Systemic therapy in colon Cancer

(Pre - immunotherapy era)

→ stage I colon cancer:

T_1N_0, T_2N_0 → No adjuvant therapy needed.
5 yr OS = 95%.

→ stage II colon cancer:

T_3N_0, $T_{4a}N_0$, $T_{4b}N_0$ → Adjuvant chemo for high risk patients.

* clinical trials in favour & against adjuvant chemo in stage II colon cancer

→ IMPACT - B2 metaanalysis:

Stage II colon cancer (Resected) → 5 FU / Observation → No significant difference in OS.

→ QUASAR trial

Stage II Resected colon cancer → 5FU + levamisole vs Observation
- 22% decrease in recurrence.
- 18% decrease in Death.
- No significant improval in OS.

→ MOSAIC trial

Stage II, III Resected colon cancer, n = 2250 patients.
→ LV5FU 2 (mayo clinic regime) Biweekly infusional (vs) FOLFOX 4 (LV5FU 2 + oxaliplatin on day 1)

TABLE 40.9
Results of The Mosaic Trial: Biweekly Infusional Fluorouracil/Leucovorin versus 5-Fluorouracil/Leucovorin Plus Oxaliplatin in Patients with Stage II and III Colon Cancer

	FOLFOX (%)	5FULV2 (%)	*P* Value
Five-y disease-free survival (stage II+III)	73.3	67.4	0.003
Six-y overall survival (stage II+III)	78.5	76.0	0.046
Six-y overall survival (stage III only)	72.9	68.7	0.023
Six-y overall survival (stage II only)	85	83.3	0.65
Grade 3–4 neutropenia	41	5	
Grade 3–4 diarrhea	11	7	
Grade 3 neuropathy	12	0	
Grade 2 neuropathy	32	0	

FOLFOX, fluorouracil/leucovorin plus oxaliplatin; 5FULV2, fluorouracil/leucovorin.

* Long term data of MOSAIC trial:
10 yr OS: ∓ oxaliplatin → 59%; ± oxaliplatin → 67%. Results irrespective of MMR & BRAF mutation status.

→ NSABP C-07 trial

Stage II & III Resected Colon Cancer — [→ FLOX regimen (vs) LV5FU2] → 8 year follow up.

- Flox had better 5yr DFS 69 vs 64%
- No significant difference in OS

→ All trials uniformly showed NO overall survival benefit with adjuvant chemotherapy in stage II color cancer.

↓

High risk for recurrence features identified in stage II colon cancer

Table 30.1 High-risk features of stage II colon cancer

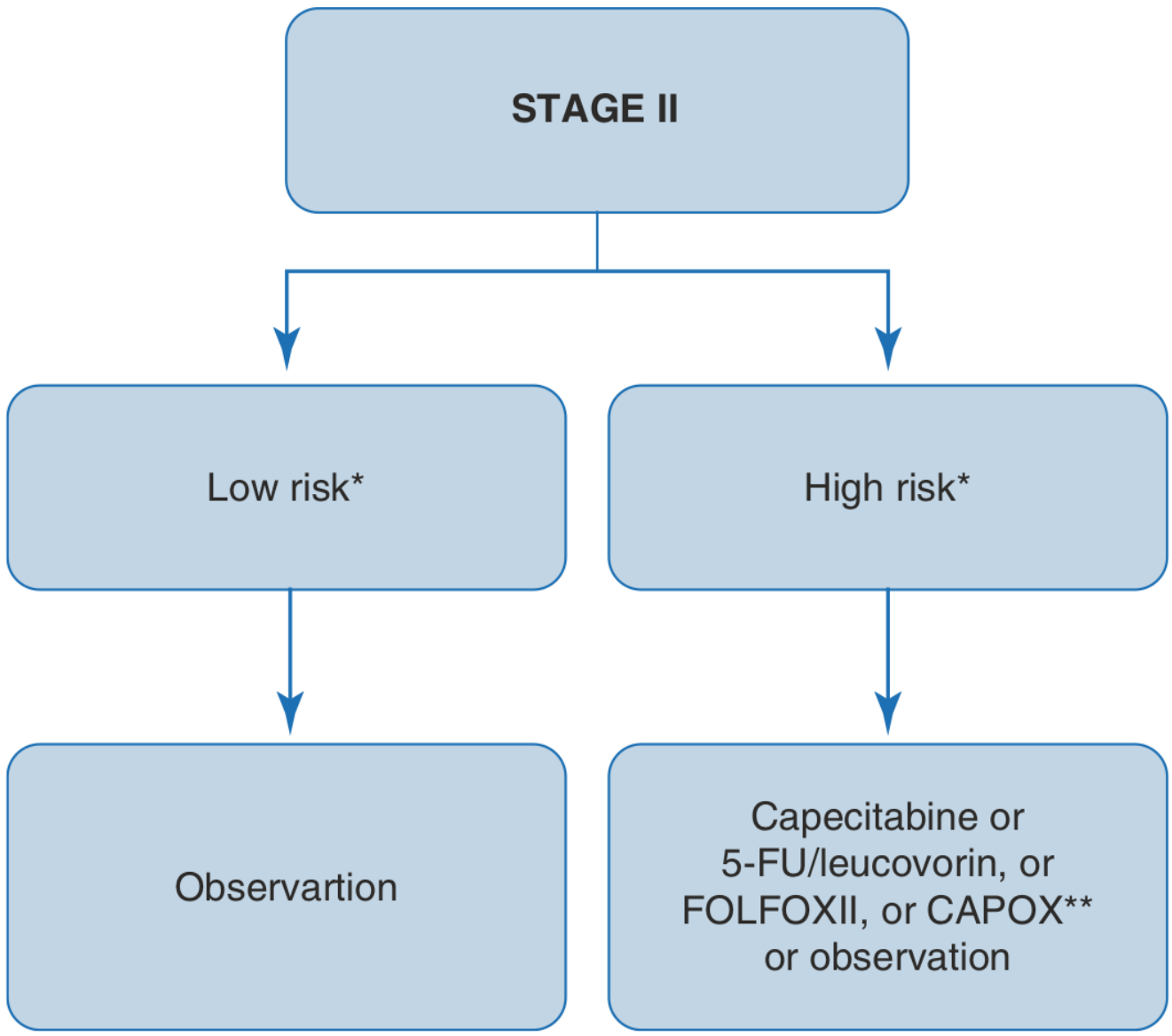
T4 tumor
Poor differentiation
Lymphovascular invasion
Perineural invasion
Close or positive margin
Bowel obstruction
<12 lymph nodes harvested

+ Impact of mutational analysis

(+)

* MSI-H / MMR deficient [Better OS, resistant to 5FU therapy.
* BRAF V600E mutation → worse OS.
* BRAF and MMR mutation NEVER coexist.
* Routine MMR testing f/b reflex testing for BRAF in MSI-low tumors.

→ All things considered, Asco / Esmo / nccn guidelines for stage II colon cancer



→ CAPOX if mmR-d | MSI-H as they are resistant to 5FU.

→ Stage III colon cancer:
T1 - T4 with Node positive

→ Always need adjuvant therapy.
Risk stratification to decide duration of therapy (3 mo vs 6 mo)

→ IMPACT analysis

Pooled analysis of 3 RCT.

Stage III Resected Colon Cancer
- → Sx alone
- → Sx + 6# LV5FU2

→
- Improved 3 yr OS (71.1% vs 62.1%)
- Levamisole superior to levamisole
- 6 months treatment offered similar benefits as 12 months treatment.

→ MOSAIC trial

Stage II, III
Resected
colon cancer

n = 2250
Patients.

→ LV5FU 2 (mayo clinic regime)
Biweekly infusional
(vs)
→ FOLFOX 4
(LV5FU 2 + oxaliplatin on day 1)

TABLE 40.9

Results of The Mosaic Trial: Biweekly Infusional Fluorouracil/Leucovorin versus 5-Fluorouracil/Leucovorin Plus Oxaliplatin in Patients with Stage II and III Colon Cancer

	FOLFOX (%)	5FULV2 (%)	*P* Value
Five-y disease-free survival (stage II+III)	73.3	67.4	0.003
Six-y overall survival (stage II+III)	78.5	76.0	0.046
Six-y overall survival (stage III only)	72.9	68.7	0.023
Six-y overall survival (stage II only)	85	83.3	0.65
Grade 3–4 neutropenia	41	5	
Grade 3–4 diarrhea	11	7	
Grade 3 neuropathy	12	0	
Grade 2 neuropathy	32	0	

FOLFOX, fluorouracil/leucovorin plus oxaliplatin; 5FULV2, fluorouracil/leucovorin.

* Long term data of MOSAIC trial:

10yr OS
- ∉ oxaliplatin → 59%
- ∈ oxaliplatin → 67%

} Results irrespective of MMR & BRAF mutation status.

→ Twelves et al & Haller et al:

Stage III
Resected
Colon
Cancer

→ Oral Capecitabine alone (or) CAPOX
(vs)
→ FOLFOX

→ - Capecitabine equivalent to 5FU in terms of survival.
- CAPOX is an acceptable alternative to FOLFOX.

→ IDEA collaboration:

Stage III
resected
colon cancer

N = 13,000
Patients.

→ 3 months FOLFOX
→ 3 months CAPOX
→ 6 months FOLFOX
→ 6 months CAPOX

(Non inferiority trial design)

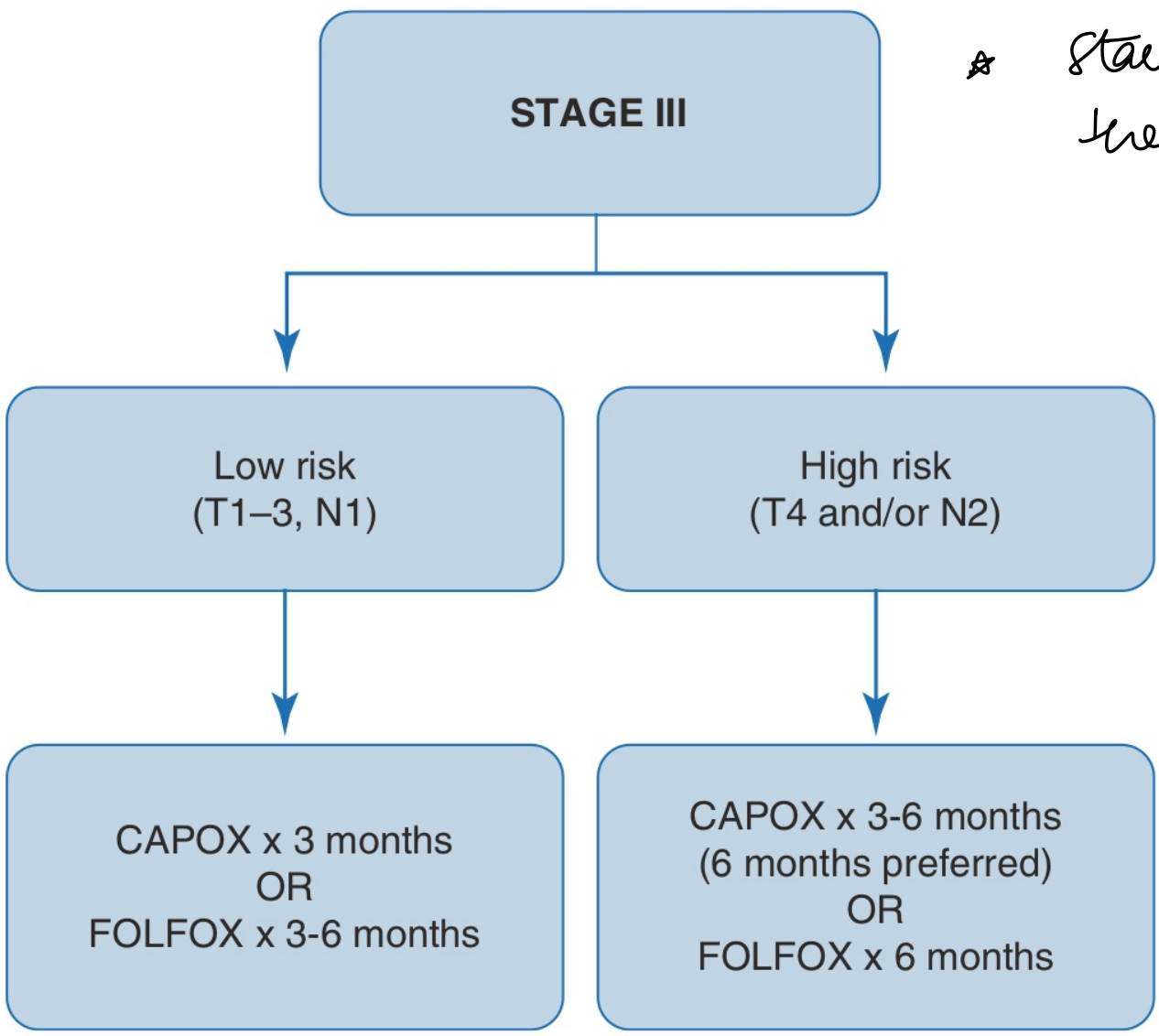
→ - overall, 3 months treatment failed to meet non inferiority criteria.
- Subgroup analysis:

Low risk stage III → 3 mo CAPOX non inferior to 6 mo FOLFOX.

High risk stage III (T4 | N2)
→ 3 mo vs 6 mo CAPOX non inferiority could not be proved.
→ 3 mo FOLFOX definitely inferior to 6 mo FOLFOX.

* Tested to reduce neuropathy toxicity related to prolonged oxaliplatin.

On things considered, NCCN / ASCO / ESMO guidelines for adjuvant therapy in stage III colon cancer



* Start adjuvant therapy within 3-8 weeks of Sx

↓

To consider complexity of CAPOX regimen:

Oral capecitabine 5 pills/day — 2 weeks on, 1 week off

+

oxaliplatin on day 1

→ Other agents which were evaluated in metastatic colon cancer, But did not improve survival in stage II / III colon cancer:

All negative trials:

* Irinotecan → CALGB trial, ACCORD 02, PETACC-3 → ↑ed lethal toxicity
* Bevacizumab → NSABP C-08, AVANT trial → No improvement in DFS/OS when Bev added to CAPOX or FOLFOX.

* Cetuximab
* Panitumumab

} No benefit in adjuvant setting.

→ Impact of MMR/MSI testing on adjuvant therapy in colon cancer:

→ study by Ribic et al:

TABLE 40.10

Microsatellite Instability versus Outcome with 5-Fluorouracil-Based Adjuvant Chemotherapy

	No. of Patients	Five-Y Disease-Free Survival (%)	*P* Value
All Patients			
Adjuvant chemotherapy	285	70	0.06
No adjuvant chemotherapy	287	62	
Patients with MSI-L/MSS			
Adjuvant chemotherapy	230	70	0.01
No adjuvant chemotherapy	245	59	
Patients with MSI-H			
Adjuvant chemotherapy	53	69	0.11
No adjuvant chemotherapy	42	83	

MSI-L, low level of microsatellite instability; MSS, microsatellite stable; MSI-H, high level of microsatellite instability.
Data from Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med* 2003;349:247–257.

→ Despite no significant improval, Adjuvant chemotherapy still preferred in stage III Colon cancer.

with the addition of oxaliplatin.

As platinum induced DNA adducts induce cytotoxicity.

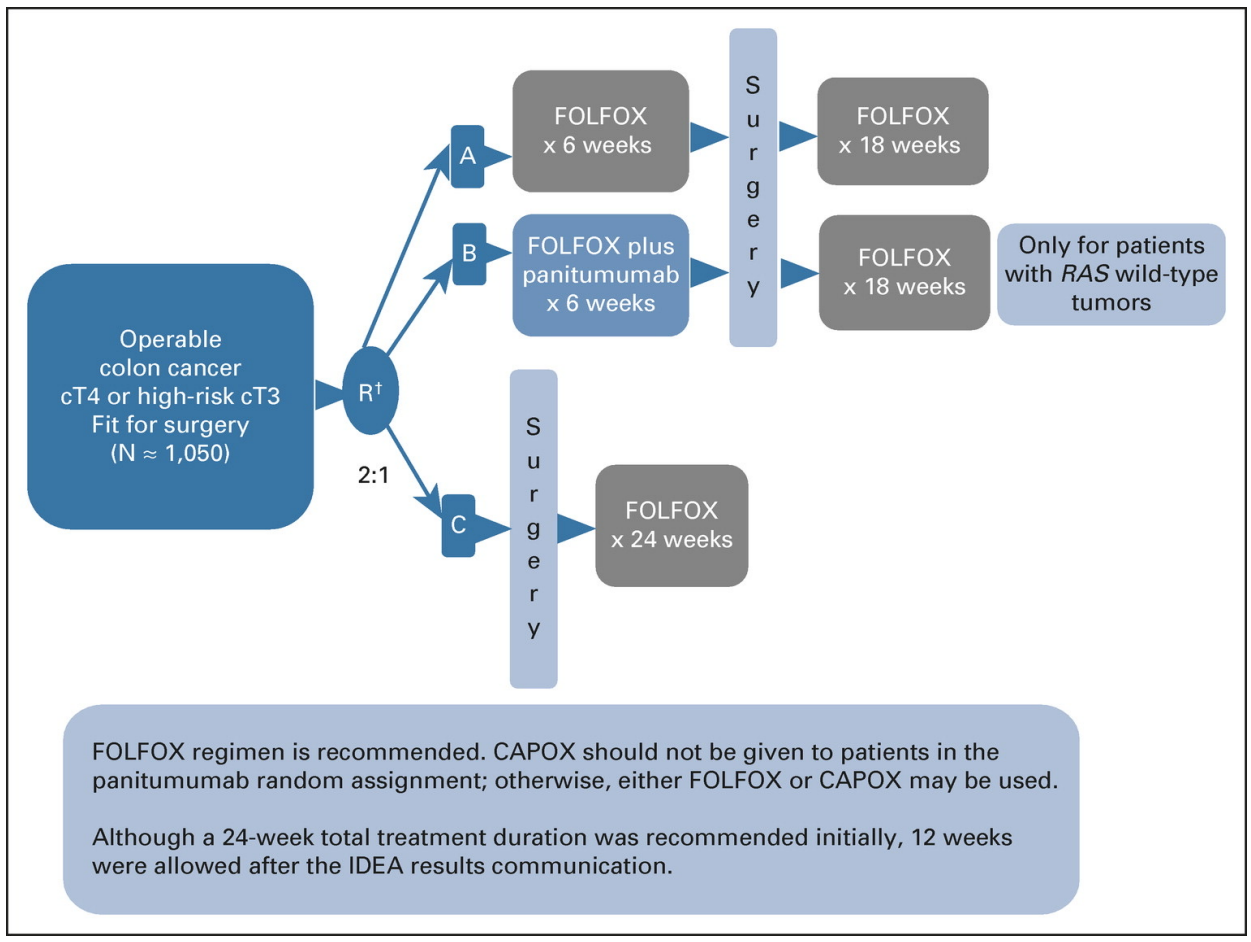
→ Other molecular markers to prognosticate:

- ctDNA
- KRAS/NRAS → only in metastatic colon cancer
- Oncotype Dx - 12 gene signature
- COLO PRINT. - 18 gene.
- Colorectal Cancer - DSA
- microRNA.

→ Investigational adjuvant therapy options

→ Neoadjuvant chemotherapy in colon cancer:

→ FoxTROT trial



→ 6 weeks preop chemotherapy significantly
- Downstaged tumor (T & N stage)
- improved Ro resection in locally advanced CA colon
- Decreased recurrence at 2 years follow up.

→ Panitumumab did not confer any additional benefits.

→ may be considered for T_{4b} tumors

→ Portal vein infusion chemotherapy:

- NSABP C-02
  - Sx alone
  - vs
  - Sx + 1 day PV infusion of 5FU
  - → No difference in hepatic recurrence.
- Swiss group → intraportal infusion of mitomycin + fl 5FU → No significant difference in DFS/OS.

PV infusion is investigational only at present.

→ Role of prophylactic HIPEC in colon cancer:

- Dutch COLOPEC trial

T4N0 / intraperitoneal perforated colon cancer

N = 204 patients

→ HIPEC ± oxaliplatin f/b adjuvant chemo

VS

→ Adjuvant chemo only

→
- No significant diff in peritoneal disease free survival @ 18 mo
- 14.1% in HIPEC arm had complications.

- Melero et al

- Patient selection for prophylactic HIPEC based on pre op circulating tumor cells.
- CTC +ve → indication of systemic disease → no benefit with HIPEC.

→ Follow up / surveillance strategy:

- CEA @ 3-6 month intervals × (3) years
  @ 6-12 month intervals × (2) years
  then annually
- CECT chest + A+P — yearly × (3) years
- Colonoscopy — @ immediately after adjuvant therapy if full length colonoscopy could not be performed pre op
  or at 1 year after completion of therapy — if normal, repeat @ 3-5 years interval.

→
* Serially rising CEA with no evidence of disease on scopy / CT
  ↓
  Indication for PET/CT scan.

* No role for CBC / LFT / chest x rays on routine follow up.