REKTUM KANSERİNDE KANITA DAYALI TEDAVİ VE RADYOTERAPİ PLANLAMASI

Neoadjuvan Radyoterapi:

Doz, Zamanlama

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Rektum Kanseri Tedavisinde Radyoterapi

Adjuvan

RT ile LR: (%13-16 vs. %25-34)

- 1990'a kadar temel yaklaşım adjuvan RT
- Cerrahi vs. cerrahi + adj. RT
- 5 randomize çalışma; GS, UM: Fark yok!

Neadjuvan

NeoRT ile LR: (%6-8 vs. %13-16)

- Tümör küçülmesi sağlayarak distal yerleşimli lezyonlarda sfinkter koruyucu cerrahiye olanak sağlamak

RT- C vs C

(radyosensitivite)

KRT- C vs RT-C

radyasyon hasarının önüne geçmek

- RT uygulanan alan cerrahide çıkarılıyor, RT'den etkilenmeyen doku ile anostomoz şansı
- Dezavantaj: Fazla tedavi riski

Rektum Kanseri Tedavisinde Radyoterapi

Adjuvan

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Neadjuvan

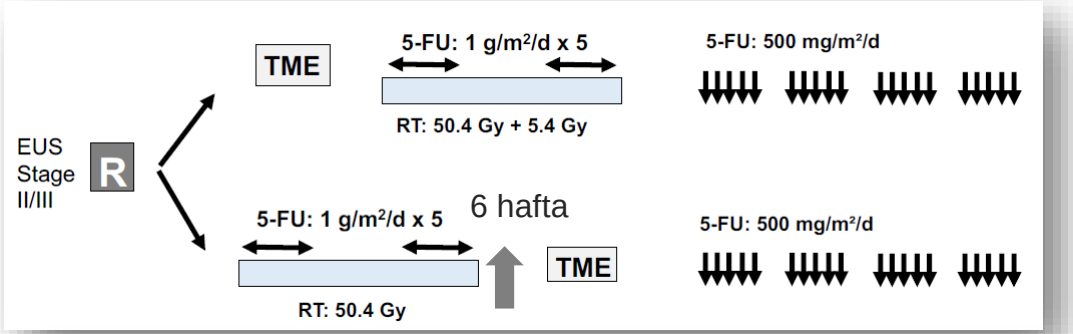
NeoRT ile LR: (%6-8 vs. %13-16)

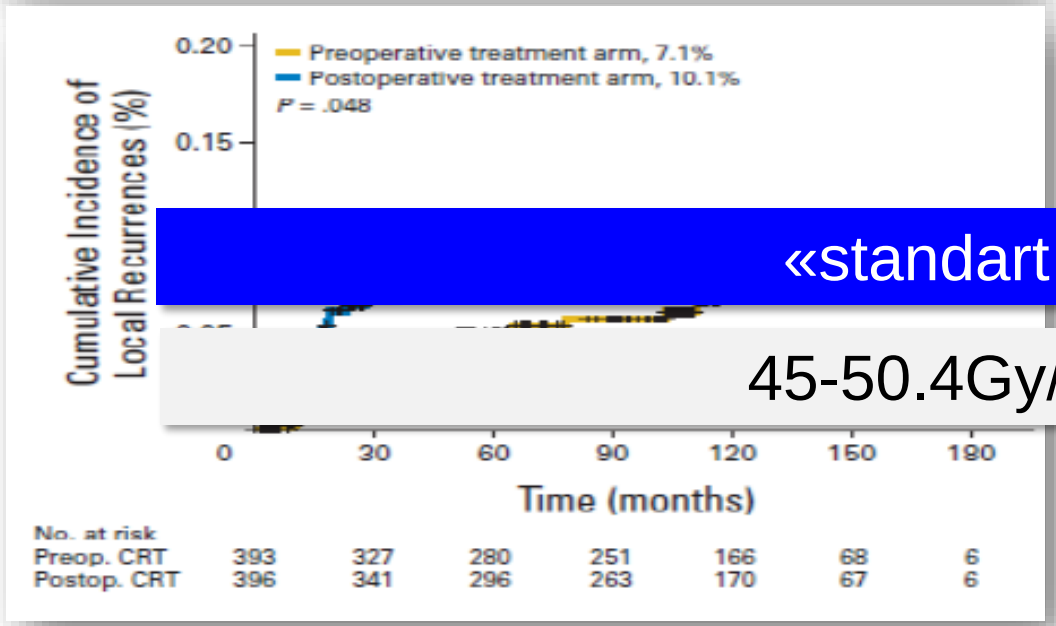
- Tümör küçülmesi sağlayarak distal yerleşimli lezyonlarda sfinkter koruyucu cerrahiye olanak sağlamak
- Pre-operatif dönemde dokularda daha iyi oksijenlenme (radyosensitivite)
- Cerrahi sonrası yapışıklıklar nedeniyle alana giren bağırsaklarda radyasyon hasarının önüne geçmek
- RT uygulanan alan cerrahide çıkarılıyor, RT'den etkilenmeyen doku ile anostomoz şansı
- Dezavantaj: Fazla tedavi riski

Rektum Kanseri Tedavisinde Radyoterapi

German CAO/ARO/AIO-94

Sauer R et al., NEJM, 2004





	Pre-op	Post-op	p
Gr 3-4 akut toks.	%27	%40	**0.001**
Gr 3-4 geç toks.	%14	%24	**0.01**
pTY	%8	%0	**<0.001**
LR	%6	%13	**0.006**
Sfinkter koruma (distal)	%20	%10	**0.004**
			NS
			NS

«standart tedavi»

45-50.4Gy/28fr - KT

Bu sırada «!»

İsveç Protokolü

25Gy/5fr

1 hafta bekleme

The New England Journal of Medicine

IMPROVED SURVIVAL WITH PREOPERATIVE RADIOTHERAPY
RECTAL CANCER

Swedish Rectal Cancer Trial., NEJM, 1997

Swedish Rectal Cancer Trial: Long Lasting Benefits From Radiotherapy on Survival and Local Recurrence Rate

Joakim Folkesson, Helgi Birgisson, Lars Pahlman, Bjorn Cedermark, Bengt Glimelius, and Ulf Gunnarsson

Folkesson et al, JCO, 2005

1168 cT1-T3 rektum ca

R

25 Gy / 5 Fx
1 hafta sonra cerrahi
(RT→C)

Cerrahi
(C)

TME yok!

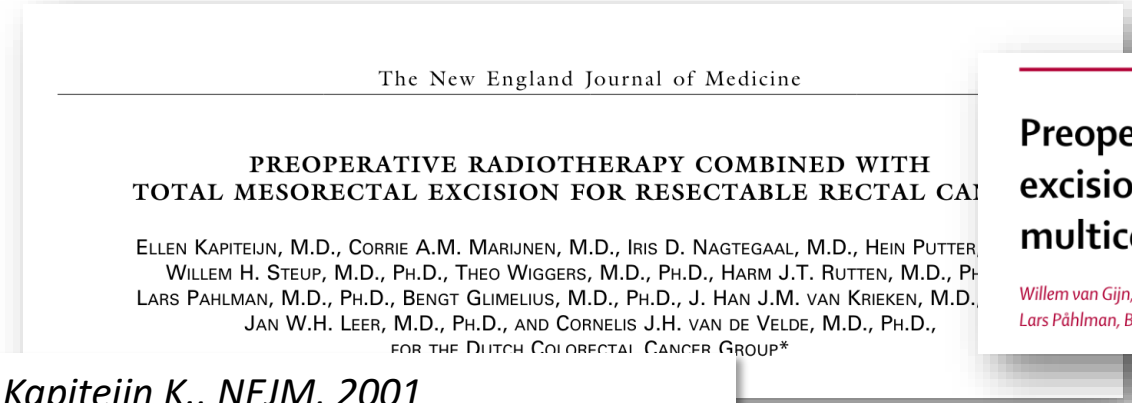
13 yıllık sonuçlar;

	RT→C	C	p
LR	%9	%26	**<0.001**
GS	%38	%30	**0.008**
HSS	%72	%62	**0.03**

Birgisson et al, JCO, 2005

Toksisite: İB obs. (13.9 vs. 5.5%, p < 0.01)

Hollanda Çalışması


The New England Journal of Medicine

PREOPERATIVE RADIOTHERAPY COMBINED WITH TOTAL MESORECTAL EXCISION FOR RESECTABLE RECTAL CA

ELLEN KAPITEIJN, M.D., CORRIE A.M. MARIJNEN, M.D., IRIS D. NAGTEGAAL, M.D., HEIN PUTTER, WILLEM H. STEUP, M.D., PH.D., THEO WIGGERS, M.D., PH.D., HARM J.T. RUTTEN, M.D., PH. LARS PAHLMAN, M.D., PH.D., BENGT GLIMELIUS, M.D., PH.D., J. HAN J.M. VAN KRIEKEN, M.D., JAN W.H. LEER, M.D., PH.D., AND CORNELIS J.H. VAN DE VELDE, M.D., PH.D., FOR THE DUTCH COLORECTAL CANCER GROUP*

Kapiteijn K., NEJM, 2001


Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial

Willem van Gijn, Corrie A M Marijnen, Iris D Nagtegaal, Elma Meershoek-Klein Kranenbarg, Hein Putter, Theo Wiggers, Harm J T Rutten, Lars Påhlman, Bengt Glimelius, Cornelis J H van de Velde, for the Dutch Colorectal Cancer Group

Van Gijn et al., Lancet Oncol, 2011

1861 Evrel-III rektum ca

R

25 Gy / 5 Fx 1 hafta sonra cerrahi (RT→C)	**Cerrahi (C)**
RT basl-C : 10 gün	**c.s.+: 50.4Gy/28fr**

12 yıllık sonuçlar;

		RT→C	C	p
LR		%5	%11	**<0.001**
CRD		%16.9	%21.5	**0.04**
GS	Evre III	%50.1	%40.3	**0.03**

«standart tedavi»

KRT

Kısa dönem RT

45-50.4Gy/25-28fr + KT

25Gy/5fr

Konvansiyonel Fr

Hipofraksiyonasyon

Toplam doz

Eş değer doz ‘?’

Doz/fr

Yan etki ‘?’ – *Radiation Induced Fibrosis*

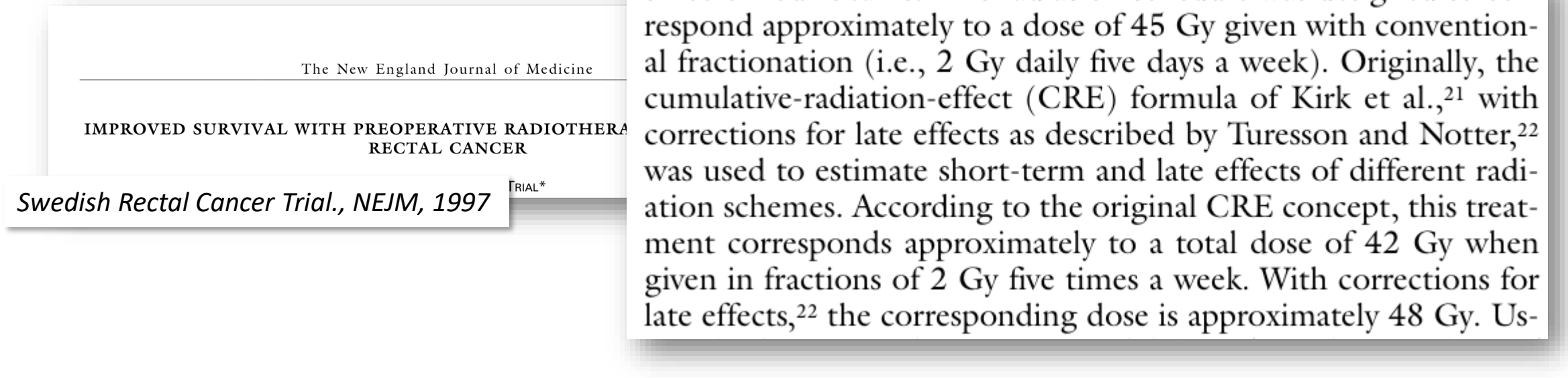
Toplam doz

Eş değer doz '?'

BED

Total dose x (1 + ((Dose rate factor x Fraction dose) / αβ))

BED	45Gy/25fr	25Gy/5fr
BED_{10}	53.10Gy	37.50Gy
BED_{3}	72.00Gy	66.67Gy



The New England Journal of Medicine

IMPROVED SURVIVAL WITH PREOPERATIVE RADIOTHERA
RECTAL CANCER

TRIAL*

three or four beams. This radiation schedule was designed to correspond approximately to a dose of 45 Gy given with conventional fractionation (i.e., 2 Gy daily five days a week). Originally, the cumulative-radiation-effect (CRE) formula of Kirk et al.,[21] with corrections for late effects as described by Turesson and Notter,[22] was used to estimate short-term and late effects of different radiation schemes. According to the original CRE concept, this treatment corresponds approximately to a total dose of 42 Gy when given in fractions of 2 Gy five times a week. With corrections for late effects,[22] the corresponding dose is approximately 48 Gy. Us-

Swedish Rectal Cancer Trial., NEJM, 1997

Toplam doz

Eş değer doz '?'

BED

Total dose x (1 + ((Dose rate factor x Fraction dose) / αβ))

BED	45Gy/25fr	25Gy/5fr
BED_{10}	53.10Gy	37.50Gy
BED_3	72.00Gy	66.67Gy

CRE

Swedish Rectal Cancer T

IMPROVED SURVIVAL

Clin. Radiol. (1971) **22**, 145-155

CUMULATIVE RADIATIO
PART I: FRACTIONATED TREA

J. KIRK, W. M. GRAY and E. I

From the Regional Department of Clinical Phy
Scottish Western Regional Hospital Board and the Glas
Western Infirmary, Glas

Kirk et al., Clin Radiol. 1971

The equation describing the iso-effect curves for fractionated radiation (equation (1)) can be written as a

In ar as

given in fractions of 2
late effects,[22] the corr

(2)

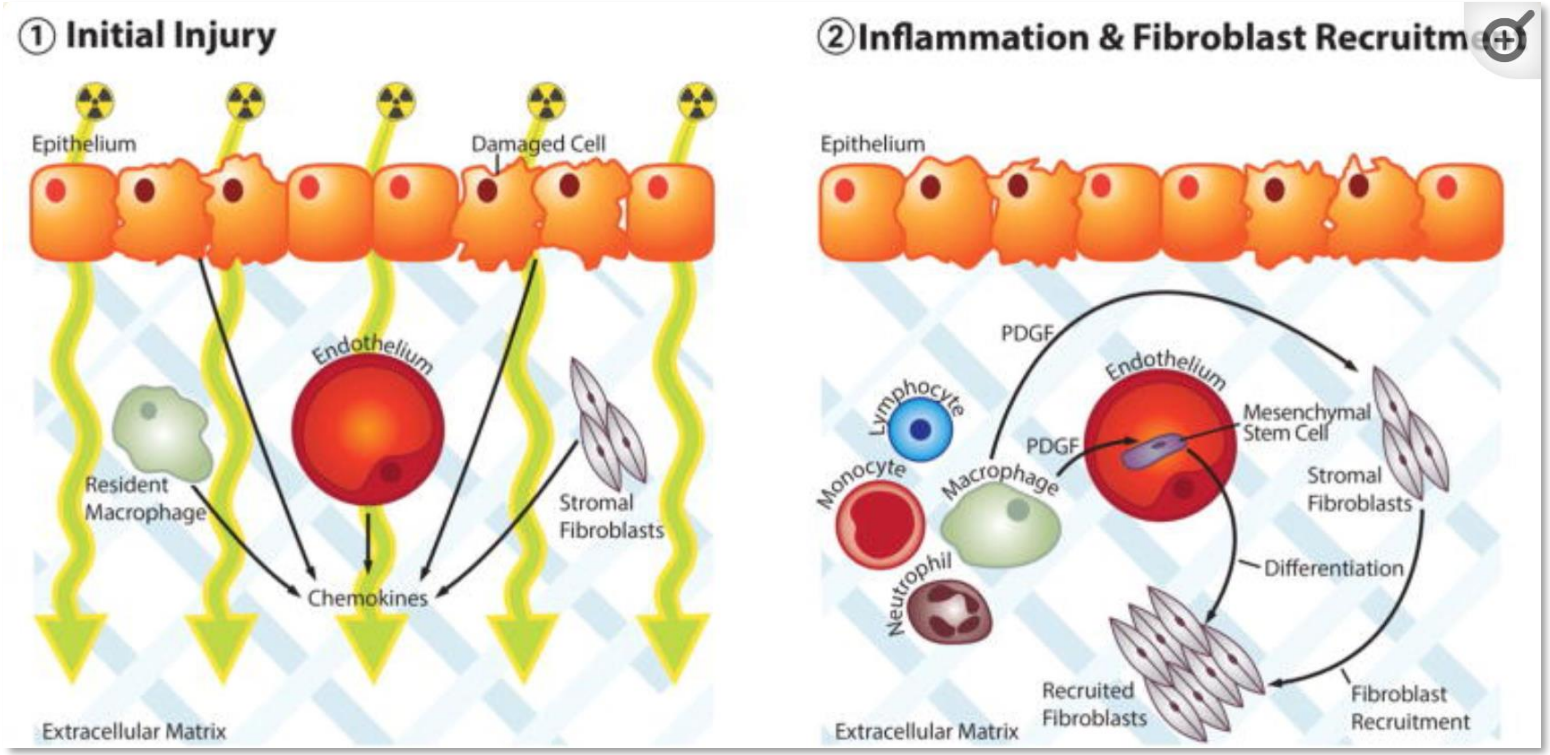
where R_F is a positive constant of proportionality.

CRE	25Gy/5fr
CRE tm	42Gy
CRE ye	45Gy

Doz/fr

Yan etki ‘?’

- Doz/fr
- Volum
- Süre



«standart tedavi»

KRT

Kısa dönem RT

45-50.4Gy/25-28fr + KT

Konvansiyonel Fr

25Gy/5fr

Hipofraksiyonasyon

«standart tedavi»

KRT

Kısa dönem RT

Randomized clinical trial

Bujko et al., Brit J Surg, 2006

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

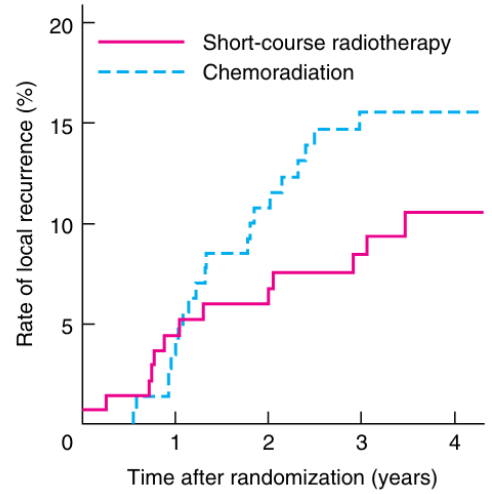
312 hasta cT3-T4rez rektum ca

R

25 Gy / 5fr
1 hafta sonra cerrahi
Adj KT

50.4 Gy/28 fr+KT
4-6 hafta cerrahi
Adj Kt

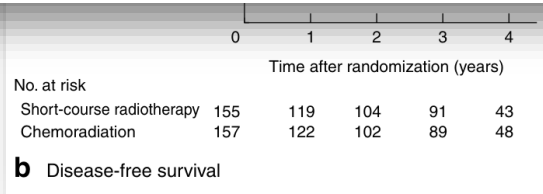
cCR (SC %2 vs. LC%,13 p < 0.001)
pCR (SC %1 vs. LC %16 p < 0.001)



No. at risk

Short-course radiotherapy	146	125	118	100	46
Chemoradiation	149	136	116	98	53

Fig. 3 Intention-to-treat analysis of actuarial cumulative incidence of local recurrence ($P = 0{\cdot}210$, log rank test)



No. at risk

Short-course radiotherapy	155	119	104	91	43
Chemoradiation	157	122	102	89	48

b Disease-free survival

Akut G3 toks: LC%18 vs.SC% 3, p < 0.001

Ngan et al., JCO, 2012

CLINICAL INVESTIGATION | VOLUME 108, ISSUE 5, P1257-1264, DECEMBER 01, 2020

Should Short-Course Neoadjuvant Radiation Therapy Be Applied for Low-Lying Rectal Cancer? A Systematic Review and Meta-Analysis of the Randomized Trials

Joanna Socha, MD, PhD • Laura Kairevice, MD, PhD • Lucyna Kępka, MD, PhD • ...
Mateusz Spałek, MD, PhD • Karol Paciorek, MD • Krzysztof Bujko, MD, PhD • Show all authors

Published: July 04, 2020 • DOI: https://doi.org/10.1016/j.ijrobp.

25 Gy / 5fr
1 hafta sonra cerrahi
Adj KT

50.4 Gy/28 fr+KT
4-6 hafta cerrahi
Adj KT

- 4 randomize çalışmanın meta-analizi
- 421 hasta, distal yerleşimli tm (0-5 cm)
- Kısa şema ile LR farkı yok

SC	162	155	143	129	104	76	46	22	0
LC	161	152	143	130	100	71	50	21	0

Fig 3. (A) Recurrence-free survival curves by allocated treatment arm. (B) Overall survival curves by allocated treatment arm. HR, hazard ratio; LC, long course; SC, short course.

G3-4 gec toksisite : SC, %5.8 vs ; LC, %8.; p .53

Primer sonlanım 3y LR : SCRT %7.5 vs. LCCRT %4.4, p = 0.24

< 5 cm - anal verge 3y LR: SCRT %12.5 vs. LCCRT %3.2, p = 0.21

Ngan et al., JCO, 2012

Randomized Trial of Short-Course Radiotherapy Versus Long-Course Chemoradiation Comparing Rates of Local Recurrence in Patients With T3 Rectal Cancer: Trans-Tasman Radiation Oncology Group Trial 01.04

Samuel Y. Ngan, Bryan Burmeister, Richard J. Fisher, Michael Solomon, David Goldstein, David Joseph, Stephen P. Ackland, David Schache, Bev McClure, Sue-Anne McLachlan, Joseph McKendrick, Trevor Leong, Cris Hartopeanu, John Zalcberg, and John Mackay

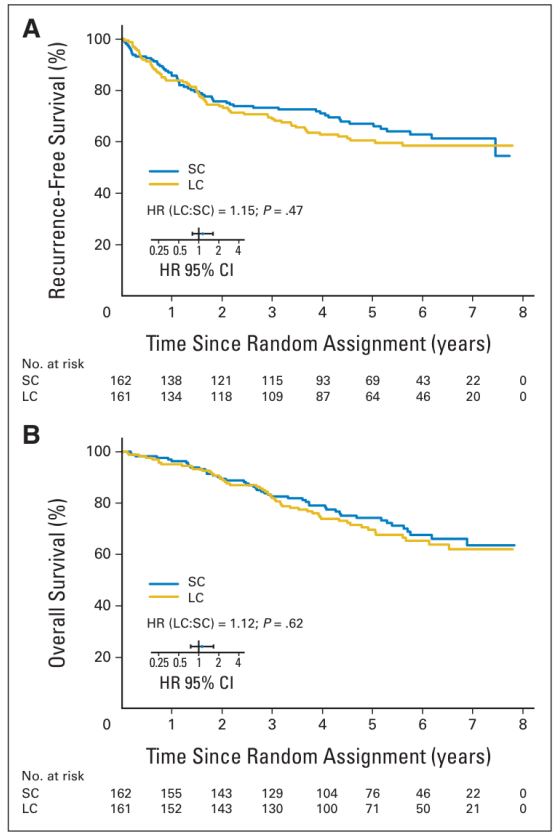


Fig 3. (A) Recurrence-free survival curves by allocated treatment arm. (B) Overall survival curves by allocated treatment arm. HR, hazard ratio; LC, long course; SC, short course.

326 hasta cT3-N0-2 rektum ca

R

25 Gy / 5fr
1 hafta sonra cerrahi
Adj KT

50.4 Gy/28 fr+KT
4-6 hafta cerrahi
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«standart tedavi»

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Kısa dönem RT

45-50.4Gy/25-28fr + KT

25Gy/5fr

Konvansiyonel Fr

Hipofraksiyonasyon

Regresyon

Endikasyon ‘?’

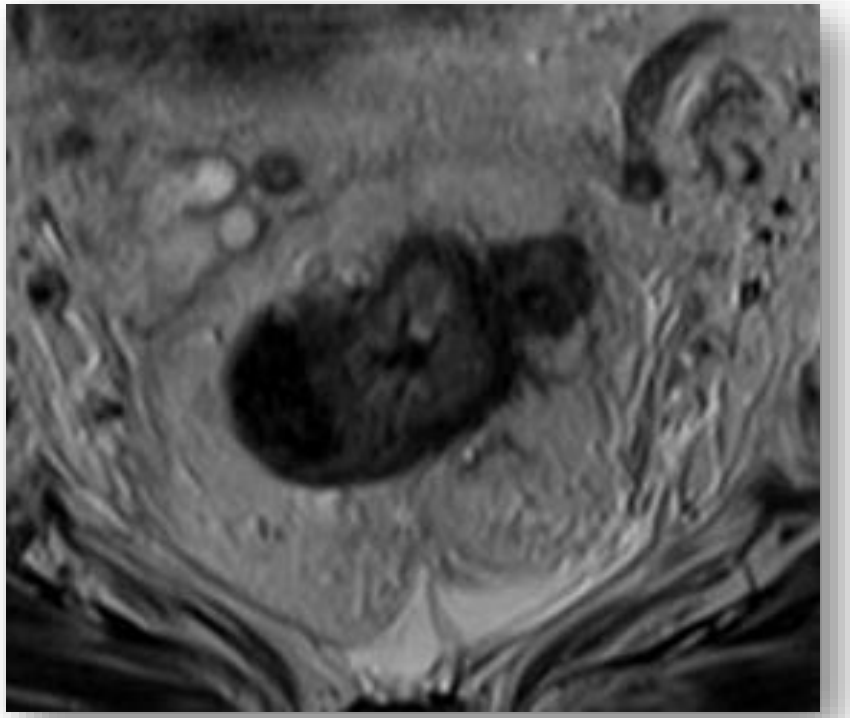
T4 – CRM (+)

‘!’

Circumferential Radial Margin

MRF<1mm

Ekstramural Venöz Invazyon



«standart tedavi»

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Kısa dönem RT

45-50.4Gy/25-28fr + KT

25Gy/5fr

Konvansiyonel Fr

Hipofraksiyonasyon

Regresyon

Endikasyon ‘?’

‘!’

T4 – CRM (+)

RT- cerrahi zamanlama

RT- cerrahi zamanlama

Sloothaak et al., Br J Surg , 2013

1593 hasta
13w vs 13-14 w vs 15-16wvs 16w

pCR: 15-16 w: %18 : p-0.013

Table 4 Studies comparing the effects of the time interval between neoadjuvant chemoradiotherapy/radiotherapy and surgery in locally

Moore *et al.* 2003	82/73		
Tulchinsky *et al.*, 2008	48/84	Retrospective	33 (6-80)
de Campos-Lobato *et al.*, 2011	83/94	Retrospective	48
Wolthius *et al.*, 2012	201/155	Retrospective	58.8 (12-130.8)
Saglam *et al.* 2013	76/77	Prospective, randomized	57.6 (6-94)

[a], shorter interval/longer interval; [b], unless otherwise stated, weeks; [c], months, median (range); NA, not available.

.,JCO, 2016

n et al.,JGO, 2014

Chemotherapy regimen

CPT-11 weekly bolus

	4 hafta	8 hafta	p
CS +	%9.2	%5.1	**0.33**
OS	%76.5	%74.2	**0.60**
LR	%11.8	%10.3	**0.77**

Erlandsson et al., Lancet Oncol, 2017

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, Hemming Johansson, Mikael Machado, Fredrik Hjern, Olof Hallböök, Ingvar Syk, Bengt Glimelius, Anna Martling

pTY:	%0.3	%10.4	%2.2
Post-op ≥Gr 3 toks:	%53	%39	%41
Akut RT toks:	%<1	%7	%5

*İkili analizde anlamlı.

Erlandsson et al: Lancet Oncol 18:336-46, 2017
Erlandsson et al: Radiother Oncol 135:178-86, 2019

Optimal fractionation of preoperative r
to surgery for rectal cancer (Stockholr
randomised, non-blinded, phase 3, nc

Johan Erlandsson, Torbjörn Holm, David Pettersson, Åke Berglund, Björn Cedermark, Calin Ra
Olof Hallböök, Ingvar Syk, Bengt Glimelius, Anna Martling

25 Gy / 5 fr
1 h sonra cerrahi

129
228

	SRT (*n* = 234)	SRT-delay (*n* = 228)	*P*¶
Tumour stage			0·001
ypT0	4 (1·7)	27 (11·8)	
ypI	69 (29·5)	76 (33·3)	
ypII	71 (30·3)	53 (23·2)	
ypIII	74 (31·6)	55 (24·1)	
ypIV	5 (2·1)	6 (2·6)	
ypx†	11 (4·7)	11 (4·8)	
Tumour category			< 0·001
ypT0	5 (2·1)	27 (11·8)	
ypT1	12 (5·1)	27 (11·8)	
ypT2	74 (31·6)	60 (26·3)	
ypT3‡			
ypT3ab	88 (37·6)	67 (29·4)	
ypT3cd	41 (17·5)	26 (11·4)	
ypT3x	3 (1·3)	1 (0·4)	
ypT4‡			
ypT4a	1 (0·4)	5 (2·2)	
ypT4b	3 (1·3)	3 (1·3)	
ypTx†	7 (3·0)	12 (5·3)	
Node category			0·059
ypN0	149 (63·7)	163 (71·5)	
yp N1	52 (22·2)	41 (18·0)	
ypN2	28 (12·0)	19 (8·3)	
ypNx†	5 (2·1)	5 (2·2)	
Tumour regression*			< 0·001
Grade 0	17 (7·3)	15 (6·6)	
Grade 1	165 (70·5)	104 (45·6)	
Grade 2	41 (17·5)	64 (28·1)	
Grade 3	2 (0·9)	11 (4·8)	
Grade 4	4 (1·7)	23 (10·1)	
Grade x†	5 (2·1)	11 (4·8)	
Circumferential resection margin§	*n* = 170	*n* = 150	1·000#
Positive (≤ 1 mm)	11	9	
Negative (> 1 mm)	159	141	

*İkili analizde anlamlı.

pTY: %0.3

Post-op ≥Gr 3 toks: %53

Akut RT toks: %<1

Lancet Oncol 18:336-46, 2017
...liother Oncol 135:178-86, 2019

«standart tedavi»

KRT

Kısa dönem RT

Structure	CRT		Short-course RT	
	Volume	Dose	Volume	Dose
Bowel	V35Gy	< 180cc	V25Gy	< 180cc
	V40Gy	< 100cc	Dmax	<105%PD
	V45Gy	< 65cc		
Bladder	Dmax	<50Gy		
	V40Gy	< %40	D45%	21Gy
	V45Gy	< %15		
Femoral Heads	V40Gy	< %40	D45%	21Gy
	V45Gy	< %25		
	Dmax	< 50Gy		

«standart tedavi»

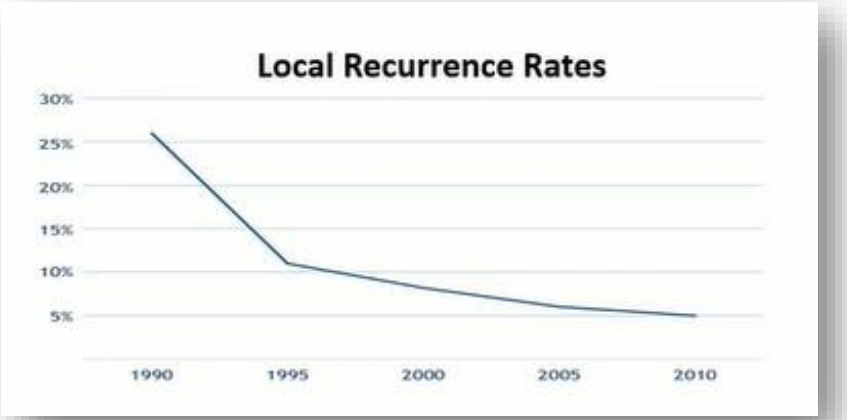
KRT

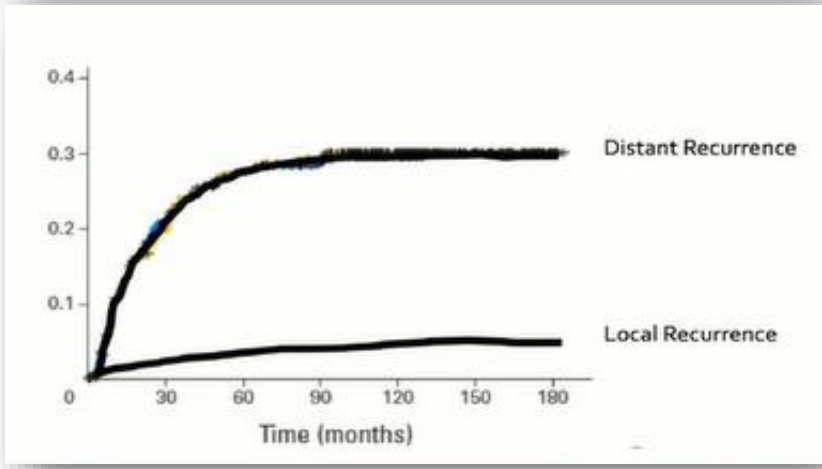
Kısa dönem RT

- Lokal rekürens düşük (<%6-8)
- Sağkalım iyi (DFS: ~%75-5y)
- Metastaz gelişimi en sık rekürens paterni

DR, LR'in **3-6 kat** fazla

- Uzun dönem morbidite





Dutch Rectal Cancer Registry.Sauer et al: J Clin Oncol, 2012

«standart tedavi»

KRT

Kısa dönem RT

Doz, Zamanlama – Nasıl Karar Vereceğiz?

«standart tedavi»

KRT

Kısa dönem RT

Doz, Zamanlama – Nasıl Karar Vereceğiz?

WJG 20th Anniversary Special Issues (5): Colorectal cancer

Neo-adjuvant radiotherapy in rectal cancer

Bengt Glimelius

Glimelius et al., WJG, 2013

Table 2 Subgrouping of localized rectal cancer assessed by magnetic resonance imaging[1] and the recommended primary treatment

Favourable "good" group	Intermediate "bad" group	Advanced "ugly" group
Mid/upper rectum T1-3b Low rectum T1-2, T3a N0 mrf clear	Mid/upper rectum T3c/d low rectum also includes T3b T4 with peritoneal or vaginal involvement only N1/N2 mrf clear	T3 mrf positive T4 with overgrowth to prostate, seminal vesicles, base of urinary bladder, pelvic side walls or floor, sacrum positive lateral lymph nodes
5 yr LFR[2] < 10% 5 yr DFR[3] < 15% Primary surgery (TME)[4]	5 yr LFR[2] 10%-20% 5 yr DFR[3] 15%-60% Preop 5 × 5 Gy with immediate surgery[5]	5 yr LFR[2] 20%-100% 5 yr DFR 30%-80% Preop CRT or 5 × 5 Gy with delayed surgery[6]

Clinical Practice Guideline

Radiation Therapy for Rectal Cancer: Executi
Summary of an ASTRO Clinical Practice Guideline

Wo et al., PRO, 2021

Jennifer Y. Wo, MD,[a] Christopher J. Anker, MD,[b]
Jonathan B. Ashman, MD, PhD,[c] Nishin A. Bhadkamkar, MD,[d]
Lisa Bradfield, BA,[e] Daniel T. Chang, MD,[f] Jennifer Dorth, MD,[g]
Julio Garcia-Aguilar, MD,[h] David Goff,[i] Dustin Jacqmin, PhD,[j]
Patrick Kelly, MD,
Ann C. Raldow, M
Karyn B. Stitzenb
Q. Jackie Wu, PhD

1. For patients with rectal cancer receiving neoadjuvant chemoradiation, conventional fractionation from 5000-5040 cGy in 25-28 fractions with concurrent chemotherapy is recommended.	Strong	High 9,21,22
2. For patients with rectal cancer receiving neoadjuvant short-course RT, 2500 cGy in 5 fractions without concurrent chemotherapy is recommended.	Strong	High 7,11
5. For patients with rectal cancer undergoing neoadjuvant therapy ***without*** tumor factors that portend increased recurrence risk, (1) chemoradiation or (2) short-course RT are recommended. Implementation remark: Risk factors for increased recurrence include cT3 tumors ≤5 cm from the anal verge or mrCRM <2 mm; cT4 tumor or cN2 disease, presence of mrEMVI.	Strong	High 7,11,30-35

«standart tedavi»

KRT

Kısa dönem RT

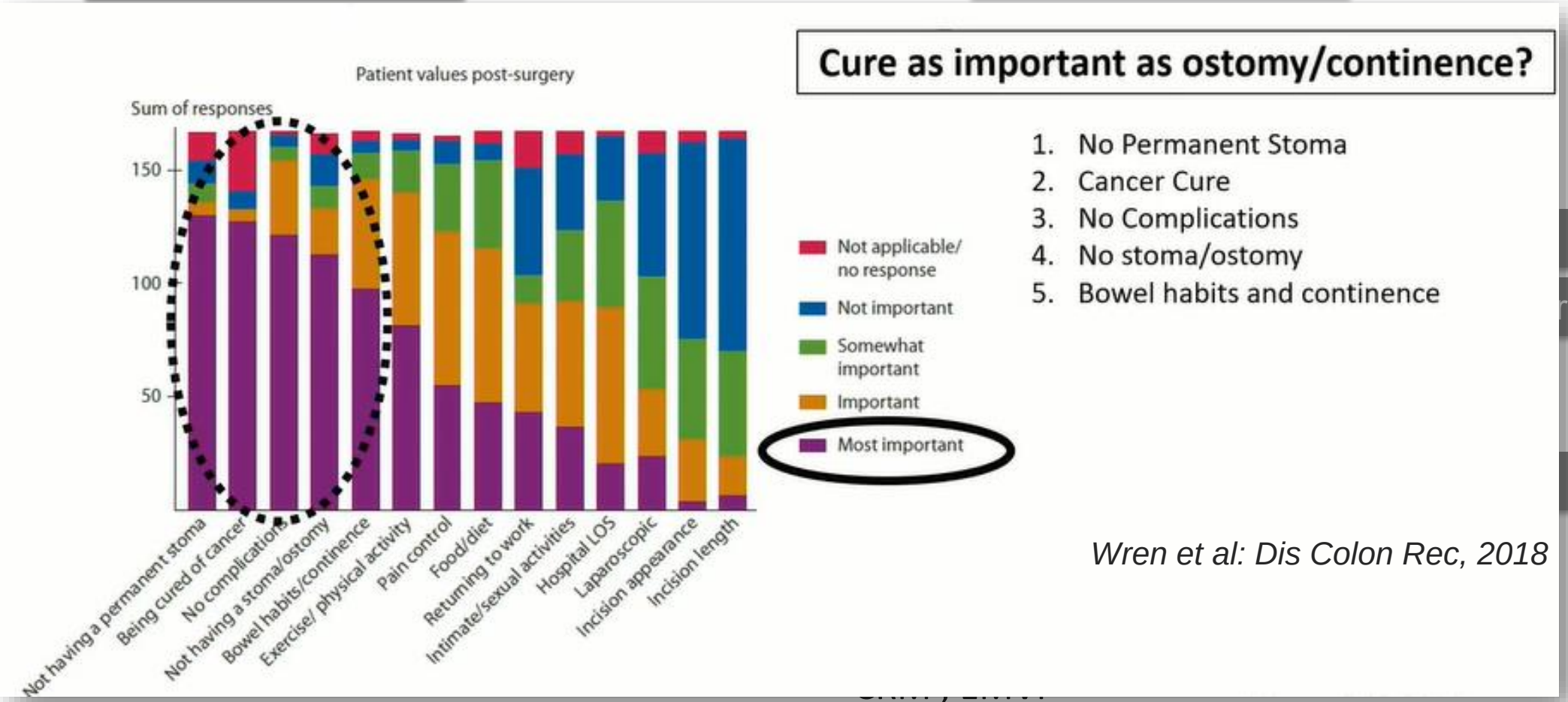
Doz, Zamanlama – Nasıl Karar Vereceğiz?

- Multidisipliner bir süreçtesiniz
  - SCRT: cerrahi açıdan deneyim gerektiriyor
  - SCRT- geç C : cerrahi açıdan dafa çok deneyim gerektiriyor
- Asıl sorununuz UM
  - KT uyumu / KT erişimi
- Hasta bazında karar verilmeli
  - CRM , EMVI
  - TNM
  - Sfinkter anatomi

«standart tedavi»

KRT

Kısa dönem RT



riyor

- TNM
- Sfinkter anatomi

Rektum Kanseri Tedavisinde Radyoterapi

Adjuvan

RT ile LR: (%13-16 vs. %25-34)

- 1990'a kadar temel yaklaşım adjuvan RT
- Cerrahi vs. cerrahi + adj. RT
- 5 randomize çalışma; GS, UM: Fark yok!

Neadjuvan

NeoRT ile LR: (%6-8 vs. %13-16)

- SCRT vs LCCRT
- Gec vs Erken cerrahi
- UM sorunu
- Morbidite

TNT

Definitif

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