging system
AJCC/UICC 7th edition 2010
Stage II Colon Cancer

T3	Tumour invades through the muscularis propria into the pericolorectal tissues
T4a	Tumour penetrates into the surface of the visceral peritoneum[b]
T4b	Tumour directly invades or is adherent to other organs or structures[b,c]

IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0

N0: 0 node involved out of at least 12 lymph nodes

Stage II colon cancer

- The quality of the pathology report is ESSENTIAL
  - T size 3 or 4
  - T4a or T4b
  - Number of lymph nodes retrieved and examined

- Additional features to be described:
  - Perineural invasion
  - Lympho-Vascular invasion
  - Lymphocytic reaction?
  - Stroma reaction?

High risk group according to ASCO NCCN and ESMO

Definitions of "high risk" stage II colon cancer from expert groups*

	ASCO (2004)	NCCN (2013)	ESMO (2012)
T4 primary tumor	+	+	+
Inadequately sampled nodes	+ (<13)	+ (<12)	+ (<12)
Poorly differentiated tumor	+	+	+
Perforation	+	+ (localized)	+
Obstruction		+	+
LVI		+	+
PNI		+	+
Close/indeterminate or positive margins		+	

LVI: lymphovascular invasion; PNI: perineural invasion.
* Ie, the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the European Society for Medical Oncology (ESMO).

Adjuvant Chemotherapy for Stage II colon Cancer: for which patients?

Risk factors and outcome of stage II colon cancer

Stage II: bad factors

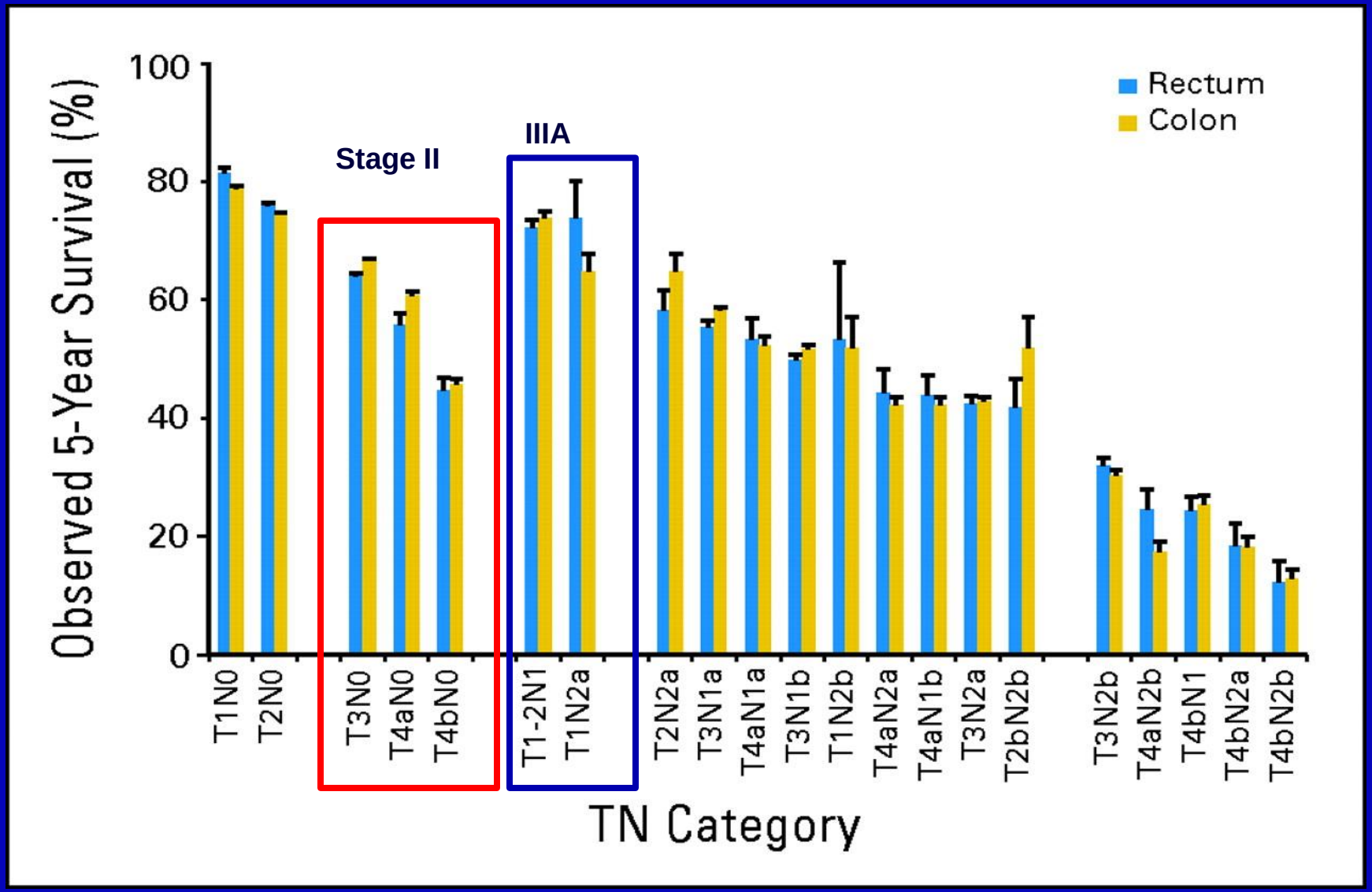
- **Clinical factors:**
  - Obstruction (subjective)
  - Perforation

- **Histological factors**: (sometime subjective)
  - Differentiation
  - Lymphovascular invasion
  - Neuro invasion

  - Depth of invasion
    - pT4a: serosal invasion
      - May be missed
      - May be difficult to recognize (mesothelial hyperplasia, inflammation)
    - pT4b: invasion of adjacent organs
      - May be difficult to differenciate from inflammatory adhesion

Most of the studies published refer to previous TNM Classifications and not to TNM 7 (AJCC 2010)

SEER data base 48 500 stage II colon cancer
Observed 5-year survival by TN category. (TNM VI)



Gunderson L L et al. JCO 2010;28:264-271

SEER data base 48 500 stage II colon cancer Observed 5-year survival by T category.(TNM VI)

Revised TN Classification for Colon Cancer Based On National Survival Outcomes Data

NT Category	Number of Patients	5-Yr Overall Survival
N0	74,690	
Tis	2,383	95.6%
T1-2	23,861	97.1%
T1	10,930	97.4%
T2	13,931	96.8%
T3	40,338	87.5%
T4	8,108	71.5%
T4a	5,020	79.6%
T4b	3,088	58.4%

Gunderson LL, Jessup JM, Sargent DJ, Greene FL, Stewart AK, *J Clin Oncol*, 28 264-71, 2009

A dapted from Goldberg R ASCO GI 2014

VOLUME 29 · NUMBER 23 · AUGUST 10 2011

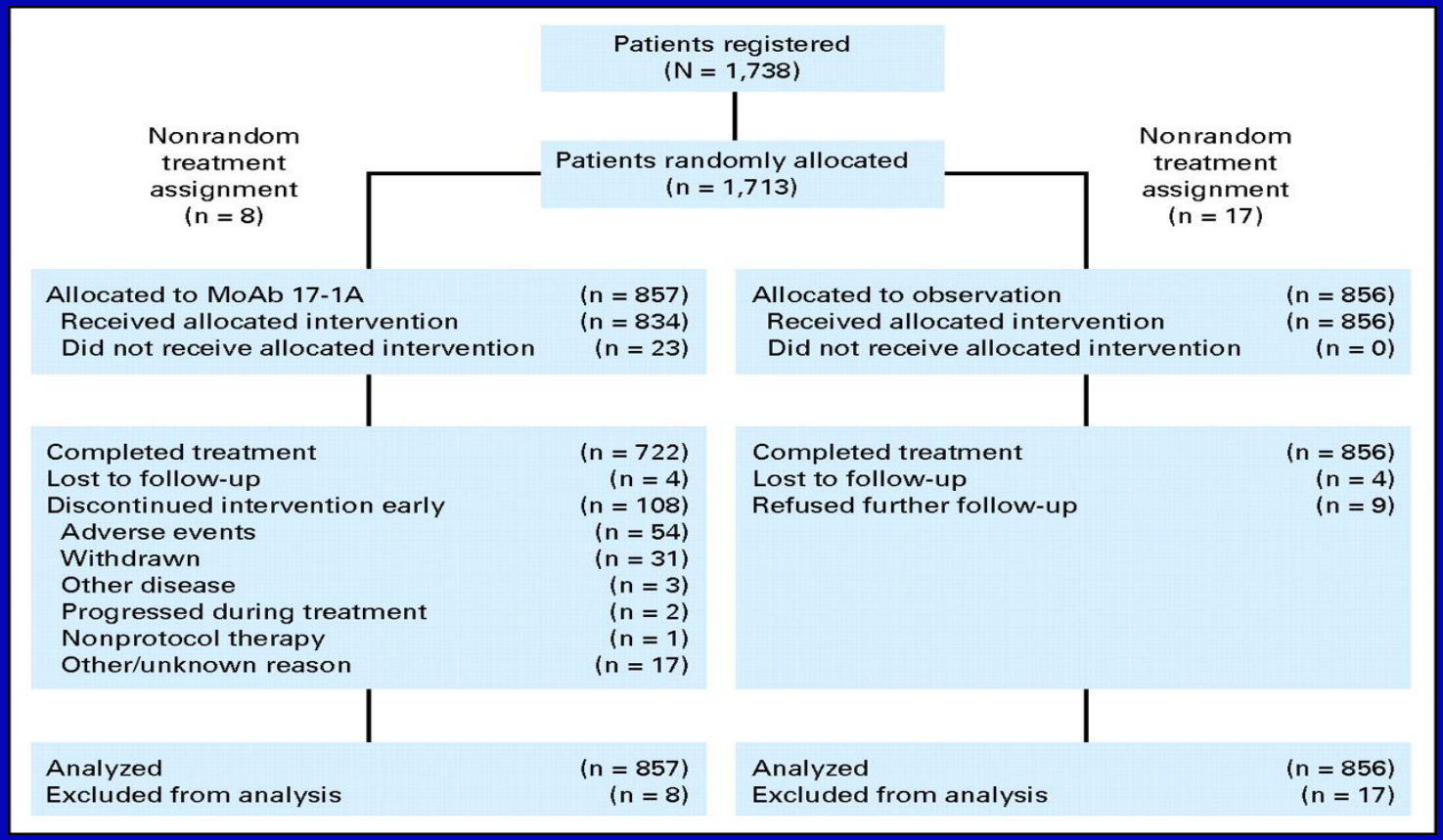
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

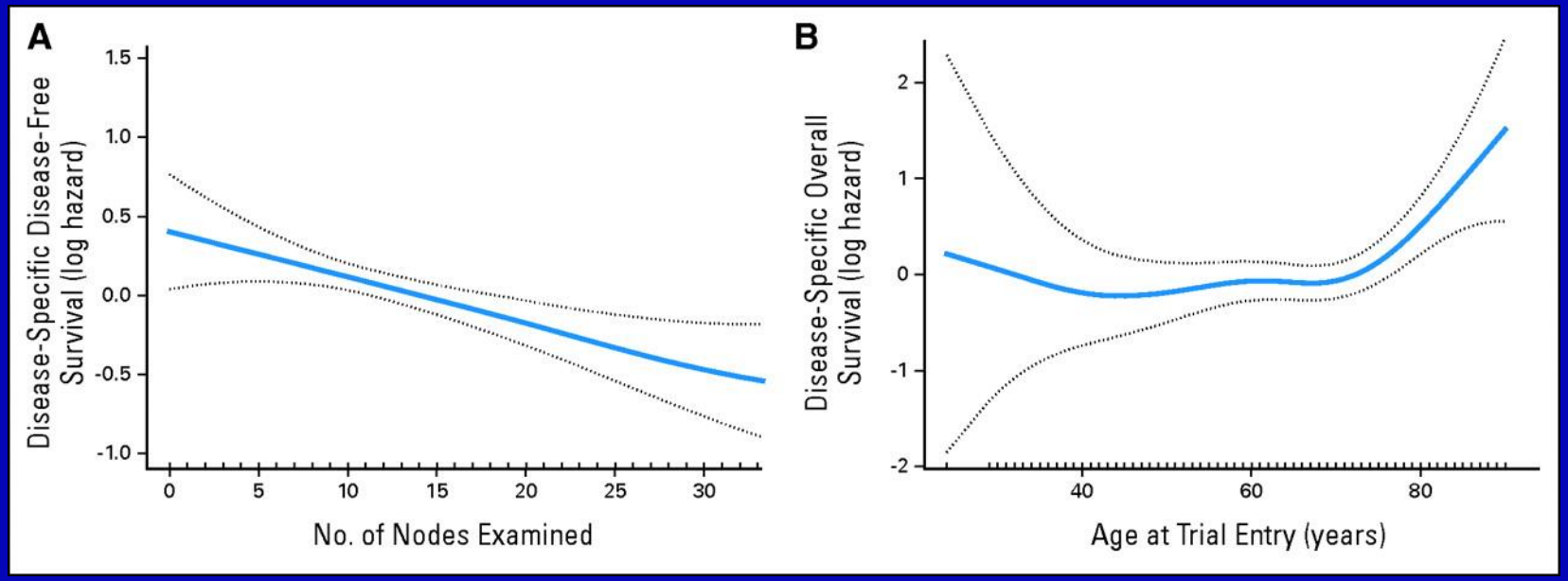
Documenting the Natural History of Patients With Resected Stage II Adenocarcinoma of the Colon After Random Assignment to Adjuvant Treatment With Edrecolomab or Observation: Results From CALGB 9581

Donna Niedzwiecki, Monica M. Bertagnolli, Robert S. Warren, Carolyn C. Compton, Nancy E. Kemeny, Al Bowen Benson III, S. Gail Eckhardt, Steven Alberts, Gity N. Porjosh, David J. Kerr, Anthony Fields, Philippe Rougier, J. Marc Pipas, Joel H. Schwartz, James Atkins, Mark O'Rourke, Michael C. Perry, Richard M. Goldberg, Robert J. Mayer, and Thomas A. Colacchio

From the Cancer and Leukemia Group B Statistical Center; Duke University Medical Center, Durham; Southeast Cancer Control Consortium, Goldsboro; University of North Carolina, Chapel Hill, NC; Brigham and Women's Hospital; Eastern Cooperative Oncology Group; Dana-Farber Cancer Insti-



Smoothing splines of (A) the log hazard for disease-specific disease-free survival by number of nodes examined truncated at 32 nodes, representing 95% of the data, and (B) the log hazard for disease-specific overall survival by age at trial entry



Niedzwiecki D et al. JCO 2011;29:3146-3152

Risk factors in CALGB 9581

Variable	Cancer Specific Survival
Race	0.004
Age ≥ 70	0.03
Differenciation	0.004
Lympho-Vascular Invasion	0.013
Perineural Invasion	0.001
Depth of invasion T 3 vs 4	0.001

Stage II colon cancer subgroups

Low risk

- T3
- T4a?
- No obstruction (subjective)
- No perforation
- No lymphovascular invasion
- No perineural invasion
- Well differenciated

High risk

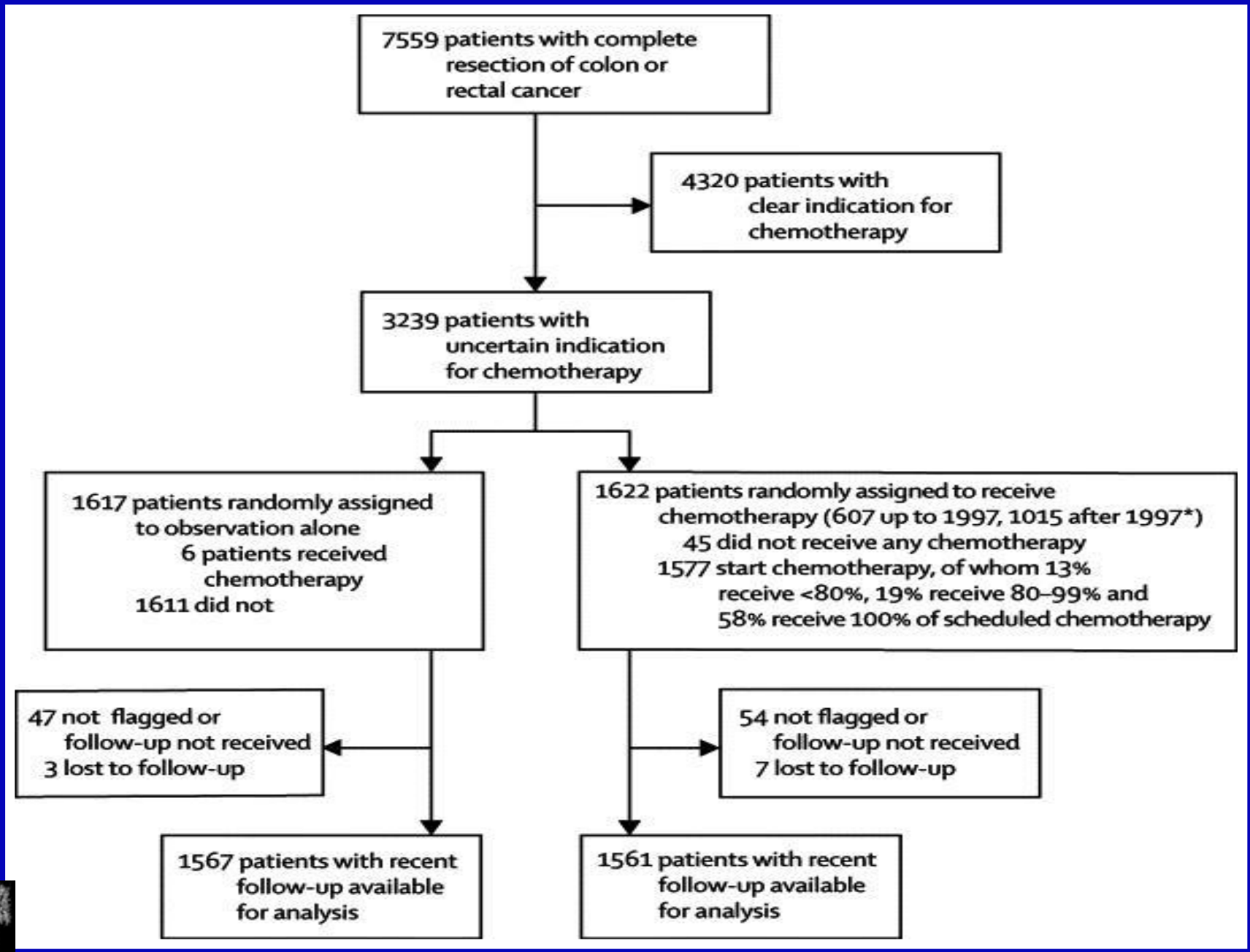
- T4b
- T4a?
- Obstruction (subjective)
- Perforation
- Lymphovascular invasion
- Perineural invasion
- Poorly differenciated

Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study

QUASAR Collaborative Group

The Lancet 2007 370 2020-2029

QUASAR Patient consort diagram

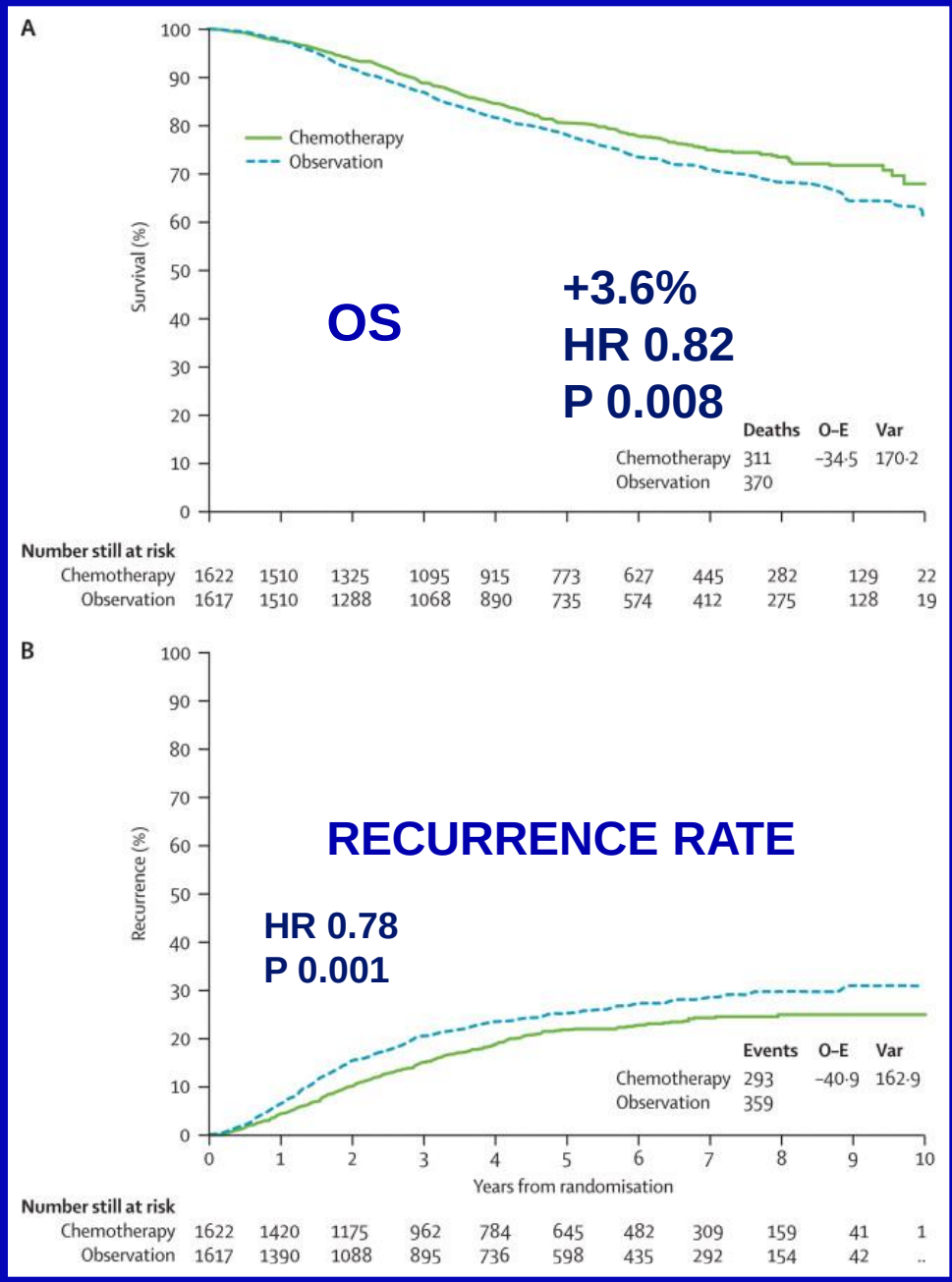


The Lancet 2007 370 2020-2029

QUASAR

	CT* 1622	No CT 1617
Stage % I II III	 0.5 91 8	 0.5 92 8
Site Colon Rectum or Both	 71 29	 71 29
Gender male	62	60
Age <70 >70	80 20	79 21

***All CT was 5FU/LV**
27% with levamisol



The Lancet 2007 370 2020-2029

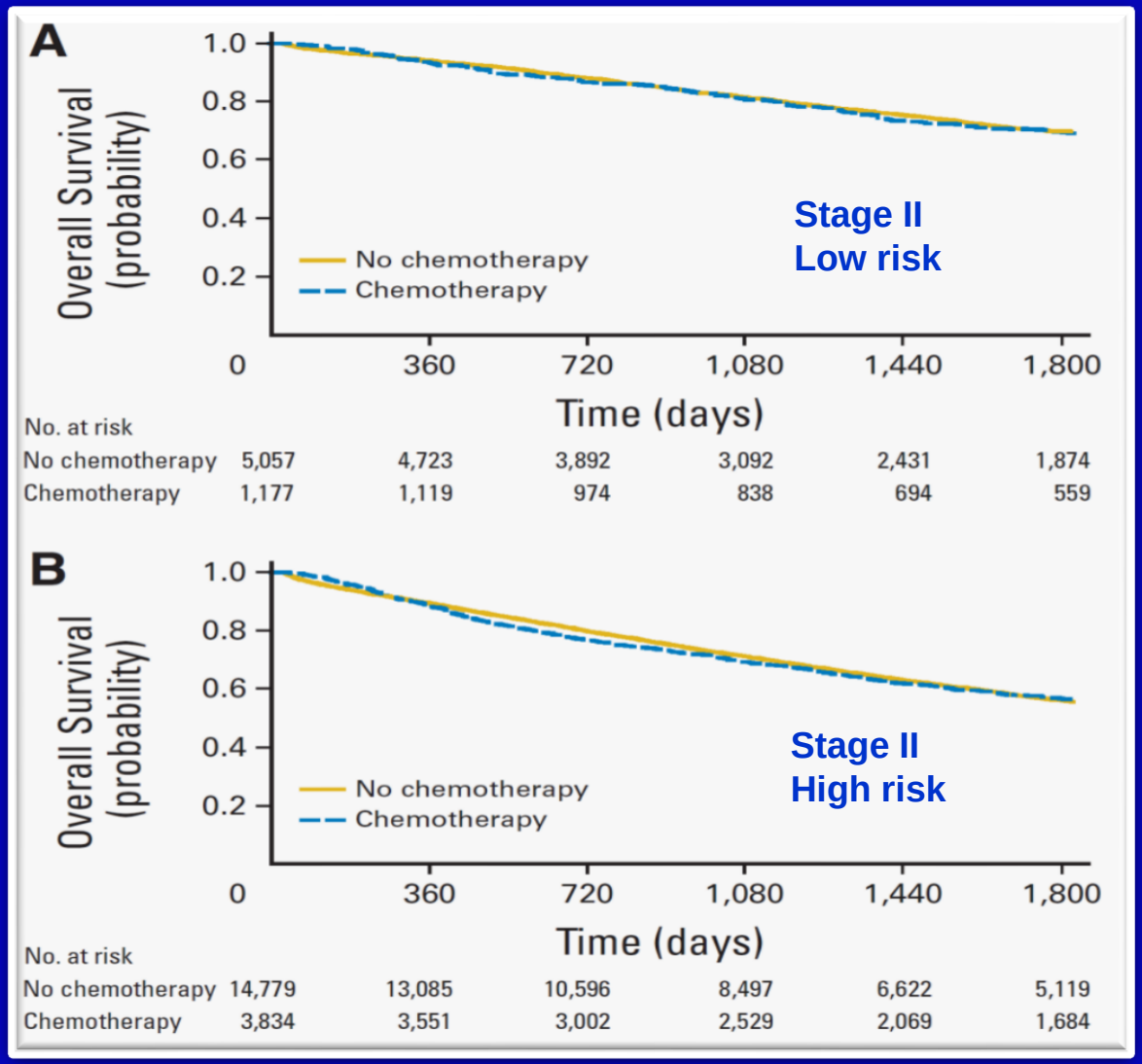
QUASAR CONCLUSION

- Improvement of borderline clinical significance
  - Significant reduction in recurrence rate
    - Mostly early recurrences (2 years)
    - More pronounced in rectum
- In colon cancer stage II:
  - 18% reduction in the risk of death (absolute benefit + 3.6%)
  - No benefit > 70 years of age
- No data on benefit in high-risk patients (T4, vascular invasion, < 8 LN)

QUASAR vs. older trials

- 5FU/Levamisol (MOERTEL 1990)
  - Stage II: 3.5y Recurrence-free survival:
    - 84 vs. 77% (ns)
- IMPACT B2 (1999)
  - Stage II: 5y Relapse-free survival:
    - 76 vs. 73% (ns)
- Meta-analysis (Figueredo JCO 2004)
  - 37 trials, 11 meta-analysis
    - HR for recurrence: 0.87 (ns)

SEER (Medicare) Database
24 847 Patients > 65y Stage II



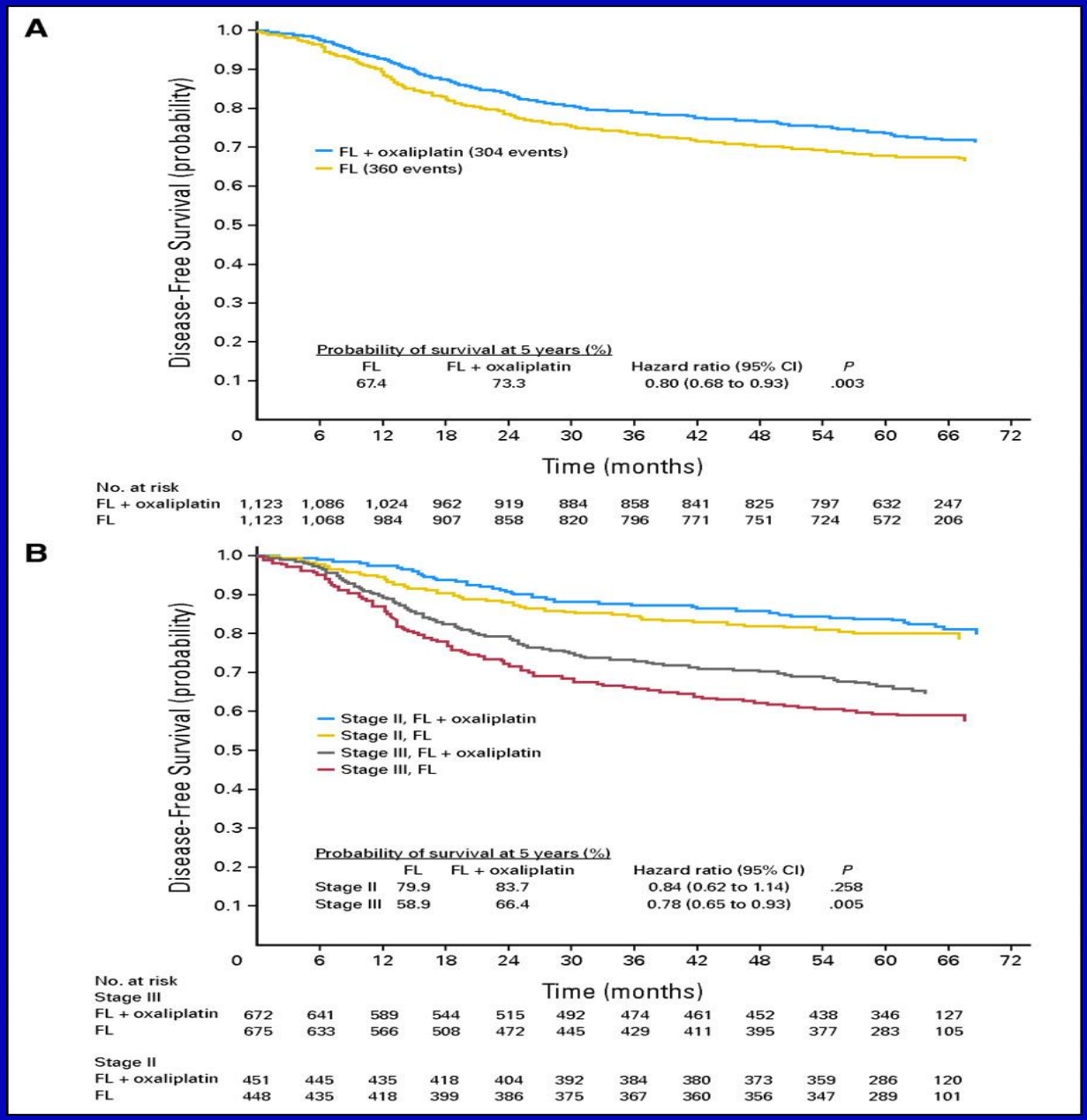
O'Connor E S et al. JCO 2011;29:3381-3388

Adjuvant chemotherapy for stage II

The issue of Oxaliplatin

DFS (A) by treatment arm and (B) by treatment arm and by stage

MOSAÏC



André T et al. JCO 2009;27:3109-3116
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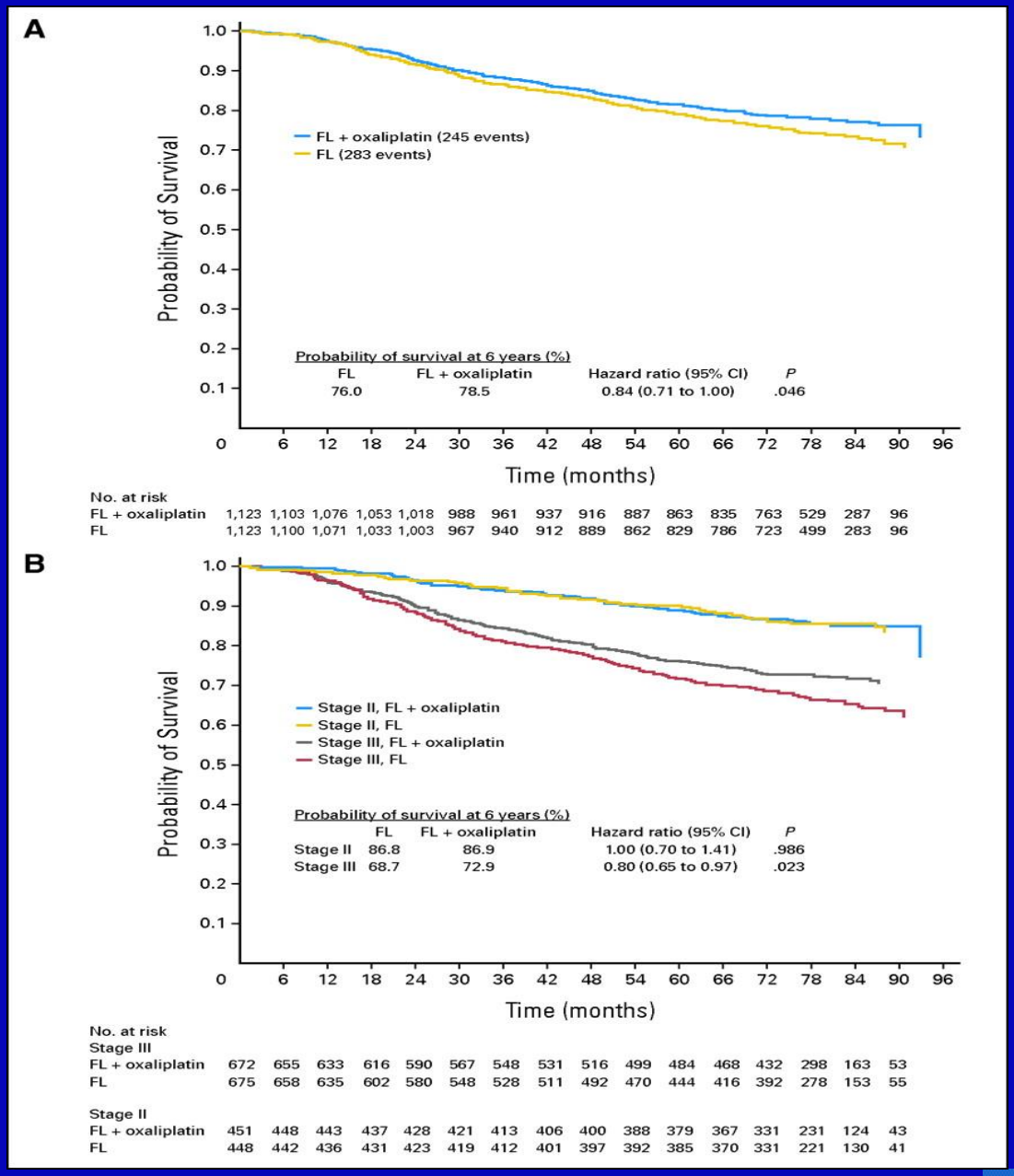
OS (A) by treatment arm and (B) by treatment arm and by stage

MOSAÏC



André T et al. JCO 2009;27:3109-3116

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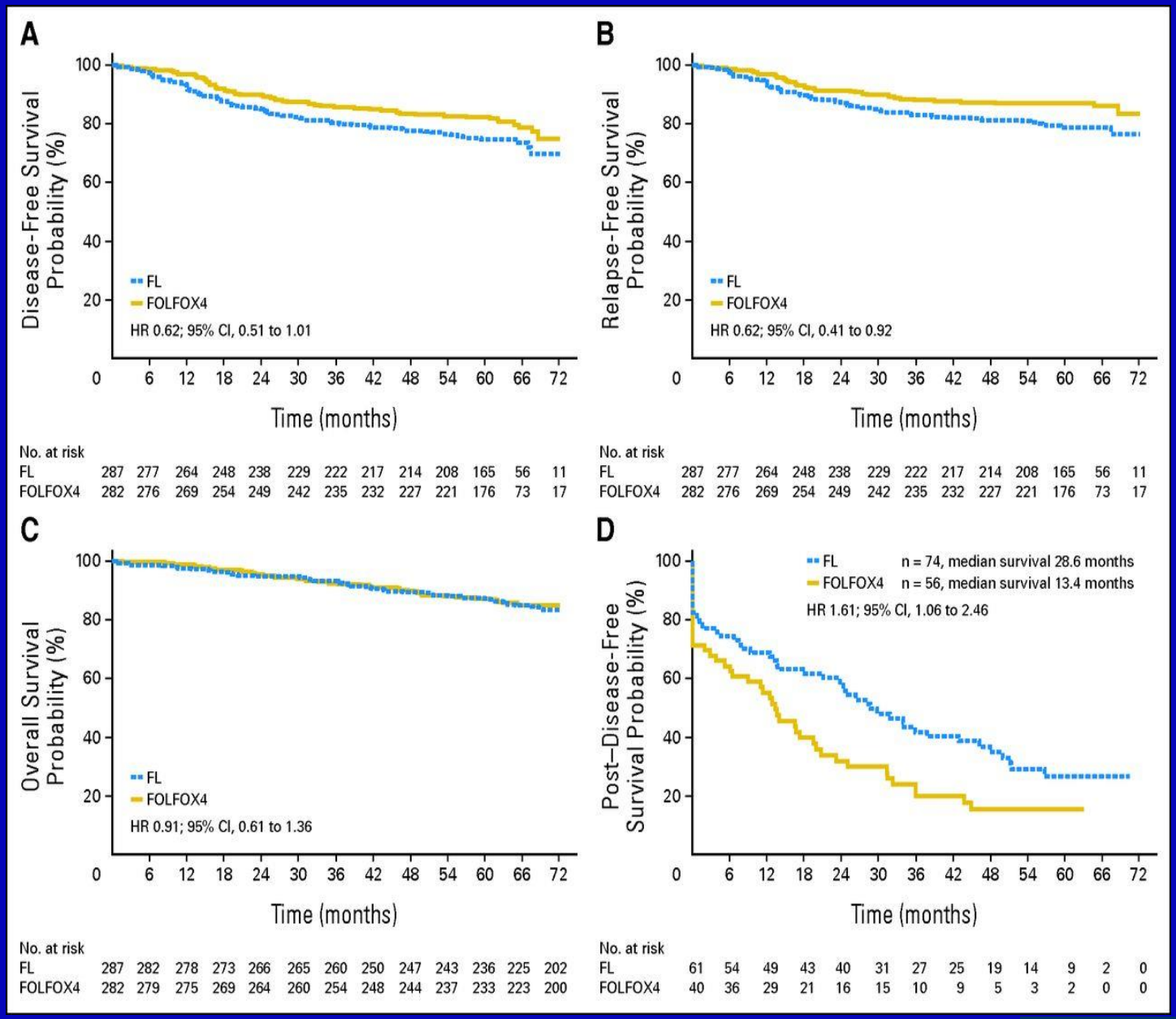
MOSAÏC outcome according to subgroup stage II TNM VII + clinical factors

FOLFOX4 *v* FL by Subgroup	No. of Patients	Five-Year DFS			Five-Year TTR			Six-Year OS		
		HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Stage II	899	0.84	0.62 to 1.14	.258	0.70	0.49 to 0.99	.045	1.00	0.7 to 1.41	.986
High risk	569	0.72	0.51 to 1.01	.062	0.62	0.41 to 0.92	.002	0.91	0.61 to 1.36	.648
Low risk	330	1.36	0.76 to 2.45	.305	1.01	0.5 to 2.05	.972	1.36	0.67 to 2.5	.399

Tournigand C et al. JCO 2012;30:3353-3360

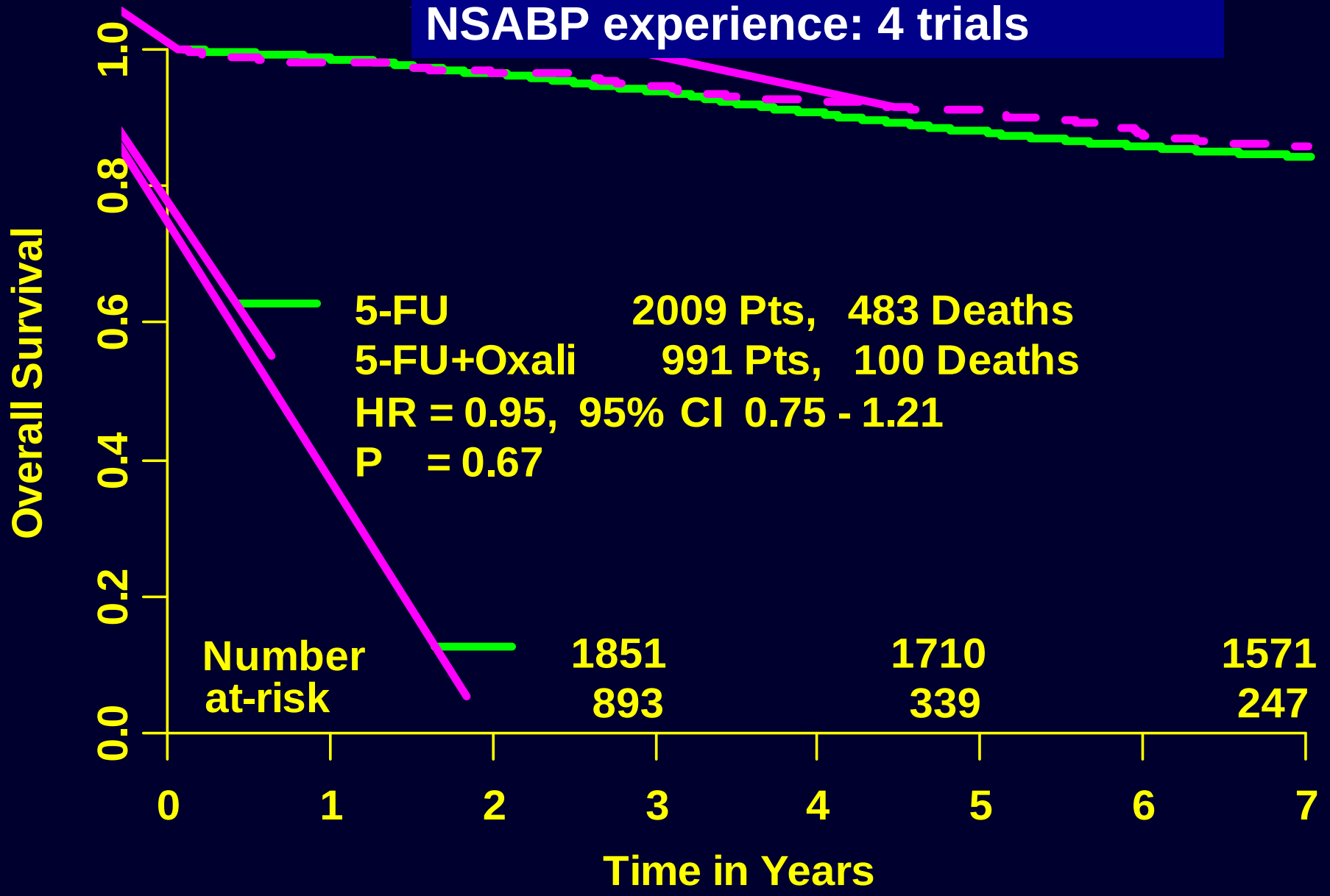
Rates of (A) disease-free, (B) relapse-free, (C) overall, and (D) post–disease-free survival in high-risk stage II colon cancer treated with LV5FU2 or FOLFOX4.



Tournigand C et al. JCO 2012;30:3353-3360

Adjusted* Kaplan Meier Estimate of OS in Stage II

NSABP experience: 4 trials



*Adjusted for age, gender, race, nodes examined, and T-stage

Yothers ASCO 2011

Adjuvant colon cancer: stade II
NSABP C05-06-07-08

- ➔ 3000 patients stage II high (HR) and low risk (LR) treated in NSABP studies
- ➔ 2009 pts treated with 5-FU and 901 with 5-FU+ oxaliplatine

At 5 years	oxaliplatin	No oxaliplatin
DFS HR	81%	76%
DFS LR	83%	80%
OS HR	90%	87%
OS LR	91%	89%

➔ Minimal benefit, Risk/benefit questionable, no consensus…

GA Yothers et al., *ASCO 2011, A#3507*

Adjuvant treatment of colon cancer stage II

The issue of age

Adjuvant chemotherapy of stage II colon cancer issues in the elderly

- Recent analysis showed that elderly (>70 years-old) may not benefit from adjuvant chemotherapy
  - Already seen in the Quasar trial (stage II)
  - Already seen in the Mosaïc trial (stage II and III)
  - Recently reported in NO 16968 (stage III, Xelox vs. 5FU/LV)

Adjuvant chemotherapy in the elderly with colon cancer

- **XELOX versus 5FU/LV (NO16968)**

DFS	3 years		4 years	5 years
XELOX	71,0%	HR 0,80	68,4%	66,1%
5-FUL/LV	67,0%	P=0,004	62,3%	59,8%
Analysis according to age				
<70 ans	HR 0,79 (95% CI 0,66-0,94)			
> 70 ans	HR 0,87 (95% CI 0,63-1,18)			

- **Mosaic**

> 70 y.	FOLFOX	LV5FU2
n=315	155	160
DFS	HR 0,91 (95% IC 0,62-1,34)	
OS	HR 1,10 (95% IC 0,73-1,65)	

➔ **Relapse in FOLFOX in Elderly:**
- **fewer patients resected (p=0,01)**
- **fewer patients treated with combined therapy (p=0,01)**

➔ **More 2nd cancer in FOLFOX**

D.G. Haller *et al.* ASCO 2010. Abstract 3521
C. Tournigand *et al.* ASCO 2010. Abstract 3522

Cross-trial comparison: Age

	NSABP C-07[1]		MOSAIC[2]		NO16968	
	FLOX*		FOLFOX*		XELOX*	
Age, years	<70	≥70	<70	≥70	<70	≥70
DFS						
HR (95% CI)	0.76 (0.66–0.88)	1.03 (0.77–1.36)	na	0.91 (0.62–1.34)	0.80 (0.67–0.94)	0.86 (0.64–1.16)
OS						
HR (95% CI)	0.80 (0.68–0.95)	1.18 (0.86–1.62)	na	1.10 (0.73–1.65)	0.82 (0.67–1.01)	0.91 (0.66–1.26)

*Comparison vs 5-FU/LV

na: not available

1. Yothers et al. JCO 2011;28:3768–74
2. Tournigand et al. JCO 2010;28:15s (abstr 3522)

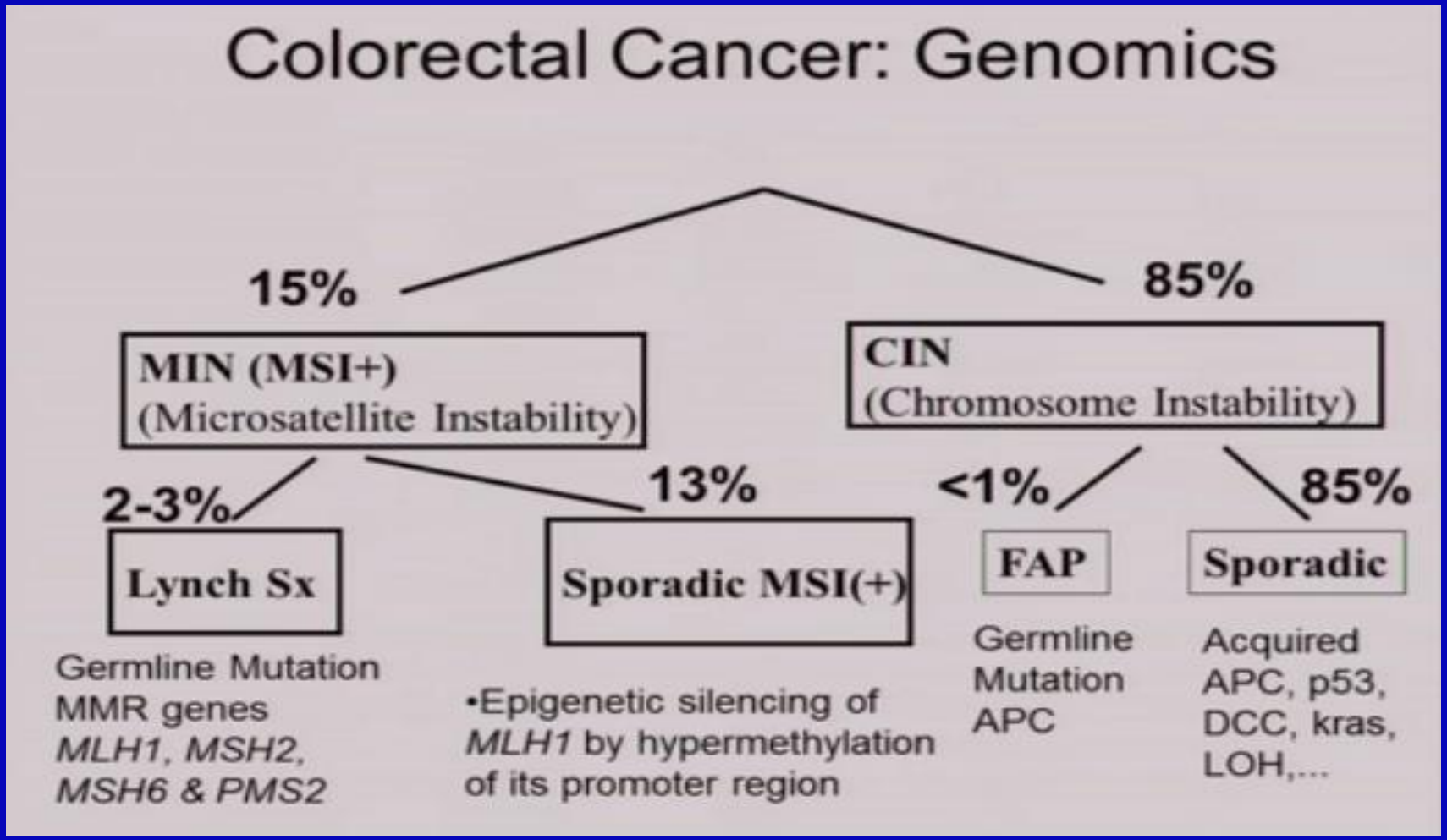
Adjuvant chemotherapy of stage II colon cancer issues in the elderly

- Recent analysis showed that elderly (>70 years-old) may not benefit from adjuvant chemotherapy
  - Already seen in the Quasar trial (stage II)
  - Already seen in the Mosaïc trial (stage II and III)
  - Recently reproted in NO 16968 (stage III, Xelox vs. 5FU/LV)
- Considering the absence of clear benefit of adjuvant chemotherapy in stage II, elderly patients > 70 years of age should not be treated

Adjuvant chemotherapy for stage II colon cancer

Can we get help from biomarkers?

Microsatellite instability



Goldberg R ASCO GI January 2014

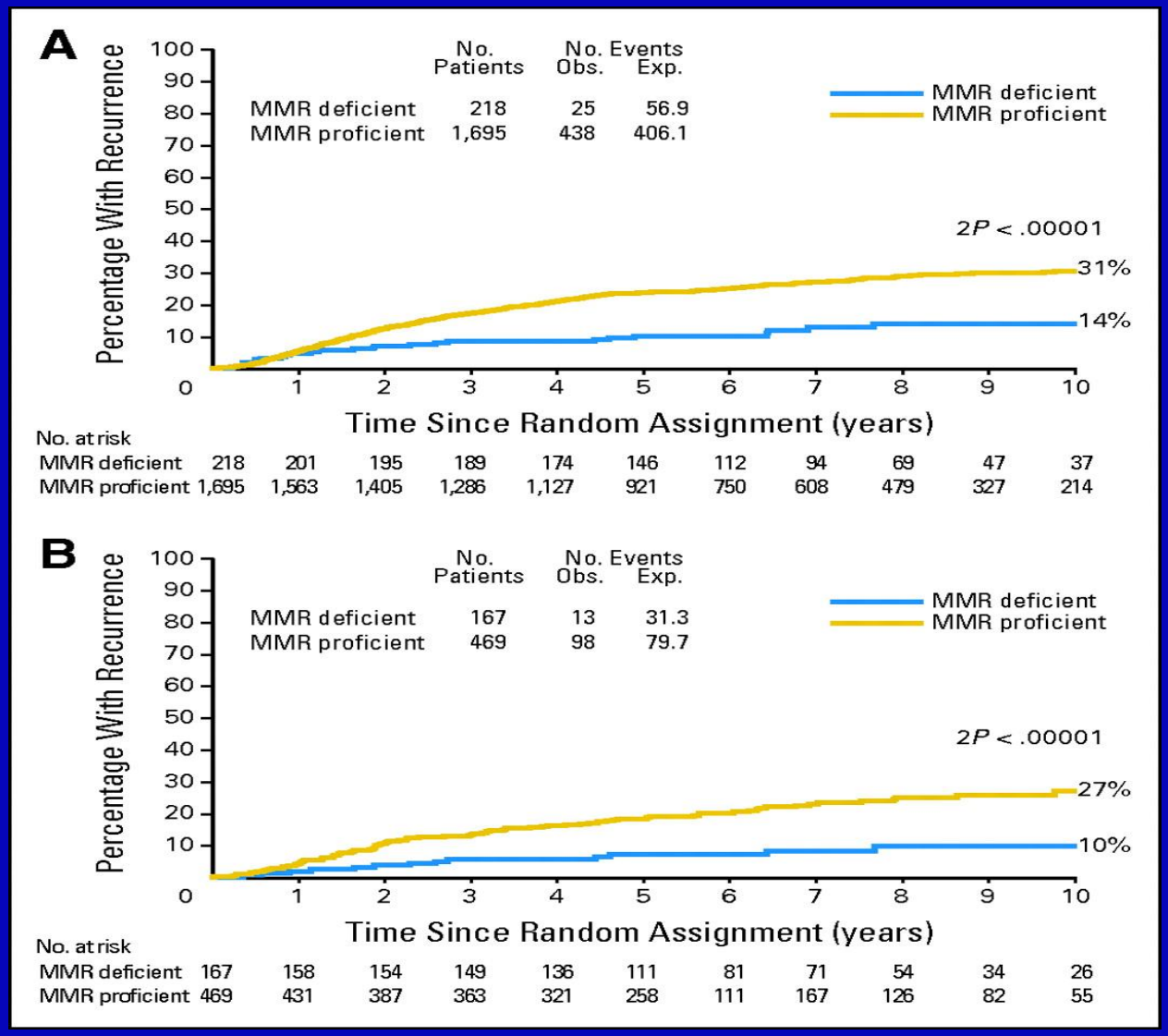
MSI-H as a consistent favorable prognostic marker

Source	Stage / Treatment	Endpoint	MMR-D vs MMR-P HR	p-value
Ribic et al[1]	II/III Surgery alone	Overall survival	0.31	0.004
Sargent et al[2]	II/III Surgery alone	Disease-free survival Overall survival	0.46 0.51	0.03 0.06
Gray et al[3] (QUASAR)	II Surgery alone	Recurrence-free interval	0.31	0.001
Roth et al[4] (PETACC-3)	II 5FU ± irinotecan	Relapse-free survival	0.30	0.004

1. Ribic CM, et al. *N Engl J Med*. 349:247-57, 2003
2. Sargent DJ, et al. *J Clin Oncol*. 28:3219-26, 2010
3. Gray R, et al. *J Clin Oncol*. 29:4611-9, 2011.
4. Roth AD, et al. *J Natl Cancer Inst*. 104, 1635-46, 2012.

QUASAR

Recurrence by mismatch repair (MMR) status: (A) all patients, (B) colon stage II only.



Hutchins G et al. JCO 2011;29:1261-1270

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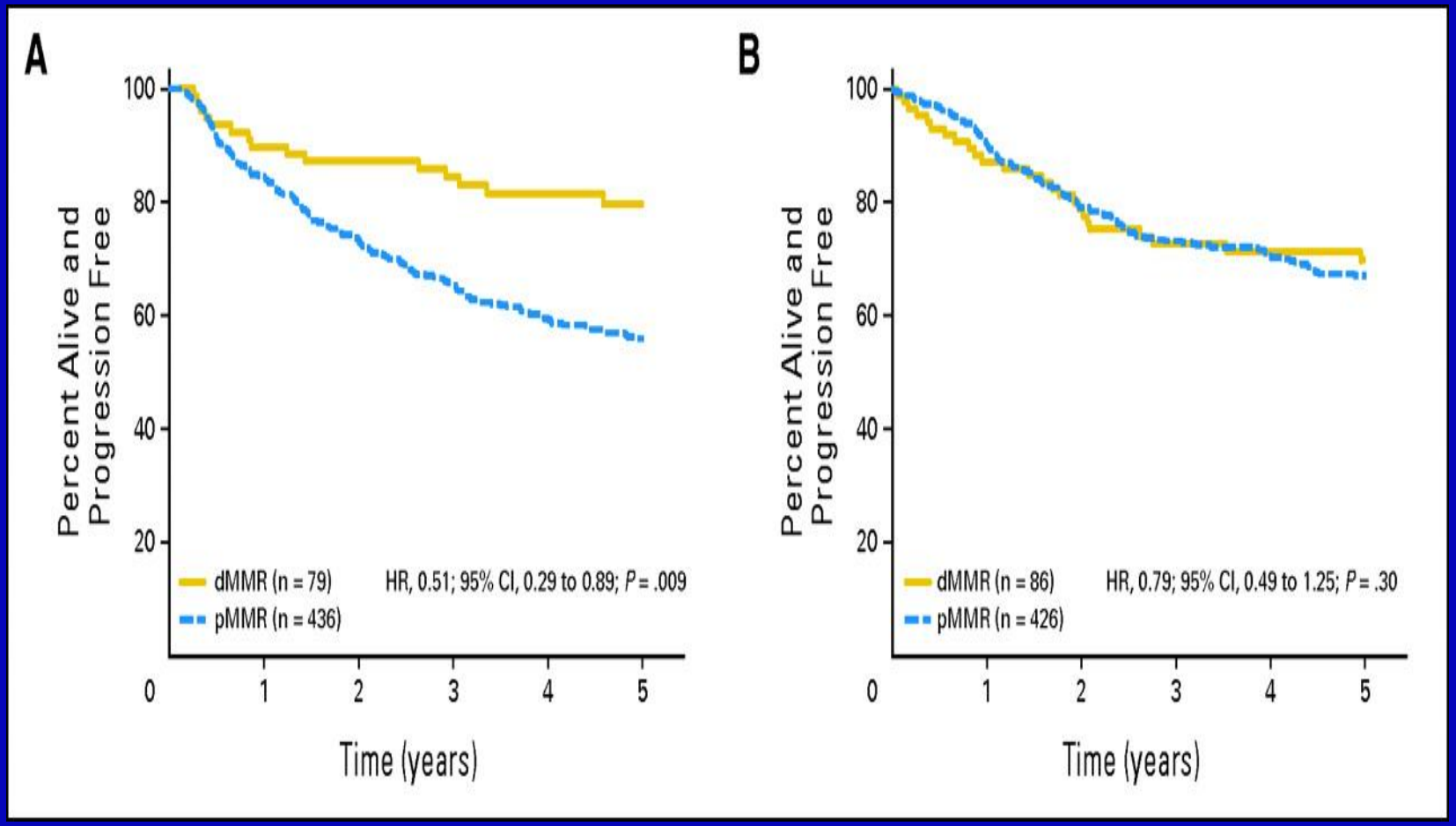
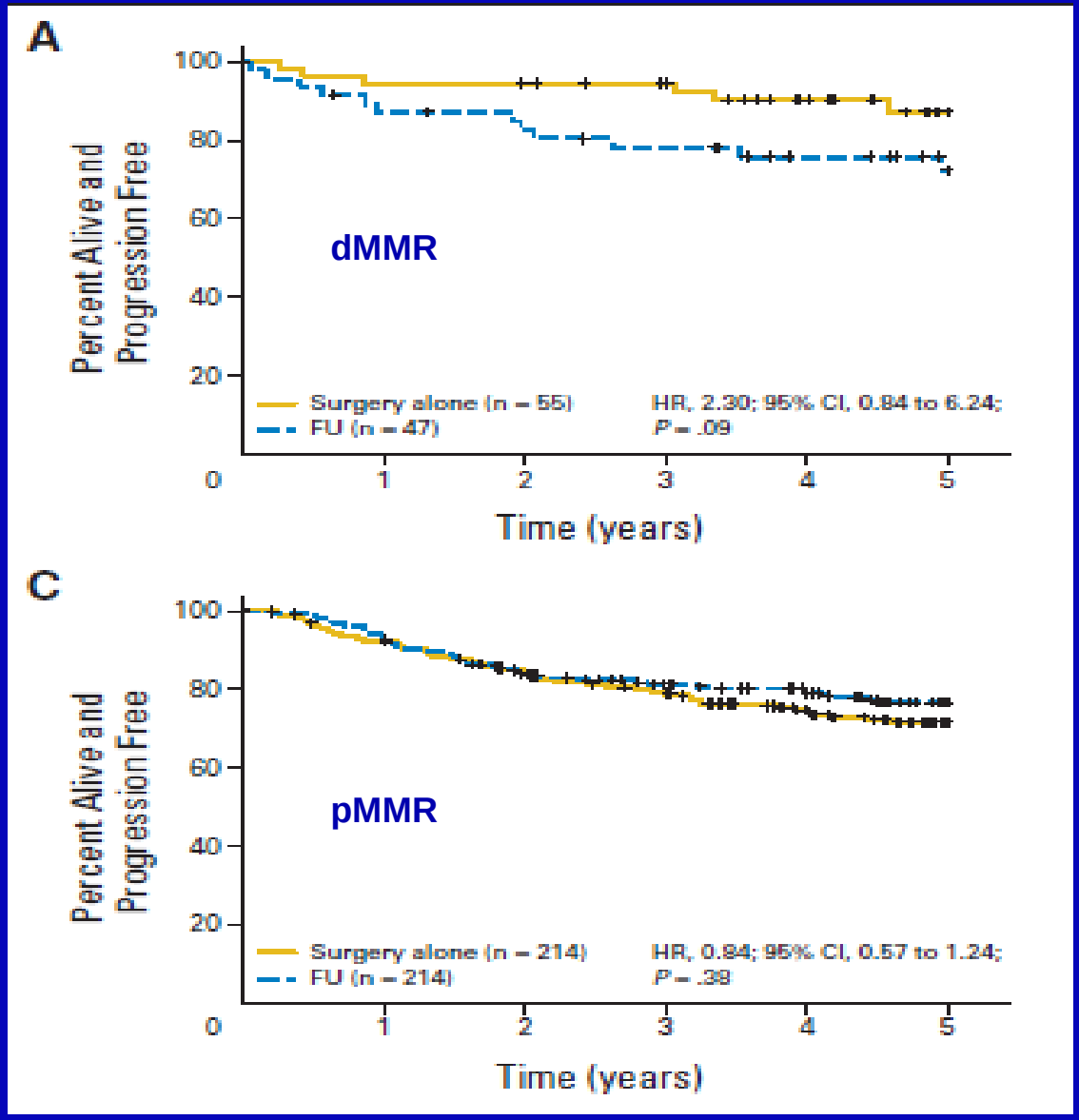
A. DFS in untreated patients by DNA mismatch repair (MMR) status.
B. DFS in treated patients by DNA mismatch repair (MMR) status



Sargent D J et al. JCO 2010;28:3219-3226

Predictive value of MMR status in stage II colon cancer



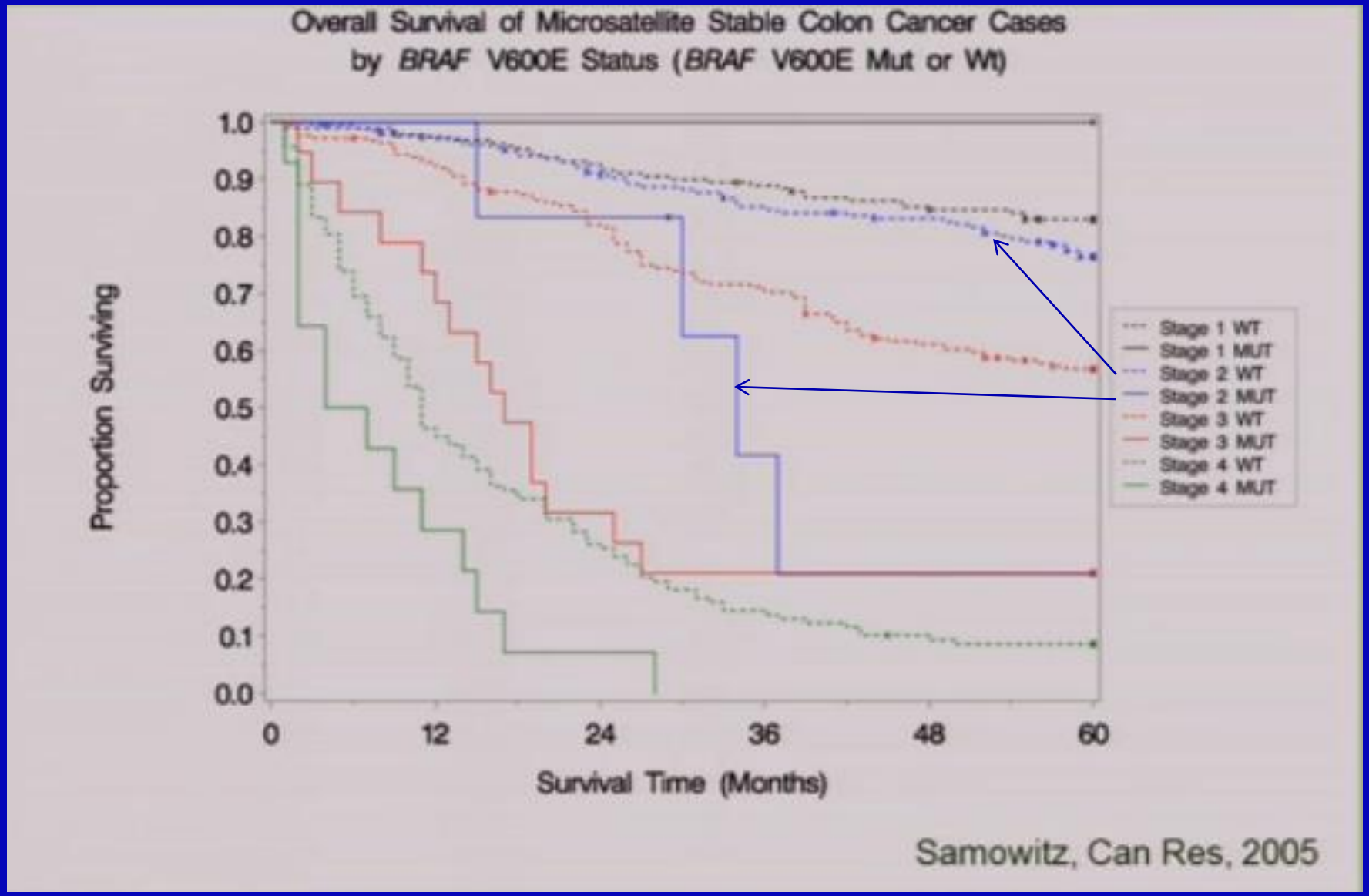
Sargent D J et al. JCO 2010;28:3219-3226

MSI as an indicator for adjuvant CT in stage II

Conclusions

- dMMR is a prognostic marker in untreated patients
- No suggestion of benefit from 5-FU based treatment in dMMR patients
- Significant OS decrement to 5-FU based treatment in stage II patients

Braf as a prognostic biomarker

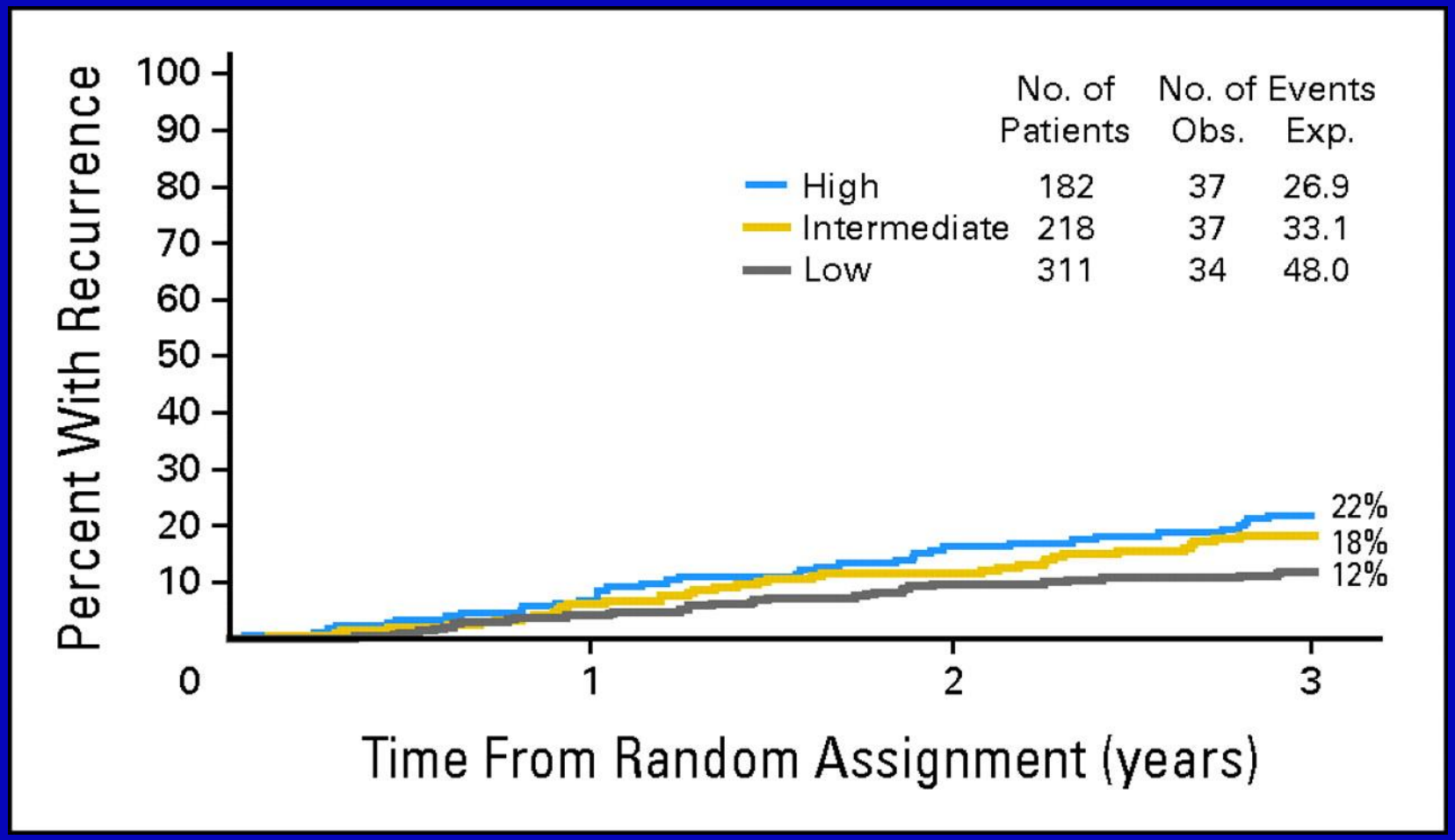


Gene signature in colon cancer

- Oncotype Dx (Genomic Health)
- ColDx (Almac)
- ColonPRS (Signal Genetics LLC)
- ColoPrint (Agendia NV)
- GeneFx Colon (Precision Therapeutics)
- Onco-Defender-CRC (Everist Genomics)

  - Still under investigation, Not approved
  - Not routinely available
  - Costly

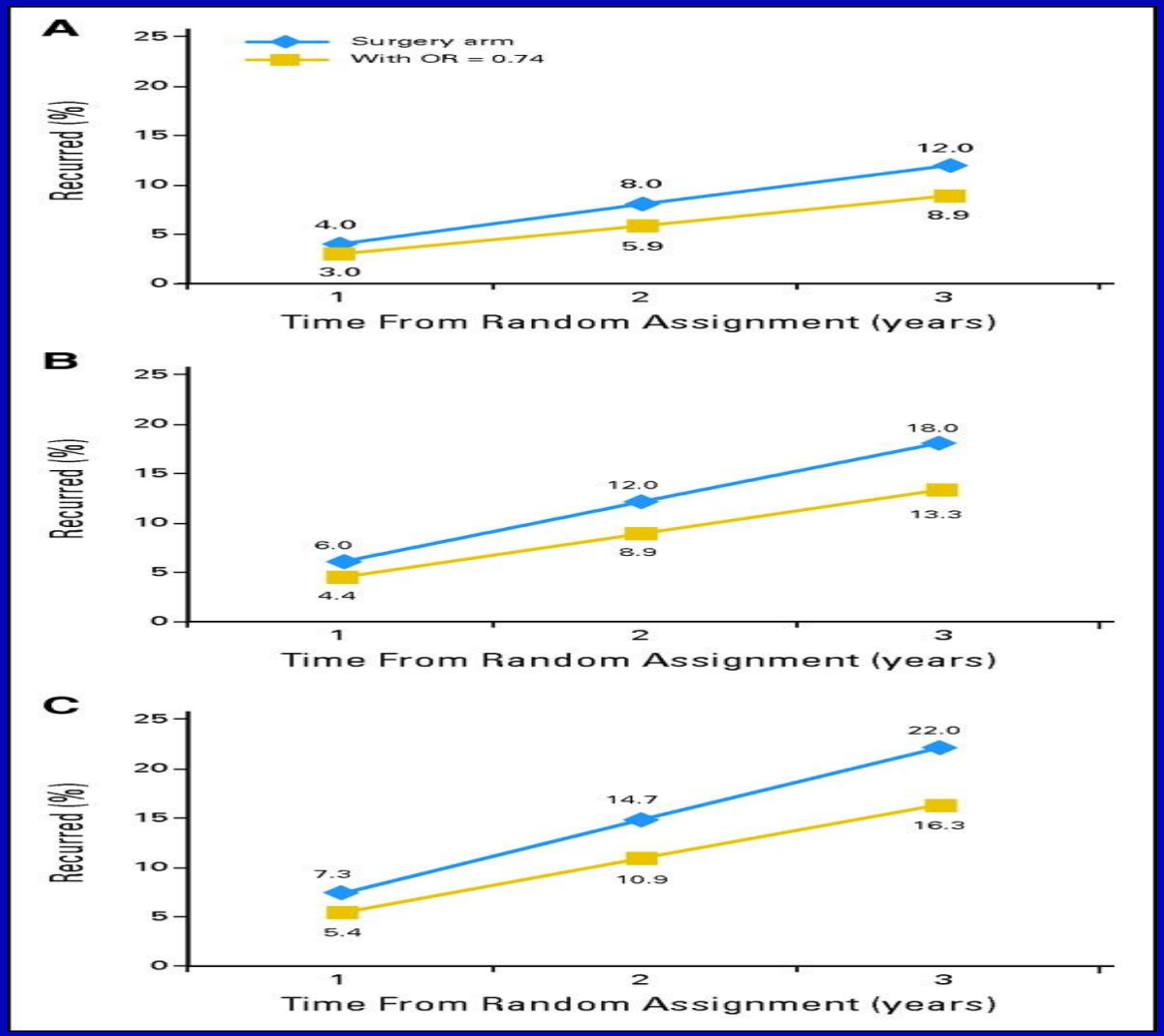
Kaplan-Meier estimates of 3-year recurrence in surgery-alone patients by risk group. (Oncotype *DX)*



Gray R G et al. JCO 2011;29:4611-4619

JOURNAL OF CLINICAL ONCOLOGY ASCO

Estimated absolute risk of recurrence at 3 years with and without FUFA chemotherapy, assuming the overall treatment effect for all stage II colon cancer patients in QUASAR (Quick and Simple and Reliable) Oncotype *DX*



Low risk
- 3.1%

Intermediate risk
- 4.7%

High risk
- 5.7%

Gray R G et al. JCO 2011;29:4611-4619

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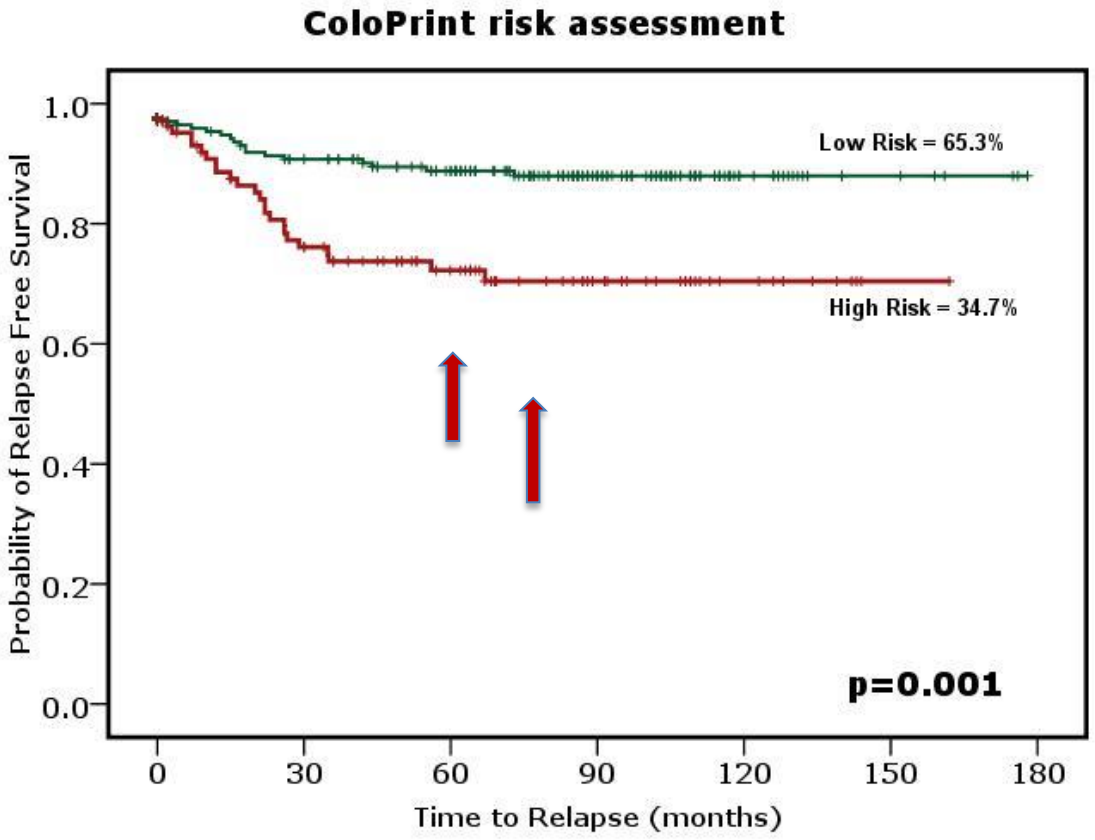
ColoPrint identifies patients at risk of distant and local-regional relapse (RFS)

Local, Regional and Distant Relapse



3-year RFS
Low Risk = 91% (86-95%)
High Risk = 74% (64-83%)

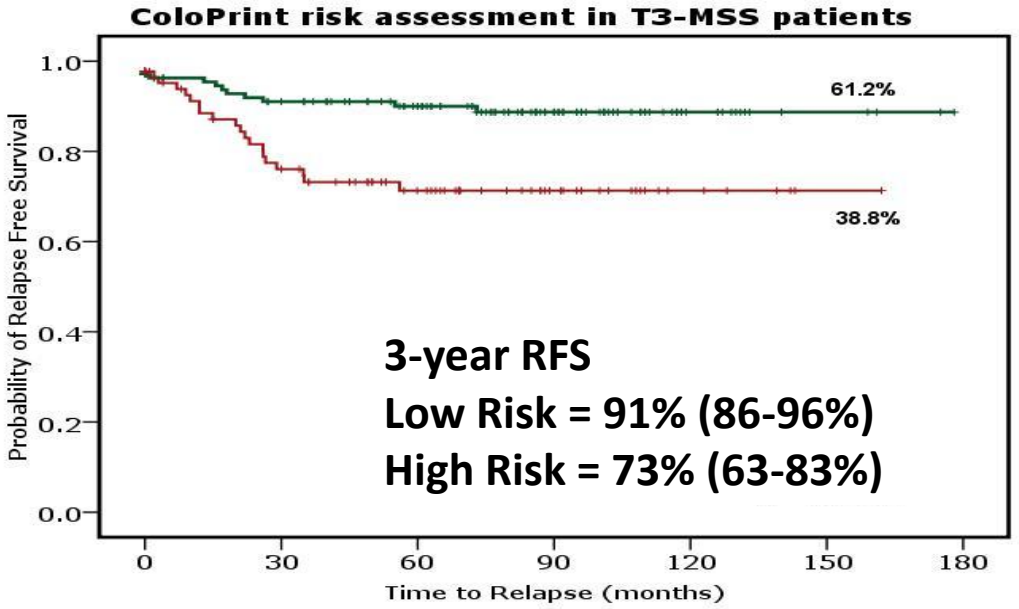
5-year RFS
Low Risk = 88% (83-93%)
High Risk = 71% (62-80.5%)

Tabernero J et al ASCO GI 2012

Subgroup analysis in T3-MSS patients (n=227)

Univariate Analysis of 3-year RFS

Variable	HR	95% CI	P-value
ColoPrint	3.04	1.45-6.34	0.003
Age	1.01	0.97-1.05	0.59
Localization	1.34	0.59-3.06	0.48
Grade	0.71	0.22-2.26	0.27
Gender	0.46	0.19-1.061	0.07
LN > 12	0.83	0.37-1.85	0.65

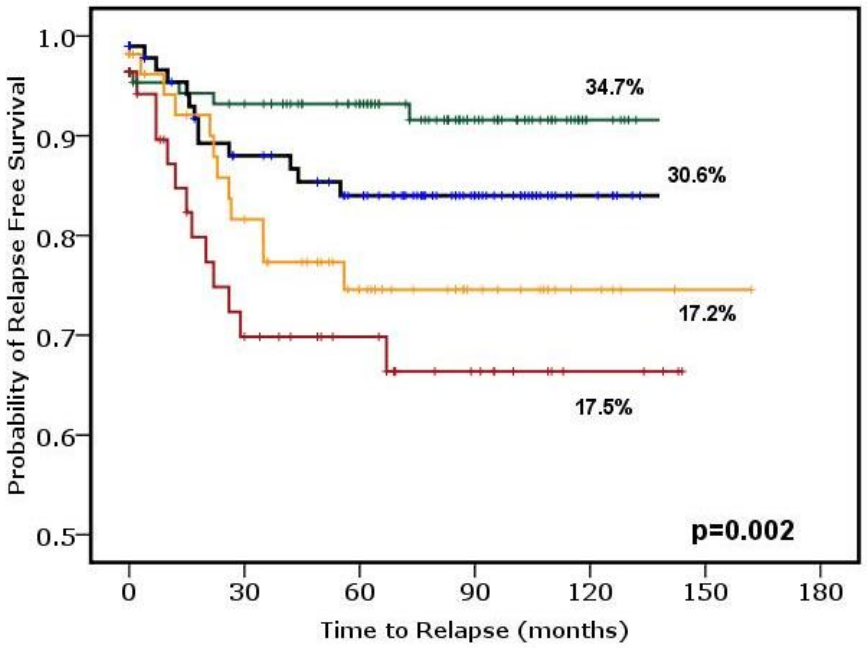


Tabernero J et al ASCO GI 2012

ColoPrint in combination with clinical factors might give best risk stratification

ColoPrint + NCCN clinical factors

All patients



3-year RFS

93 %	Low Risk ColoPrint, low risk NCCN
88 %	Low Risk ColoPrint, high risk NCCN
76 %	High Risk ColoPrint, low risk NCCN
71 %	High Risk ColoPrint, high risk NCCN

Tabernero J et al ASCO GI 2012

Adjuvant chemotherapy for stage II colon cancer

ESMO recommendations (Annals of Oncology 2010)

Standard treatment options: (i) wide surgical resection and anastomosis; (ii) following surgery, in high-risk patients (who present at least one of the previously mentioned features) adjuvant therapy could be considered in clinical practice [II, B]. Even better, all patients should be considered for entry into randomized clinical trials evaluating new options for adjuvant treatment.

ASCO recommendation

Direct evidence from randomized controlled trials does not support the routine use of adjuvant chemotherapy for patients with stage II colon cancer.

Features associated with an increased risk of recurrence include inadequate lymph node sampling, T4 disease, perforation and a poorly differentiated histology

Possible algorithm for stage II colon cancer