INNOVATE, COLLABORATE, TRANSFORM

ASTRO ANNUAL MEETING 2019

ASTRO'S 61ST ANNUAL MEETING

September 15-18, 2019

McCormick Place | Chicago, Illinois

Management of Advanced Rectal Cancer

Sebastián Solé M. D.

Clínica IRAM

Universidad Diego Portales

udp
UNIVERSIDAD DIEGO PORTALES

Clínica IRAM
Expertos en oncología

Objetivos de aprendizaje

- Conocer la evidencia que apoya el uso de adyuvancia en cáncer de recto localmente avanzado

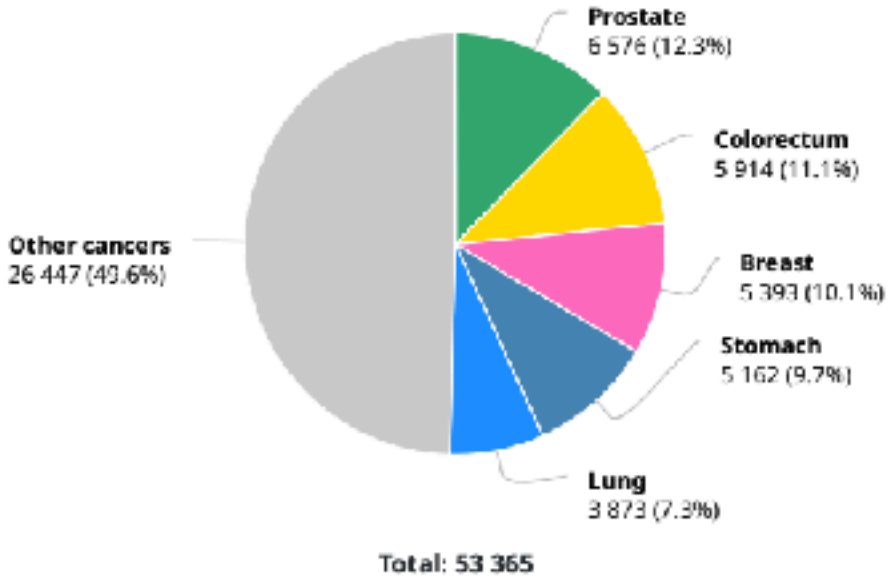
- Comprender los beneficios y la evidencia detrás de las nuevas tendencias en adyuvancia en cáncer de recto localmente avanzado

Cáncer de Recto en Chile

International Agency for Research on Cancer
World Health Organization

Chile
Source: Globocan 2018

Number of new cases in 2018, both sexes, all ages



Colorectum
5 914 (11.1%)

Es necesario hacer tratamientos adyuvantes

The New England
Journal of Medicine

Volume 312 JUNE 6, 1985 Number 23

PROLONGATION OF THE DISEASE-FREE INTERVAL IN SURGICALLY TREATED RECTAL CARCINOMA

GASTROINTESTINAL TUMOR STUDY GROUP

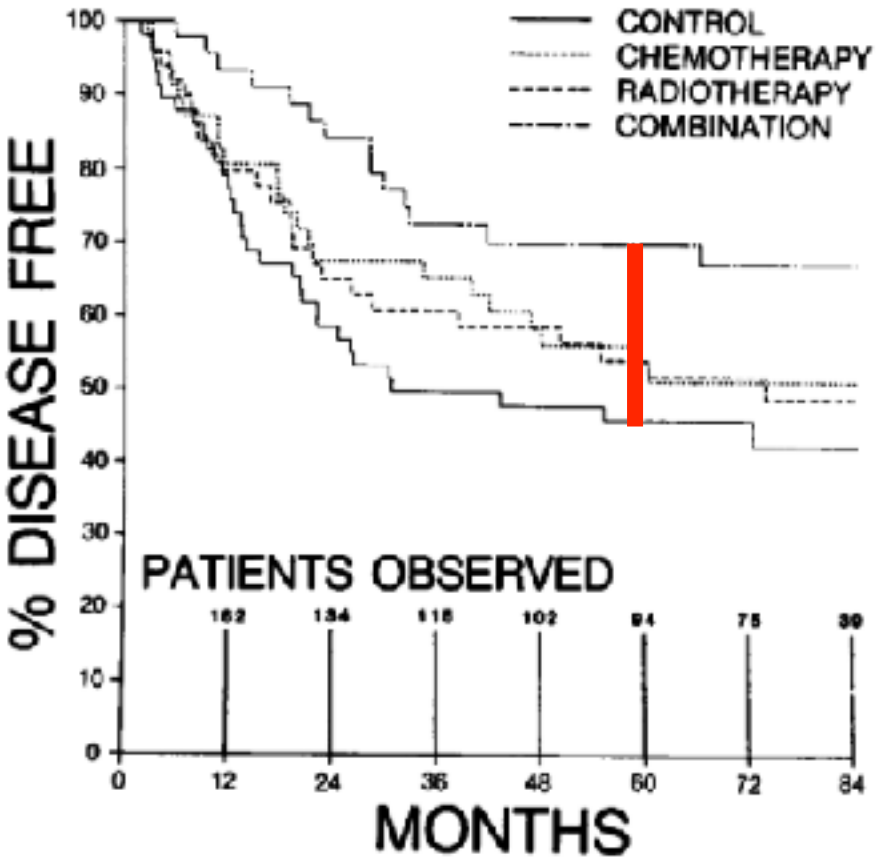


Figure 2. Time to Recurrence, According to Treatment.

GTSG, NEJM 1985

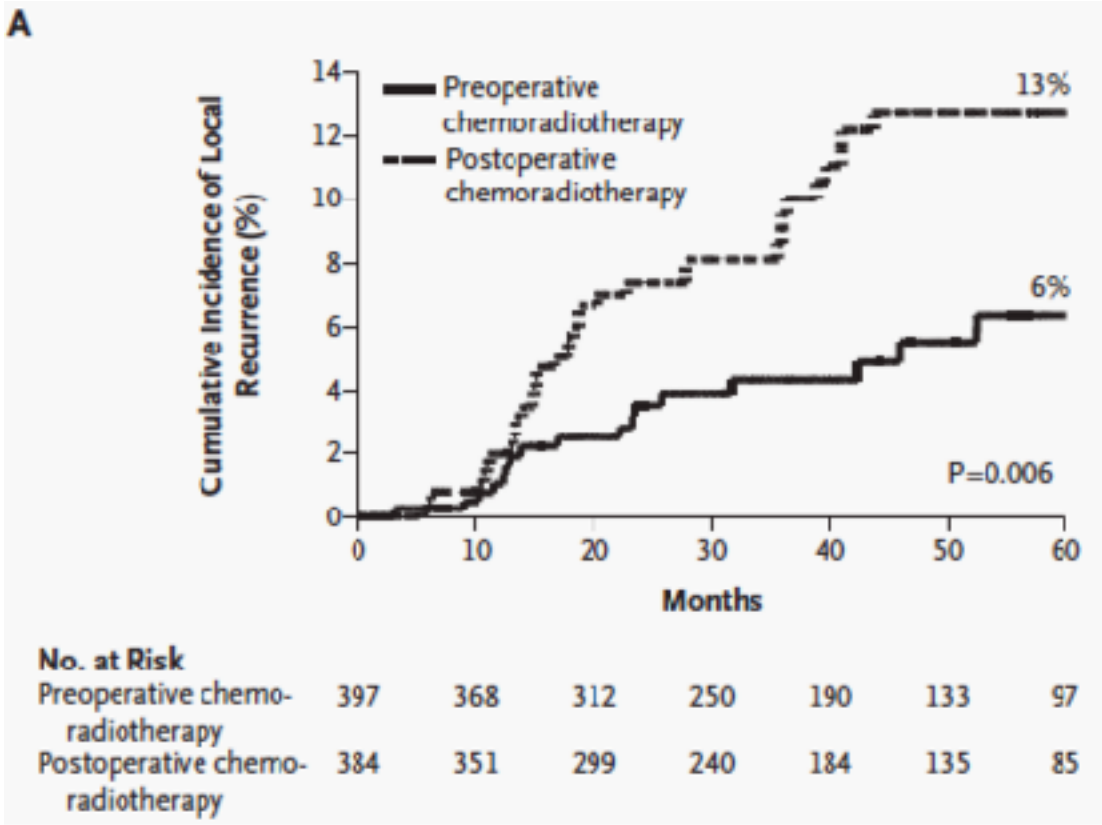
Es mejor la neoadyuvancia que la adyuvancia

ORIGINAL ARTICLE

Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer

Rolf Sauer, M.D., Heinz Becker, M.D., Werner Hohenberger, M.D., Claus Rödel, M.D., Christian Wittekind, M.D., Rainer Fietkau, M.D., Peter Martus, Ph.D., Jörg Tschmelitsch, M.D., Eva Hager, M.D., Clemens F. Hess, M.D., Johann-H. Karstens, M.D., Torsten Liersch, M.D., Heinz Schmidberger, M.D., and Rudolf Raab, M.D., for the German Rectal Cancer Study Group*

RTQT por 5-6 semanas



Sauer, NEJM 2004

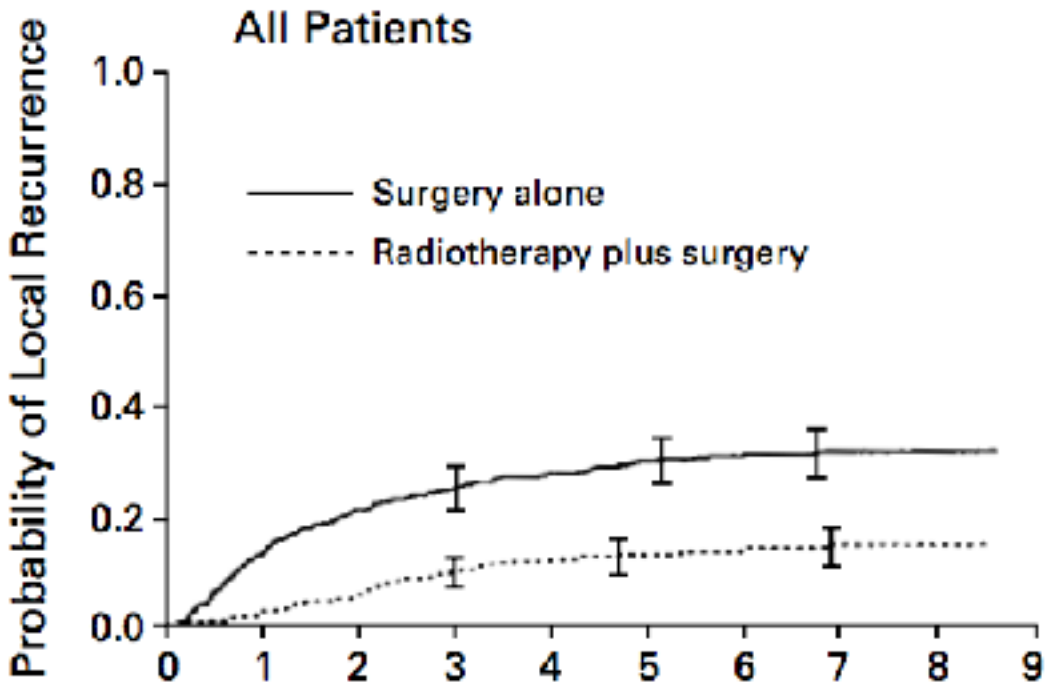
Otro tipo de neoadyuvancia efectiva

The New England Journal of Medicine

IMPROVED SURVIVAL WITH PREOPERATIVE RADIOTHERAPY IN RESECTABLE RECTAL CANCER

SWEDISH RECTAL CANCER TRIAL*

RT corta (1 semana)
sin QT



Pahlman, NEJM 1997

¿Cuál neoadyuvancia es mejor?

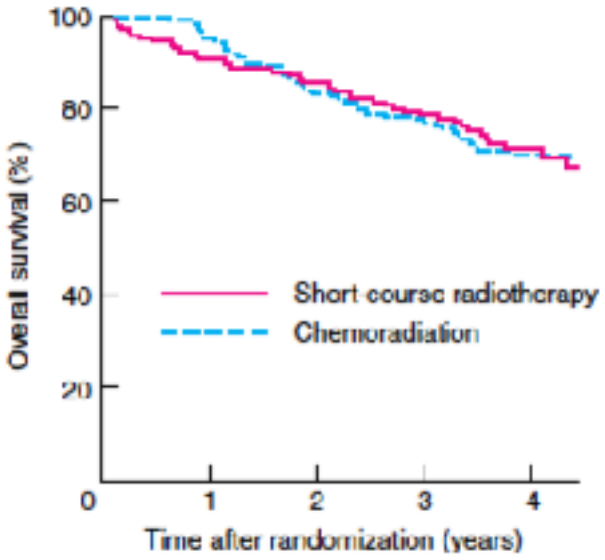
Randomized clinical trial

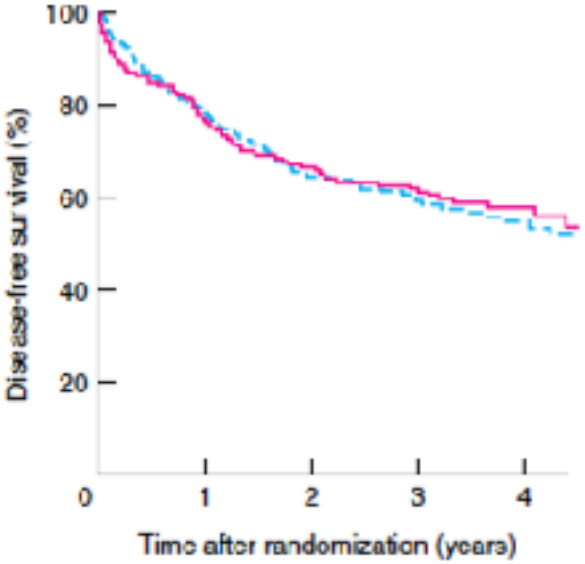
Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer

K. Bujko[1], M. P. Nowacki[2], A. Nasierowska-Guttmejer[3], W. Michalski[4], M. Bebenek[5] and M. Kryj[6] for the Polish Colorectal Study Group

Departments of [1]Radiotherapy, [2]Colorectal Cancer, [3]Pathology and [4]Biostatistics, Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, [5]Department of Surgery, Silesian Oncological Center, Wroclaw and [6]Department of Surgery, Maria Sklodowska-Curie Memorial Cancer Center, Gliwice, Poland

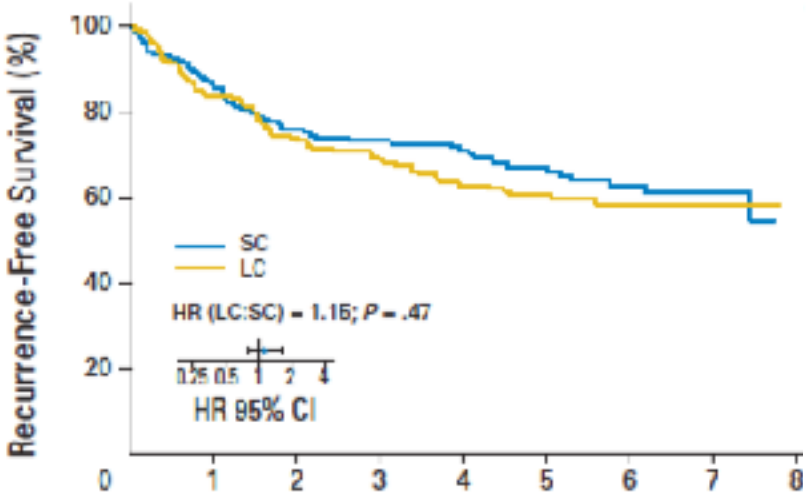
Correspondence to: Dr K. Bujko, The Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, W. K. Roentgena 5, 02 781 Warsaw, Poland (e-mail: bujko@coi.waw.pl)

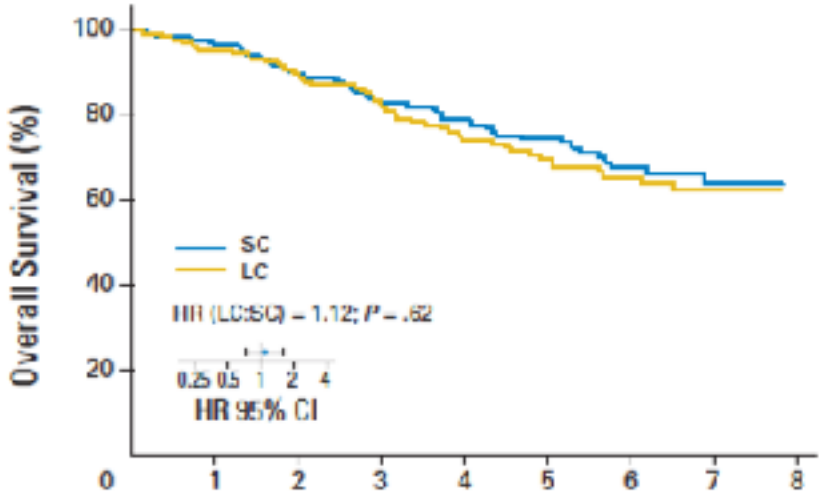




Bujko, Br J Surg 2006

¿Cuál neoadyuvancia es mejor?





Ngan, JCO 2012

¿Cómo se explica esto?

Radiobiología

Esquema	Tumor α/β= 5	Tumor c/ corrección de t	Tejido Sano α/β=3
5x5 Gy	35,7 Gy	35,7 Gy	40Gy
25x2 Gy	50Gy	50-15,6 =34,4 Gy	50Gy

EQD2 $(\alpha/\beta) = (d+\alpha/\beta) / (2+\alpha/\beta)$
Time correction: EQD2 (α/β) – (OTT-delay) D_{prolif}
Repair rate= D_{prolif}=0,6Gy/day
Proliferation delay: 7 days

25 Gy en 5 fx es un poco más dosis en tumor que 50 Gy en 25 fx

Guckenberger et al. Radiat Oncol 2009;4:67

Diapositiva Dra. Verónica López
Instituto Nacional del Cáncer - Chile

25 Gy en 5 fx tiene 4 veces más pCR

Radiotherapy and Oncology 135 (2019) 178–186

Contents lists available at ScienceDirect

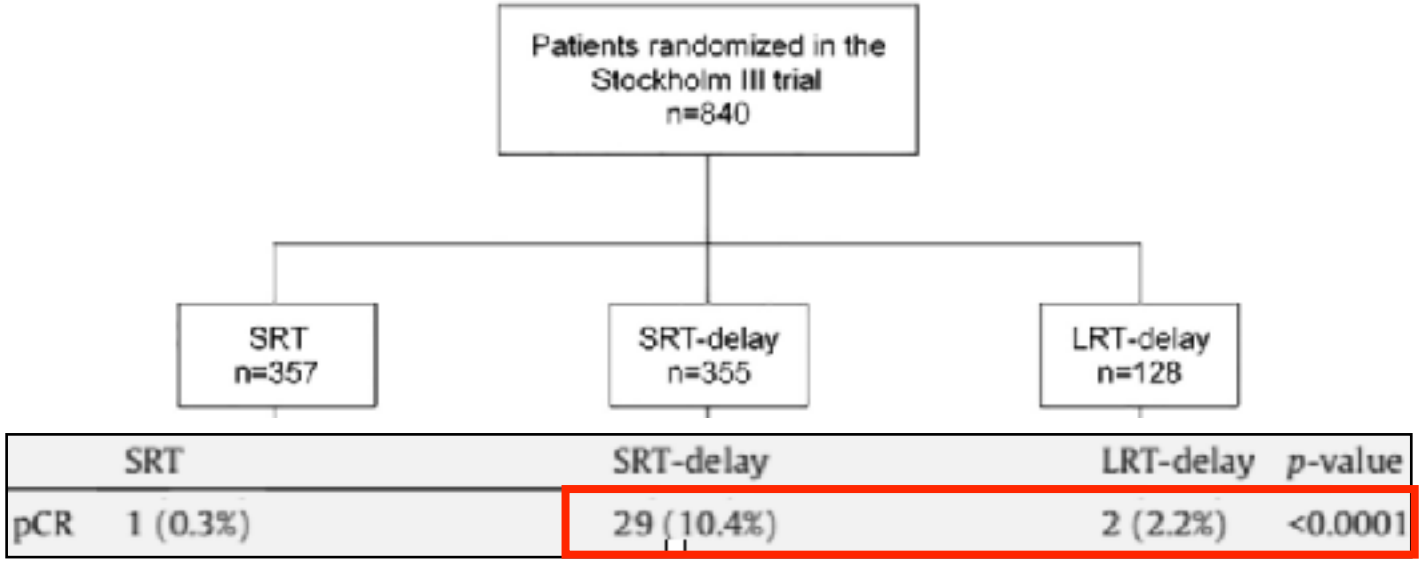
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Tumour regression after radiotherapy for rectal cancer – Results from the randomised Stockholm III trial

Johan Erlandsson, Ester Lörinc, Madelene Ahlberg, David Pettersson, Torbjörn Holm, Bengt Glimelius, Anna Martling

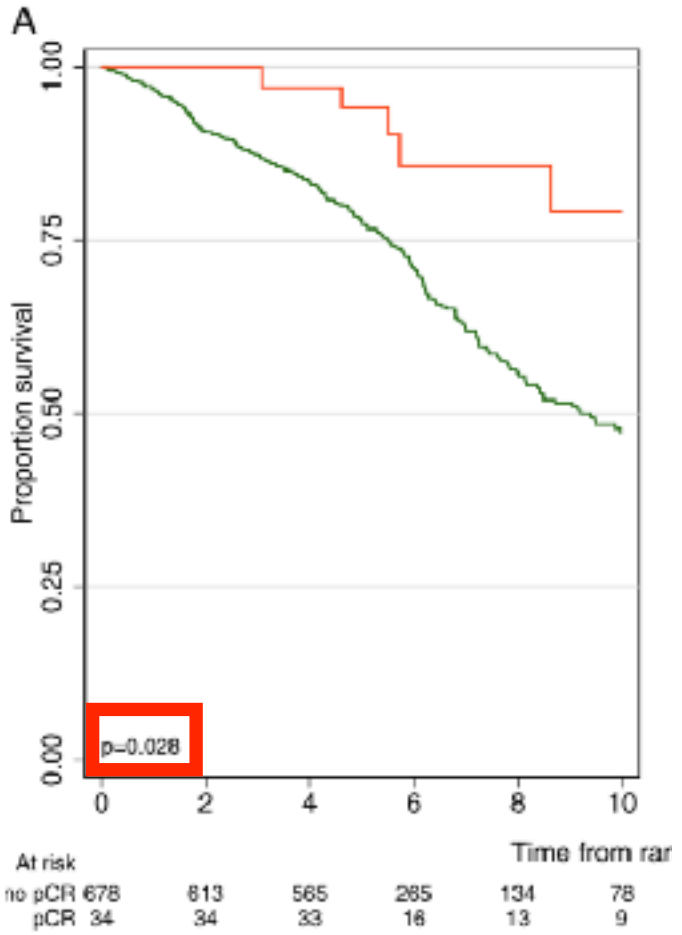


	SRT	SRT-delay	LRT-delay	*p*-value
pCR	1 (0.3%)	29 (10.4%)	2 (2.2%)	<0.0001

Erlandsson, Radiother Oncol 2019

pCR se asoció a mejor sobrevida

In conclusion, 5 × 5 Gy in one week with a delay of surgery between 4 and 8 weeks induces pCR in about 10 per cent of the patients and is in this respect superior to 2 Gy × 25 in five weeks. A very good RT response in the tumour, TRG 4 using the Dworak system, or a pCR, is associated with superior OS and TTR.



Erlandsson, Radiother Oncol 2019

Por Radiobiología y pCR:

25 Gy en 5 fx es mejor que 50 Gy en 25 fx

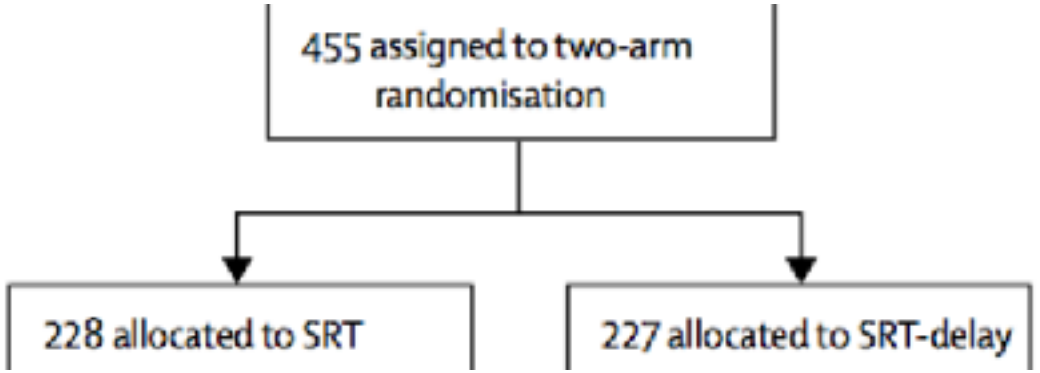
25 Gy en 5 fx: ¿Cirugía inmediata o delay?

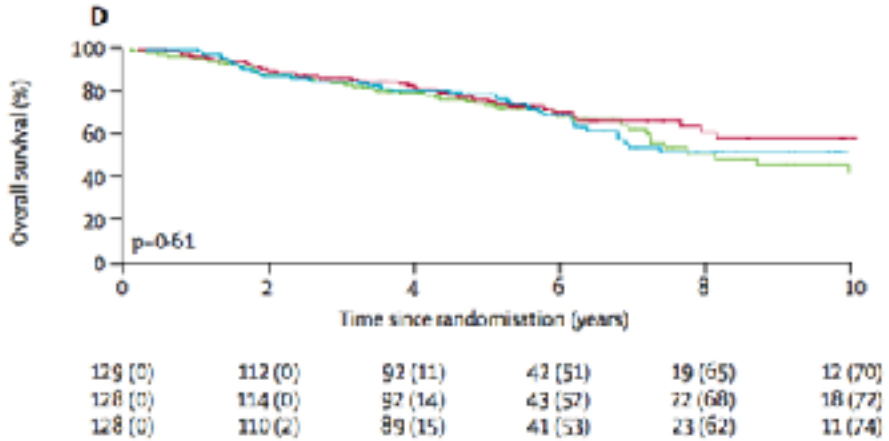
Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial

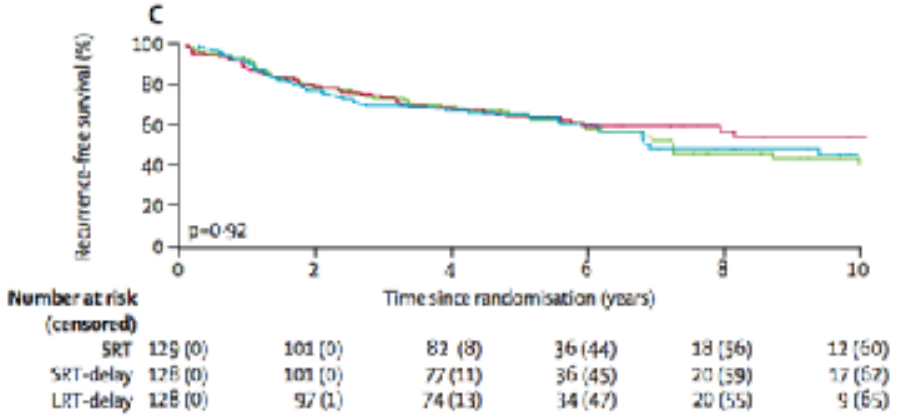
Johan Erlandsson, Torbjörn Holm, David Pettersson, Åke Berglund, Björn Cedermark, Calin Radu, Hamming Johansson, Mikael Machado, Fredrik Hjern, Olof Hallböök, Ingvar Syk, Bengt Glimelius, Anna Martling

Summary

Background Radiotherapy reduces the risk of local recurrence in rectal cancer. However, the optimal radiotherapy







Erlandsson, Lancet Oncol 2017

25 Gy en 5 fx: ¿Cirugía inmediata o delay?

	SRT (n=357)	SRT-delay (n=355)	p value
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†

Erlandsson, Lancet Oncol 2017

25 Gy en 5 fx con delay para cirugía tiene menos complicaciones

¿Y que hacemos durante el delay?

surgery. Thus, short-course radiotherapy with delay presents the opportunity to give neoadjuvant chemotherapy during the interval between radiotherapy and surgery.

Erlandsson, Lancet Oncol 2017

¿Debemos mejorar lo que hacemos?

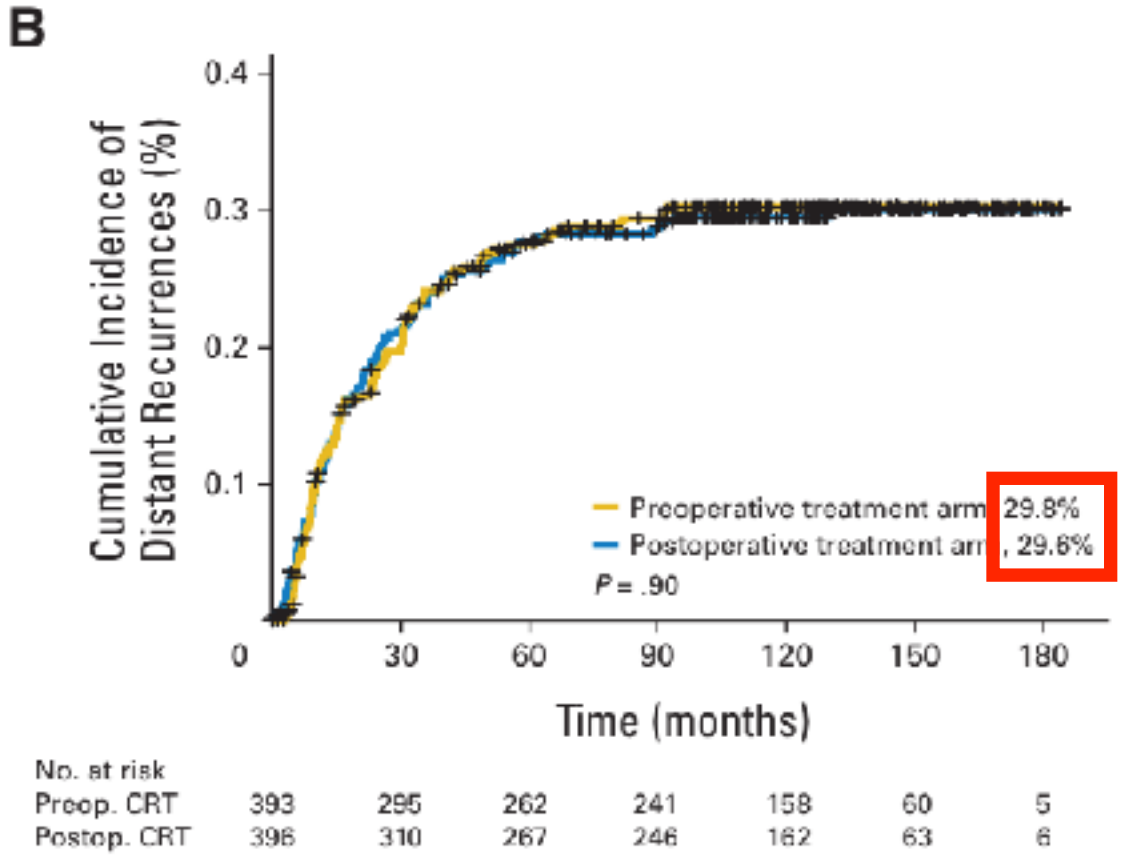
VOLUME 30 · NUMBER 16 · JUNE 1 2012

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

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

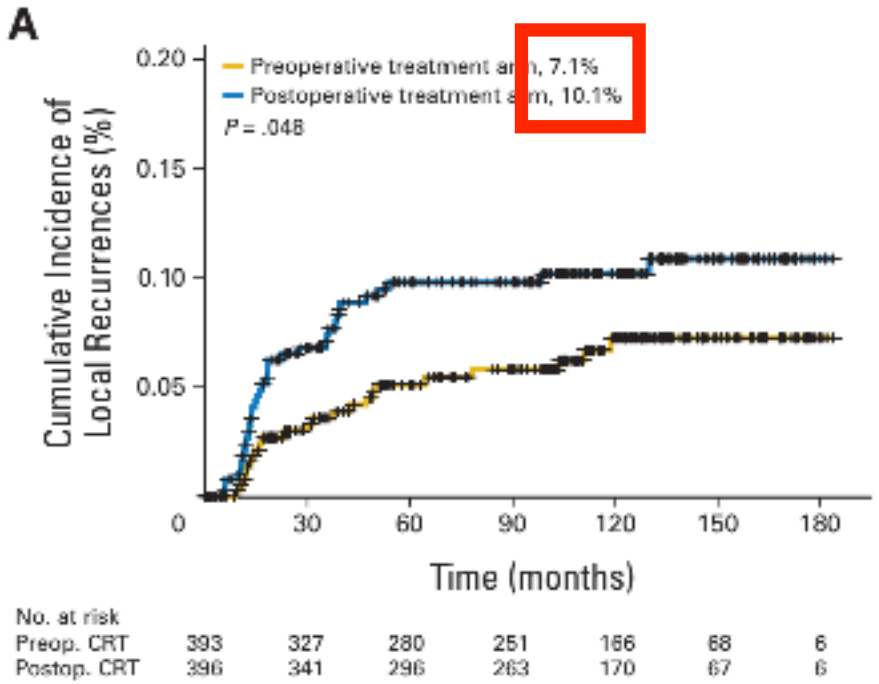
30% de recurrencia a distancia



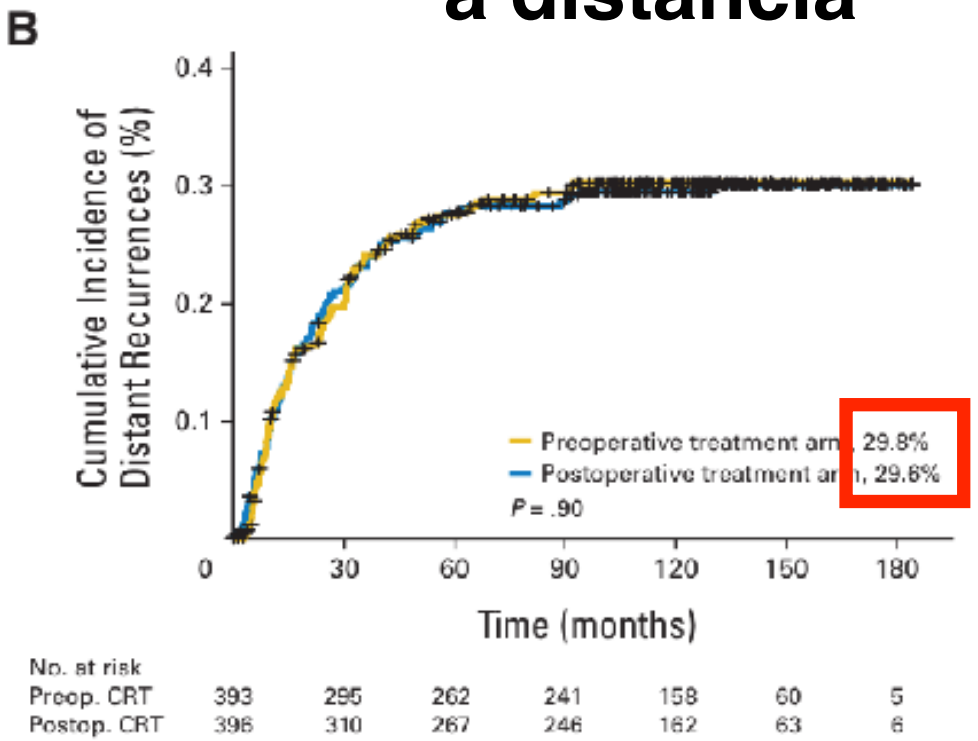
Sauer, JCO 2012

¿Cómo mejorar lo que hacemos?

7-10% de recurrencia local

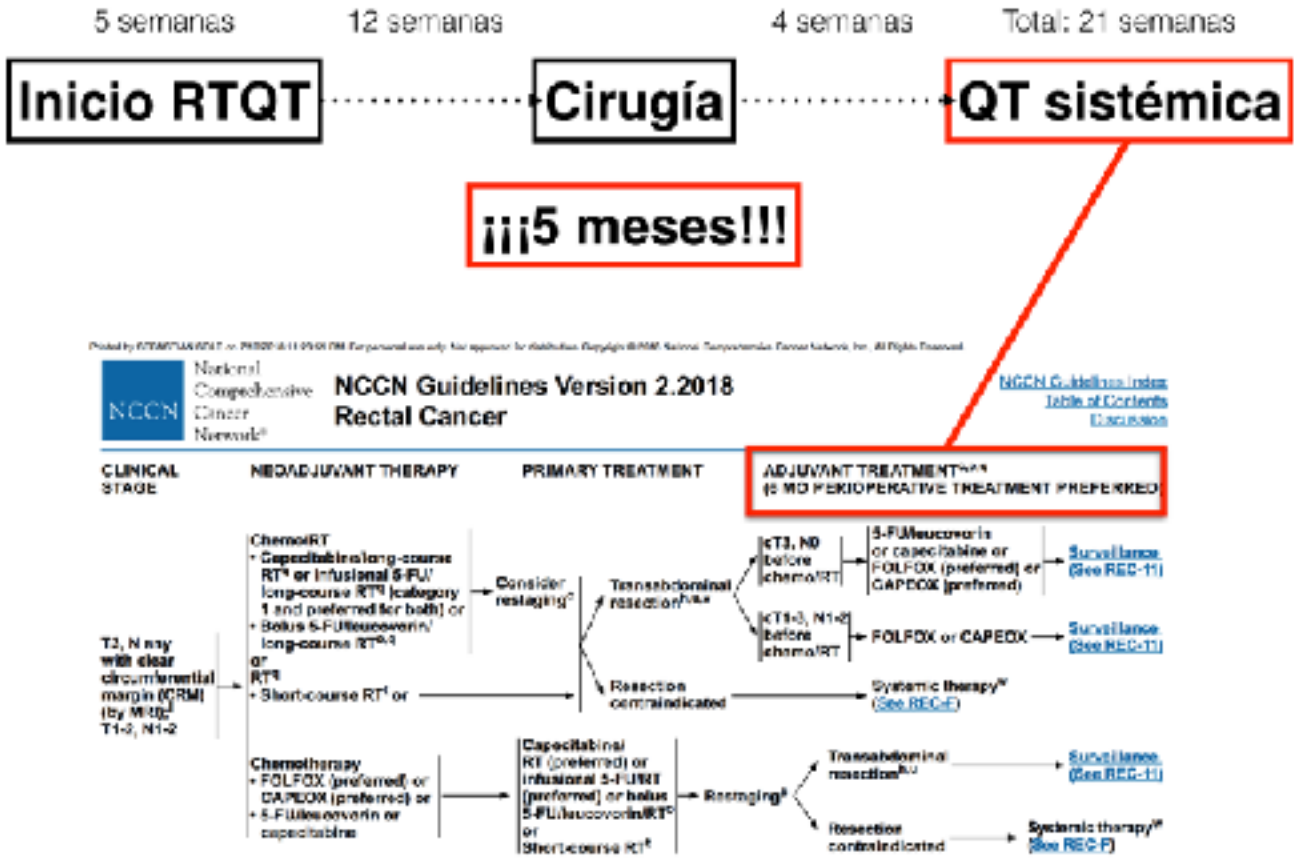


30% de recurrencia a distancia



Sauer, JCO 2012

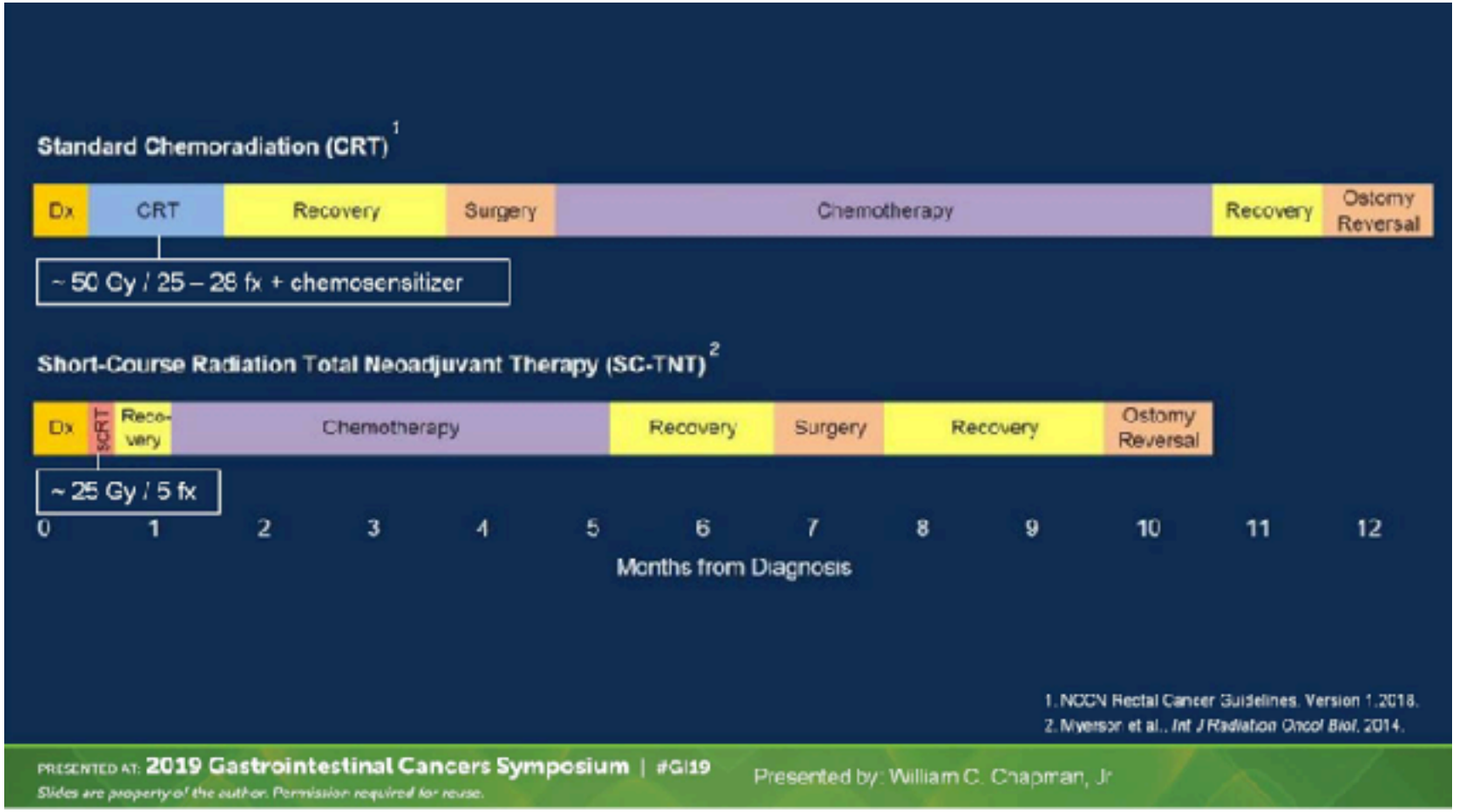
Nuestros esfuerzos deben ir en disminuir la recurrencia a distancia



¿Cómo dar QT efectiva antes en el curso de la enfermedad sin perder el control local?

Tratamiento **N**eoadyuvante **T**otal

¿Cómo dar QT efectiva antes en el curso de la enfermedad sin perder el control local?



¿Estudios randomizados?

Resultados iniciales del estudio STELLAR

The initial results for a phase III study of short-term versus long-term chemoradiotherapy in locally advanced rectal cancer (STELLAR trial)

Y. Tang[1], J. Jin[1], S. Li[1], N. Li[1], Y. Zhu[2], S-X. Liu[3], W-L. Wang[4], J. Wang[5], X. Wang[6], G-F. Li[7], M. Shi[8], L. Fan[9], K. Zhang[10], H. Ren[1], Y-X. Li[1], H. Fang[1], W-H. Wang[1], Y-W. Song[1], Y-P. Liu[1], S-L. Wang[1], Y. Tang[1], B. Chen[1]

Corresponding Author: Jing Jin[1]

[1]Radiation Oncology, Cancer Hospital and Institute, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, China
[2]Radiation Oncology, Zhejiang Provincial Cancer Hospital, Hangzhou, China
[3]Radiation Oncology, Jilin Provincial Cancer Hospital, Changchun, China
[4]Radiation Oncology, Guizhou Provincial Cancer Hospital, Guiyang, China
[5]Radiation Oncology, Hebei Provincial Cancer Hospital, Shijiazhuang, China
[6]Radiation Oncology, West China Hospital, Sichuan University, Chengdu, China
[7]Radiation Oncology, Beijing Hospital, Beijing, China
[8]Radiation Oncology, Xijing Hospital, Xi'an, China
[9]Radiation Oncology, Sichuan Provincial Cancer Hospital, Chengdu, China
[10]Radiation Oncology, Qinghai Red Cross Hospital, Xining, China

Trial Design

Control group
Experimental group

- Aged 18-70
- Distal or middle third rectal adenocarcinomas
- T3-T4 and/or N+ diagnosed by MRI
- ECOG PS 0-1
- No previous anti-cancer treatments

Estimated Enrollment: 552

Randomize 1:1

Long-term CRT → **TME** → **CAPOX** 6#, q21

SCRT → **CAPOX** 4#, q21 → **TME** → **CAPOX** 2#, q21

- **Primary Endpoint**
  3y-DFS
- **Secondary Endpoints**
  OS, LC, DM, Surgical complications, Toxicities, QOL

- Stratified by status of mesorectal fascia (MRF) : (MRF- vs. MRF+)
- Non inferiority comparison

ASTRO 2016 ENHANCING VALUE IMPROVING OUTCOMES

Tang, ASTRO 2016

Resultados iniciales del estudio STELLAR

Surgery and Histopathology		SCRT + CT(N=37)		CRT(N=38)	
		No.	%	No.	%
Operative model	Anterior resection	15	40.5%	16	42.1%
	Abdominoperineal resection	21	56.7%	22	57.9%
	Hartmann's	1	2.8%	0	0
R0 resection	Yes	34	91.9%	34	89.5%
	No	3	8.1%	4	10.5%
pCR rate		9	25.7%	3	7.9%

Treatment after neoadjuvant radiotherapy or chemotherapy	SCRT + CT(N=60)		CRT(N=58)	
	No.	%	No.	%
Radical surgery	37	61.7%	38	65.5%
Wating for surgery	13	21.6%	10	17.2%
Wait and watch due to CCR of tumor	7	11.7%	0	0

Tang, ASTRO 2016

Actualización STELLAR

496P **Short-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally advanced rectal cancer (STELLAR): A planned interim analysis**

J. Jin[1], Y. Tang[1], S. Liu[2], Y. Zhu[3], W. Wang[4], G. Li[5], X. Wang[6], J. Wang[7], J. Yang[8], S. Li[1], N. Li[1], W. Liu[1], Y. Li[1], Y. Chi[9], A. Zhou[10], J. Huang[9], X. Wang[11], L. Jiang[12], J. Jiang[12], S. Zou[13]

Conclusions: The interim analysis revealed the acute toxicity and surgical complication were acceptable and comparable in both groups, however, the people in experimental group showed better treatment completion.

Clinical trial identification: NCT02533271.

26.2% vs 5.3% of them achieved $_{yp}T_0N_0$ (p = 0.011).

Jin, ESMO 2018

¿Por qué es importante lograr CR?

Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study

Maxime J M van der Valk, Denise E Hilling, Esther Bastiaannet, Elma Meershoek-Klein Kranenbarg, Gerrard L Beets, Nuno L Figueiredo, Angelita Habr-Gama, Rodrigo O Perez, Andrew G Renehan, Cornelis J H van de Velde, and the IWWD Consortium*

Summary

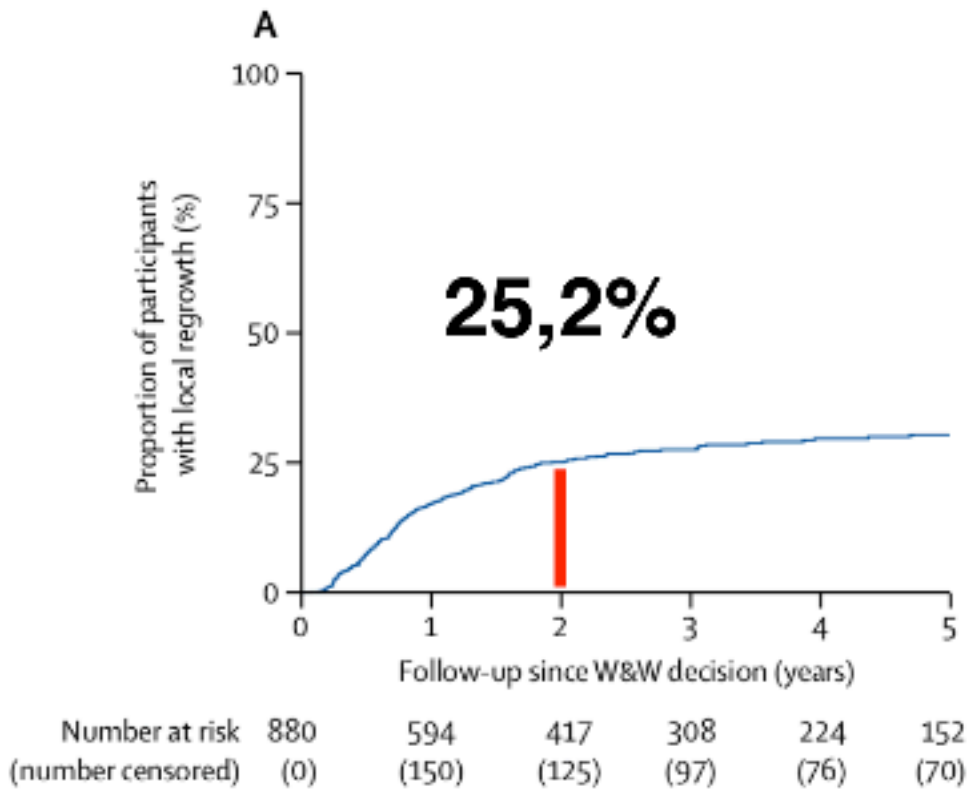
Background The strategy of watch and wait (W&W) in patients with rectal cancer who achieve a complete clinical response (cCR) after neoadjuvant therapy is new and offers an opportunity for patients to avoid major resection surgery. However, evidence is based on small-to-moderate sized series from specialist centres. The International Watch & Wait Database (IWWD) aims to describe the outcome of the W&W strategy in a large-scale registry of pooled individual patient data. We report the results of a descriptive analysis after inclusion of more than 1000 patients in the registry.

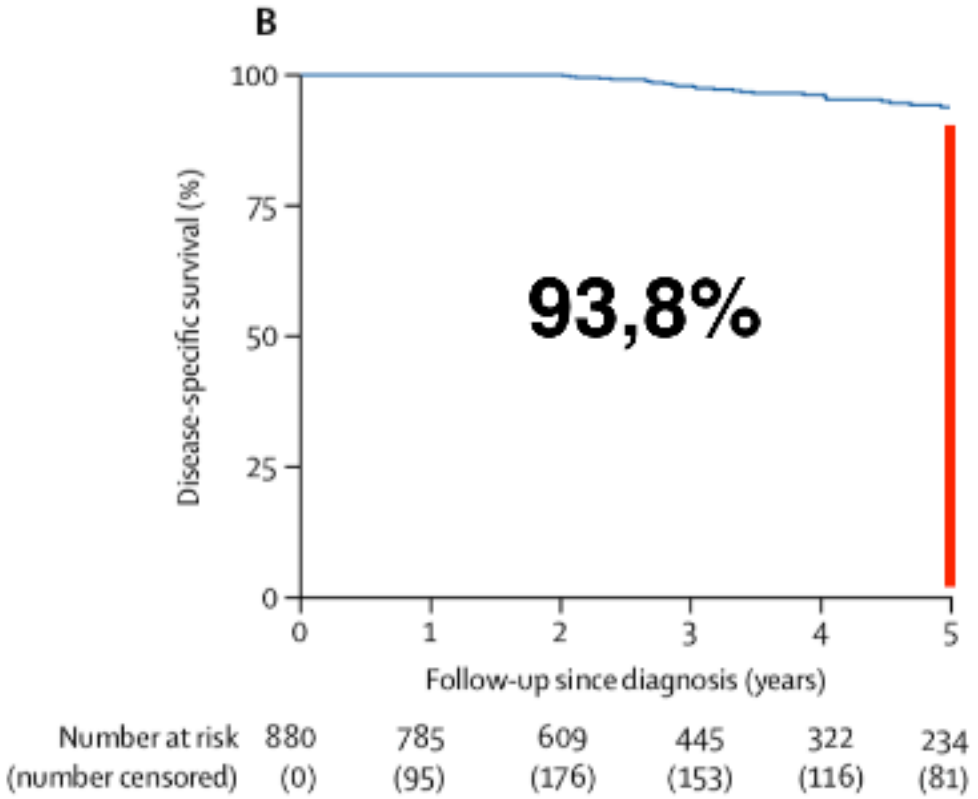
Total number of patients (N=880)	
cT3	451 (51%)
cT4	30 (3%)
cN1	271 (31%)
cN2	167 (19%)

Mediana de seguimiento 3,3 años

van der Valk, Lancet 2018

¿Por qué es importante lograr CR?



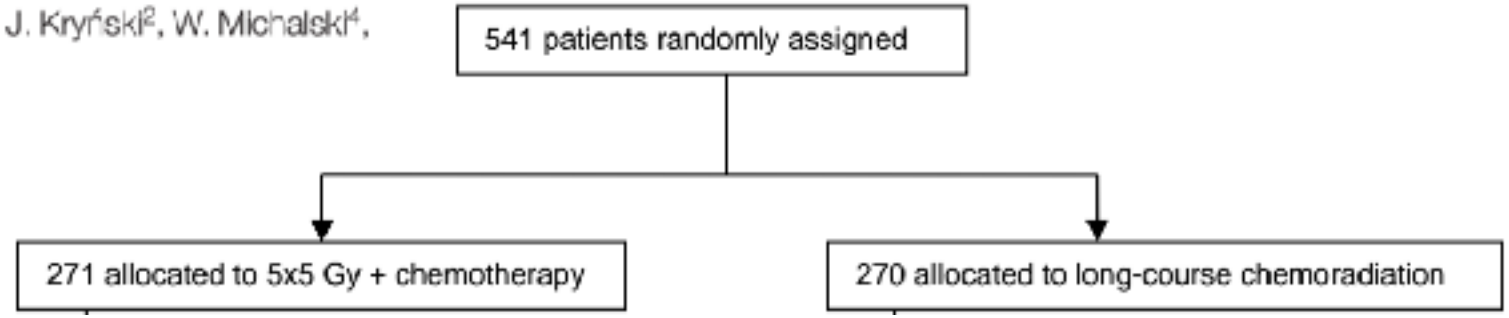


van der Valk, Lancet 2018

Estudio Polaco II

Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study

K. Bujko[1*], L. Wyrwicz[2], A. Rutkowski[2], M. Malinowska[3], L. Pietrzak[1], J. Kryński[2], W. Michalski[4],



RT 1 semana + QT

RTQT 5 semanas

Bujko, Ann Oncol 2016

Estudio Polaco II

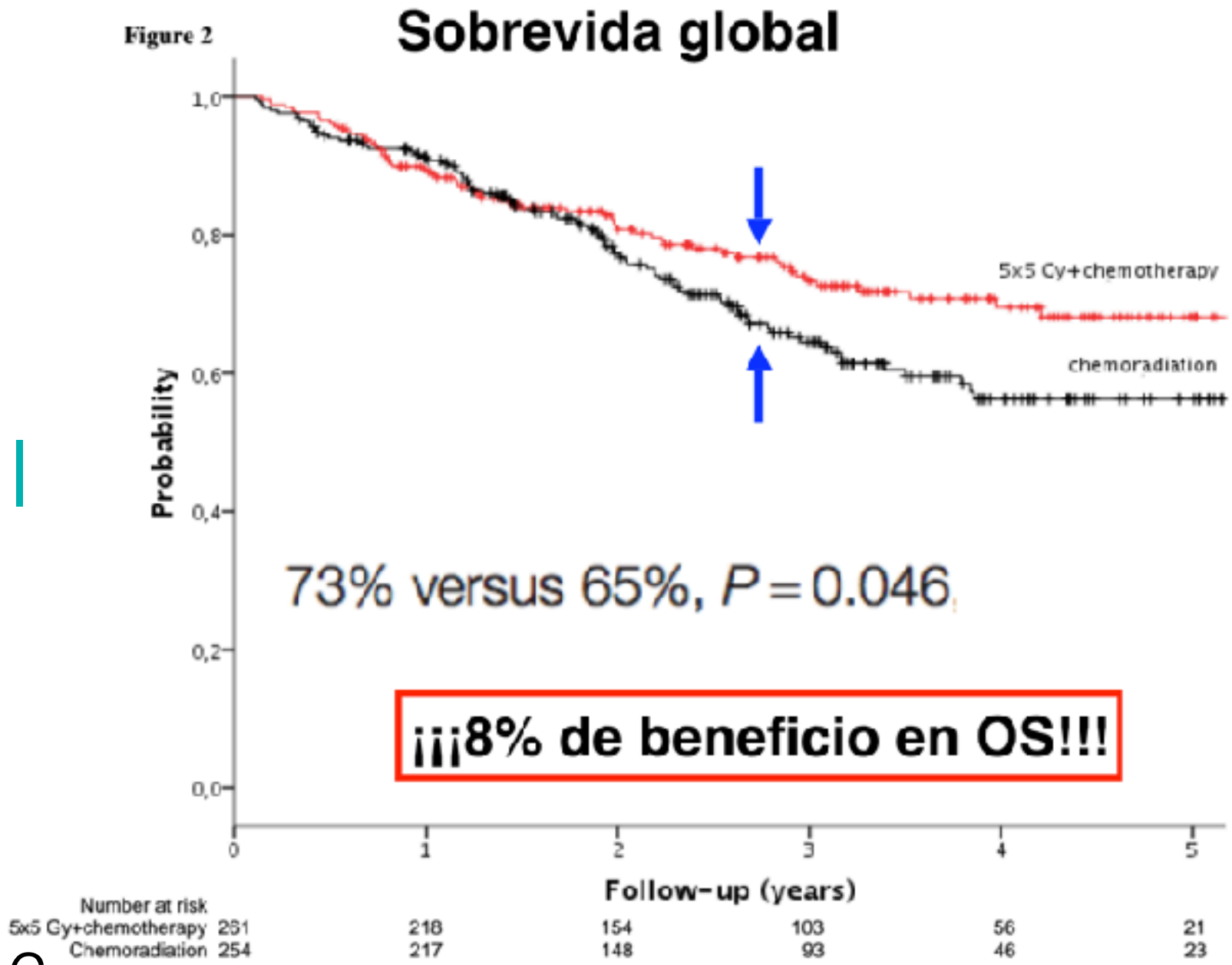
Table 1. Patients' characteristics.

	5+5 Gy + chemotherapy *N=261*	Long-course chemoradiation *N=254*
Gender		
Female	78 (30)	85 (33)
Male	183 (70)	169 (67)
Age in years, median (IQR)	60 (54 - 66)	60 (56 - 65)
Pelvic MRI		
Yes	172 (66)	164 (65)
No	88 (34)	89 (35)
No data	1	1
Type of tumour		
Primary fixed cT3 [diagnosed on MRI]	88 (34) [57 (33)]	83 (33) [59 (36)]
Primary cT4 [diagnosed on MRI]	165 (63) [112 (65)]	163 (64) [101 (62)]
Recurrent [diagnosed on MRI]	8 (3) [3 (2)]	8 (3) [4 (2)]
Who performance score		
0	129 (49)	126 (50)
1	120 (46)	115 (45)
2	11 (4)	13 (5)
3	1 (0.5)	0
Distance between tumour and anal verge in cm		
0-5	148 (57)	138 (55)
>5-10	106 (41)	99 (39)
>10-15	7 (3)	16 (6)
No data		1

Numbers in the table denote number of patients (%) unless otherwise stated.

Bujko, Ann Oncol 2016

Estudio Polaco II

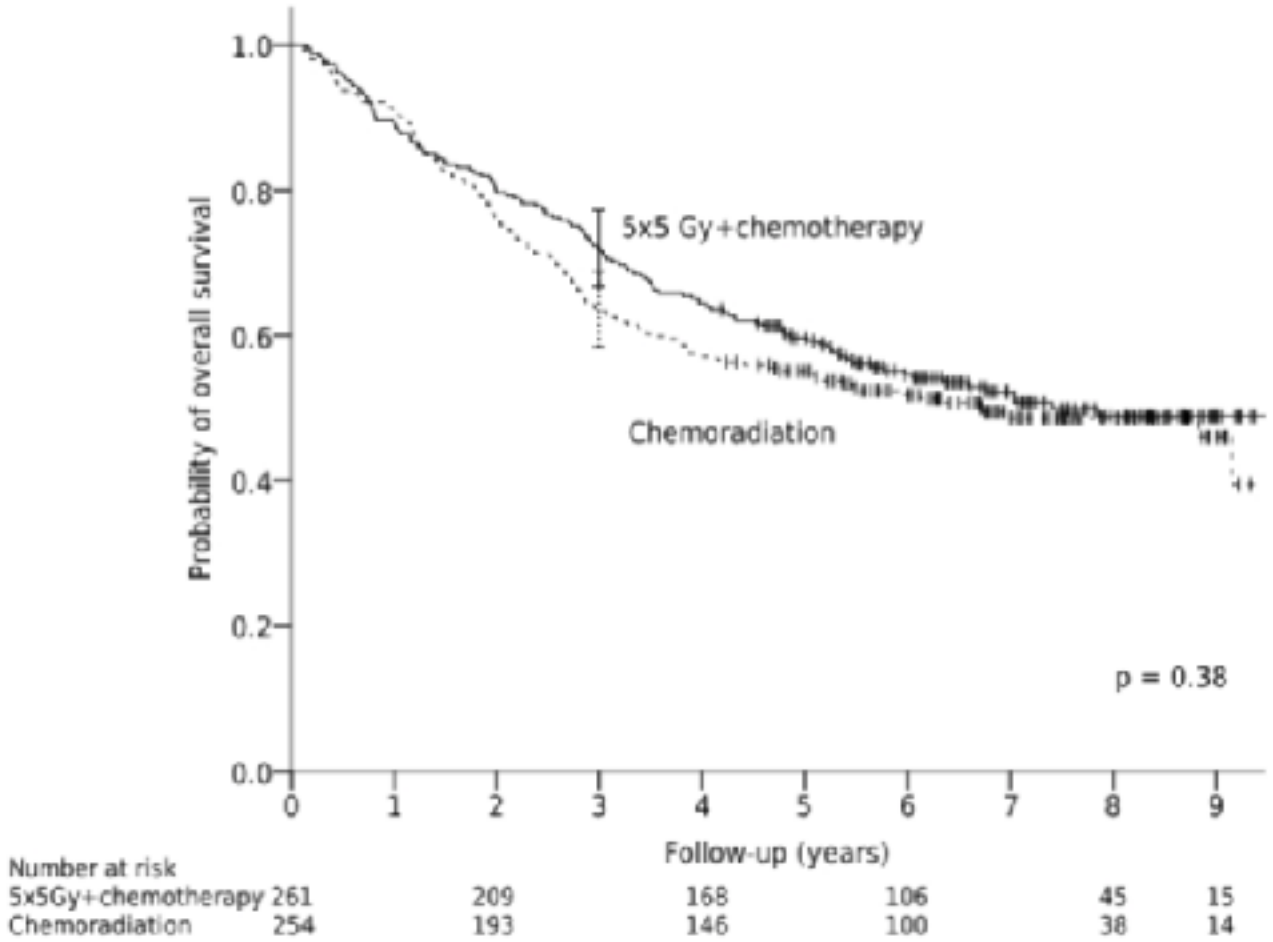


Bujko, Ann Oncol 2016

Actualización estudio Polaco II

Long-course preoperative chemoradiation vs. 5 x 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: Long-term results of the randomized Polish II study

B. Cisel[1], L. Pietrzak[2], W. Michalski[3], L. Wyrwicz[4], A. Rutkowski[5], E. Kosakowska[5], A. Cencelewicz[5], M. Spałek[2], W. Polkowski[1], M. Jankiewicz[1,6], R. Styliński[7], M. Bębenek[8], B. Kapturkiewicz[8], A.Maciejczyk[9], J. Sadowski[10], J. Zygulska[11], W. Zegarski[12], M. Jankowski[12]; M. Las-Jankowska[13]; Z. Toczko[14]; U. Żelazowska-Omiotek[15], L. Kępka[16], J. Socha[16,17], E. Wasilewska-Tesluk[18,19], W. Markiewicz[20], J. Kładny[21], A. Majewski[22], W. Kapuściński[23], R. Suwiński[24] and K. Bujko[2] for the Polish Colorectal Study Group



Cisel, Ann Oncol 2019

Actualización estudio Polaco II

The calculation of the sample size showed that to detect at least a 10% benefit in radical surgery rate, 540 patients were needed.

Twenty-six patients were excluded, leaving 515 patients for analysis.

The corresponding values for radical resection rate were **77% vs. 71%, *P* = 0.07** and for pCR (ypT0N0) 16% vs. 12%, *P* = NS.

Oxaliplatin was given to 70% of patients.

Median OS was 89 months vs. 81 months in the short-course/CCT group vs. the chemoradiation group, respectively; for 8 months difference, 95% CI was –23 to 38 months. *P* = NS.

Median follow-up for living patients was 7.0 years.

Acute toxicity of preoperative treatment was lower in the short-course/CCT group than in the chemoradiation group, *P* = 0.006.

Cisel, Ann Oncol 2019

¿Cómo se explica esto?

Radiobiología

Esquema	Tumor α/β= 5	Tumor c/ corrección de t	Tejido Sano α/β=3
5x5 Gy	35,7 Gy	35,7 Gy	40Gy
25x2 Gy	50Gy	50-15,6 =34,4 Gy	50Gy

EQD2 (α/β) = (d+α/β) / (2+α/β)
Time correction: EQD2 (α/β) – (OTT-delay) D_{prolif}
Repair rate= D_{prolif}=0,6Gy/day
Proliferation delay: 7 days

25 Gy en 5 fx es un poco menos dosis en tejido sano que 50 Gy en 25 fx

Guckenberger et al. Radiat Oncol 2009;4:67

Diapositiva Dra. Verónica López
Instituto Nacional del Cáncer - Chile

Datos de Clínica IRAM, Santiago, Chile

Revisión retrospectiva de 58 pacientes operados luego de RT 25 Gy en 5 fx y 4 ciclos de FOLFOX (2 meses)

total pac 58	n	%
N0	8	13,8
N1	32	55,1
N2	11	18,9
N positivo no clasificado	7	12,1
N +	50	86,2

45 pacientes T3-4 (77,5%)

Gabler, Datos No Publicados

Datos de Clínica IRAM, Santiago, Chile

22,4 % de respuesta patológica completa

total pac 58	n	%
pT 0	13	22,4
pT 1	5	8,6
pT2	15	25,9
pT3	22	37,9
pT 4	2	3,4
pT no evaluado	1	1,7

Gabler, Datos No Publicados

Datos de Clínica IRAM, Santiago, Chile

65,5 % de downstage (de etapa III a menor)

total pac 58	n	%
pN0	42	72,4
pN1	10	17,2
pN2	2	3,4
pN no evaluado	4	6,9
pN+	12	20,7

Gabler, Datos No Publicados

IRAM vs Sauer

Table 3. Postoperative Pathological Tumor Stage, Type of Surgery, and Completeness of Resection, According to Actual Treatment Given.*

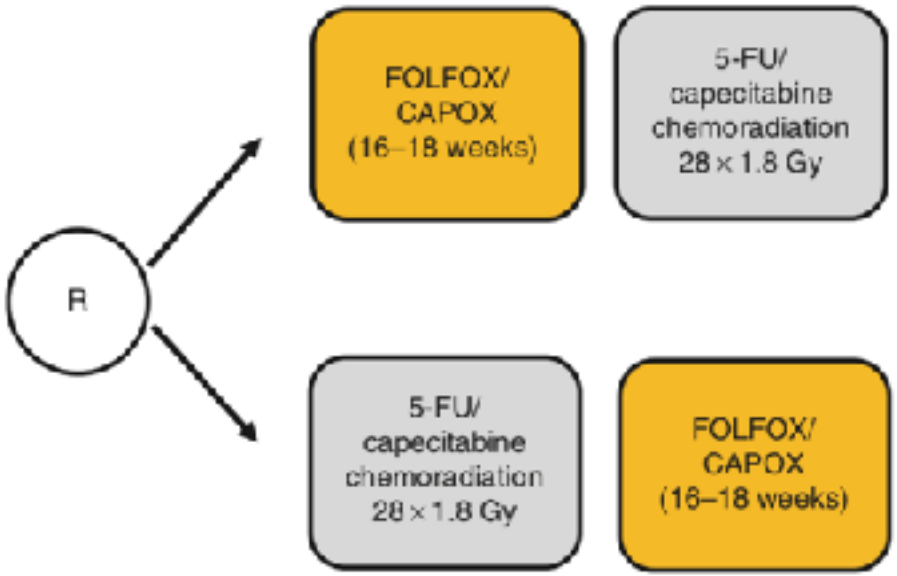
Variable	Preoperative Chemoradiotherapy (N=415)	Postoperative Chemoradiotherapy (N=384)	P Value
Histopathological finding (%)			<0.001
Complete response	8	0	
TNM stage			
I	25	18	
II	29	29	
III	25	40	

Sauer, NEJM 2004

	IRAM	Sauer
pCR	22,4 %	8 %
Downstage (III a menor)	65,5 %	15 %

Gabler, Datos No Publicados

Otras estrategias de TNT



Radioterapia corta (1 semana) y luego Oxaliplatino es una mejor estrategia de TNT:

1. Alargar el tratamiento local en 4 semanas no mejorará los resultados oncológicos

2. Comenzar con RT evita la probabilidad de que el tumor progrese durante QT

3. Comenzar con RT produce rápido alivio de los síntomas

4. Evita retraso en entrega de QT efectiva lo que podría reducir la progresión sistémica

¿Las guías clínicas apoyan el uso de RT corta + FOLFOX?

Annals of Oncology 28 (Supplement 4): iv22–iv40, 2017
doi:10.1093/annonc/mdx224

CLINICAL PRACTICE GUIDELINES

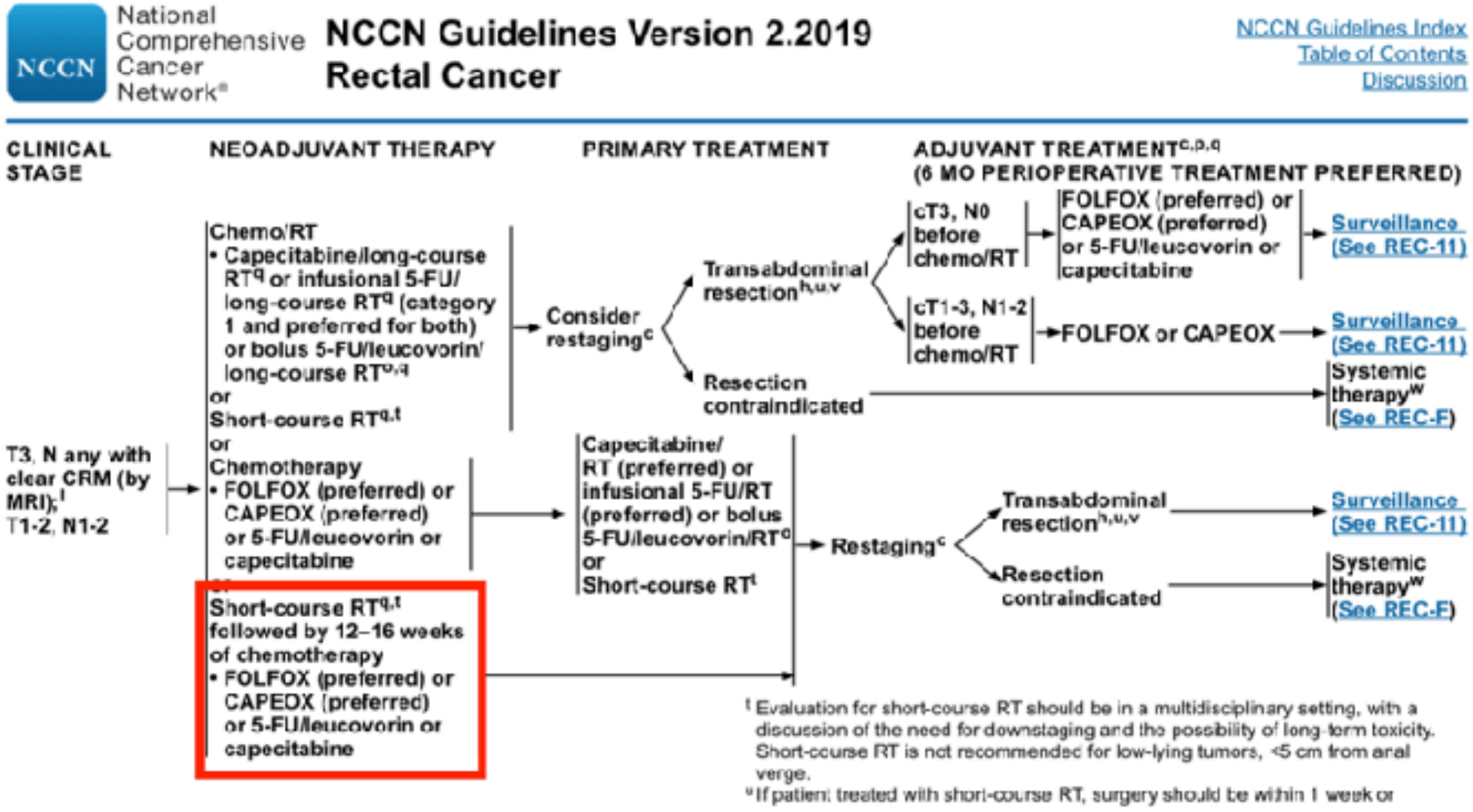
Clinical Practice Guidelines

Annals of Oncology

Table 6. Recommended choice of treatment options within TNM risk category of primary rectal cancer without distant metastases

Advanced (Ugly)	cT3 with any MRF involved, any cT4a/b, lateral node+	Preoperative CRT followed by surgery (TME and more extended surgery if needed due to tumour overgrowth), or preoperative SCPRT (5×5 Gy) plus FOLFOX and delay to surgery	Alternatively, 5×5 Gy alone with a delay to surgery in fragile/elderly or in patients with severe comorbidity who cannot tolerate CRT

¿Las guías clínicas apoyan el uso de RT corta + FOLFOX?



Nuevo estándar

Invited Commentary

Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer—The New Standard of Care?

Theodore S. Hong, MD; David P. Ryan, MD

In summary, TNT can be considered standard of care for select patients with high-risk, locally advanced disease. Further studies are needed to help patients balance the benefits of sphincter preservation vs toxic effects of overtreatment in lower-risk disease.

Hong, JAMA Oncol 2018

Mensajes para la casa

- **Es necesario mejorar los resultados en cáncer de recto localmente avanzado**
- **Para hacer esto debemos enfocarnos en disminuir el riesgo de recurrencia a distancia (30% Sauer, JCO 2012)**
- **Adelantar la QT útil (Oxaliplatino) a la neoadyuvancia es la mejor forma de lograr de disminuir la recurrencia a distancia (TNT)**

Mensajes para la casa

- **TNT con RT corta (1 semana) y oxaliplatino acorta el tiempo total de tratamiento, esto es IMPORTANTE para TODOS pacientes**
- **TNT con RT corta (1 semana) y oxaliplatino produce mayor pCR y cCR (STELLAR), esto puede ser MUY IMPORTANTE para ALGUNOS pacientes (tumor de recto bajo, pacientes con co-morbilidades)**
- **TNT con RT corta (1 semana) y oxaliplatino tiene menor toxicidad aguda y al menos equivalente outcome oncológico (POLACO II), esto es MUY IMPORTANTE para TODOS pacientes**

Para mayor lectura

Rev Chil Cir. 2017;69(2):181–183

Revista Chilena de cirugía

www.elsevier.es/rchic

ARTÍCULO DE REVISIÓN

Nueva estrategia terapéutica en cáncer de recto localmente avanzado

Sebastián Solé Z., Francisco Larsen E.* y Claudio Solé P.

Solé, Rev Chil Cir 2017

INNOVATE, COLLABORATE, TRANSFORM

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