SACRO CUORE DON CALABRIA
IRCCS
Istituto di Ricovero e Cura a Carattere Scientifico
Sacro Cuore - Don Calabria
Ospedale Classificato e Presidio Ospedaliero Accreditato - Regione Veneto

# Incontri di aggiornamento del Dipartimento Oncologico

**Responsabile Scientifico:**
**DOTT.SSA STEFANIA GORI**

**26 ottobre - 9 novembre**
**23 novembre - 30 novembre**
**2022**

**SEDE:**
*"Centro Formazione e Solidarietà"*
*Sala Convegni "Fr. Francesco Perez"*
IRCCS Sacro Cuore - Don Calabria
Via Don Angelo Sempreboni, 5 - 37024 Negrar di Valpolicella (VR)

**Mercoledì 26 ottobre**
*- Centro Formazione e Solidarietà -*

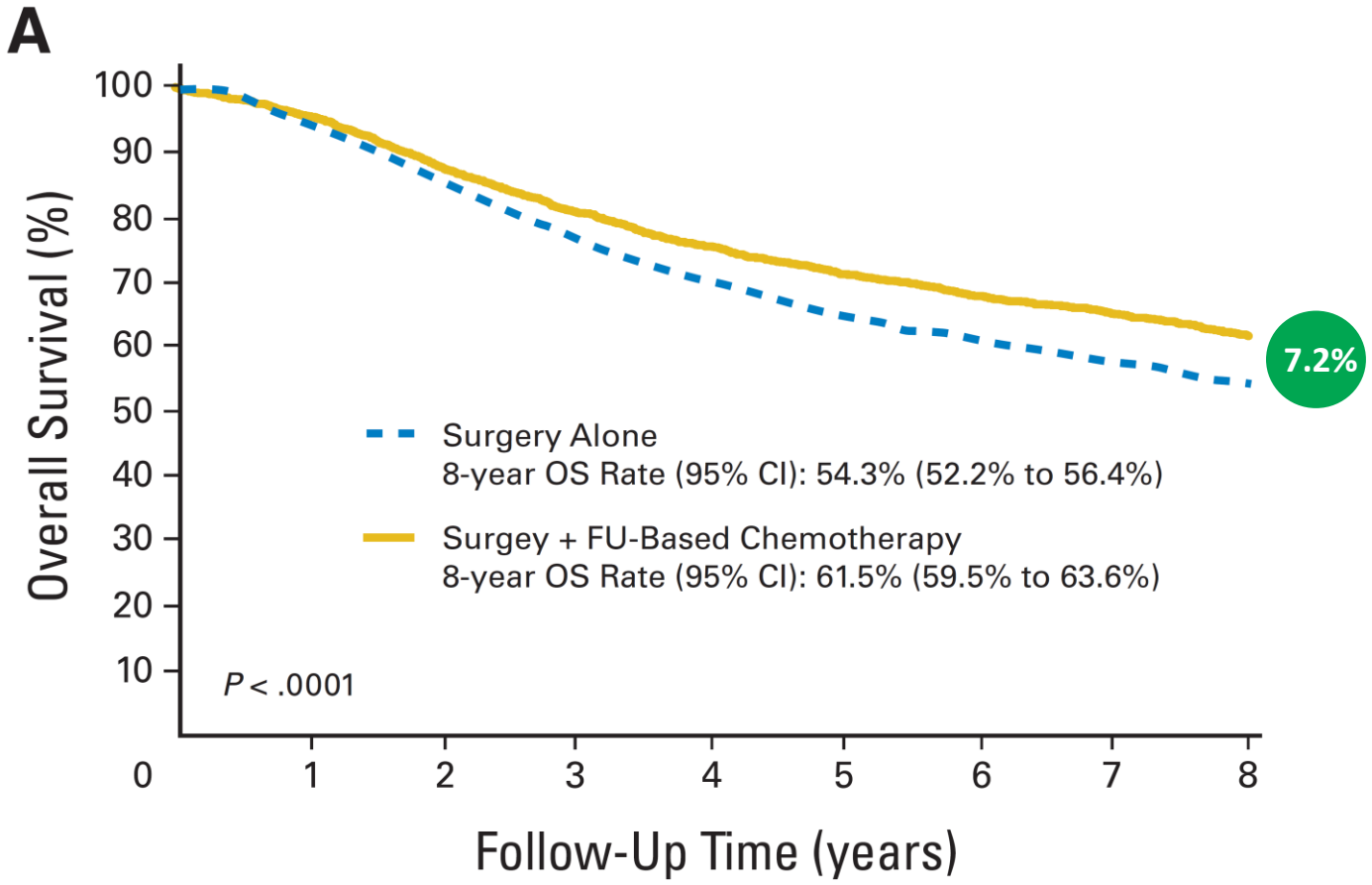
## Il carcinoma del colon retto

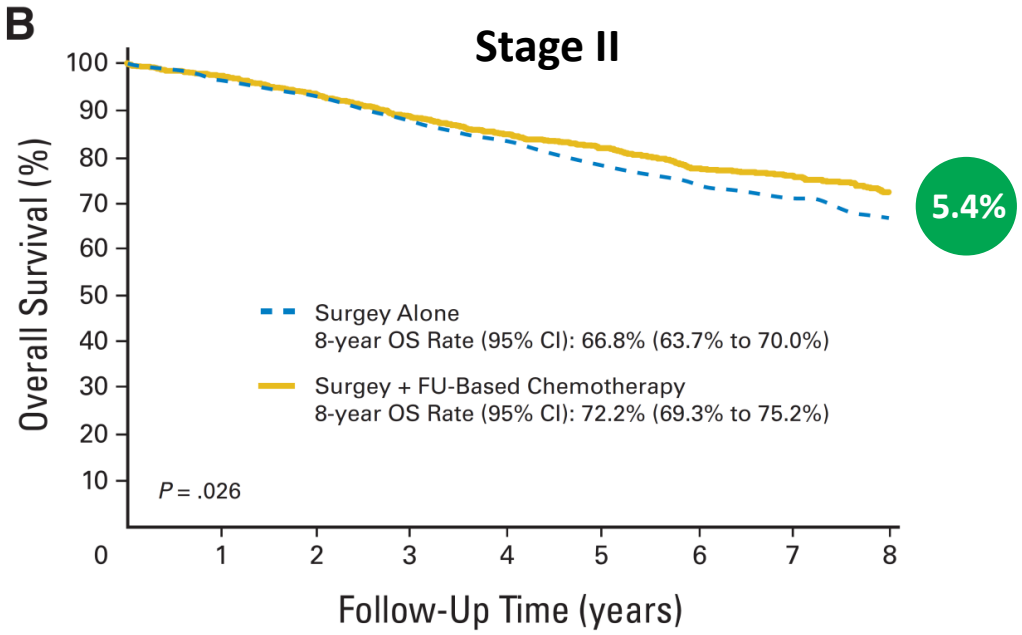
# Terapia sistemica adiuvante e follow up

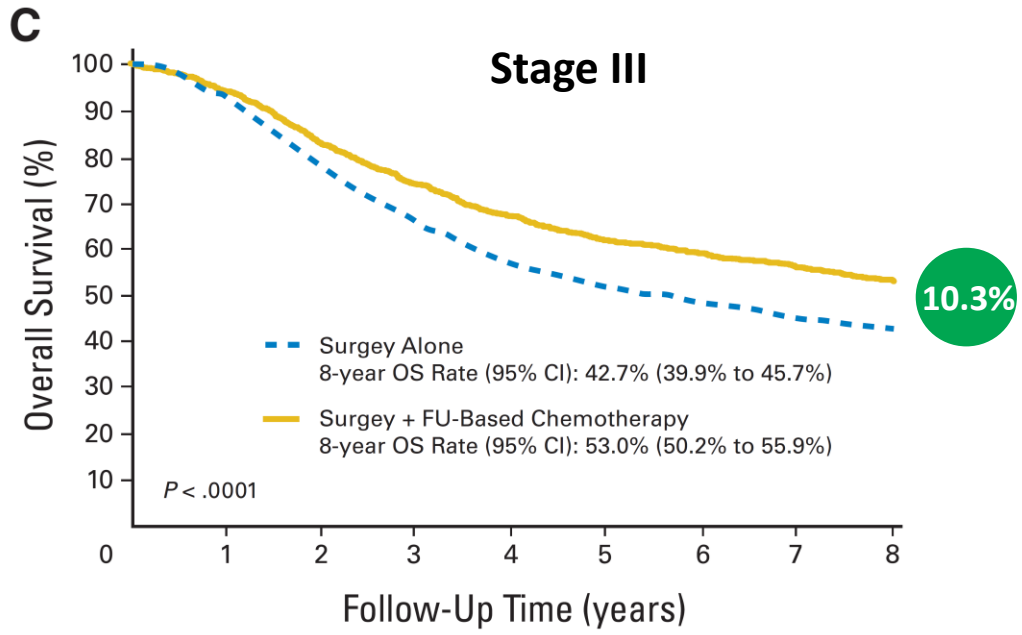

*Alessandro Inno*

SACRO CUORE DON CALABRIA
Oncologia Medica
IRCCS Ospedale Sacro Cuore Don Calabria
Negrar di Valpolicella (VR)

# Chemioterapia adiuvante a base di 5-FU negli stadi II-III

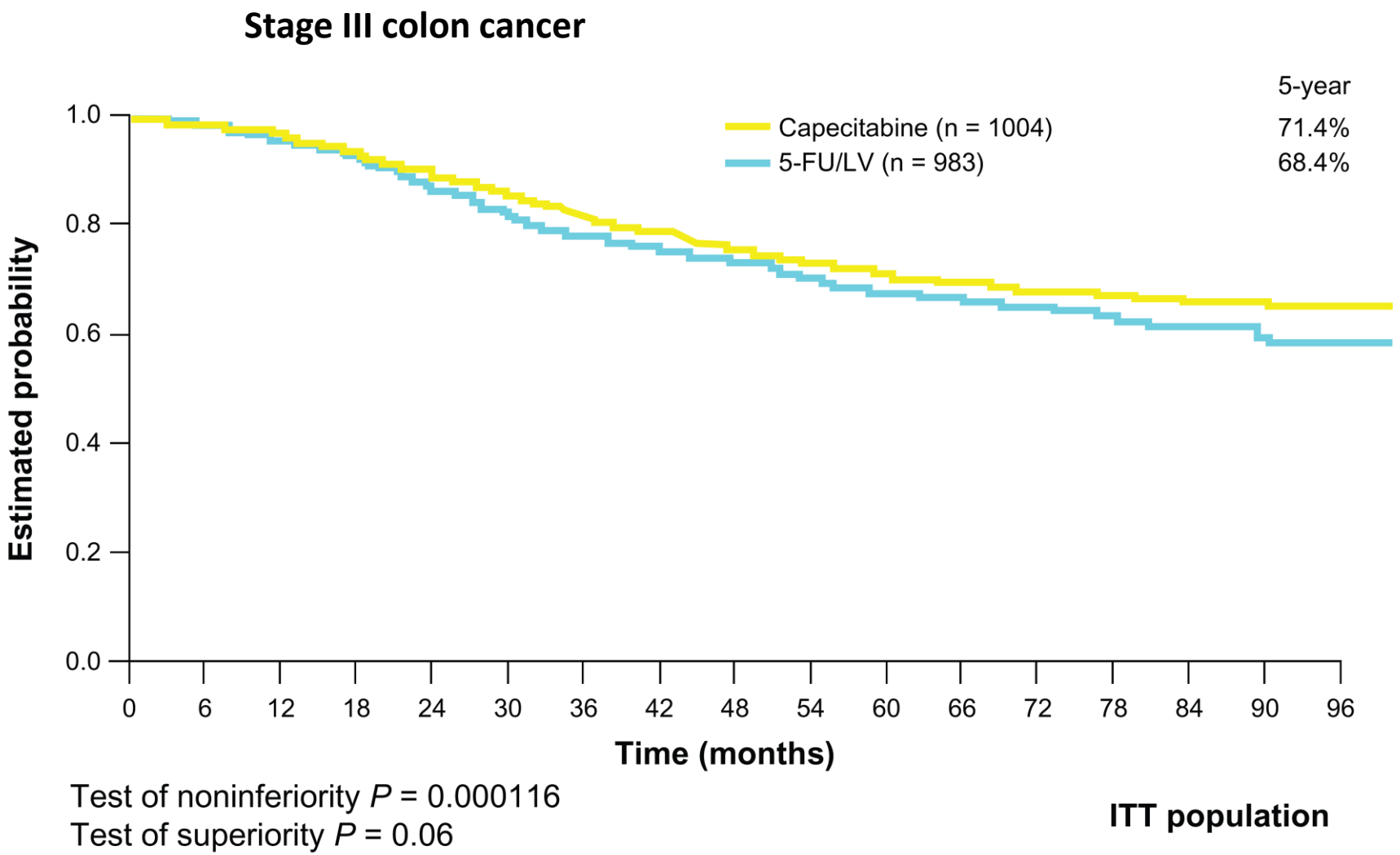


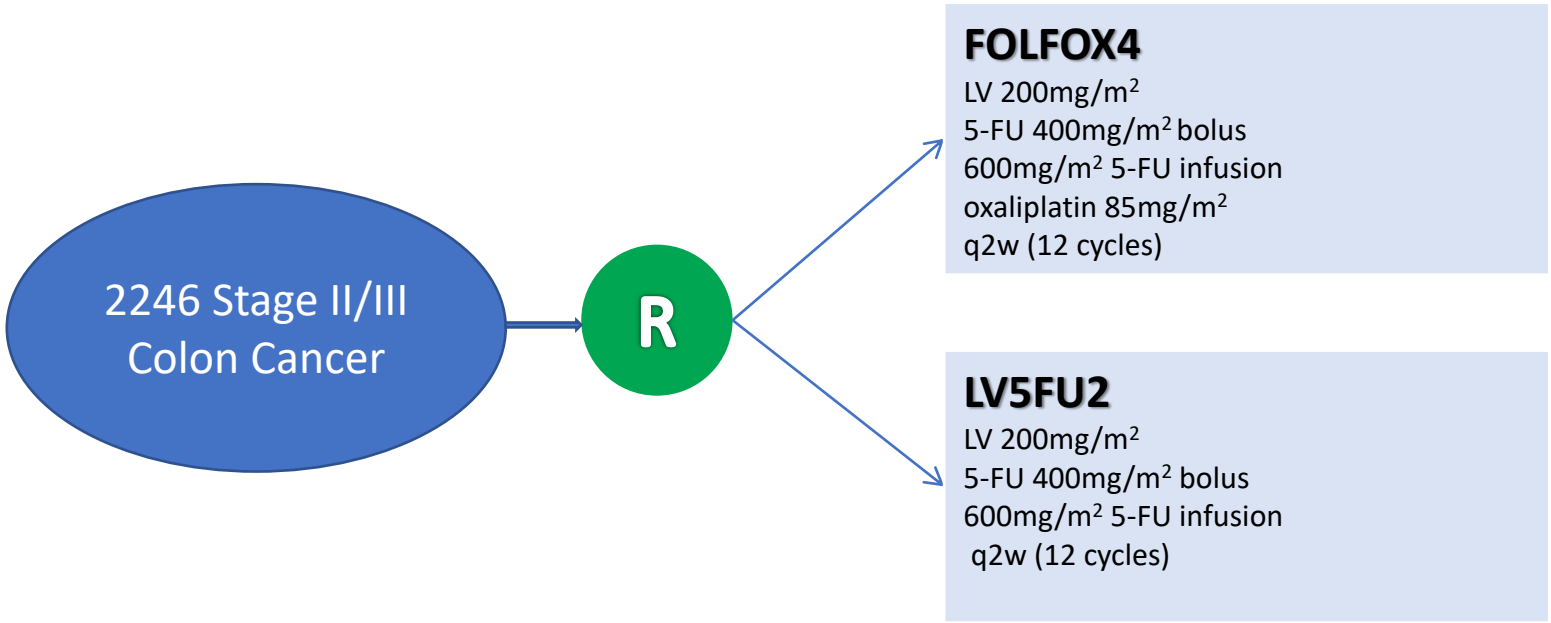

Sargent D, et al. J Clin Oncol 2009;27(6):872-7.

# Capecitabina non inferiore a 5-FU




Twelves C, et al. N Engl J Med. 2005 Jun 30;352(26):2696-704.

# Chemioterapia di combinazione: studio MOSAIC

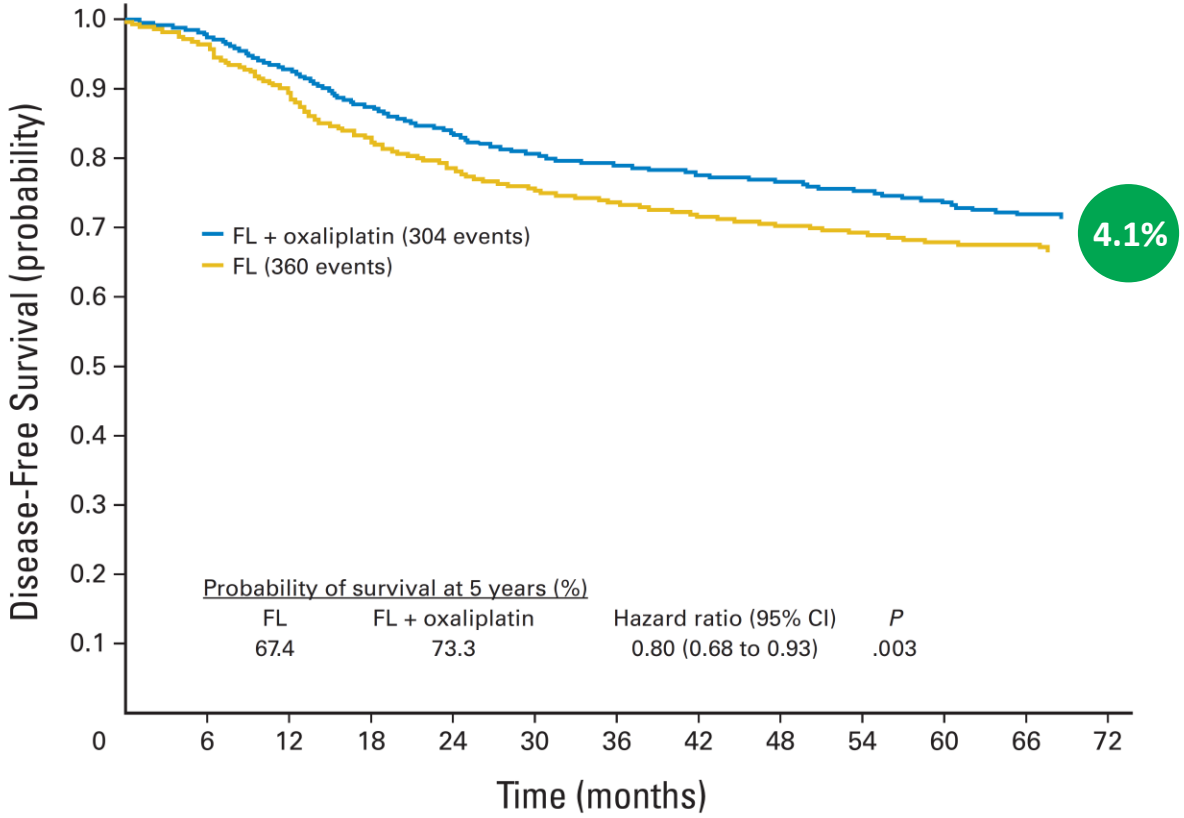



- Primary endpoint: DFS
- Stage II / III ratio = 40 / 60%
- 2.3 year enrolment (10/1998→01/2001)
- Expected 3-year DFS: 79% for test arm and 73% for control arm or 25% reduction in risk of recurrence

N = 2200 for a statistical power of 90% (a=0.05)

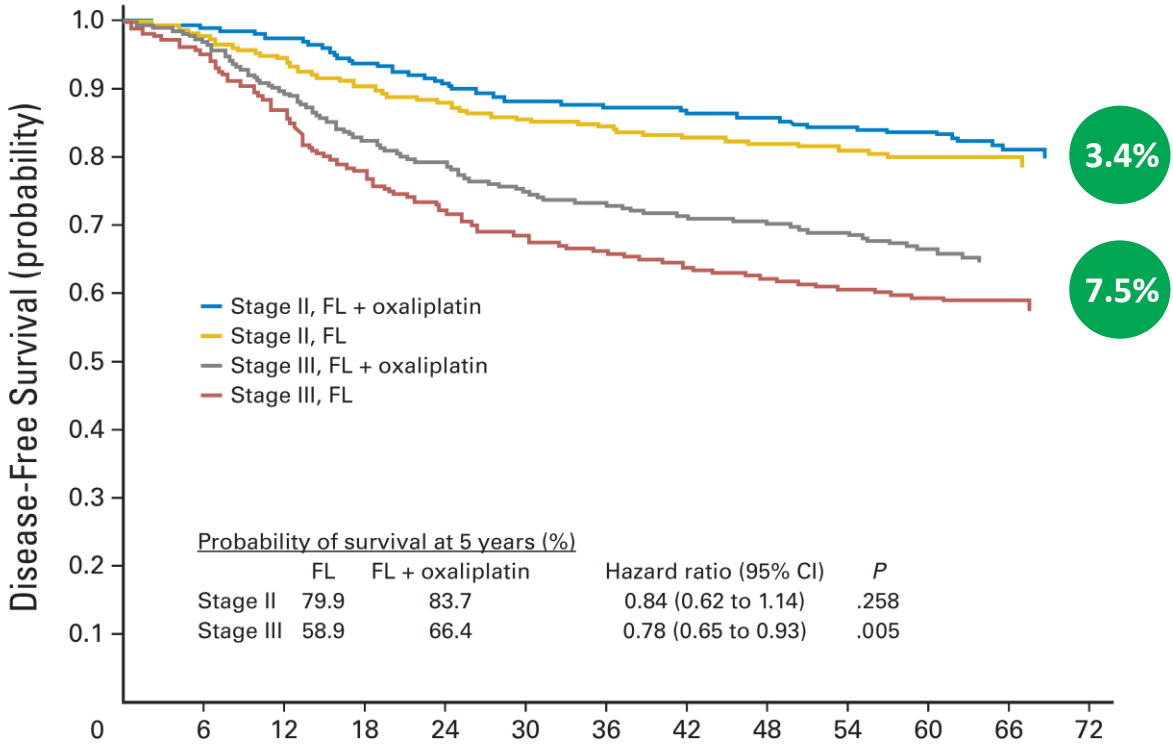
# MOSAIC: DFS a 5 anni

## DFS in ITT population




| No. at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FL + oxaliplatin | 1,123 | 1,086 | 1,024 | 962 | 919 | 884 | 858 | 841 | 825 | 797 | 632 | 247 |
| FL | 1,123 | 1,068 | 984 | 907 | 858 | 820 | 796 | 771 | 751 | 724 | 572 | 206 |

## DFS by stage

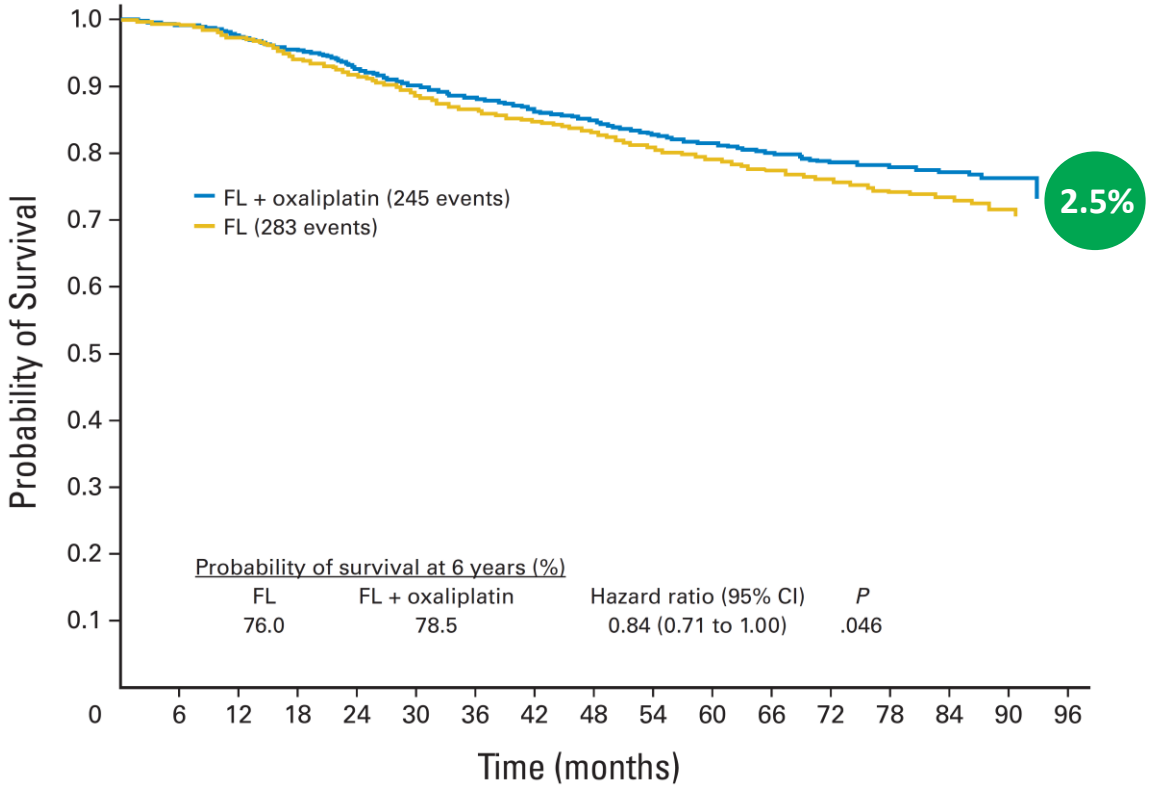



| No. at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stage III | | | | | | | | | | | | |
| FL + oxaliplatin | 672 | 641 | 589 | 544 | 515 | 492 | 474 | 461 | 452 | 438 | 346 | 127 |
| FL | 675 | 633 | 566 | 508 | 472 | 445 | 429 | 411 | 395 | 377 | 283 | 105 |
| Stage II | | | | | | | | | | | | |
| FL + oxaliplatin | 451 | 445 | 435 | 418 | 404 | 392 | 384 | 380 | 373 | 359 | 286 | 120 |
| FL | 448 | 435 | 418 | 399 | 386 | 375 | 367 | 360 | 356 | 347 | 289 | 101 |

André T, et a. J Clin Oncol 2009;27(19):3109-16.

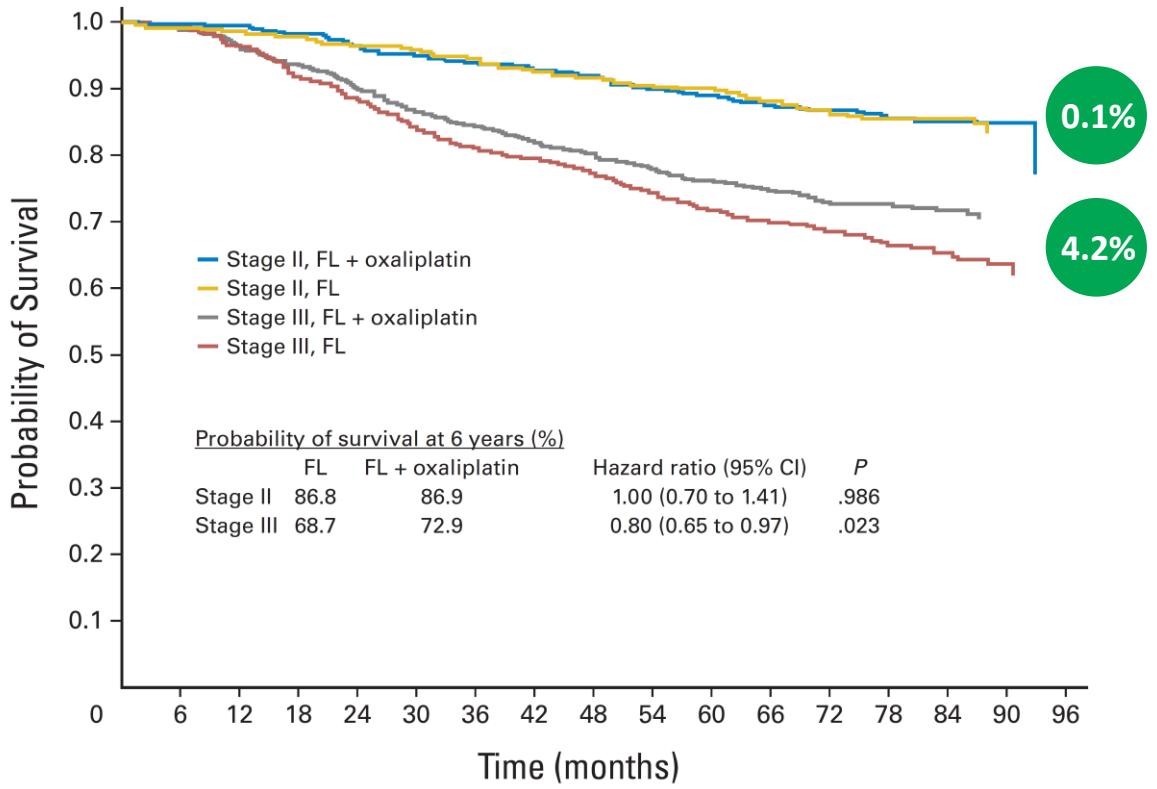
# MOSAIC: OS a 8 anni

## OS in ITT population




| No. at risk | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FL + oxaliplatin | 1,123 | 1,103 | 1,076 | 1,053 | 1,018 | 988 | 961 | 937 | 916 | 887 | 863 | 835 | 763 | 529 | 287 | 96 |
| FL | 1,123 | 1,100 | 1,071 | 1,033 | 1,003 | 967 | 940 | 912 | 889 | 862 | 829 | 786 | 723 | 499 | 283 | 96 |

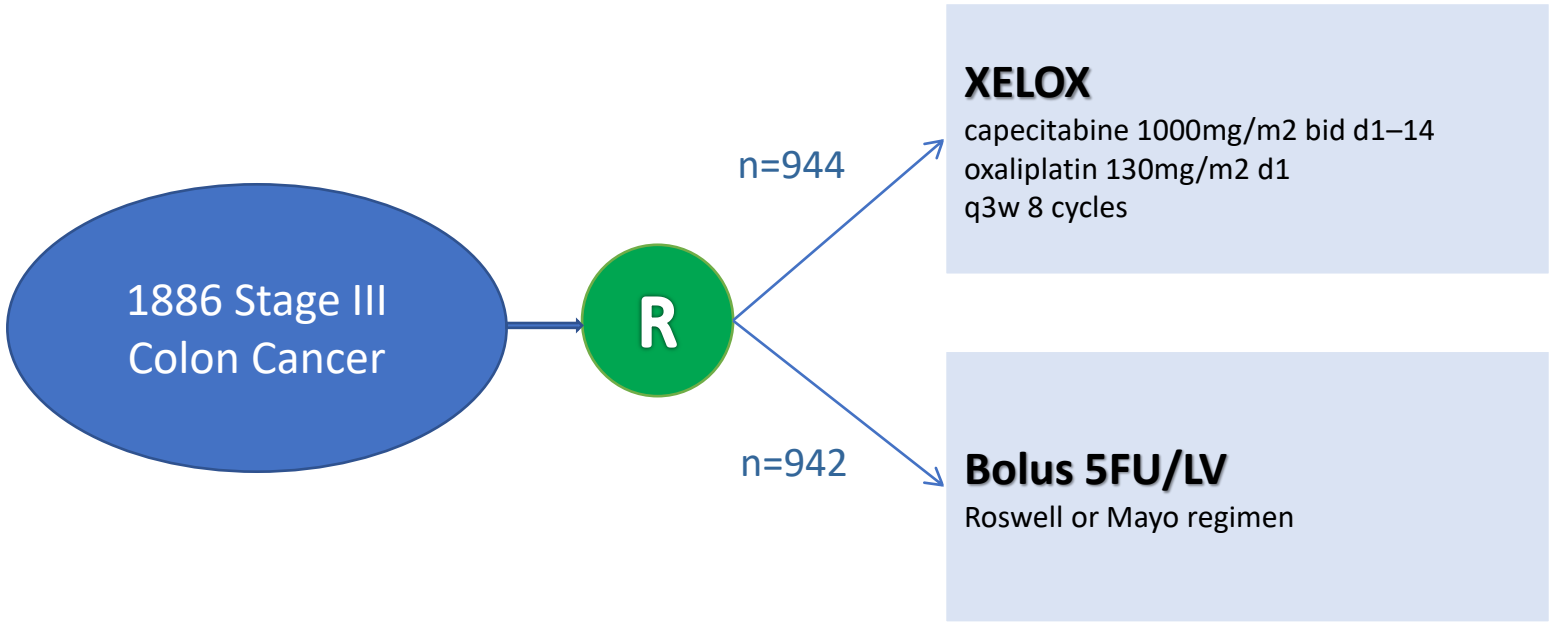
## OS by Stage




| No. at risk | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stage III | | | | | | | | | | | | | | | | |
| FL + oxaliplatin | 672 | 655 | 633 | 616 | 590 | 567 | 548 | 531 | 516 | 499 | 484 | 468 | 432 | 298 | 163 | 53 |
| FL | 675 | 658 | 635 | 602 | 580 | 548 | 528 | 511 | 492 | 470 | 444 | 416 | 392 | 278 | 153 | 55 |
| Stage II | | | | | | | | | | | | | | | | |
| FL + oxaliplatin | 451 | 448 | 443 | 437 | 428 | 421 | 413 | 406 | 400 | 388 | 379 | 367 | 331 | 231 | 124 | 43 |
| FL | 448 | 442 | 436 | 431 | 423 | 419 | 412 | 401 | 397 | 392 | 385 | 370 | 331 | 221 | 130 | 41 |

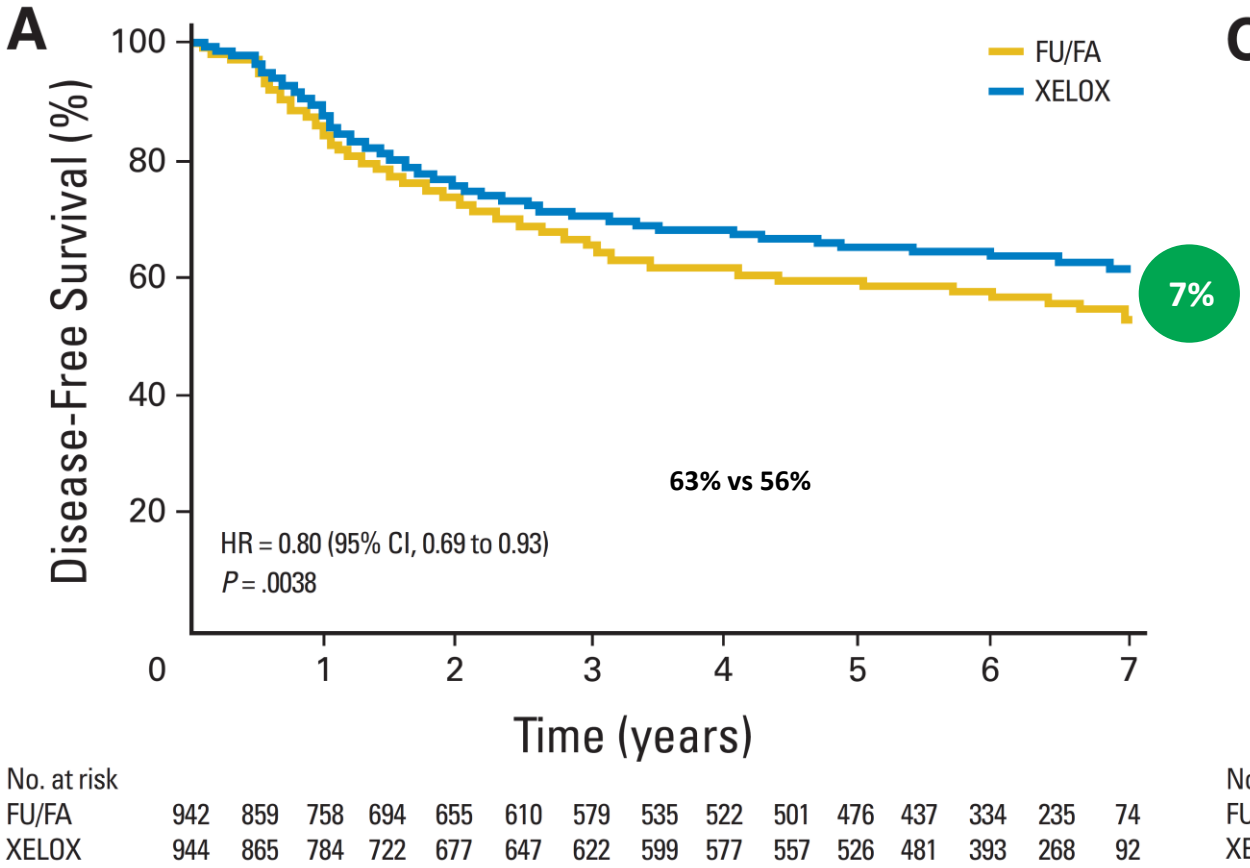
André T, et a. J Clin Oncol 2009;27(19):3109-16.

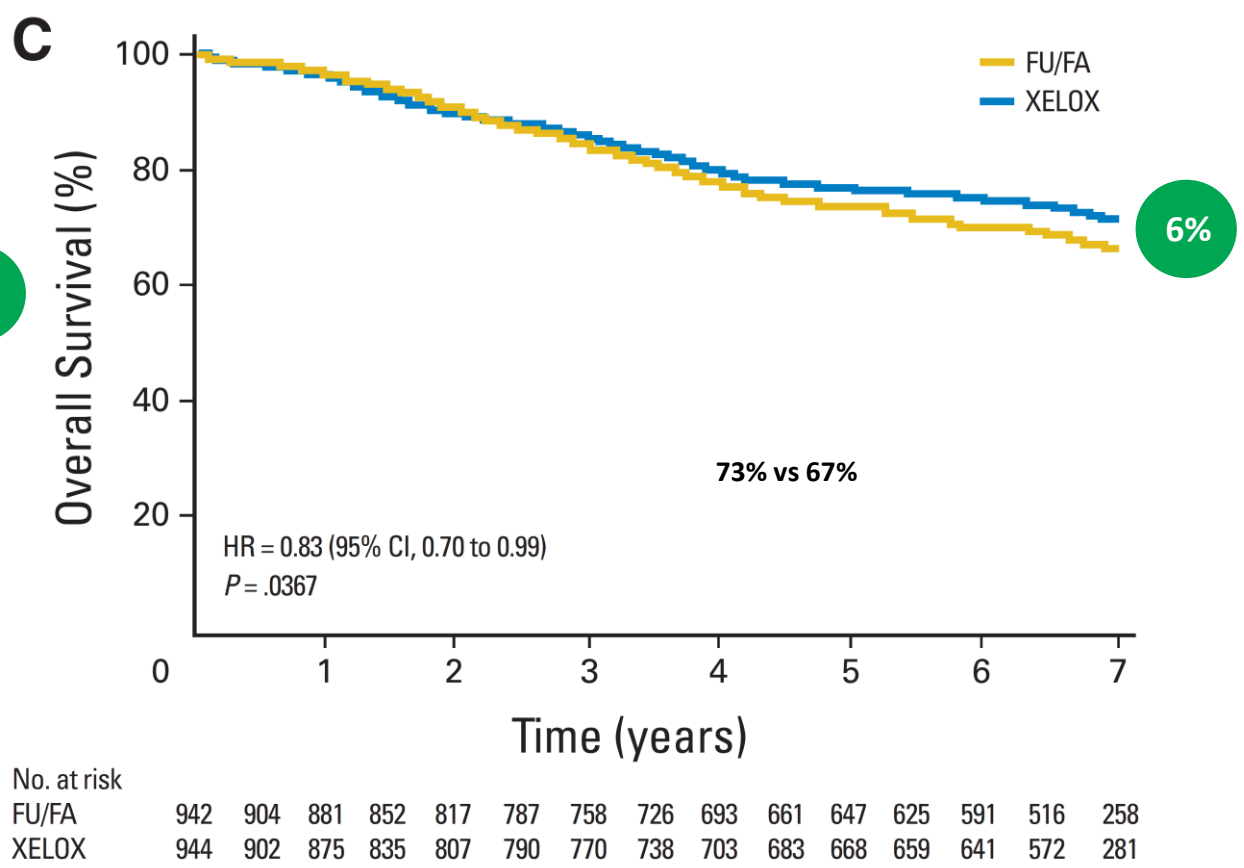
# Chemioterapia di combinazione: studio XELOX-A




- Primary endpoint: 3 year-DFS
- Secondary endpoints: RFS, OS, tolerability

# XELOX-A: OS e DFS a 7 anni



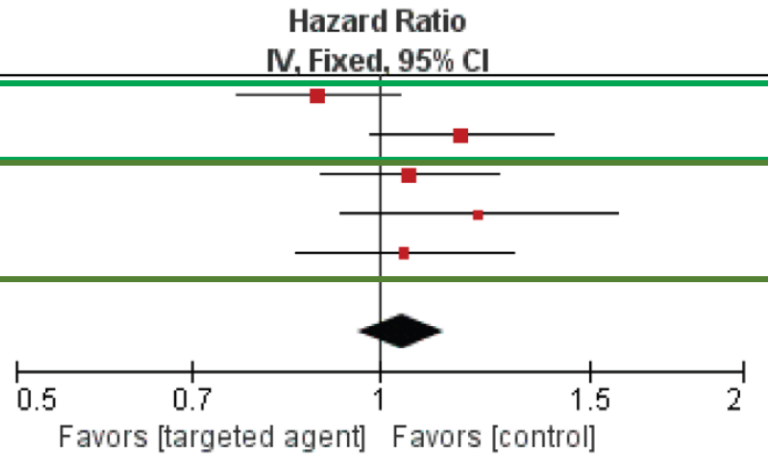

Schmoll HJ, et al. J Clin Oncol 2015;33(32):3733-40.

# Target therapies nella terapia adiuvante

**3-yr DFS**

| | Study or Subgroup | log[Hazard Ratio] | SE | targeted agent Total | control Total | Weight | Hazard Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| Bevacizumab | NSABP C-08 (2011) | -0.1165 | 0.08 | 1334 | 1338 | 28.0% | 0.89 [0.76, 1.04] |
| | AVANT (2012) | 0.157 | 0.0892 | 960 | 955 | 22.5% | 1.17 [0.98, 1.39] |
| Cetuximab | QUASAR2 (2016) | 0.0583 | 0.0867 | 972 | 967 | 23.8% | 1.06 [0.89, 1.26] |
| | NCCTG N-0147 (2012) | 0.1906 | 0.135 | 954 | 909 | 9.8% | 1.21 [0.93, 1.58] |
| | PETACC-8 (2014) | 0.0488 | 0.1064 | 791 | 811 | 15.8% | 1.05 [0.85, 1.29] |
| | **Total (95% CI)** | | | **5011** | **4980** | **100.0%** | **1.04 [0.96, 1.13]** |

Heterogeneity: Chi² = 6.84, df = 4 (P = 0.14); I² = 42%
Test for overall effect: Z = 1.02 (P = 0.31)



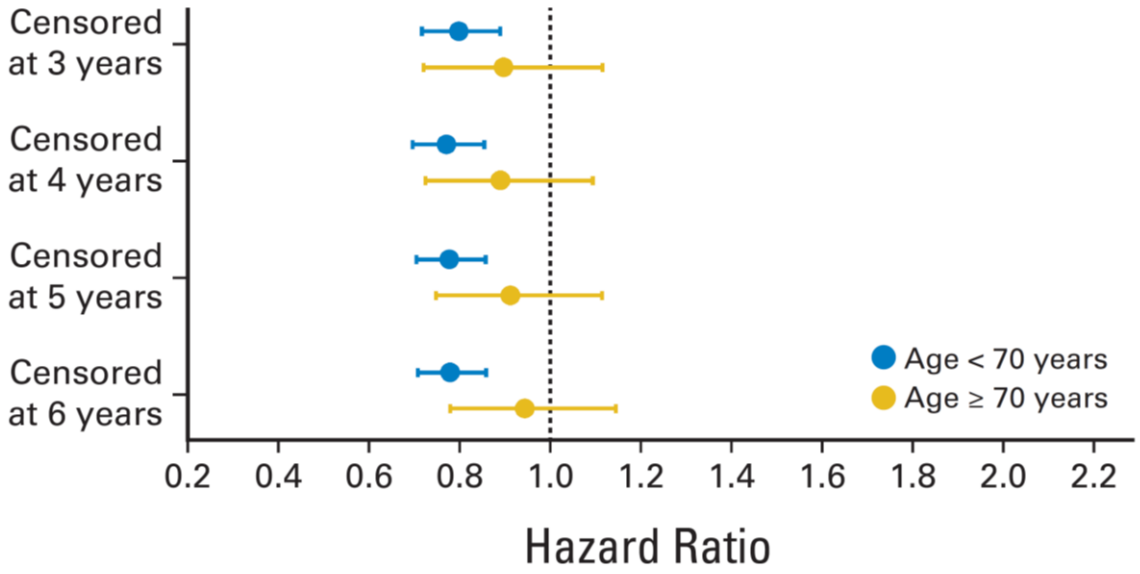

Kim BJ, et al. Oncotarget 2017;8(19):31112-31118.

# Chemioterapia adiuvante nel III stadio: sintesi delle evidenze (3-y DFS)

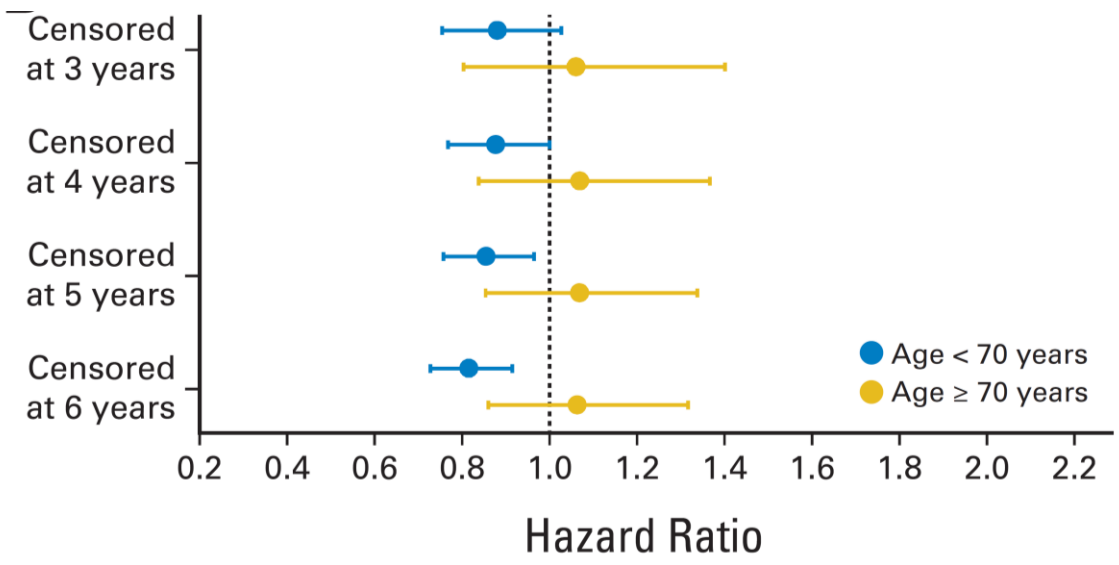
| | Study, year | Treatment | 3-y DFS |
|---|---|---|---|
| **Surgery alone** | Moertel, 1990 | Surveillance | 52% |
| | IMPACT, 1993 | Surveillance | 44% |
| **Mono-CTx** | IMPACT, 1993 | 5-FU | 62% |
| | André, 2003 | 5-FU | 63% |
| | MOSAIC, 2004 | 5-FU | 65% |
| | INT0089, 2005 | 5-FU | 63% |
| | XELOX-A, 2010 | 5-FU | 66% |
| | X-ACT, 2005 | Capecitabine | 64% |
| **Poli-CTx** | MOSAIC, 2004 | FOLFOX4 | 73% |
| | XELOX-A, 2010 | XELOX | 71% |

# Chemioterapia adiuvante con oxaliplatino nel paziente anziano (>70 anni)

**DFS**




**OS**




McCleary NJ, et al. J Clin Oncol 2013;31(20):2600-6.

# Neuropatia da oxaliplatino: tossicità a lungo termine

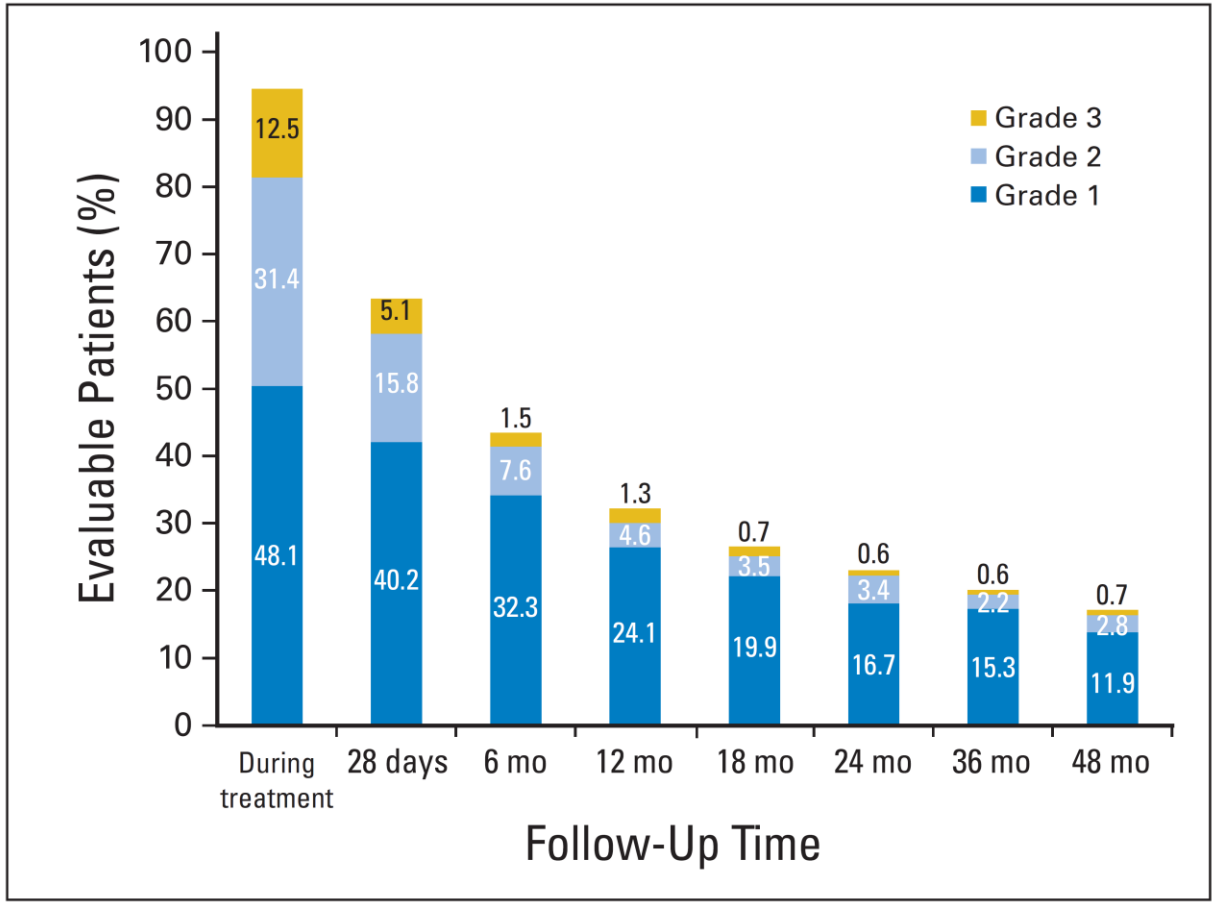
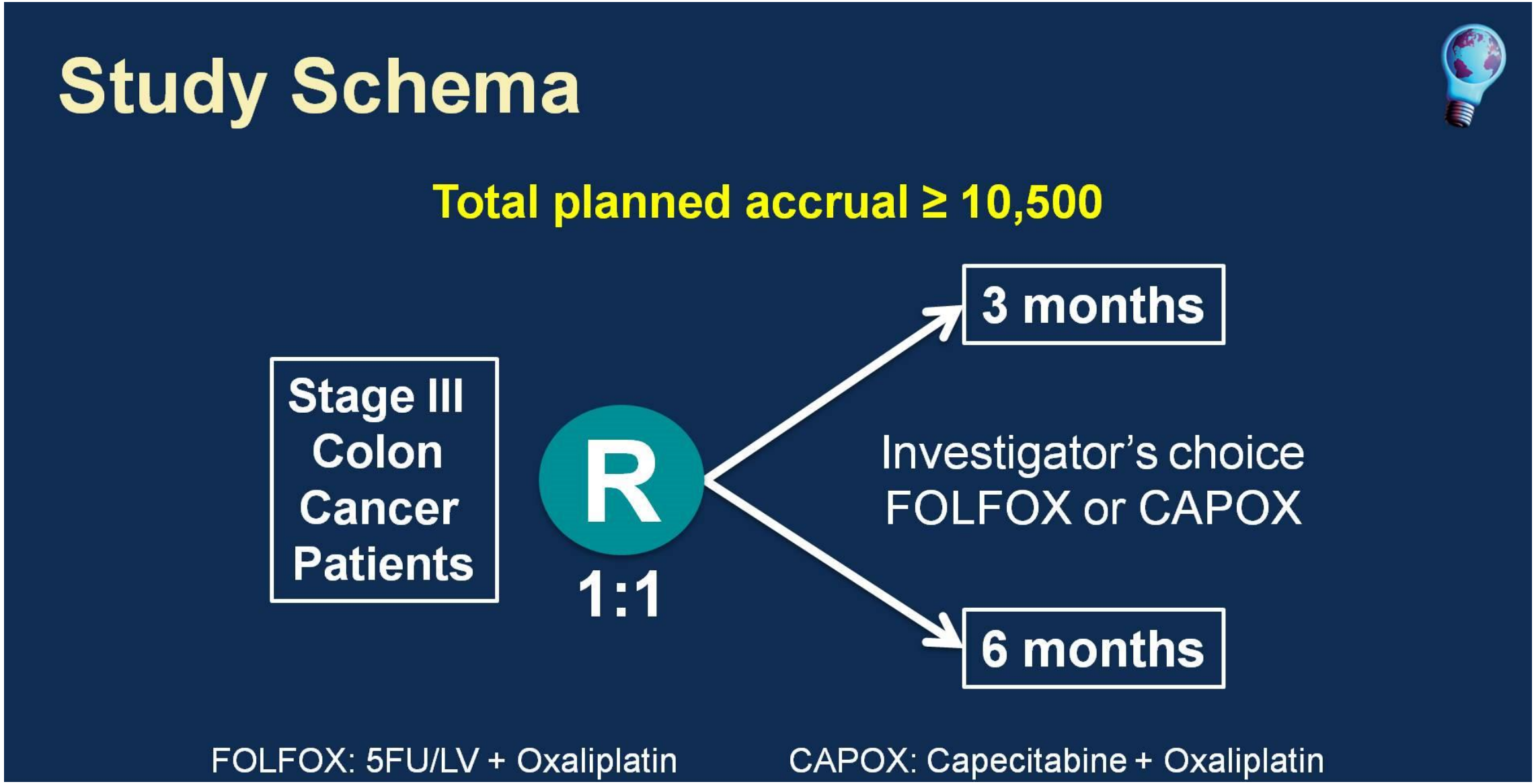



**Fig 5.** Proportion of patients treated with oxaliplatin plus fluorouracil and leucovorin with grade 1, 2, or 3 peripheral sensory neuropathy during treatment and after follow-up to 4 years.

André T, et a. J Clin Oncol 2009;27(19):3109-16.

# Durata del trattamento: 3 vs 6 mesi

## International Duration Evaluation od Adjuvant Chemotherapy (IDEA) collaboration



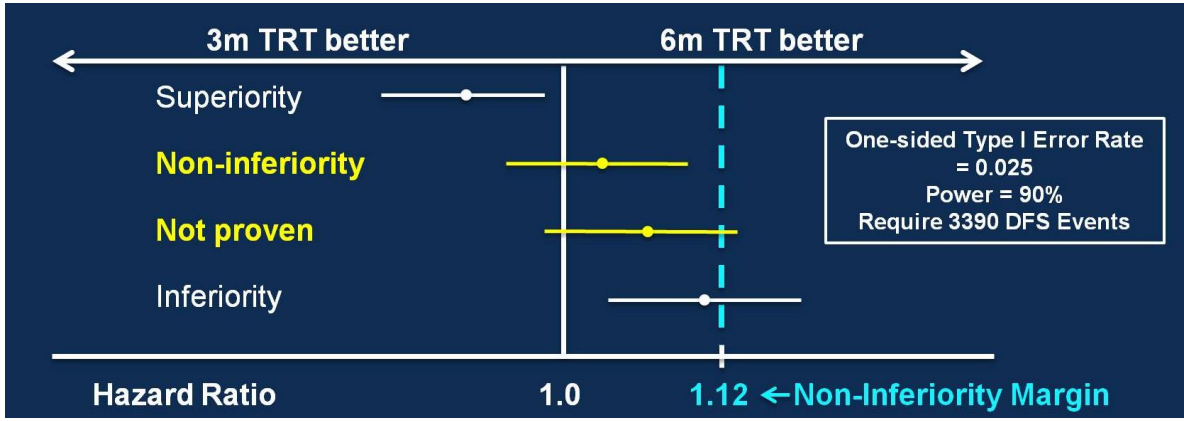

Shi Q, Asco 2017

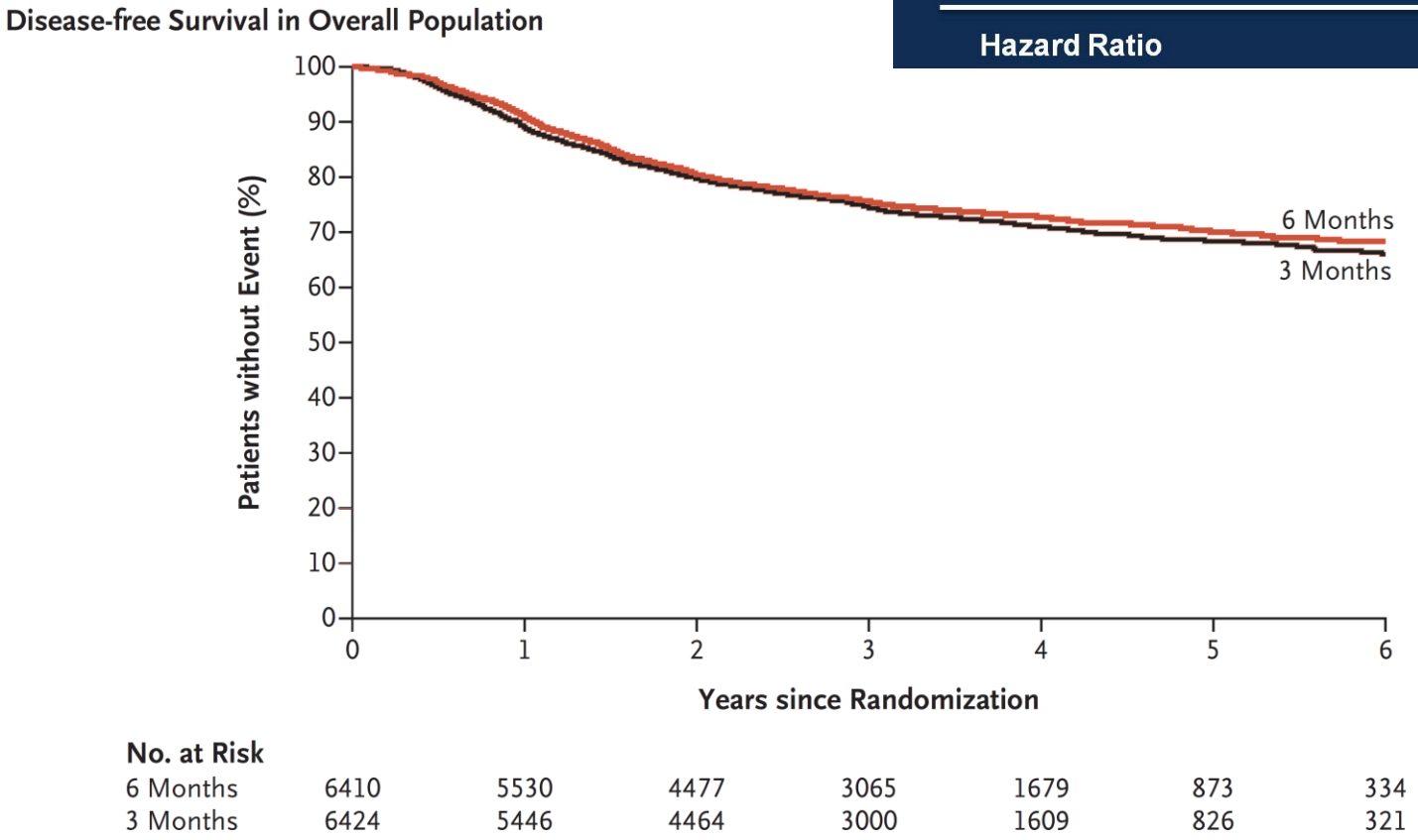
# IDEA Trials Summary

| Trial | Regimen(s) | Stage III Colon Cancer Patients* | Enrolling Country |
|---|---|---|---|
| TOSCA | CAPOX or FOLFOX4 | 2402 | Italy |
| SCOT | CAPOX or mFOLFOX6 | 3983 | UK, Denmark, Spain, Australia, Sweden, New Zealand |
| IDEA France | CAPOX or mFOLFOX6 | 2010 | France |
| C80702 | mFOLFOX6 | 2440 | US, Canada |
| HORG | CAPOX or FOLFOX4 | 708 | Greece |
| ACHIEVE | CAPOX or mFOLFOX6 | 1291 | Japan |

*Only stage III colon cancer patients were included in the pooled primary analysis

# IDEA: Risultati nella ITT population




**HR 1.07 (1.00 -1.15)**

**Non-inferiority: not proven**

Grothey A,et al. N Engl J Med 2018;378(13):1177-1188.

# IDEA: Risultati per schema e gruppo di rischio

| 3 yr DFS rate (%) and HR by regimen and risk group | | Regimen | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | CAPOX | | | FOLFOX | | | CAPOX/FOLFOX combined | | |
| | | 3 yr DFS, % (95% CI) | | *HR (95% CI)* | 3 yr DFS, % (95% CI) | | *HR (95% CI)* | 3 yr DFS, % (95% CI) | | *HR (95% CI)* |
| | | 3 m | 6 m | | 3 m | 6 m | | 3 m | 6 m | |
| Risk group | Low-risk (T1-3 N1) ~60% | **85.0** (83.1-86.9) | **83.1** (81.1-85.2) | ***0.85*** *(0.71-1.01)* | **81.9** (80.2-83.6) | **83.5** (81.9-85.1) | ***1.10*** *(0.96-1.26)* | **83.1** (81.8-84.4) | **83.3** (82.1-84.6) | ***1.01*** *(0.90-1.12)* |
| | High-risk (T4 and / or N2) ~40% | **64.1** (61.3-67.1) | **64.0** (61.2-67.0) | ***1.02*** *(0.89-1.17)* | **61.5** (58.9-64.1) | **64.7** (62.2-67.3) | ***1.20*** *(1.07-1.35)* | **62.7** (60.8-64.4) | **64.4** (62.6-66.4) | ***1.12*** *(1.03-1.23)* |
| | Risk groups combined | **75.9** (74.2-77.6) | **74.8** (73.1-76.6) | ***0.95*** *(0.85-1.06)* | **73.6** (72.2-75.1) | **76.0** (74.6-77.5) | ***1.16*** *(1.06-1.26)* | **P-value interaction test: Regimen: 0.0061 Risk group: 0.11** | | |

Non-inferior | Not proven | Inferior

Grothey A,et al. N Engl J Med 2018;378(13):1177-1188.

# IDEA: Eventi avversi

**Table 3.** Selected Adverse Events, According to Treatment and Duration of Therapy.*

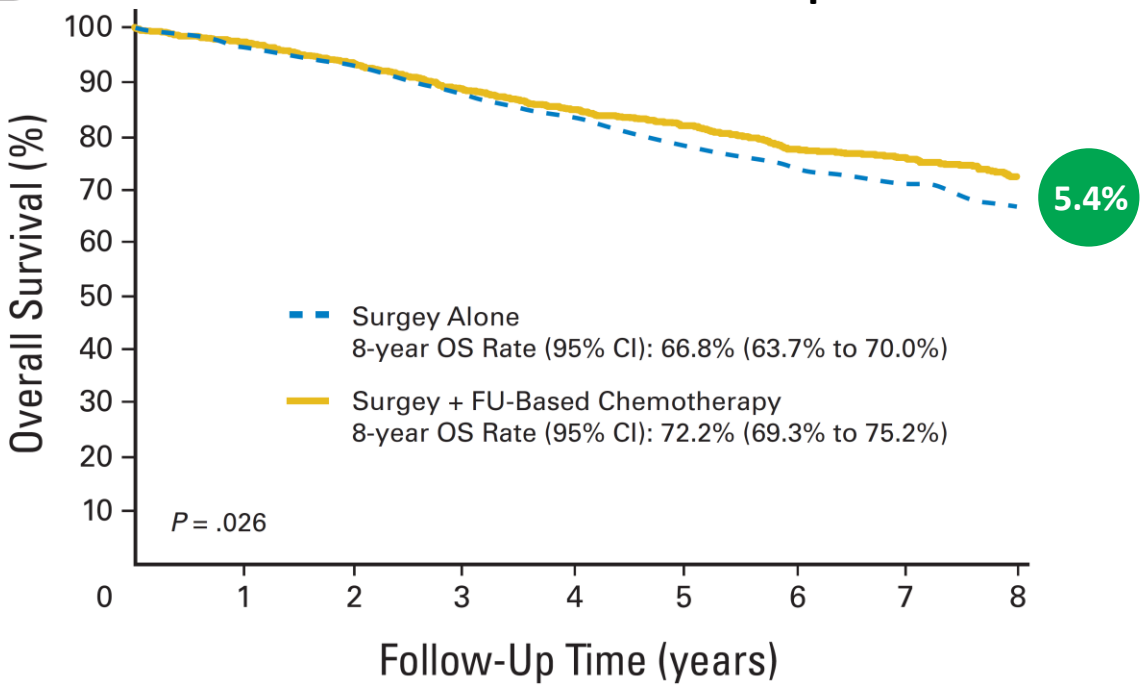
| Adverse Event | FOLFOX | | | | CAPOX | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 or 4 | P Value | Grade 1 | Grade 2 | Grade 3 or 4 | P Value |
| | *number (percent)* | | | | *number (percent)* | | | |
| Any adverse event | | | | <0.001 | | | | <0.001 |
| 3 mo | 1008 (30.7) | 1039 (31.6) | 1236 (37.6) | | 496 (35.0) | 578 (40.8) | 342 (24.2) | |
| 6 mo | 363 (11.0) | 1056 (32.1) | 1874 (56.9) | | 203 (14.6) | 674 (48.5) | 512 (36.9) | |
| Peripheral sensory neurotoxicity† | | | | <0.001 | | | | <0.001 |
| 3 mo | 2661 (83.4) | 450 (14.1) | 80 (2.5) | | 1211 (85.8) | 164 (11.6) | 37 (2.6) | |
| 6 mo | 1700 (52.2) | 1036 (31.8) | 519 (15.9) | | 763 (55.0) | 500 (36.0) | 124 (8.9) | |

Grothey A,et al. N Engl J Med 2018;378(13):1177-1188.

# Chemioterapia adiuvante nello stadio II

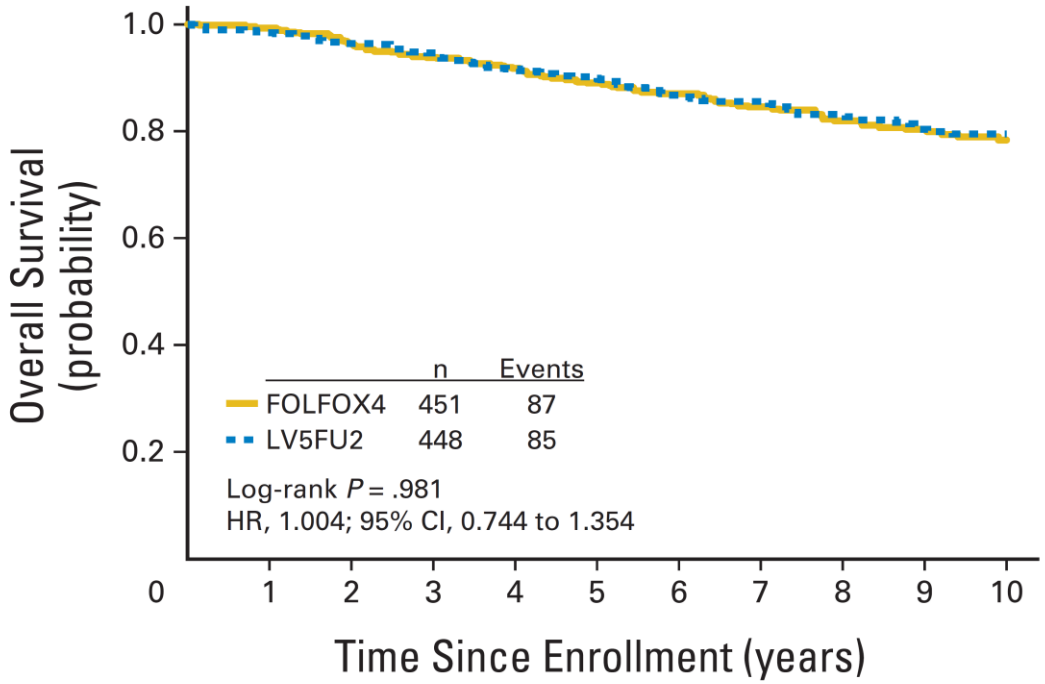
B

## Modesto beneficio delle fluoropirimidine




B

## Nessun vantaggio dall'aggiunta di Oxali



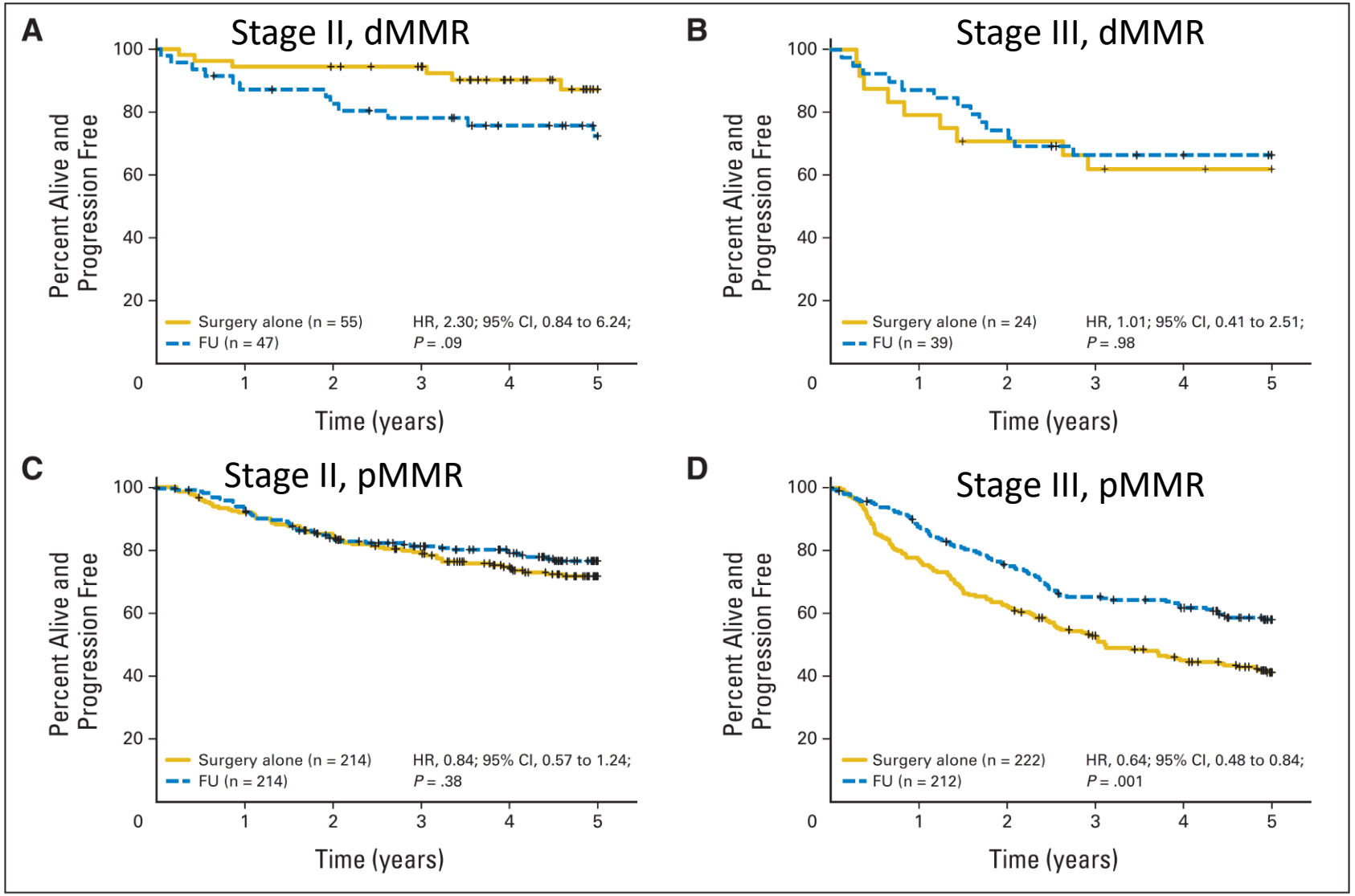

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| FOLFOX4 | | | | | | | | | | | |
| No. at risk | 451 | 445 | 432 | 418 | 404 | 390 | 358 | 282 | 200 | 183 | 144 |
| Events | 0 | 4 | 17 | 29 | 38 | 49 | 58 | 67 | 74 | 78 | 82 |
| LV5FU2 | | | | | | | | | | | |
| No. at risk | 448 | 439 | 425 | 416 | 399 | 392 | 364 | 271 | 193 | 174 | 138 |
| Events | 0 | 7 | 16 | 25 | 38 | 45 | 59 | 63 | 70 | 76 | 78 |

Sargent D, et al. J Clin Oncol 2009;27(6):872-7. André T, et a. J Clin Oncol 2009;27(19):3109-16.

# Instabilità dei microsatelliti e 5-FU adiuvante

**MSI (n=165)**

**MSS (n=863)**

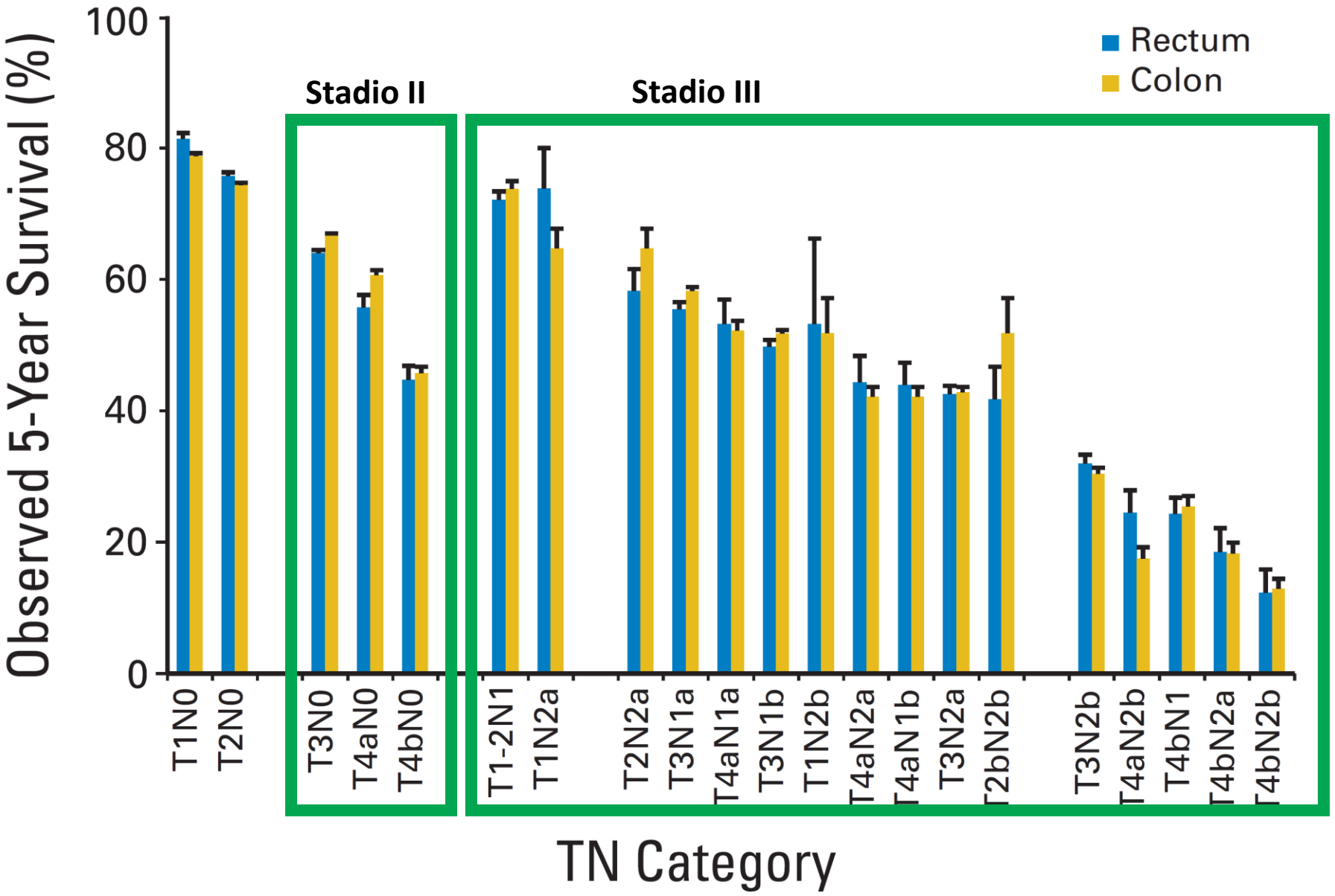



In pz con deficit del MMR:

- Nessuna differenza nello stadio III
- Può essere detrimentale nello stadio II

Sargent DJ, et al. J Clin Oncol 2010;28(20):3219-26.

# Alcuni stadi II hanno prognosi sfavorevole



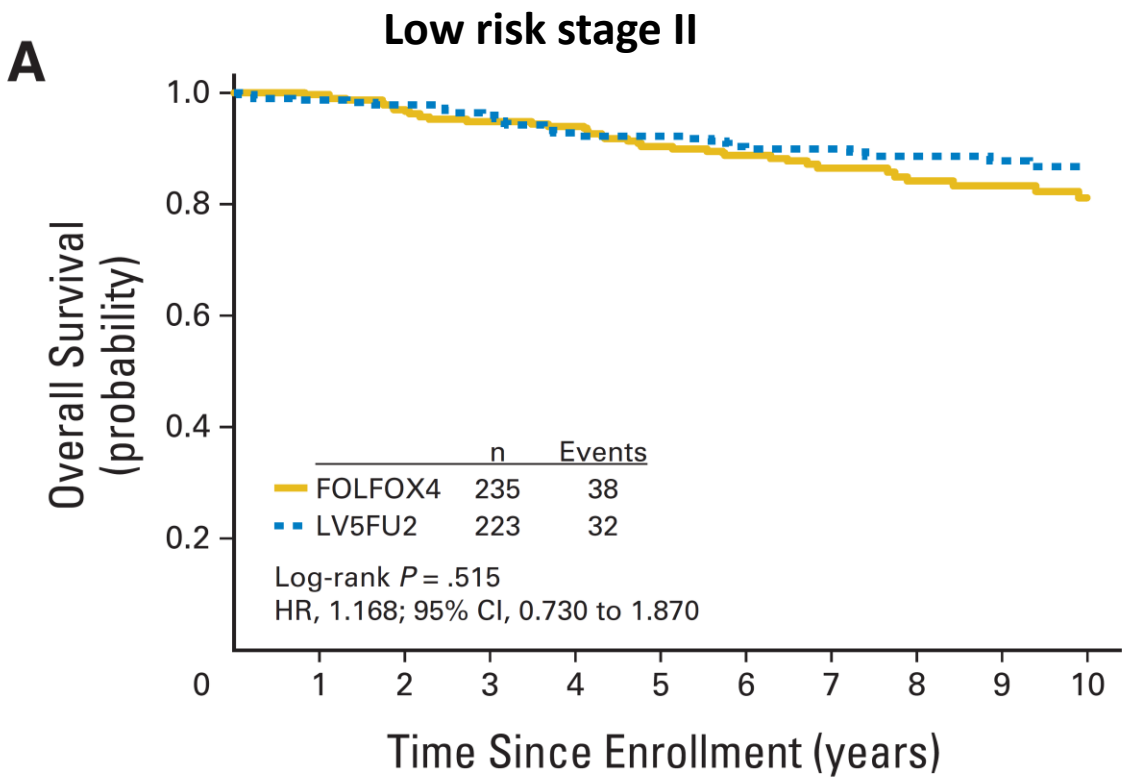

Gunderson LL, et al. J Clin Oncol 2010;28(2):264-71.

# Fattori di rischio nello stadio II

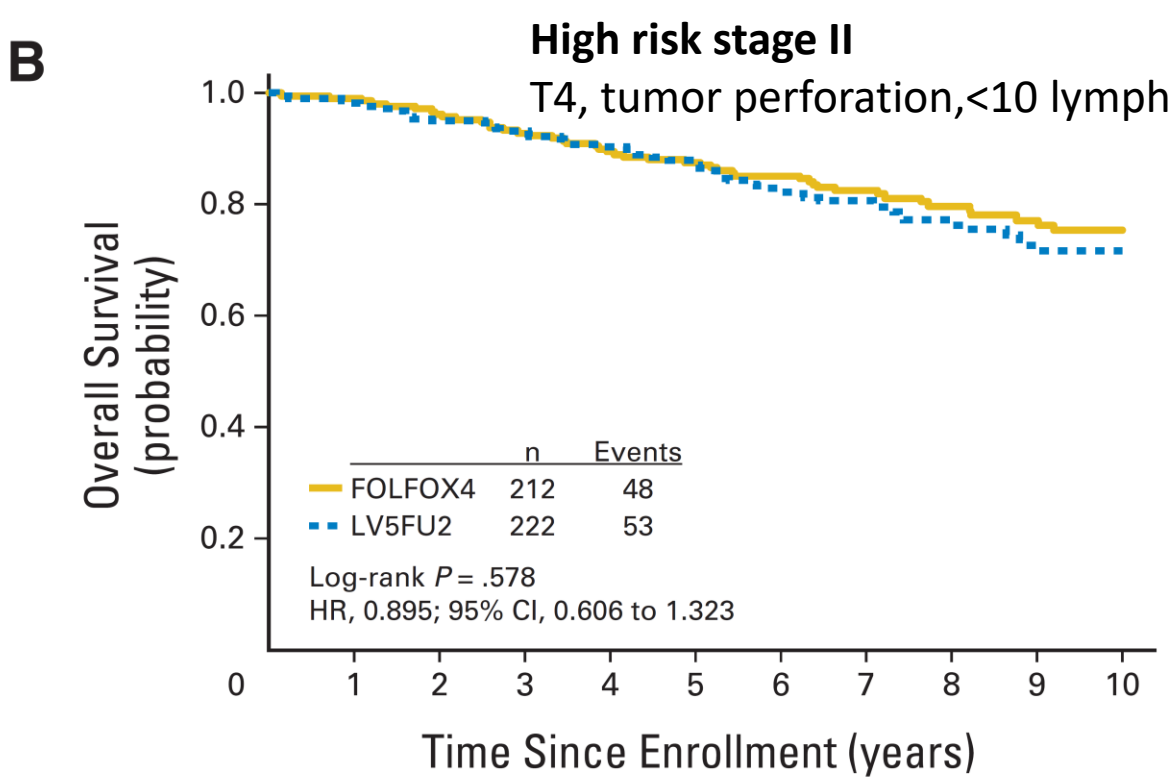
- pT4 (inclusa perforazione)
- Inadeguato sampling linfonodale (<12)
- Alto grado di differenziazione (G3-G4)
- Invasione linfatica/vascolare/perineurale
- Margini positivi, vicini o indeterminati
- Esordio con occlusione intestinale
- Elevati livelli preoperatori di CEA

Argilés G, et al. Ann Oncol 2020;31(10):1291-1305. Baxter NN, et al. J Clin Oncol 2022;40(8):892-910.

# Oxaliplatino adiuvante nello stadio II ad alto rischio




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| FOLFOX4 | | | | | | | | | | | |
| No. at risk | 235 | 232 | 226 | 219 | 215 | 205 | 188 | 149 | 101 | 94 | 68 |
| Events | 0 | 2 | 8 | 13 | 15 | 22 | 26 | 30 | 33 | 34 | 36 |
| LV5FU2 | | | | | | | | | | | |
| No. at risk | 223 | 220 | 216 | 211 | 203 | 202 | 190 | 142 | 104 | 94 | 77 |
| Events | 0 | 4 | 5 | 10 | 17 | 18 | 22 | 22 | 24 | 25 | 27 |

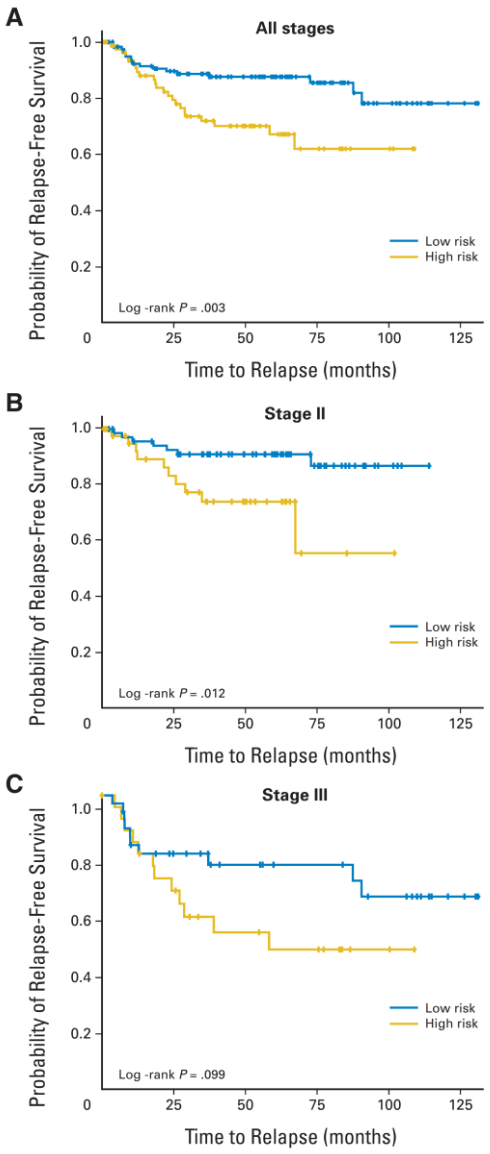



| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| FOLFOX4 | | | | | | | | | | | |
| No. at risk | 212 | 209 | 203 | 196 | 186 | 182 | 168 | 131 | 98 | 88 | 75 |
| Events | 0 | 3 | 9 | 16 | 23 | 27 | 31 | 36 | 40 | 44 | 45 |
| LV5FU2 | | | | | | | | | | | |
| No. at risk | 222 | 216 | 206 | 202 | 193 | 187 | 171 | 126 | 87 | 78 | 59 |
| Events | 0 | 4 | 12 | 16 | 22 | 28 | 38 | 41 | 46 | 51 | 52 |

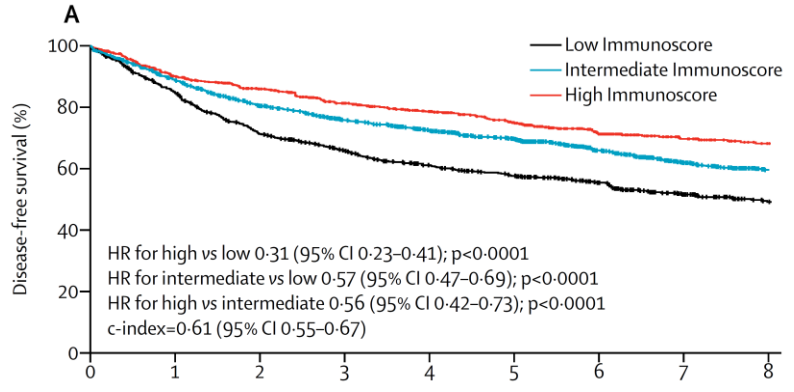
André T, et al. J Clin Oncol. 2015;33(35):4176-87.

# Nuovi strumenti per la stratificazione del rischio

## Multigene assays (ex. Colprint)



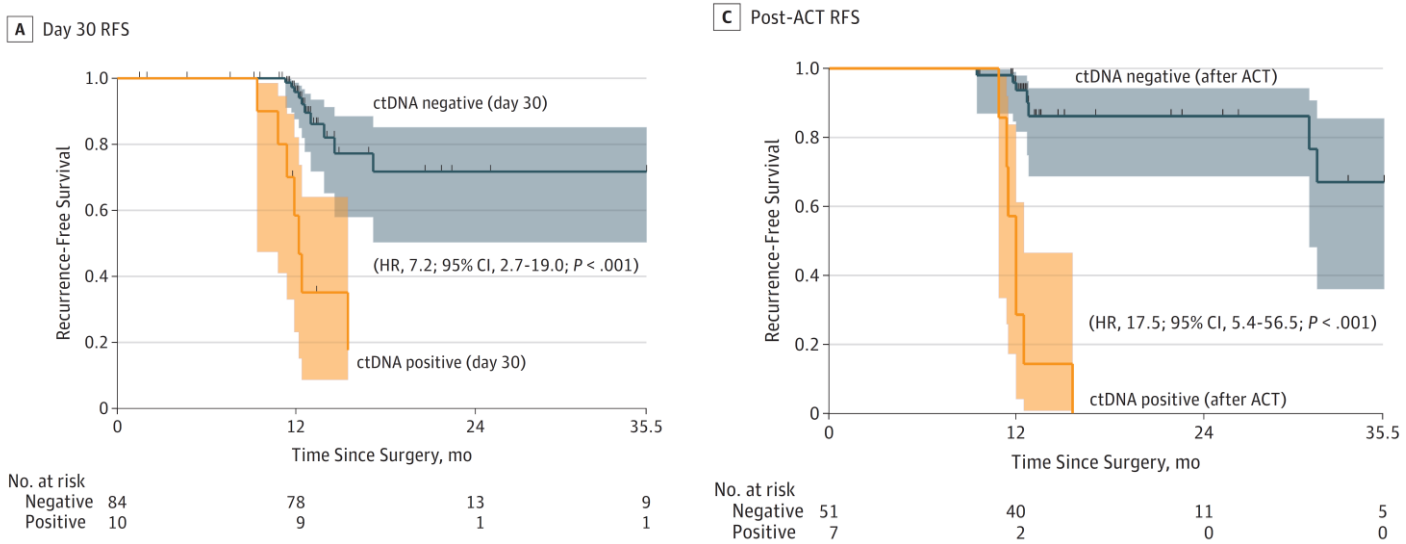

## Immunoscore




**Number at risk**

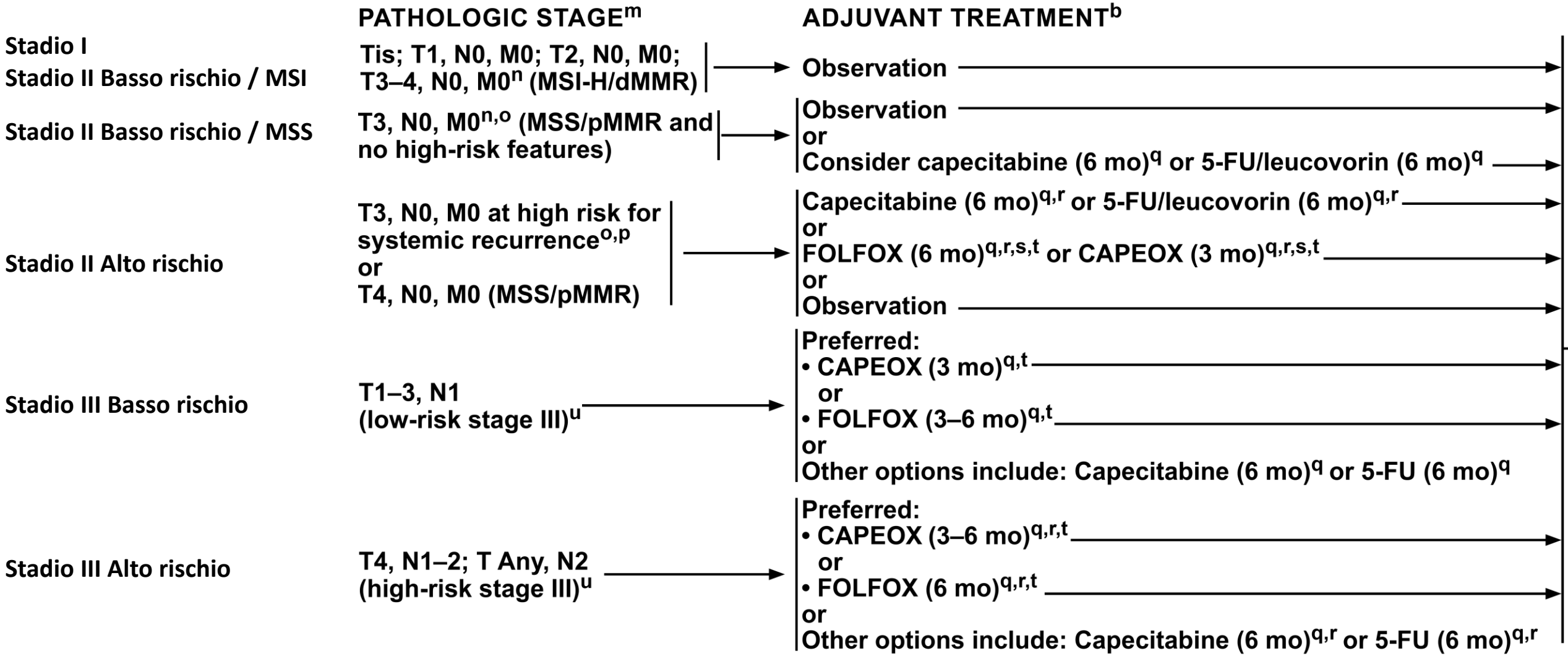
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Low Immunoscore | 702 | 566 | 468 | 411 | 358 | 321 | 259 | 194 | 150 |
| Intermediate Immunoscore | 1271 | 1069 | 930 | 839 | 763 | 675 | 526 | 406 | 324 |
| High Immunoscore | 708 | 594 | 535 | 469 | 417 | 359 | 273 | 208 | 172 |

## ctDNA




Salazar R, et al. J Clin Oncol 2011;29(1):17-24. Pagès F, et al. Lancet 2018;391(10135):2128-2139. Reinert T, et al. JAMA Oncol.2019;5(8):1124-1131.

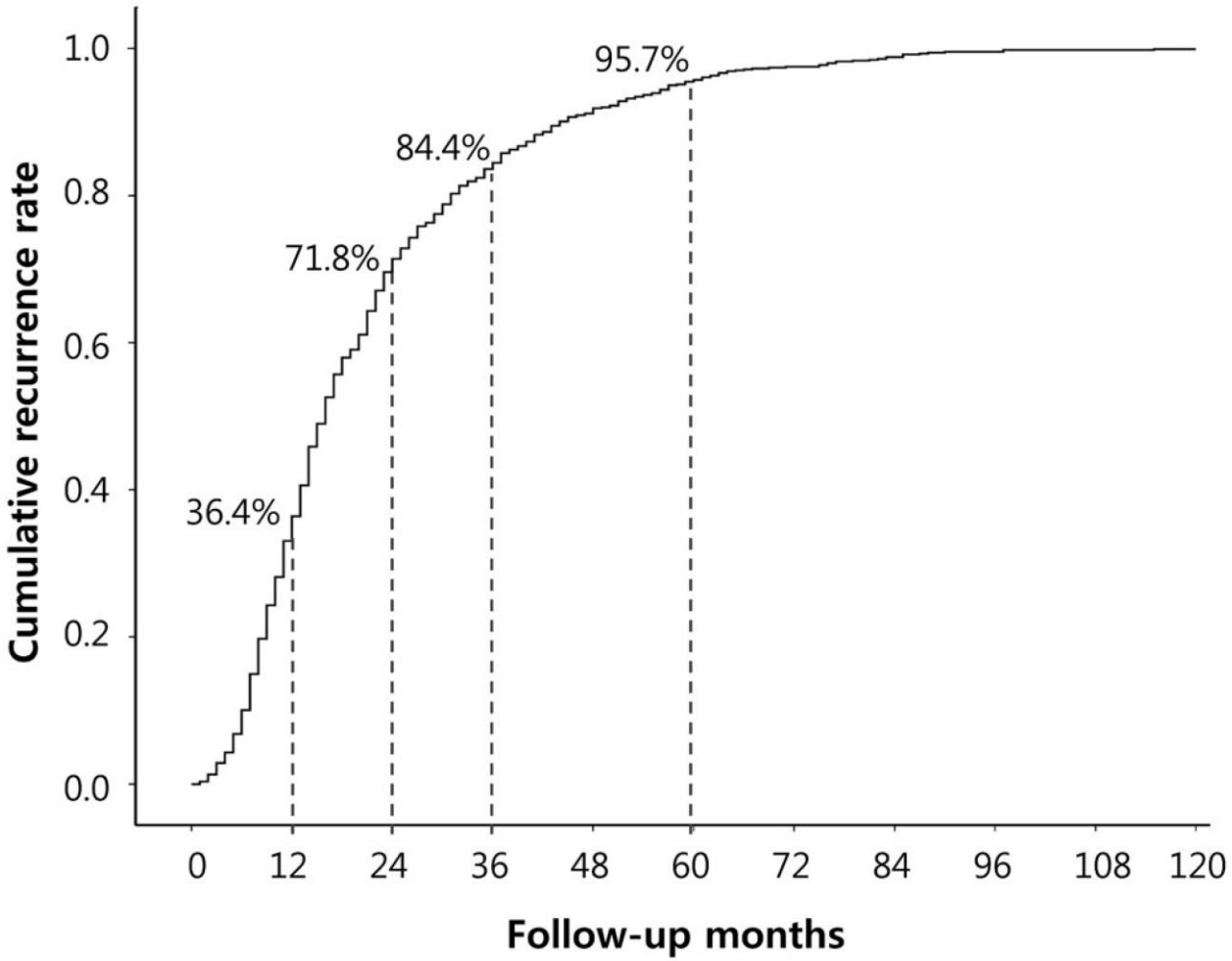
# Tumori del colon operati: Algoritmo di terapia adiuvante




NCCN Guidelines 2022

# Follow-up: durata del follow-up

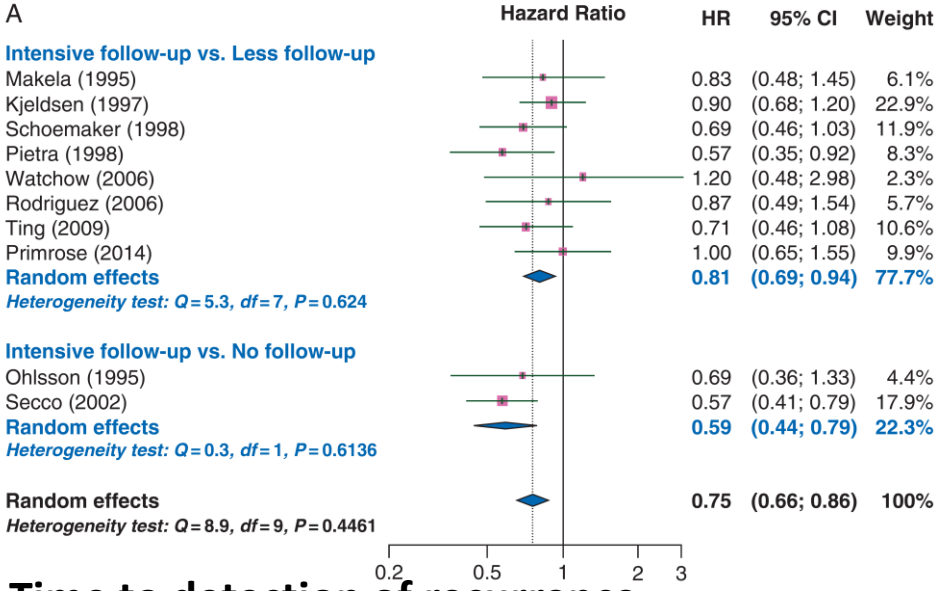
**Il 95% delle ricadute avviene entro i 5 anni**



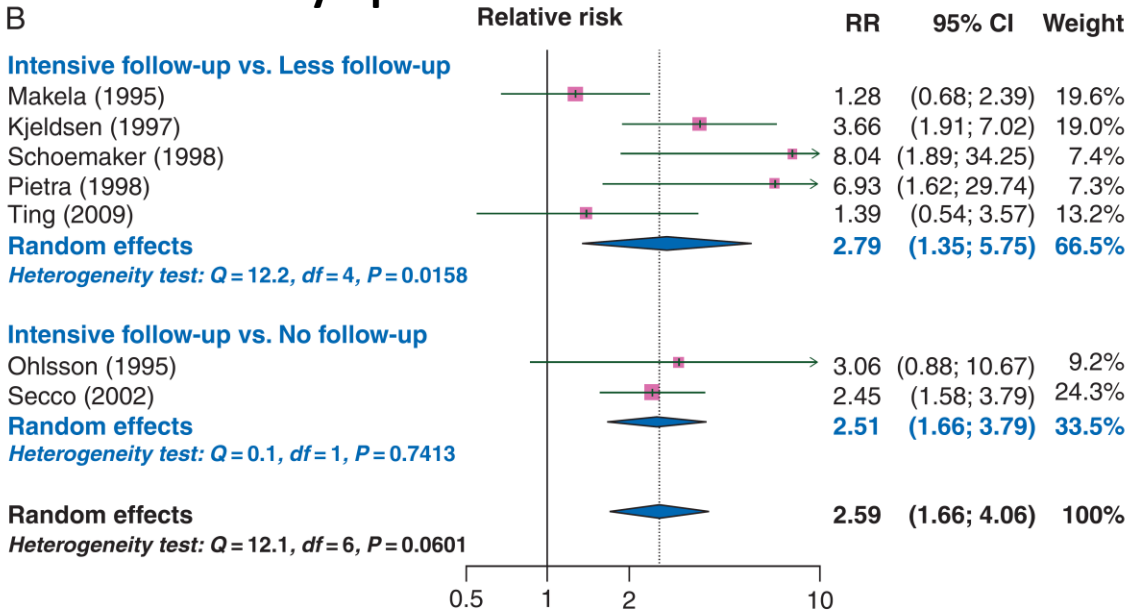

Seo SI, et al. J Surg Oncol 2013;108(1):9-13.

# Follow-up: ruolo del follow-up «intensivo»

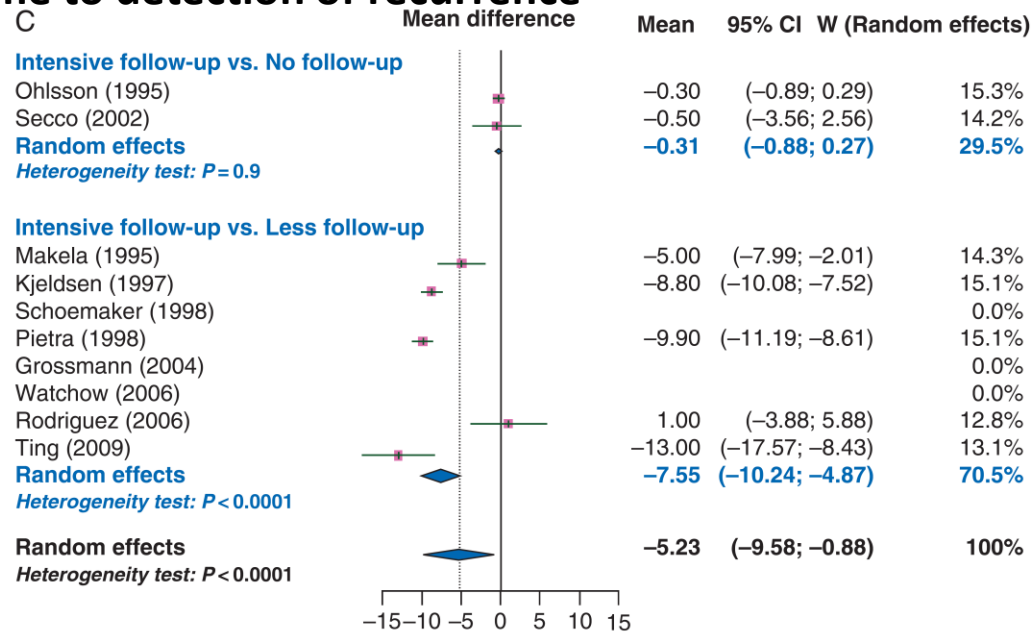
## Overall survival



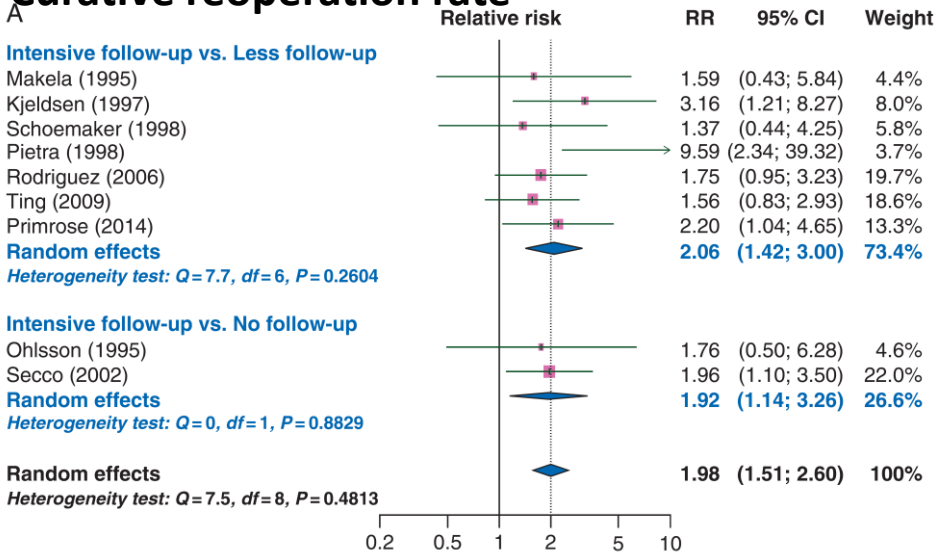

## Detection of asymptomatic recurrence




## Time to detection of recurrence




## Curative reoperation rate




Pita-Fernández S, et al. Ann Oncol 2015;26(4):644-656.

# Follow-up: linee guida AIOM 2021

| Qualità globale delle prove | Raccomandazione clinica | Forza della raccomandazione |
|---|---|---|
| **Moderata** | Il dosaggio del CEA ogni 4-6 mesi per i primi 3 anni e ogni 6 mesi per i due anni successivi può essere preso in considerazione (18) | **Condizionata a favore** |
| **COI: Nessun conflitto dichiarato** | | |

| Qualità globale delle prove | Raccomandazione clinica | Forza della raccomandazione |
|---|---|---|
| **Moderata** | Una prima colonscopia di controllo dovrebbe essere presa in considerazione come prima opzione dopo 1 anno dall'intervento, in seguito dopo 3 anni in assenza di adenomi e quindi ogni 5 anni, qualora età e comorbidità non lo controindichino (15;26). | **Forte a favore** |
| **COI: Nessun conflitto dichiarato** | | |

| Qualità globale delle prove | Raccomandazione clinica | Forza della raccomandazione |
|---|---|---|
| **Moderata** | Seppure non esistano indicazioni universalmente condivise sulla modalità ideale di follow-up, le seguenti indicazioni dovrebbero essere prese in considerazione come prima opzione:<br>- Esame Clinico ogni 4-6 mesi per i primi 3 anni; ogni 6 mesi per i due anni successivi<br>- TC Torace-Addome con contrasto: ogni 6-12 mesi per i primi 3-5 anni in funzione dell'entità del rischio.<br>Ecografia Addome e Rx Torace possono rappresentare un' opzione alternativa alla TC considerando però la minore sensibilità (13;18;20). | **Forte a favore** |
| **COI: Nessun conflitto dichiarato** | | |

| Qualità globale delle prove | Raccomandazione clinica | Forza della raccomandazione |
|---|---|---|
| **Bassa** | L'uso della FDG PET nei programmi di follow-up non deve essere presa in considerazione, se non come metodica di secondo livello in caso di dubbi (25). | **Forte a sfavore** |
| **COI: Nessun conflitto dichiarato** | | |

| Qualità globale delle prove | Raccomandazione clinica | Forza della raccomandazione |
|---|---|---|
| **Bassa** | Può essere indicato consigliare ai pazienti di evitare uno stile di vita sedentario praticare nel corso della settimana attività fisica di moderata intensità per almeno 150 minuti o 75 minuti di attività fisica intensa (45-48). | **Condizionata a favore** |
| **COI: Nessun conflitto dichiarato** | | |

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Grazie per l'attenzione

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