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

SACRO CUORE DON CALABRIA
I R C C S
Cancer Care Center

Incontri di aggiornamento del Dipartimento Oncologico

Responsabile Scientifico:
DOTT.SSA STEFANIA GORI

Mercoledì 26 ottobre
- Centro Formazione e Solidarietà -

Il carcinoma del colon retto

Carcinoma del retto: trattamento neoadiuvante

Elisa Bertocchi
U.O.C. Chirurgia Generale
IRCCS Ospedale Sacro Cuore Don Calabria
Negrar di Valpolicella (VR)

Terapia neoadiuvante: standard di cura nel paziente con carcinoma del retto localmente avanzato

JOURNAL OF CLINICAL ONCOLOGY

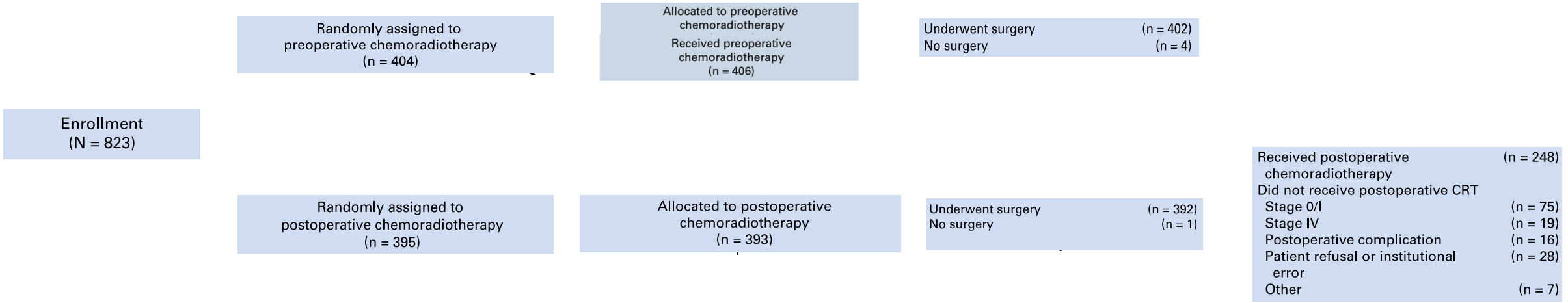
Preoperative Versus Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial After a Median Follow-Up of 11 Years

Rolf Sauer, Torsten Liersch, Susanne Merkel, Rainer Fietkau, Werner Hohenberger, Clemens Hess, Heinz Becker, Hans-Rudolf Raab, Marie-Therese Villanueva, Helmut Witzigmann, Christian Wittekind, Tim Beissbarth, and Claus Rödel

German Rectal Cancer Study Group (GRCSG) trial – 2004/2011

Concetto moderno dello «standard of care» nel cancro del retto localmente avanzato

Adenocarcinoma del retto (< 16 cm) - T3-T4 o N+



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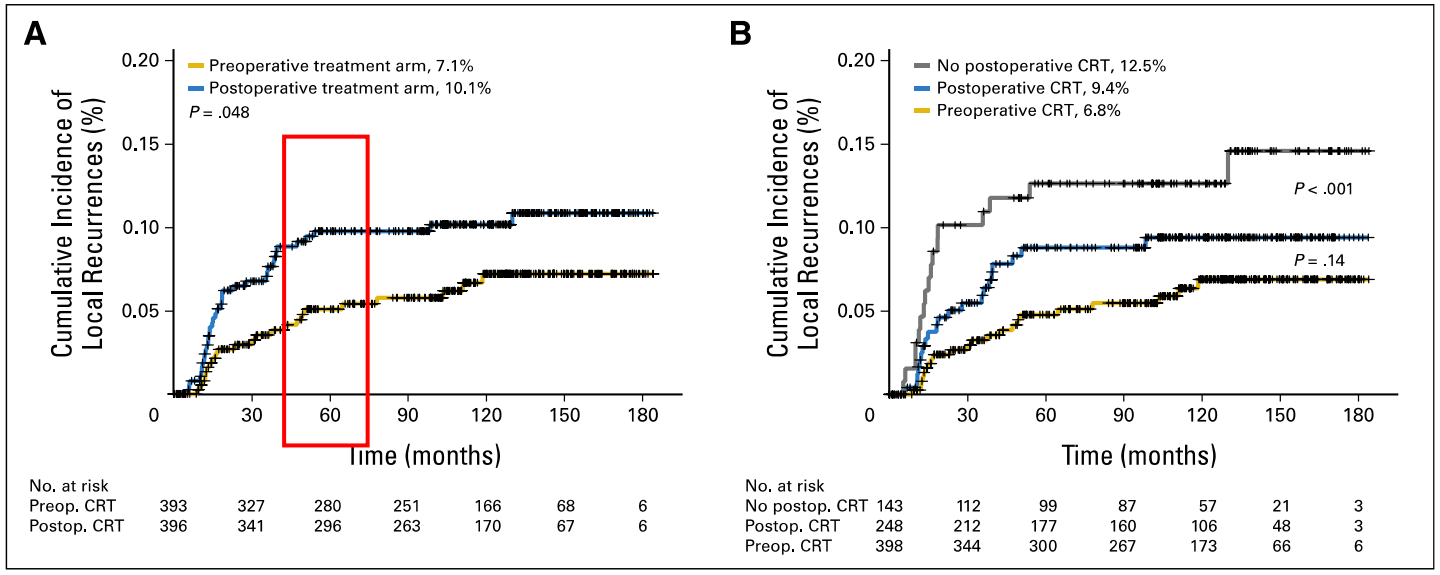

Follow-up a 5 anni:

- Overall Survival non differente (76% VS 74%)
- **Ripresa locale di malattia più bassa nel gruppo sottoposto a terapia neoadiuvante (6% VS 13%** - p < 0.006)

Terapia neoadiuvante: standard di cura nel paziente con carcinoma del retto localmente avanzato

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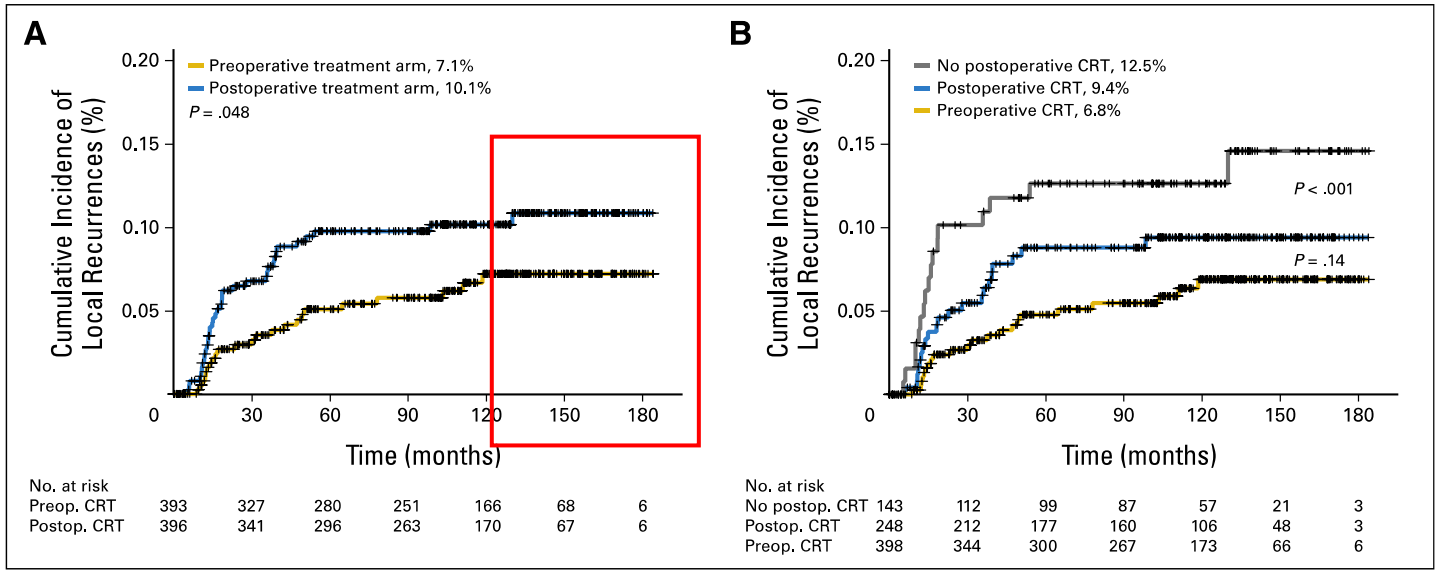


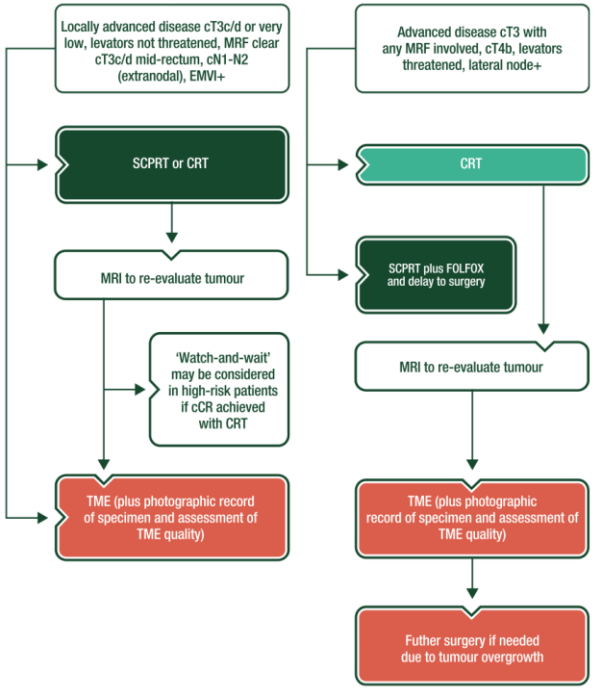
Follow-up a 10 anni:

- Non differenze nei due gruppi in:
  - Overall Survival (59.6% VS 59.9%)
  - Disease-free survival (68.1% VS 67.8%)
  - Metastasi a distanza (29.8% VS 29.6%)
- **Ripresa locale di malattia 7.1% nel braccio terapia neoadiuvante VS 10.1% nel braccio terapia adiuvante - p < 0.048**

Terapia neoadiuvante: standard di cura nel paziente con carcinoma del retto localmente avanzato

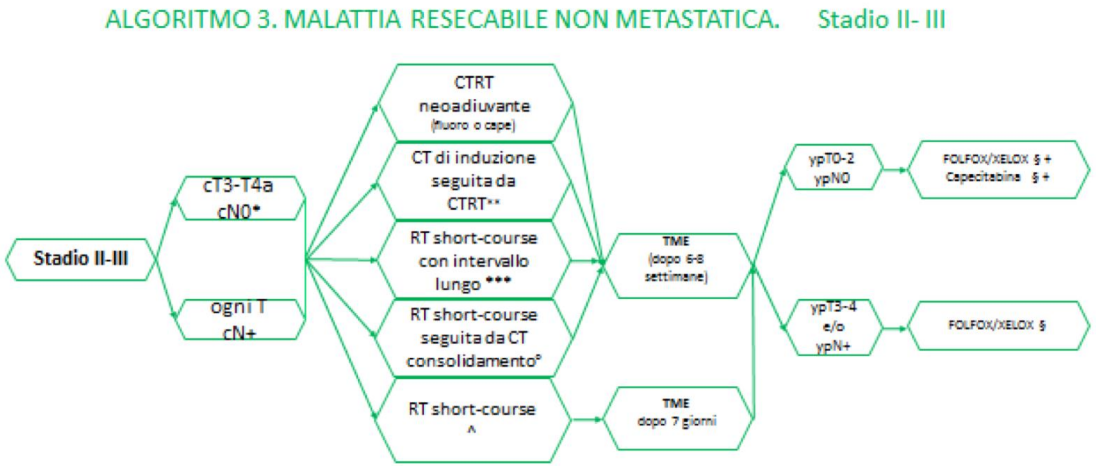
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

2018



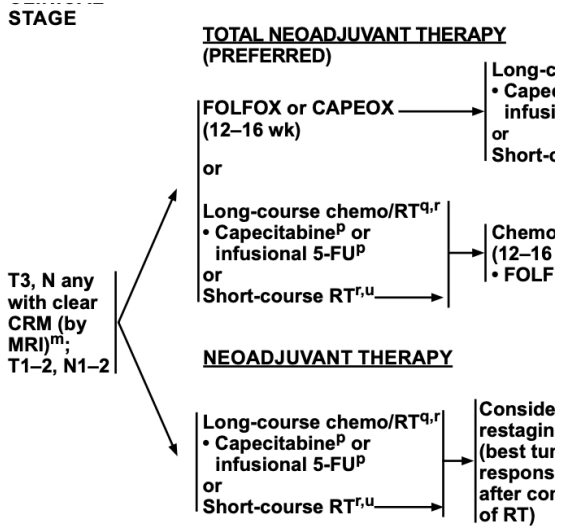
AIOM Associazione Italiana di Oncologia Medica

2021



NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY

2022



Terapia neoadiuvante

Radioterapia

Chemioterapia

Total Neoadjuvant Therapy

De-escalation della terapia neoadiuvante

Terapia neoadiuvante

Radioterapia

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Terapia neoadiuvante

Il chirurgo?

Terapia neoadiuvante

Presa in carico del paziente

Stadiazione

Il chirurgo?

Terapia neoadiuvante

Presa in carico del paziente

Stadiazione

Il chirurgo?

Sintomi

Anamnesi - comorbidità

Valutazione funzionale iniziale

T2N1 sottoposto a terapia neoadiuvante

T2N0 non sottoposto a terapia neoadiuvante

Terapia neoadiuvante

Presa in carico del paziente

Stadiazione

Il chirurgo?

Chirurgia

Gestione di eventuali complicanze

Gestione degli esiti funzionali anche del trattamento neoadiuvante

Sintomi

Anamnesi - comorbidità

Valutazione funzionale iniziale

Terapia neoadiuvante

Radioterapia

Chemioterapia
Total Neoadjuvant Therapy

De-escalation della terapia neoadiuvante

Table 1. Review of Key Neoadjuvant Therapy in Rectal Cancer Trials and Outcomes

Trial	Year	Patients	Experimental	Control	Local Recurrence	Overall Survival
Swedish Rectal Cancer Trial[17]	1987–1990	1,168 Resectable	Preoperative SCRT	Surgery alone	5-y: 11% vs 27% *P*<.0001	5-y: 58% vs 48% *P*=.004
Dutch Colorectal Cancer Group study[19]	1996–1999	1,861 Resectable	Preoperative SCRT	Surgery alone	2-y: 2.4% vs 8.2% *P*<.0001	2-y: 82.0% vs 81.8% *P*=.84
German Rectal Cancer Study Group trial[10]	1995–2002	823 cT3–4/N+	Preoperative CRT	Postoperative CRT	5-y: 6% vs 13% *P*=.006	5-y: 76% vs 74% *P*=.80
TROG 01.04[20]	2001–2006	326 T3N0–2	Preoperative SCRT	Preoperative CRT	3-y: 7.5% vs 4.4% *P*=.24	5-y: 74% vs 70% *P*=.62
CAO/ARO/AIO-12[35]	2015–2018	311 Stage II–III	Induction chemotherapy then CRT	CRT then consolidation chemotherapy	3-y: 6% vs 5% *P*=.67	3-y: 92% vs 92% *P*=.81
Stockholm III[22]	1998–2013	840 Resectable	1. Preoperative SCRT 2. Preoperative SCRT with 4- to 8-wk delay of surgery	Preoperative CRT with 4- to 8-wk delay of surgery	Median time: 28.3 vs 22.1 vs 33.3 mo *P*>.05	5-y: 73% vs 76% vs 78% *P*>.05
UNICANCER-PRODIGE 23[25]	2012–2017	461 cT3–4M0	TNT FOLFIRINOX, CRT, TME, adjuvant FOLFOX ×6	Neoadjuvant CRT, TME, adjuvant FOLFOX ×9	(pCR) 3-y: 28% vs 12% *P*<.0001	3-y: 91% vs 88% *P*=.0773
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Anurag S et al. Optimal Neoadjuvant strategies for locally advanced rectal cancer by risk assessment and tumor location. J Nat Compr Netw 2022

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Terapia neoadiuvante

Radioterapia

Short-course RT: 25 Gy in 5 Gy per frazione per un totale di 5 sedute

Long-course RT: 50.0 – 54.0 Gy in 1.8 – 2.0 Gy per frazione per un totale di 5-6 settimane

Terapia neoadiuvante

Radioterapia

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Long-course RT: 50.0 – 54.0 Gy in 1.8 – 2.0 Gy per frazione per un totale di 5-6 settimane

Incremento dosaggio RT

→ Migliore riposta patologica tumorale

→ Più elevata tossicità

- Incremento complicanze post-operatorie
- Incremento leak anastomotico
- Peggiori outcomes funzionali

Terapia neoadiuvante

Radioterapia

Acute Adverse Events and Postoperative Complications in a Randomized Trial of Preoperative Short-course Radiotherapy Versus Long-course Chemoradiotherapy for T3 Adenocarcinoma of the Rectum

Trans-Tasman Radiation Oncology Group Trial (TROG 01.04)

2017

Trial randomizzato

2001 – 2006: 326 pazienti

Adenocarcinoma del retto medio-basso T3N0–2

Short Course radiotherapy (SCRT)
25Gy in 5 Gy per frazione
Chirurgia immediata entro 3 – 7 giorni dalla fine della RT
Chemioterapia adiuvante (5-FU per 6 cicli)

Long Course radiotherapy (LCRT)
50.4 Gy in 1.8 Gy per frazione + 5-FU
Chirurgia ritardata a 4-6 settimane dopo la fine della RT
Chemioterapia adiuvante (5-FU per 4 cicli)

Terapia neoadiuvante

Radioterapia

Short Course radiotherapy (SCRT)

Long Course radiotherapy (LCRT)

Acute Adverse Events and Postoperative Complications in a Randomized Trial of Preoperative Short-course Radiotherapy Versus Long-course Chemoradiotherapy for T3 Adenocarcinoma of the Rectum

Trans-Tasman Radiation Oncology Group Trial (TROG 01.04)

TABLE 4. Postoperative Complications

Complication	Category	Actual Treatment SC (158) N	SC (158) %	LC (161) N	LC (161) %
Any	None	74	46.8	80	49.6
($P = 0.68$) *	One or more	84	53.2	81	50.4
Perineal wound complication	Not applicable	98		113	
(Time to wound healing) for APRs	No	37	61.6	24	50.0
($P = 0.26$) *	Yes—no intervention	19	31.6	17	35.4
	≤3 wks	6	10.0	0	
	>3 wks and ≤3 mo	7	11.6	10	20.8
	>3 mo	6	10.0	7	14.5
	Yes—nonsurgical intervention	2	3.3	7	14.5
	≤3 wks	0		0	
	>3 wks and ≤3 mo	0		2	4.1
	>3 mo	2	3.3	5	10.4
	Yes—secondary suturing	2	3.3	0	
	≤3 wks	0		0	
	>3 wks and ≤3 mo	1	1.6	0	
	>3 mo	1	1.6	0	
Abdominal wound complication	No	142	89.8	147	91.3
($P = 0.71$)*	Yes—conservative management	15	9.5	14	8.7
	Yes—secondary suturing	1	0.6	0	
Bowel obstruction	No	143	90.5	146	90.7
($P = 1.00$)*	Yes—mechanical, conservative	7	4.4	2	1.2
	Yes—mechanical, surgery	2	1.3	4	2.5
	Yes—prolonged ileus (>5 days)	6	3.8	9	5.6
Anastomosis breakdown	Not applicable	60		48	
(excluding APRs) ($P = 0.26$)*					
	No	91	92.9	109	96.5
	Yes—conservative management	4	4.1	4	3.5
	Yes—secondary suturing	3	3.0	0	
Deep vein thrombosis ($P = 0.26$)*	No	153	96.8	159	98.8
	Yes	5	3.2	2	1.2
Other (Table 5)	No	103	65.2	111	68.9
($P = 0.53$) *	Yes	55	34.8	50	31.1

*All P values refer to the comparison of proportions of patients with and without the complication by actual treatment group.

- No differenze in OS, DFS e tossicità tardiva
- Eventi avversi acuti più alti nel braccio LCRT (99.4% vs 72.3%; P=0.001 - dermatite, proctite, nausea e diarrea)
- **Nel braccio LCRT**:
  - **percentuali più alte di stomie permanenti** (38.0% vs 29.8%; P=0.13) **e deiscenza anastomotica (7.1% vs 3.5%; P=.26)**
  - **Maggiore downstaging (45% vs 28%; P=.002)**
  - **Maggiore risposta patologica completa (pCR) (15% vs 1%)**

Terapia neoadiuvante

Radioterapia

Timing alla chirurgia

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

… the optimal timing of surgical resection of LARC after preoperative CRT or SCPRT ***remains controversial and is addressed in trials …***

… In the case of SCPRT in resectable cancers, where downstaging is not required, 'immediate' surgery is recommended to take place within 7 days from the end of neoadjuvant treatment, and ideally within 0–3 days if the patient is 75 years ***(<10 days from the first radiation fraction)*** *….*

… longer intervals after SCPRT or CRT may enhance pCR rates (with unknown prognostic implications), but risks repopulation delays the use of postoperative systemic adjuvant ChT and risks subsequent metastases. In practice, ***there is a wide variation in the timing of surgery (4–12 weeks) due to patient/surgeon choice, recovery from treatment and/or waiting list issues …***

Terapia neoadiuvante

Radioterapia

Timing alla chirurgia

Qual è **miglior intervallo** per ottenere la **maggiore risposta patologica completa** (pCR) che impatti sugli indici di **sopravvivenza in modo favorevole** e che **non impatti negativamente sulla chirurgia**?

Terapia neoadiuvante

Radioterapia

Timing alla chirurgia dopo short course

Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial

Studio randomizzato (1:1:1)

1998 – 2013: 840 pazienti

Adk del retto < 15 cm dal margine anale chirurgicamente resecabile e non metastatico

End-point primario: ripresa locale di malattia e suo timing

Short Course radiotherapy (SCRT)
25Gy in 5 Gy per frazione
Chirurgia immediata a 7 giorni dalla fine della RT

Short Course radiotherapy (SCRT)
25Gy in 5 Gy per frazione
Chirurgia ritardata a 4-8 settimane dalla fine della RT

Long Course radiotherapy (LCRT)
50.4 Gy in 25 frazioni
Chirurgia ritardata a 4-6 settimane dopo la fine della RT

Terapia neoadiuvante

Radioterapia

Timing alla chirurgia dopo short course

Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial

- Non differenze nella percentuale di ripresa di malattia locale tra i gruppi SCRT e LCRT
- **Minori complicanze post-operatorie** (41% versus 53%; OR 0·61 [95% CI 0·45–0·83] p=0·001) **e maggiore downstaging nel braccio SCRT e chirurgia ritardata rispetto al braccio SCRT e chirurgia immediata**

	SRT (n=357)	SRT-delay (n=355)	p value
Local recurrence			
As the first recurrence event	7	6	..
HR (90% CI)	1·00 (ref)	0·91 (0·36–2·27)	0·59*
As any event	8	10	..
HR (90% CI)	1·00 (ref)	1·30 (0·59–2·85)	0·58*
Distant metastases			
As the first recurrence event	77	77	..
HR (95% CI)	1·00 (ref)	1·02 (0·74–1·40)	0·91*
As any event	80	79	..
HR (95% CI)	1·00 (ref)	1·00 (0·73–1·38)	0·98*
Survival			
Deaths	110	108	..
Overall survival HR (95% CI)	1·00 (ref)	0·90 (0·70–1·15)	0·46*
Number of patients with any event	141	130	..
Recurrence-free survival HR (95% CI)	1·00 (ref)	0·90 (0·69–1·18)	0·39*
Number of patients with intercurrent death	57	47	..
Intercurrent death HR (95% CI)	1·00 (ref)	0·73 (0·49–1·10)	0·13*
Complications			
Any postoperative complication	188 (53%)	144 (41%)	..
OR (95% CI)	1·00 (ref)	0·61 (0·45–0·83)	0·001†
Any surgical complication	128 (36%)	100 (28%)	..
OR (95% CI)	1·00 (ref)	0·70 (0·51–0·96)	0·03†
Reoperation	43 (15%)	37 (14%)	..
OR (95% CI)	1·00 (ref)	0·88 (0·55–1·41)	0·59†

Data are n (%) if not otherwise specified. SRT=short-course radiotherapy 5 × 5 Gy surgery within 1 week. SRT-delay=short-course radiotherapy, 5 × 5 Gy, with a delay of 4–8 weeks to surgery. HR=hazard ratio. OR=odds ratio. Postoperative complication was defined as any cardiovascular, infectious, neurologic, or surgical complication observed within 30 days after surgery. Surgical complication was defined as any surgical site infection, deep infection, anastomotic leak, postoperative bleeding, stoma related complications, wound dehiscence, or other surgical complication. *Cox regression stratified by including centre, log-rank test. †Logistic regression with χ^2 test.

***Table 3*: Oncological outcomes and postoperative complications by allocated treatment in the pooled short-course radiotherapy comparison at the end of follow-up**

Terapia neoadiuvante

Radioterapia

Timing alla chirurgia dopo long course

Timing to achieve the highest rate of pCR after preoperative radiochemotherapy in rectal cancer: a pooled analysis of 3085 patients from 7 randomized trials

Maria Antonietta Gambacorta [1], Carlotta Masciocchi [2], Giuditta Chiloiro [3], Elisa Meldolesi [2], Gabriella Macchia [4], Johan van Soest [5], Fenke Peters [6], Laurence Collette [7], Jean-Pierre Gérard [8], Samuel Ngan [9], C Claus Rödel [10], Andrea Damiani [2], Andre Dekker [5], Vincenzo Valentini [1]

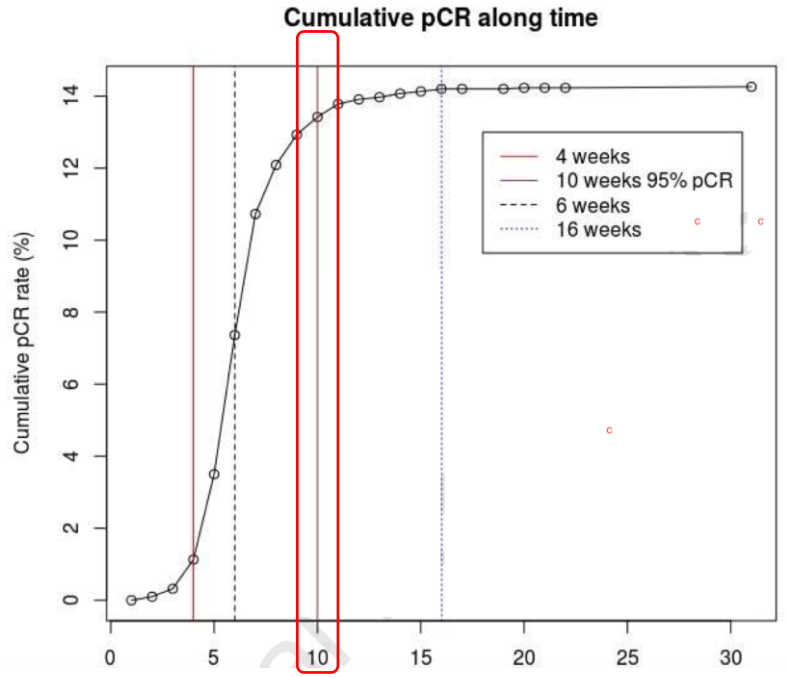
Accord12/0405
EORTC22921
FFCD9203
CAO/ARO/AIO-94
CAO-ARO-AIO-04
INTERACT
TROG01.04.

cT3-T4 and cN0-2

No metastasi a distanza

Chemio-radioterapia long-course seguita da chirurgia

- 3085 pazienti
- pCR 14% ad una media di 6 settimane di intervallo dalla fine della RT (range 1-31).
- **95% di pCR a 10 settimane dalla fine terapia neoadiuvante**
- Intervallo alla chirurgia non impattante su recidiva locale, OS e metastasi a distanza



Terapia neoadiuvante

Radioterapia

Timing alla chirurgia dopo long course

BMC

Standard (8 weeks) vs long (12 weeks) timing to minimally-invasive surgery after NeoAdjuvant Chemoradiotherapy for rectal cancer: a multicenter randomized controlled parallel group trial (TiMiSNAR)

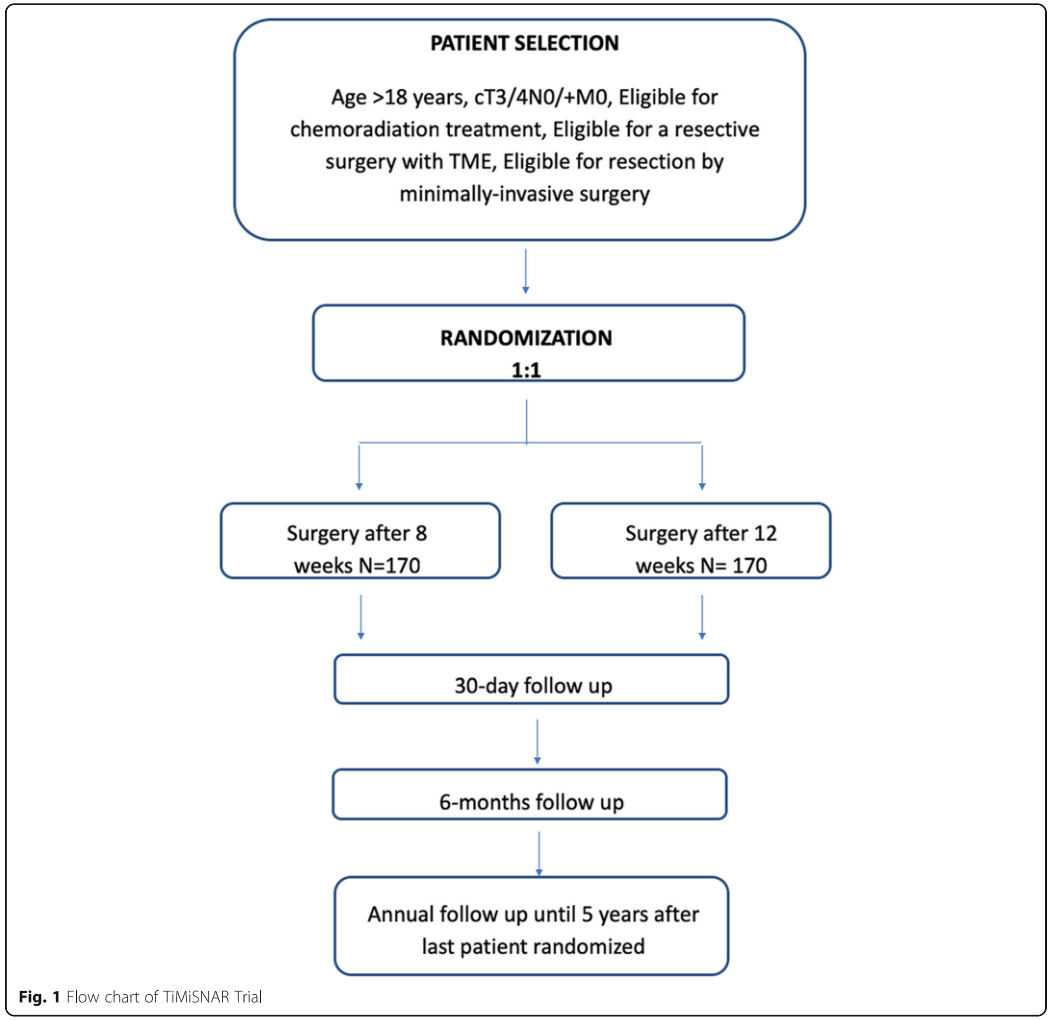


Fig. 1 Flow chart of TiMiSNAR Trial

Terapia neoadiuvante

Chemioterapia
Total Neoadjuvant Therapy

Somministrazione sia di chemioterapia sistemica sia di chemio-radio-terapia neoadiuvante prima dell'(eventuale) intervento chirurgico.

Obiettivi:

- Migliorare la sopravvivenza e ridurre il tasso di metastasi a distanza
- Trattamento precoce delle micrometastasi
- Migliore controllo sistemico della malattia
- Conservazione dell'organo

Terapia neoadiuvante

Chemioterapia
Total Neoadjuvant Therapy

Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial

*Thierry Conroy, Jean-François Bosset, Pierre-Luc Etienne, Emmanuel Rio, Éric François, Nathalie Mesgouez-Nebout, Véronique Vendrely, Xavier Artignan, Olivier Bouché, Dany Gargot, Valérie Boige, Nathalie Bonichon-Lamichhane, Christophe Louvet, Clotilde Morand, Christelle de la Fouchardière, Najib Lamfichekh, Béata Juzyna, Claire Jouffroy-Zeller, Eric Rullier, Frédéric Marchal, Sophie Gourgou, Florence Castan, Christophe Borg, on behalf of the Unicancer Gastrointestinal Group and Partenariat de Recherche en Oncologie Digestive (PRODIGE) Group**

2021

Studio multicentrico randomizzato di fase III

2012 – 2017: 461 pazienti

cT3–4 M0

WHO performance status 0 – 1

18 – 75 anni

End-point primario: 3 anni DFS

Terapia neoadiuvante

Chemioterapia
Total Neoadjuvant Therapy

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Braccio «Standard of care - SoC»

50 Gy/25 + capecitabine (800 mg/mq)

Chirurgia TME a 6-8 settimane

Terapia adiuvante 5-12 settimane dopo FOLFOX6 o Capecitabine

Braccio sperimentale - TNT

Chemioterapia di induzione FOLFIRINOX – 6 cicli

50 Gy/25 + capecitabine (800 mg/mq)

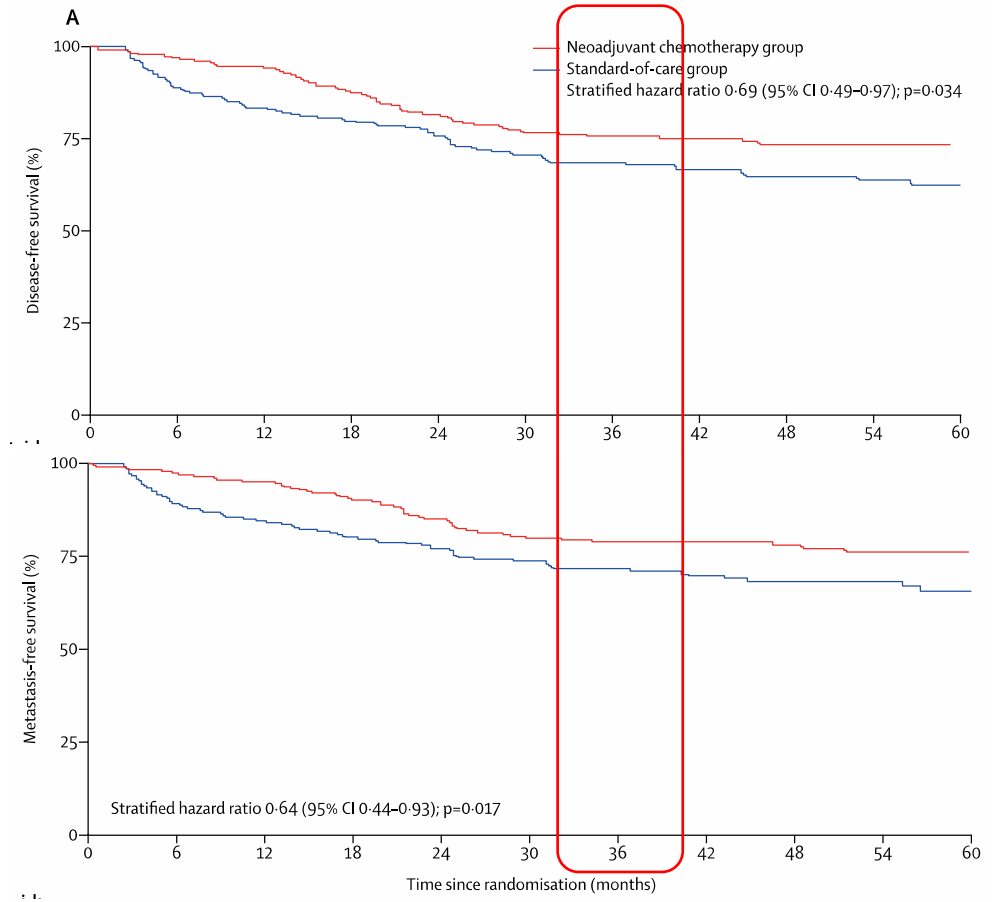
Terapia neoadiuvante

Chemioterapia
Total Neoadjuvant Therapy

- Follow-up medio 46.5 mesi
- **DFS a tre anni incrementata nel gruppo TNT versus SoC** (76% vs 69%; P=0.034) → metastasi-free survival a 3 anni
- **Percentuale pCR incrementata nel braccio TNT** (28% vs 12%; P=0.0001)
- Elevata compliance alla terapia con 92% dei pazienti nel braccio TNT che hanno completato i 6 cicli di FOLIFIRNOX, 95% che hanno completato CRT e 75% la terapia adiuvante in entrambi i bracci

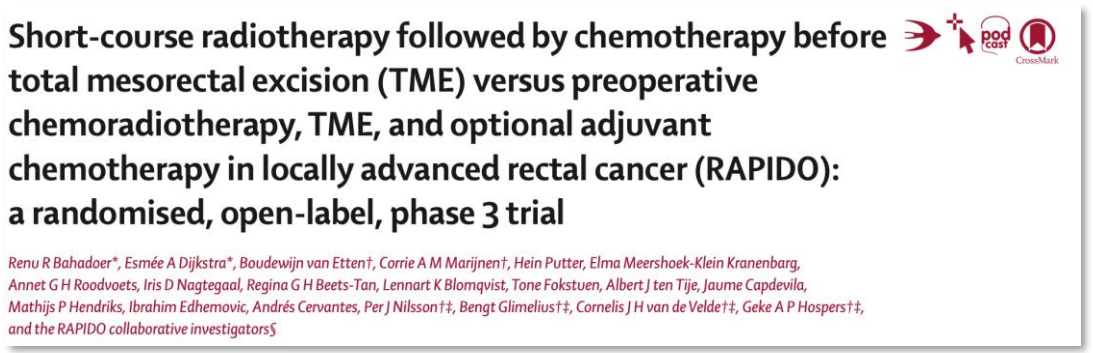
Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial

*Thierry Conroy, Jean-François Bosset, Pierre-Luc Etienne, Emmanuel Rio, Éric François, Nathalie Mesgouez-Nebout, Véronique Vendrely, Xavier Artignan, Olivier Bouché, Dany Gargot, Valérie Boige, Nathalie Bonichon-Lamichhane, Christophe Louvet, Clotilde Morand, Christelle de la Fouchardière, Najib Lamfichekh, Béata Juzyna, Claire Jouffroy-Zeller, Eric Rullier, Frédéric Marchal, Sophie Gourgou, Florence Castan, Christophe Borg, on behalf of the Unicancer Gastrointestinal Group and Partenariat de Recherche en Oncologie Digestive (PRODIGE) Group**



Terapia neoadiuvante

Chemioterapia
Total Neoadjuvant Therapy



Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial

Renu R Bahadoer, Esmée A Dijkstra*, Boudewijn van Etten†, Corrie A M Marijnen†, Hein Putter, Elma Meershoek-Klein Kranenbarg, Annet G H Roodvoets, Iris D Nagtegaal, Regina G H Beets-Tan, Lennart K Blomqvist, Tone Fokstuen, Albert J ten Tije, Jaume Capdevila, Mathijs P Hendriks, Ibrahim Edhemovic, Andrés Cervantes, Per J Nilsson†‡, Bengt Glimelius†‡, Cornelis J H van de Velde†‡, Geke A P Hospers†‡, and the RAPIDO collaborative investigators§*

2021

Studio multicentrico randomizzato di fase III

2011 – 2016: 920 pazienti

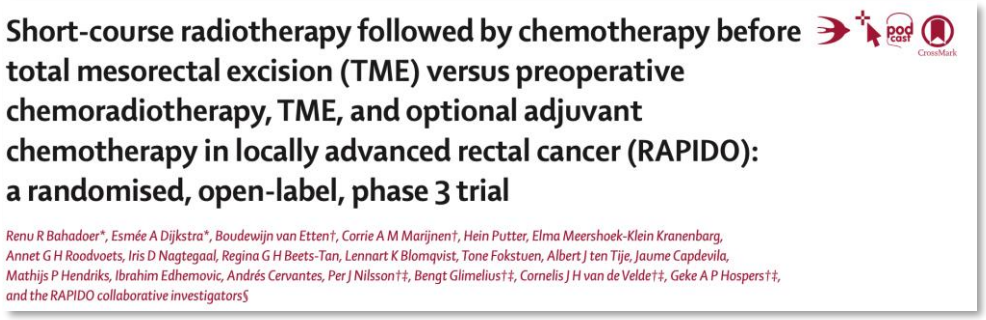
cT4 a/b, N2, EMVI +, MRF+, linfonodi pelvici laterali radiologicamente sospetti

ECOG performance status 0 – 1

End-point primario: fallimento correlato al trattamento a 3 anni (recidiva locale, metastasi a distanza, morte correlata al trattamento)

Terapia neoadiuvante

Chemioterapia
Total Neoadjuvant Therapy



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Braccio «Standard of care - SoC»	50.4 Gy in 25 frazioni + capecitabine (800 mg/mq)	Chirurgia TME a 6-10 settimane	Possibile terapia adiuvante 8 cicli CAPOX o 12 cicli FOLFOX4
Braccio sperimentale - TNT	Short course RT 25Gy in 5 Gy per frazione	6 cicli CAPOX o 9 cicli FOLFOX4	Chirurgia TME a 2-4 settimane

Terapia neoadiuvante

Chemioterapia
Total Neoadjuvant Therapy

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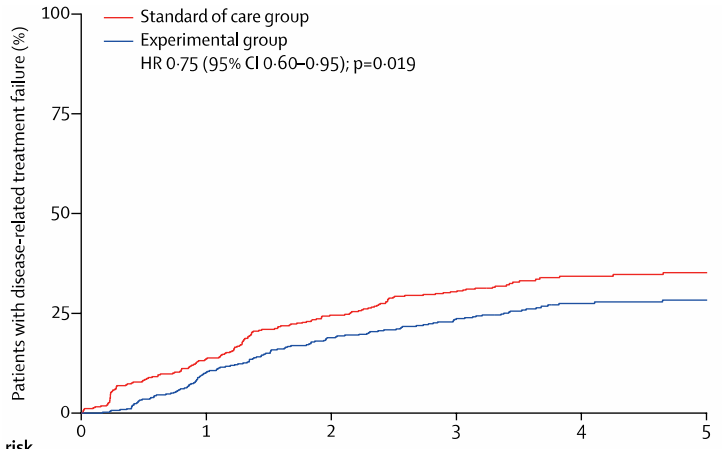

- Media follow-up 4.6 anni
- **Probabilità di fallimento correlato al trattamento a 3 anni inferiore nel gruppo TNT versus SoC (23.7% vs 30.4%; P=0.019)**
- **pCR più elevata nel gruppo TNT (28% vs 14%; P=.0001)**

Terapia neoadiuvante

Chemioterapia
Total Neoadjuvant Therapy

Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial

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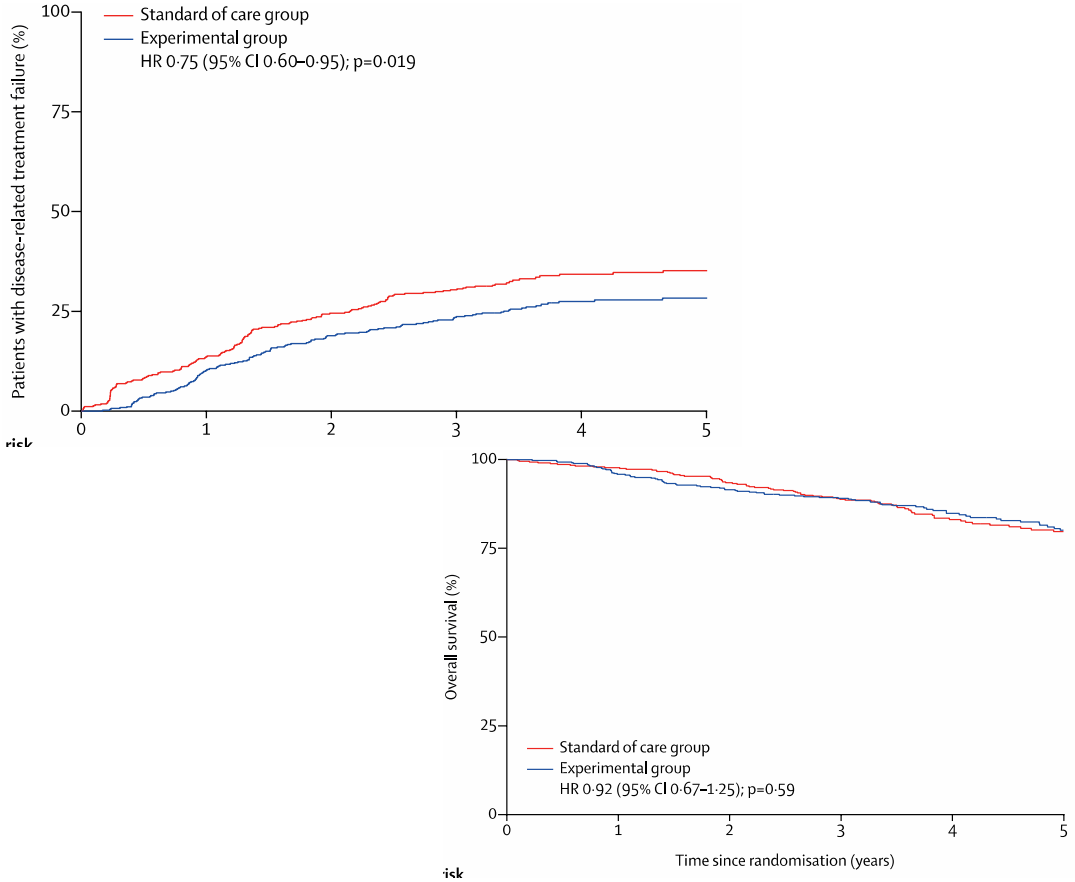
- **pCR più elevata nel gruppo TNT (28% vs 14%; P=.0001)**
- Non differenze in OS



Terapia neoadiuvante

Radioterapia

2021

PRODIGE 23
RAPIDO Trial

Chemioterapia
Total Neoadjuvant Therapy

- Diminuzione del tasso di fallimento correlato alla terapia
- Maggiore sopravvivenza libera da metastasi
- Migliore sopravvivenza libera da malattia
- Maggiori possibilità di ottenere una risposta patologica completa
- Apparente ridotta neurotossicità → ipotesi che il trattamento perioperatorio sia più efficiente e meglio tollerato dai pazienti rispetto alla chemioterapia postoperatoria

Terapia neoadiuvante

Radioterapia

2021

PRODIGE 23
RAPIDO Trial

Chemioterapia
Total Neoadjuvant Therapy

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NCCN Clinical Practice Guidelines, 2018

Total Neoadjuvant Therapy
Short Course Radiotherapy

↓

I risultati di questi due recenti trial hanno costruito concrete basi per cambiare la pratica clinica con un algoritmo terapeutico più rigoroso

Conclusioni

- Non chiari risultati a favore netto di short VS long course radiotherapy
- Ad oggi il regime di Total Neoadjuvant Therapy ideale deve ancora essere definito
- RAPIDO e PRODIGE23 includono popolazioni diverse e quindi non è possibile trarre conclusioni definitive e univoche
- Quali pazienti traggono maggior vantaggio dalla Total Neoadjuvant Therapy ?
  - ❖ RAPIDO include tumori cT4, N2, invasione venosa extramurale (EMVI), coinvolgimento/minaccio della fascia mesorettale (MRF) e linfonodi pelvici laterali ingrossati.
  - ❖ PRODIGE23 include tutti gli stadi II e III

Conclusioni

- Molti tumori restano resistenti ai farmaci e alla radioterapia → meccanismi di resistenza molecolare ancora poco conosciuti

- Con la Total Neoadjuvant Therapy il lasso di tempo tra la diagnosi e il trattamento chirurgico viene allungato ed in tale fase temporale bisognerebbe compiere maggiori sforzi nel monitoraggio della risposta del tumore durante la terapia neoadiuvante al fine di non prorogare troppo interventi chirurgici che è utile eseguire prima in caso di tumori resistenti a radioterapia e chemioterapia

Conclusioni

- Molti tumori restano resistenti ai farmaci e alla radioterapia → meccanismi di resistenza molecolare ancora poco conosciuti.

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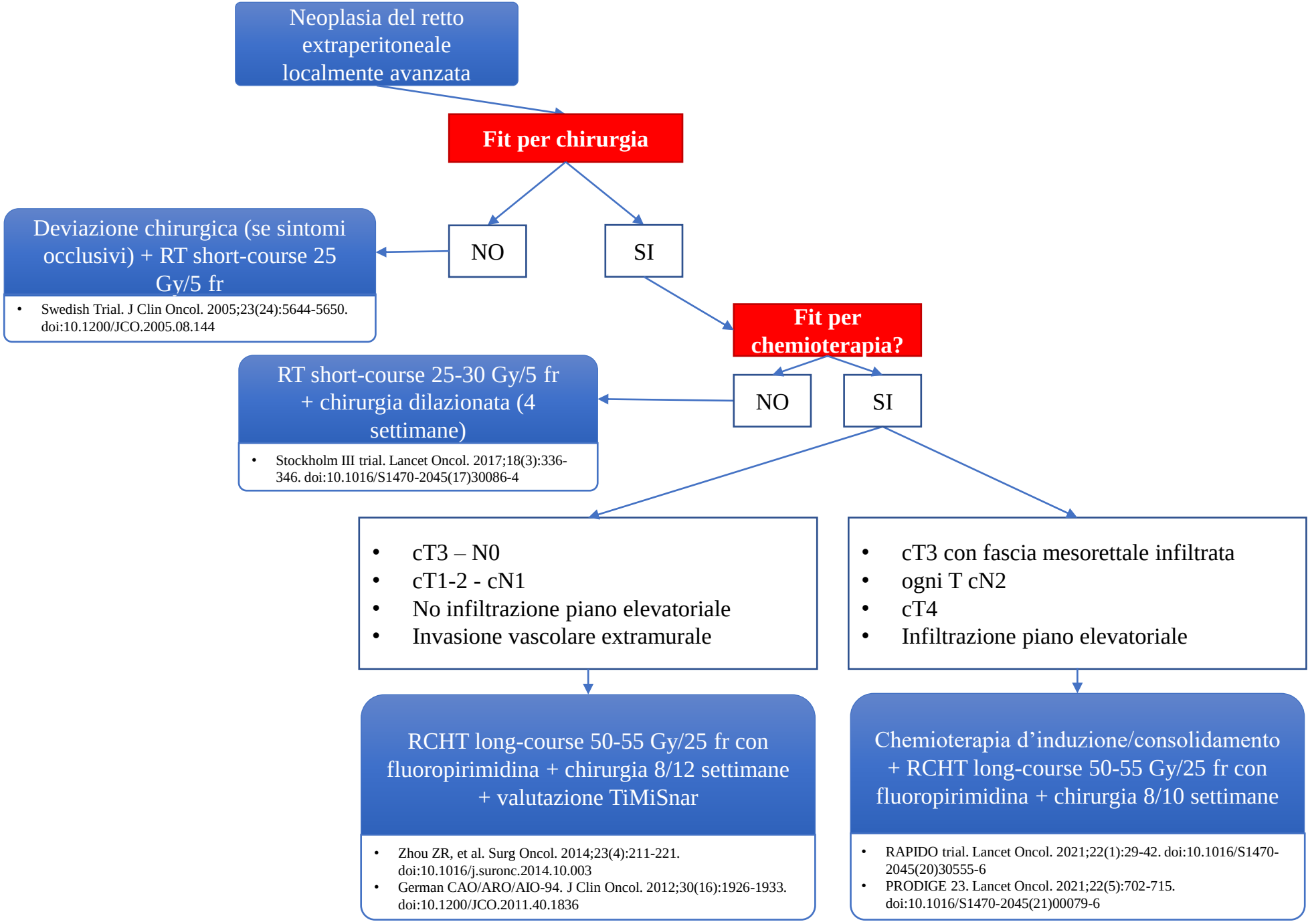
- **Ruolo del team multidisciplinare**


Neoplasia del retto extraperitoneale localmente avanzata
Fit per chirurgia
NO
SI
Deviazione chirurgica (se sintomi occlusivi) + RT short-course 25 Gy/5 fr
• Swedish Trial. J Clin Oncol. 2005;23(24):5644-5650. doi:10.1200/JCO.2005.08.144
Fit per chemioterapia?
NO
SI
RT short-course 25-30 Gy/5 fr + chirurgia dilazionata (4 settimane)
• Stockholm III trial. Lancet Oncol. 2017;18(3):336-346. doi:10.1016/S1470-2045(17)30086-4
• cT3 – N0
• cT1-2 - cN1
• No infiltrazione piano elevatoriale
• Invasione vascolare extramurale
• cT3 con fascia mesorettale infiltrata
• ogni T cN2
• cT4
• Infiltrazione piano elevatoriale
RCHT long-course 50-55 Gy/25 fr con fluoropirimidina + chirurgia 8/12 settimane + valutazione TiMiSnar
• Zhou ZR, et al. Surg Oncol. 2014;23(4):211-221. doi:10.1016/j.suronc.2014.10.003
• German CAO/ARO/AIO-94. J Clin Oncol. 2012;30(16):1926-1933. doi:10.1200/JCO.2011.40.1836
Chemioterapia d'induzione/consolidamento + RCHT long-course 50-55 Gy/25 fr con fluoropirimidina + chirurgia 8/10 settimane
• RAPIDO trial. Lancet Oncol. 2021;22(1):29-42. doi:10.1016/S1470-2045(20)30555-6
• PRODIGE 23. Lancet Oncol. 2021;22(5):702-715. doi:10.1016/S1470-2045(21)00079-6