Meta analysis in Rectal Cancer

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Areas of meta analysis in rectal cancers

- Epidemiology and risk factors
- Diagnostics
- Molecular pathology and Genetics
- Surgical approach and techniques
- Timing of RT/chemo
- Efficacy of chemotherapy
- Wait and watch

Epidemiology and risk factors





Analysing research on cancer prevention and survival



Diet, nutrition, physical activity and colorectal cancer 2017

Processed meat and colorectal cancer

ble 14: Summary of CUP 2016 cancer site dose-response meta-analyses – ocessed meat

nalysis	Sex	Increment	RR (95% CI)	ľ	No. Studies	No. Cases
olorectal ancer	М	Per 50 g/day	1.11 (0.86–1.43)	34%	2	-
	W	Per 50 g/day	1.18 (0.99–1.41)	19%	5	-
olon ancer	M/W	Per 50 g/day	1.23 (1.11–1.35)	26%	12	8,599
ectal ancer	M/W	Per 50 g/day	1.08 (1.00–1.18)	0%	10	3,029

Figure 8: Dose-response meta-analysis of processed meat and colorectal cancer per 50 grams per day

Author	Year	Sex		Per 50 g RR (95% CI)	% Weight
Ollberding	2012	M/W	H	1.09 (0.94, 1.26)	18.77
Cross	2010	M/W		1.26 (1.13, 1.40)	26.51
Balder	2006	M/W	+ -	1.21 (0.91, 1.61)	6.44
Sato	2006	M/W	<	0.77 (0.24, 2.42)	0.45
Larsson	2005	W	-++	1.13 (0.85, 1.51)	6.39
Norat	2005	M/W		1.15 (1.02, 1.29)	24.21
English	2004	M/W	<u></u>	1.61 (1.12, 2.30)	4.24
Lin	2004	W	« <u> </u>	0.56 (0.24, 1.23)	0.88
Flood	2003	W	<u>+</u>	1.17 (0.76, 1.81)	2.99
Pietinen	1999	M		1.01 (0.80, 1.27)	9.13
Overall (I-squared 20.1	1%, p = 0.25	8)	\$	1.16 (1.08, 1.26)	100.00
NOTE: Weights are from r	andom effec	ts analysis			
			.5 1 1.5 3	3	

Fruit intake and CRC

Figure 5: Non-linear dose-response association of fruit intake and colorectal cancer



Alcohol and CRC

Figure 18: Non-linear dose-response associations of alcohol (as ethanol) intake and colorectal cancer



Figure 17: Dose-response meta-analysis of alcohol (as ethanol) and colorectal cancer per 10 grams per day

Author	Year	Sex	Per 10 g/day RR (95% Cl)	% Weight
Shin	2014	M	1.07 (1.05, 1.08)	25.39
Bamia	2013	M/W	1.04 (1.01, 1.08)	13.49
Everatt	2013	M H	 1.10 (0.98, 1.24) 	1.63
Nan	2013	M	1.10 (1.04, 1.15)	7.90
Nan	2013	w 🖷	1.03 (0.97, 1.09)	6.14
Razzak	2011	w 📥	1.01 (0.95, 1.07)	5.77
Bongaerts	2008	M/W -	1.10 (0.84, 1.44)	0.31
Mizoue	2008	M/W	1.07 (1.06, 1.09)	28.15
Toriola	2008	M	 1.21 (0.95, 1.55) 	0.38
Akhter	2007	M	 1.11 (1.06, 1.17) 	7.05
Glynn	1996	M	- 1.10 (1.00, 1.22)	2.17
Wu	1987	M/W	 1.16 (1.04, 1.31) 	1.62
Overall (I-squared = 27.7%, p	= 0.172)		1.07 (1.05, 1.08)	100.00
NOTE: Weights are from random	effects analys	is		
		.8 1	1.5	

Association Between Dietary Inflammation Index and The Risk of Colorectal Cancer: A Meta-Analysis

Caixia Zhang, Weijing Wang & Dongfeng Zhang

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017	DIET, NUTRITION, PHYSICAL ACTIVITY AND COLORECTAL CANCER 2017								
Ň		DECREASES RISK	INCREASES RISK						
STRONG	Convincing	Physical activity ^{1,2}	Processed meat ³ Alcoholic drinks ⁴ Body fatness ⁵ Adult attained height ⁶						
EVIDENCE	Probable	Wholegrains Foods containing dietary fibre ⁷ Dairy products ⁸ Calcium supplements ⁹	Red meat ¹⁰						
	Limited – suggestive	Foods containing vitamin C ¹¹ Fish Vitamin D ¹² Multivitamin supplements ¹³	Low intakes of non-starchy vegetables ¹⁴ Low intakes of fruits ¹⁴ Foods containing haem iron ¹⁵						
LIMITED EVIDENCE	Limited – no conclusion	Cereals (grains) and their products; potatoes; animal fat; poultry; shellfish and other seafood; fatty acid compositie cholesterol; dietary n-3 fatty acid from fish; legumes; garlic; non-dairy sources of calcium; foods containing added sugars; sugar (sucrose); coffee; tea; caffeine; carbohydrate; total fat; starch; glycaemic load; glycaemic index; folate; vitamin A; vitamin B6; vitamin E; selenium; fat; methionine; beta-carotene; alpha-carotene; lycopene retinol; energy intake; meal frequency; dietary pattern							

World Cancer Research Fund International/American Institute for Cancer Research. Continuous Update Project Report: Diet, Nutrition, Physical Activity and Colorectal Cancer. 2017. Available at: wcrf.org/colorectal-cancer-2017.

Colorectal cancer prevalence linked to human papillomavirus: a systematic review with meta-analysis

	C		6	Proportion
Studies	Cancer/HP	V (CE95%)	Cancer/	Randomized effect model, CI95%
Dedeebiet al. 2005	Prevalenc	e (22 0 (05)	Total	
Bodagni et al., 2005	0.564	(0.433 - 0.695)	31/35	
Buyru, Tezol e Dalay 2006	0.116	(0.020-0.212)	5/53	
Cheng et al., 1995	0.703	(0.555 - 0.850)	26/37	
Damin et al., 2007	0.417	(0.292 - 0.541)	25/60	
Deschoolmeester et al., 2010	0.576	(0.407 - 0.744)	19/33	
Giuliani et al., 2008	0.182	(0.021 - 0.343)	4/22	
Karbasi et al., 2015	0.132	(0.024 - 0.239)	5/38	
Pincanço-Júnior et al., 2014	0.456	(0.346 - 0.566)	36/79	
Pérez et al., 2006	0.415	(0.282 - 0.548)	22/53	
Pérez et al., 2010	0.485	(0.314-0.655)	16/33	
Ranjbar et al., 2014	0.083	(-0.138-0.304)	0/5	
Salepci et al., 2009	0.179	(0.078-0.279)	10/56	
Sayhan et al., 2001	0.010	(-0.017-0.036)	0/51	
Soares et al., 2011	0.152	(0.029-0.274)	5/33	
Subgroup HPV16 (h2 = 95.6%; p < 0.00	0) 0.317	(0.186-0.447)	204/598	
Bodaghi et al., 2005	0.091	(0.015-0.167)	5/55	
Buyru, Tezol e Dalay, 2006	0.512	(0.362-0.661)	22/43	
Cheng et al., 1995	0.297	(0.150-0.445)	11/37	
Damin et al., 2007	0.267	(0.155-0.379)	16/60	
Deschoolmeester et al., 2010	0.455	(0.285-0.624)	15/33	
Giuliani et al., 2008	0.500	(0.291-0.709)	11/22	
Karbasi et al., 2015	0.237	(0.102 - 0.372)	9/38	
Pincanco-Júnior et al., 2014	0.245	(0.129-0.361)	13/53	
Pérez et al., 2006	0.455	(0.285-0.624)	15/33	
Pérez et al., 2010	0.006	(-0.011 - 0.024)	0/79	
Ranibar et al., 2014	0.600	(0.171 - 1.029)	3/5	
Salepci et al., 2009	0.714	(0.596 - 0.833)	40/56	
Savhan et al., 2001	0.765	(0.648-0.881)	39/51	
Soares et al., 2011	0.030	(-0.028-0.089)	1/33	
Subgroup HPV18 (1^2 = 97.02% n < 0.0	000 0.358	(0.220-0.495)	200/598	0 0.2 0.4 0.6 0.8 1
				Prevalence of colorectal cancer due to HPV 16 and HPV
Overall(^2 = 96.38%; p < 0.000)	0.334	(0.254-0.414)	404/1196	

- Colorectal cancer owing to HPV was diagnosed in 51.8% of cases.
- Of these, the majority was linked to HPV 16 and 18
- Similarity between genders.

Figure 3: Estimate of colorectal cancer due to human papillomavirus 16 and 18.

Pelizzer T et al; Rev. bras. epidemiol. vol.19 no.4 São Paulo Oct./Dec. 201

Timing of RT

Preoperative Radiotherapy for Resectable Rectal Cancer

Article in JAMA The Journal of the American Medical Association - August 2000

DOI: 10.1001/jama.284.8.1008 · Source: PubMed



Figure 3. Local Recurrence



Ann Surg Oncol (2013) 20:4169–4182 DOI 10.1245/s10434-013-3198-9 Annals of SURGICAL ONCOLOGY OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE - COLORECTAL CANCER

Neoadjuvant Radiotherapy for Rectal Cancer: Meta-analysis of Randomized Controlled Trials

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Meta analysis of Perioperative mortality

a	Neoadjuvant t	herapy	No neoadjuvant	therapy		Odds Ratio		(Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, I	Random, 959	6 CI	
Dahl	6	155	3	145	4.2%	1.91 [0.47, 7.77]				_	
Goldberg	21	228	10	239	9.9%	2.32 [1.07, 5.05]				-	
GTCCG/EORTC	2	216	2	221	2.3%	1.02 [0.14, 7.33]				_	
Illenyi	6	97	5	110	5.3%	1.38 [0.41, 4.69]			- -	-	
MRC 1	20	277	13	275	10.8%	1.57 [0.76, 3.22]			+		
MRC 2	5	139	10	140	6.2%	0.49 [0.16, 1.46]		_			
Peteren	3	47	2	46	2.6%	1.50 [0.24, 9.42]		_	· ·		
Reis Neto	1	34	1	34	1.2%	1.00 [0.06, 16.67]			-		
SRCT	22	573	15	574	11.7%	1.49 [0.76, 2.90]			+-		
Stockholm I	35	424	7	425	9.2%	5.37 [2.36, 12.24]			-		
Stockholm II	6	272	3	285	4.2%	2.12 [0.52, 8.56]				_	
TME Trial	28	897	24	908	14.0%	1.19 [0.68, 2.06]			-		
Toronto	0	60	1	65	0.9%	0.36 [0.01, 8.89]				_	
VASAG I	42	347	35	353	15.7%	1.25 [0.78, 2.01]			+-		
VASOG II	1	180	5	181	2.0%	0.20 [0.02, 1.70]	_		-		
Total (95% CI)		3946		4001	100.0%	1.48 [1.08, 2.03]			•		
Total events	198		136								
Heterogeneity: Tau ²	= 0.11; Chi ² = 20	0.54, df =	14 ($P = 0.11$); $I^2 =$	32%					_		
Test for overall effect	z = 2.44 (P = 0)	0.01)					0.01	0.1	1	10	100
							Neoa	djuvant the	rapy No neo	adjuvant t	therapy

All studies

b	Neoadjuvant t	herapy	No neoadjuvant	therapy		Odds Ratio		0	dds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, R	andom, 9	5% CI	
SRCT	241	573	190	574	19.1%	1.47 [1.15, 1.87]			-		
Stockholm I	112	424	81	425	15.7%	1.52 [1.10, 2.11]			-		
stockholm II	111	272	79	285	14.6%	1.80 [1.26, 2.56]			-	· ·	
TME Trial	336	897	297	908	21.0%	1.23 [1.02, 1.50]			-		
Toronto	0	60	1	65	0.4%	0.36 [0.01, 8.89]	·		-		2
ASAG I	184	347	187	353	16.8%	1.00 [0.74, 1.35]			+		
ASOG II	63	180	77	181	12.3%	0.73 [0.48, 1.11]			-		
Fotal (95% CI)		2753		2791	100.0%	1.25 [1.02, 1.54]			•		
Total events	1047		912								
Heterogeneity: Tau ² =	= 0.04; Chi ² = 16	5.04, df =	$6 (P = 0.01); I^2 = 6$	63%			-+				
Test for overall effect	z = 2.16 (P = 0)	.03)					0.05	0.2	1	5	20
							Neoad	juvant ther	apy No ne	eoadjuva	nt therapy





b				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Goldberg	-0.45	0.22	9.4%	0.64 [0.41, 0.98]	
GTCCG/EORTC	-0.43	0.18	10.9%	0.65 [0.46, 0.93]	
MRC 1a	0.05	0.13	12.9%	1.05 [0.81, 1.36]	+
MRC 2	-0.39	0.19	10.5%	0.68 [0.47, 0.98]	
NWRCT	-0.98	0.25	8.4%	0.38 [0.23, 0.61]	
Petersen curative	-0.94	0.53	3.1%	0.39 [0.14, 1.10]	
SRCT Curative	-0.52	0.16	11.7%	0.59 [0.43, 0.81]	
Stockholm I	-0.67	0.16	11.7%	0.51 [0.37, 0.70]	
Stockholm II	-0.78	0.2	10.1%	0.46 [0.31, 0.68]	
TME Trial curative	-0.65	0.17	11.3%	0.52 [0.37, 0.73]	
Total (95% CI)			100.0%	0.59 [0.48, 0.72]	•
Heterogeneity: Tau ² =	= 0.07; Chi ² = 26.36,	df = 9	9 (P = 0.0)	02); $I^2 = 66\%$	
Test for overall effect	Z = 5.06 (P < 0.000)	001)			0.1 0.2 0.5 1 2 5 10 Neoadjuvant therapy No neoadjuvant therapy

.3 Meta-analyses on a overall survival and b local recurrence-free survival in studies comparing neoadjuvant therapy to surgery alone

Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer (Review)

De Caluwé L, Van Nieuwenhove Y, Ceelen WP



Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD006041. DOI: 10.1002/14651858.CD006041.

Figure 1.	Forest plot of comparison:	I radiotherapy vs radiochemotherapy,	outcome: 1.10 Local Recu	rrence
		at Sy.		



ocal Recurrence at 5 yrs

Figure 2. Forest plot of comparison: I radiotherapy vs radiochemotherapy, outcome: 1.12 HR'LR.

Study or Subgroup	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI	Hazaro Exp[(O-E) / V].	l Ratio Fixed, 95% Cl
Bosset 2006	34.1%	0.69 [0.41, 1.15]		-
Bujko 2006	18.7%	0.65 [0.33, 1.30]		-
Gerard 2006	47.1%	0.74 [0.48, 1.15]	-	ł
Total (95% CI)	100.0%	0.71 [0.52, 0.95]	•	
Total events				
Heterogeneity: Chi2 =	0.12, df=	2 (P = 0.94); I ² = 0%	has also	
Test for overall effect	Z = 2.28 (P = 0.02	0.01 0.1 1	10 100

Figure 3. Forest plot of comparison: I radiotherapy vs radiochemotherapy, outcome: I.I Overall Survival at 5y.



5-ys OS

Figure 5. Forest plot of comparison: I radiotherapy vs radiochemotherapy, outcome: I.3 Disease free survival at 5 y.



5-ys DFS

Figure 7. Forest plot of comparison: I radiotherapy vs radiochemotherapy, outcome: I.6 Grade III - IV toxicity.

	CRI	ſ	RT			Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-	H, Rando	om, 95% (1
Bosset 2006	67	483	37	495	38.4%	1.99 [1.31, 3.04]				
Bujko 2006	29	157	5	155	28.0%	6.80 [2.56, 18.07]				→
Gerard 2006	55	375	10	367	33.6%	6.14 [3.08, 12.24]			-	→
Total (95% CI)		1015		1017	100.0%	4.10 [1.68, 10.00]				
Total events	151		52							
Heterogeneity: Tau ² =	0.49; Ch	i ² = 10.	57, df = 2	(P = 0.	005); I ^z =	81%		0.5	1	£ 10
Test for overall effect:	Z= 3.10	(P = 0.0)	002)				0.1 0.2	0.0	2	5 10

Toxicity

Sphincter

preservation

Figure 8. Forest plot of comparison: I radiotherapy vs radiochemotherapy, outcome: 1.7 Sphincter preservation.

	CRT		RT			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Bosset 2006	263	473	249	475	45.0%	1.14 [0.88, 1.47]	
Boulis-Wassif 1984	13	124	6	121	2.9%	2.24 [0.82, 6.11]	
Bujko 2006	87	157	87	155	14.7%	0.97 [0.62, 1.52]	
Gerard 2006	188	357	185	357	34.1%	1.03 [0.77, 1.39]	-+-
Latkauskas 2011	32	46	26	37	3.3%	0.97 [0.38, 2.49]	
Total (95% CI)		1157		1145	100.0%	1.09 [0.92, 1.30]	•
Total events	583		553				
Heterogeneity: Tau ² =	0.00; Chi ²	= 2.54	df = 4 (f)	P = 0.64	4); I ² = 0%	,	
Test for overall effect:	Z=1.00 (P = 0.3	2)				0.10.2 0.5 1 2 5 10





Figure 11. Forest plot of comparison: I radiotherapy vs radiochemotherapy, outcome: 1.9 Anastomotic leak.

	CRI	ſ	RT			Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	
Bosset 2006	2	267	0	255	3.2%	4.81 [0.23, 100.71]		• · · · · · ·
Bujko 2006	8	87	9	86	29.5%	0.87 [0.32, 2.36]		Anastomotic leak
Gerard 2006	14	188	14	185	50.0%	0.98 [0.45, 2.12]		
Latkauskas 2011	7	46	4	37	17.2%	1.48 [0.40, 5.50]		
Total (95% CI)		588		563	100.0%	1.07 [0.62, 1.84]	•	
Total events	31		27					
Heterogeneity: Tau² =	0.00; Ch	i²=1.4	0, df = 3 (P = 0.7	1); I ² = 09	6		
Test for overall effect:	Z=0.24	(P = 0.8)	31)				0.10.2 0.5 1 2 5 10	



29.4%

360

37

1154 100.0%

7

0

21

7

Û

31

Test for overall effect Z = 1.34 (P = 0.18)

Heterogeneity: Tau² = 0.00; Chi² = 1.86, df = 3 (P = 0.60); I² = 0%

359

46

1168

Gerard 2006

Total (95% CI)

Total events

-

Latkauskas 2011

Figure 9. Forest plot of comparison: I radiotherapy vs radiochemotherapy, outcome: 1.4 Mortality 30 d.

30-day mortality

5 10

Figure 12. Forest plot of comparison: I radiotherapy vs radiochemotherapy, outcome: 1.8 pCR.

	CRI	r	RT			Odds Ratio	Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	om, 95% Cl	
Bosset 2006	60	473	22	476	43.6%	3.00 [1.81, 4.97]			nCR
Boulis-Wassif 1984	6	126	3	121	11.1%	1.97 [0.48, 8.05]			pen
Bujko 2006	22	138	1	148	5.8%	27.88 [3.70, 209.90]		\longrightarrow	
Gerard 2006	41	359	13	360	34.4%	3.44 [1.81, 6.54]			
Latkauskas 2011	6	46	1	37	5.1%	5.40 [0.62, 47.03]			
Total (95% CI)		1142		1142	100.0%	3.52 [2.12, 5.84]		•	
Total events	135		40						
Heterogeneity: Tau ² =	0.09; Chi	² = 5.44	, df = 4 (F	P = 0.25	5); I ² = 269	%	0102 06	2 6 10	
Test for overall effect: 2	Z = 4.88 (P < 0.0	0001)				0.1 0.2 0.5	2 5 10	

1.00 [0.35, 2.89]

1.48 [0.83, 2.63]

Not estimable

0.1 0.2

0.5

ORIGINAL ARTICLE

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Comparison of short-course with long-course preoperative neoadjuvant therapy for rectal cancer: A meta-analysis

Ke Chen, Guoming Xie, Qi Zhang, Yanping Shen, Taoqi Zhou

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Date of Web Publication 26-Mar-2018

Chen, et al.: Short versus long preoperative treatment for rectal cancer

Study	Experim	ental Total I	Co Events	ntrol Total	Odds Ratio	OR	95%-CI	W(fixed)	W(random)
Buiko K 2005	140	155	140	157		0.50	10.21: 1.221	55.6%	41.0%
Eitta MA 2010	12	14	12	15		1.50	10.21: 10.653	6.4%	8.6%
Krainminma I 2012	64	96	63	66		1.77	10.24 12.061	6.4%	8.4%
Carried VN 2012	167	162	163	161		1.64	10.63 6 191	18.4%	25.6%
Ship 10 2012	34	34	43		1 -	1.00	10.03, 0.131	10.476	15.7%
0001002011							forest weeks	14.2.10	10.7 %
Fixed effect model Random effects model		461		456	*	0.91	[0.52; 1.60] [0.52; 1.64]	100%	100%
Helerogeneity: 3-aquared+0	PN, Anu-arq	waredH	p=0.454						
1					0.1 0.5 1 2 10				
	Experim	ental	Co	ntrol	Odds Ratio				
Study	Events	Total E	Events	Total	1:	OR	95%-CI	W(fixed)	W(random)
Buiko K 2005	132	155	130	157		1.19	10.65: 2.191	39.5%	39.2%
Eitta MA 2010		14	10	15		0.90	10.19: 4.171	7.1%	6.1%
Krajcovicova 2012	92	96	49	55		2.82	10.76: 10.461	5.4%	8.4%
Samuel YN 2012	144	162	143	161		1.01	10.50 2.011	32.9%	30.1%
Shin JS 2011	29	34	54	68		1.50	10.49 4.501	10.9%	11,6%
Yeb CH 2011	26	28	33	37		1.58	10 27 9 281	4.2%	4.0%
	20	4.0		47		1.00	fert' arol	7.4.79	
Fixed effect model		489		493	1	1.25	[0.86; 1.82]	100%	
Heterogeneity: I-squared of	11. 10-10	uared-0	p=0.818	9	T	1.25	[0.85; 1.82]		100%
			2.1	0	1 05 1 2 10				
Study	Experim	ental Total I	Co	ntrol Total	Odds Ratio	OR	95%-CI	Wiffred	W(random)
					D:				
Buiko K 2005	122	155	121	157	-10-	1.10	10.64: 1.881	40.1%	39.1%
Kraicovicova I 2012	90	96	46	55	II	2.93	10.98 8 751	5.7%	9.4%
Samuel VN 2012	133	182	132	161		1.01	10.57 1.781	37.1%	34 7%
Ship JS 2011	26	34	51	68		1.08	10.41-2.841	12.5%	12.0%
Yeh CH 2011	25	28	32	37	_ [•	1.30	[0.28: 5.98]	4.0%	4.8%
Fixed effect model		475		478	Ľ.	1.18	10.84: 1.647	100%	
Random effects model	í				-	1.18	[0.84; 1.65]		100%
Heterogeneity: I-squared+d	PS, 840-942	uareded	, p=0.544	13					
					0.2 0.5 1 2 5				
3									
1 1	Experim	ental Total I	Co	ntrol	Odds Ratio		MN -01	Wittend	Winnedowi
Study	Experim Events	ental Total I	Co Events	ntrol Total	Odds Ratio	OR	95%-CI	W(fixed)	W(random)
Study Bujko K 2005	Experim Events	ental Total I 155	Co Events	ntrol Total 157	Odds Ratio	OR 0.35	95%-CI	W(fixed) 59.2%	W(random) 24.1%
Study Bujko K 2005 Krajcovicova I 2012	Experim Events	ental Total I 155 96	Co Events 109 43	ntrol Total 157 55	Odds Ratio	OR 0.35 2.16	95%-CI [0.22; 0.56] [0.88; 5.29]	W(fixed) 59.2% 6.2%	W(random) 24.1% 19.7%
Study Bujko K 2005 Krajsovicova I 2012 Samuel YN 2012	Experim Events	ental Total 1 155 96 162	Co Events 109 43 119	ntrol Total 157 55 161	Odds Ratio	OR 0.35 2.16 1.33	95%-CI [0.22; 0.56] [0.88; 5.29] [0.79; 2.23]	W(fixed) 59.2% 6.2% 24.7%	W(random) 24.1% 19.7% 23.7%
Study Bujko K 2006 Krajcovicova I 2012 Samuel YN 2012 Shin JS 2011	Experim Events 69 85 128 26	ental Total I 155 95 162 34	Co Events 109 43 119 46	ntrol Total 157 55 161 68	Odds Ratio	OR 0.35 2.16 1.33 1.55	95%-CI [0.22; 0.56] [0.88; 5.29] [0.79; 2.23] [0.61; 3.96]	W(fixed) 59.2% 6.2% 24.7% 7.1%	W(random) 24.1% 19.7% 23.7% 19.2%
Study Bujko K 2006 Krajcovicova I 2012 Samuel YN 2012 Shin JS 2011 Yeh CH 2011	Experim Events 09 85 128 25 25	ental Total 1 155 96 162 34 28	Co Events 109 43 119 46 32	ntrol Total 157 55 161 68 37	Odds Ratio	OR 0.35 2.16 1.33 1.55 1.30	95%-CI [0.22: 0.56] [0.88: 5.29] [0.79: 2.23] [0.61: 3.98] [0.28: 5.96]	W(fixed) 59.2% 6.2% 24.7% 7.1% 2.9%	W(random) 24.1% 19.7% 23.7% 19.2% 13.4%
Study Bujko K 2006 Krajcovicova I 2012 Samuel YN 2012 Shin JS 2011 Yeh CH 2011 Fixed effect model	Experim Events 69 85 128 25 25	ental Total I 155 96 162 34 28 475	Co Events 109 43 119 46 32	ntrol Total 157 55 161 68 37 478	Odds Ratio	OR 0.35 2.16 1.33 1.55 1.30 0.82	95%-CI [0.22; 0.56] [0.79; 2.23] [0.61; 3.98] [0.28; 5.98] [0.28; 5.98]	W(fixed) 59.2% 6.2% 24.7% 7.1% 2.9% 100%	W(random) 24.1% 19.7% 23.7% 19.2% 13.4%
Study Bujko K 2006 Krajcovicova I 2012 Samuel YN 2012 Shin JS 2011 Yeh CH 2011 Fixed effect model Random effects model Random effects model	Experim Events 09 85 128 26 25	ental Total 1 155 96 162 34 28 475	Co Events 109 43 119 46 32	ntrol Total 157 55 161 68 37 478	Odds Ratio	OR 0.35 2.16 1.33 1.55 1.30 0.82 1.09	95%-CI [0.22; 0.56] [0.88; 5.29] [0.79; 2.23] [0.61; 3.96] [0.28; 5.96] [0.49; 2.41]	W(fixed) 59.2% 6.2% 24.7% 2.9% 100%	W(random) 24.1% 19.7% 19.2% 13.4%
Study Bujko K 2006 Krajcovicova I 2012 Samuel YN 2012 Shin J3 2011 Yeh CH 2011 Fixed effect model Random effects model Reterogeneity: I-squared-I	Experim Events 00 85 128 26 25 12.3%, sec-	ental Total 1 155 96 162 34 28 475	Co Events 109 43 119 46 32	ntrol Total 157 55 161 68 37 478 ,p=4.0	Odds Ratio	OR 0.35 2.16 1.33 1.55 1.30 0.82 1.09	95%-Ci [0.22; 0.56] [0.86; 5.29] [0.79; 2.23] [0.61; 3.26] [0.28; 5.96] [0.61; 1.09] [0.49; 2.41]	W(fixed) 59.2% 6.2% 24.7% 7.1% 2.9% 100%	W(random) 24.1% 19.7% 23.7% 19.2% 13.4%
Study Bujko K 2005 Krajcovicova I 2012 Samuel YN 2012 Shin JS 2011 Yeh CH 2011 Fixed effect model Random effects model Meterogeneity: P-squared-I	Experim Events 69 85 128 26 25 12.3%, sec-	ental Total 1 155 96 162 34 28 475	Co Events 109 43 119 45 32 ******	ntroi Totai 157 55 161 68 37 478 478	Odds Ratio	OR 0.35 2.16 1.33 1.55 1.30 0.82 1.09	95%-CI [0.22; 0.56] [0.78; 5.29] [0.79; 2.23] [0.61; 3.98] [0.28; 5.98] [0.61; 1.09] [0.49; 2.41]	W(fixed) 59.2% 6.2% 24.7% 7.1% 2.9% 100%	W(random) 24.1% 19.7% 23.7% 19.2% 13.4%
Study Bujko K 2005 Krajcovicova I 2012 Samuel YN 2012 Shin JS 2011 Yeh CH 2011 Fixed effect model Random effects model Meterogeneity: Fisquared-I	Experim Events 69 85 128 26 25 12.3%, ser-	ental 155 162 34 28 475 square ental	Co Events 109 43 119 46 32 ******	ntrol Total 157 55 161 65 37 478 ,p=0.0	Odds Ratio	OR 0.35 2.16 1.33 1.55 1.30 0.82 1.09	95%-CI [0.22, 0.56] [0.86, 5.29] [0.79, 2.23] [0.26, 5.96] [0.26, 5.96] [0.49; 2.41]	W(fixed) 59.2% 6.2% 24.7% 2.9% 100%	W(random) 24.1% 19.7% 23.7% 19.2% 13.4%
Study Bujko K 2006 Krajcovicova I 2012 Samuel YN 2012 Shin JS 2011 Yeh CH 2011 Fixed effect model Random effects model Anterrogeneity: /- squared-l/	Experim Events 00 85 123 25 25 12,3%, ser- Experim Events	ental 155 95 162 34 28 475 square ental Total 1	Co Events 100 43 119 46 32 #46 32 #46 32 #46 52 #46 52 #46 52 #46 52 #46 52 #46 52 #52 #52 #52 #52 #52 #52 #53 #53 #53 #53 #55 #55 #55 #55 #55 #55	ntrol Total 157 55 161 65 37 478 <i>p=</i> 0.00	Odds Ratio	OR 0.35 2.16 1.33 1.55 1.30 0.82 1.09 OR	95%-CI [0 22: 0.56] [0 36: 5.29] [0 40: 2.23] [0 40: 3.90] [0 40: 3.90] [0 40: 1.09] [0 40: 2.41] [0 40: 2.41]	W(fixed) 59.2% 6.2% 24.7% 7.1% 2.9% 100%	W(random) 24.1% 19.7% 23.7% 19.2% 13.4% 100% W(random)
Study Bujko K 2006 Krajcovicova I 2012 Samuel YN 2012 Shin JS 2011 Fixed effect model Random effects model Reterogeneity: P spuaredri Study Krajcovicova I 2012	Experim Events 00 85 128 25 25 12.3%, sec- Experim Events 74	ental 155 96 162 34 28 475 475 ental Total 1 96	Co Events 109 43 119 46 32 40 4246 32 40 4246 Co Events	ntrol 157 55 161 65 37 478 p=d.00	Odds Ratio	OR 0.35 2.16 1.33 1.55 1.30 0.82 1.09 OR	95%-CI (0.22, 0.56) (0.80, 5.20) (0.70, 2.23) (0.28, 5.96) (0.28, 5.96) (0.41, 1.09) (0.44; 1.09) (0.44; 2.41) 95%-CI	W(fixed) 59.2% 6.2% 24.7% 7.1% 2.9% 100% 	W(random) 24.1% 19.7% 23.7% 19.2% 13.4% 100% W(random) 23.7%
Study Bujko K 2005 Krajcovicova I 2012 Samuel YN 2012 Shin JS 2011 Yeh CH 2011 Fixed effect model Random effects model Random effects model Random effects model Random effects and a Krajcovicova I 2012 Study Krajcovicova I 2012	Experim Events 69 65 128 26 25 12.3%, av- Experim Events 78 129	ental Total I 155 95 162 34 28 475 475 475 spuare ental Total I	Co Events 109 43 119 46 32 46 32 46 52 Co Events 39 112	ntrol 157 55 161 68 37 478 p=d.00 ntrol Total	Odds Ratio	OR 0.35 2.16 1.33 1.55 1.30 0.82 1.09 OR	95%-CI [0.22, 0.56] [0.88, 5.29] [0.61; 3.96] [0.28, 5.99] [0.49; 2.41] 95%-CI [0.42; 2.45]	W(fixed) 59 2% 6 2% 24 7% 7 1% 2 9% 100% 	W(random) 24.1% 19.7% 23.7% 19.2% 13.4% 100% W(random) 23.7%
Study Bujko K 2005 Krajcovicova I 2012 Samuel YN 2012 Shin JS 2011 Yeh CH 2011 Fixed effect model Random effects model Atterrogeneity: /- squared-l Study Krajcovicova I 2012 Samuel YN 2012	Experim Events 09 85 128 25 12.3%, au- Experim Events 78 120 26	ental Total I 155 96 162 28 475 475 475 475 475 162 34 34	Co lvents 109 43 119 46 32 #46 32 #46 22 Events 39 112 46 24 24 24 24 24 24 24 24 24 24 24 24 24	ntrol 157 55 161 68 37 478 p=0.00 ntrol Total 55 161 68	Odds Ratio	OR 0.35 2.16 1.33 1.55 1.30 0.82 1.09 OR 1.78 1.25 1.55	95%-CI [0.22, 0.56] [0.78, 2.23] [0.77, 2.23] [0.61; 3.96] [0.45; 2.41] 95%-CI [0.82; 3.86] [0.77, 2.03] [0.61; 2.03] [0.77, 2.03]	W(fixed) 59 2% 6 2% 24 7% 7 1% 2 9% 100% 	W(random) 24.1% 19.7% 23.7% 19.2% 13.4% 100% W(random) 23.7% 60.3% 16.1%
Study Bujko K 2006 Krajcovicova I 2012 Samuel YN 2012 Shin JS 2011 Yeh CH 2011 Fixed effect model Random effects model Study Krajcovicova I 2012 Samuel YN 2012 Shin JS 2011	Experim Events 69 85 128 25 12.3% au- Experim Events 78 120 26	ental Total I 155 96 162 28 475 475 475 475 475 475 475 102 102 34	Co Events 109 43 119 46 32 e-8.4246 Events 39 112 46	ntrol 157 55 161 63 37 478 <i>p=0.0</i> ntrol 151 161 55 161 68	Odds Ratio	OR 0.35 2.16 1.33 1.55 1.30 0.82 1.09 OR 1.78 1.25 1.55	95%-Cl [0.22, 0.56] [0.78, 2.23] [0.77, 2.23] [0.61; 3.96] [0.49; 2.41] 95%-Cl [0.82; 3.86] [0.77; 2.03] [0.61; 3.96]	W(fixed) 59.2% 6.2% 24.7% 7.7% 2.9% 100% 	W(random) 24.1% 19.7% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 19.2% 10.0% W(random) 23.7% 60.3% 15.1%
Study Study Sujko K 2005 Krajcovicova I 2012 Samuel YN 2012 Shin JS 2011 Fixed effect model Random effects model Metrogeneity: Ir squaredril Study Krajcovicova I 2012 Shin JS 2011 Fixed effect model	Experim Events 00 05 128 25 12.3%, teo- Experim Events 78 120 26	ental 155 96 162 34 28 475 475 source ental 96 162 34 292	Co (vents 43 119 46 32 #4.4244, 6 Co Events 39 112 46	ntrol Total 157 55 161 68 37 478 p=0.0 70tal 55 161 68 284	Odds Ratio	OR 0.35 2.16 1.33 1.55 1.30 0.82 1.09 OR 1.78 1.25 1.55 1.41	95%-CI [0.22, 0.56] [0.58, 5.29] [0.79, 2.23] [0.61; 3.90] [0.28, 5.90] [0.49; 2.41] 95%-CI [0.82; 3.86] [0.77, 2.03] [0.61; 3.90] [0.61; 3.90]	W(fixed) 59.2% 6.2% 24.7% 2.9% 100% W(fixed) 20.4% 53.8% 15.8% 100%	W(random) 24.1% 19.7% 23.7% 19.2% 13.4% 100% W(random) 23.7% 16.1%
Study Bujko K 2006 Krajcovicova I 2012 Samuel YN 2012 Shin JS 2011 Yeh CH 2011 Fixed effect model Random effects model Netwrogeneity: /- squared-li Study Krajcovicova I 2012 Samuel YN 2012 Shin JS 2011 Fixed effect model Random effects model	Experim Events 69 85 26 25 12.3% sec- Experim Events 78 120 26	ental 1555 955 1522 34 28 475 475 475 475 475 162 34 292 292	Co Events 109 43 119 46 32 #0.4246 Events 39 112 46	ntrol Total 157 55 161 68 37 478 p=0.00 Total 55 161 68 284	Odds Ratio	OR 0.35 2.16 1.33 1.55 1.30 0.82 1.09 OR 1.78 1.25 1.55 1.41 1.41	95%-C1 [0.22, 0.56] [0.78, 2.23] [0.79, 2.23] [0.26, 5.90] [0.26, 5.90] [0.49, 2.41] 95%-C1 [0.82, 3.86] [0.77, 2.03] [0.54, 2.05] [0.96, 2.05]	W(fixed) 59.2% 6.2% 24.7% 7.1% 2.9% 100% 	W(random) 24.1% 19.7% 23.7% 19.2% 13.4% 100% W(random) 23.7% 60.3% 16.1%

Figure 3: Forest plots of comparison between short-term versus long-term treatments on survival outcomes. (a) 1-year overall survival; (b) 2-year overall survival; (c) 3-year overall survival; (d) 4-year overall survival; (e) 5-year overall survival 1-yr OS

2-yr OS

3-yr OS

4-yr OS

5-yr OS

https://www.tandfonline.com/doi/full/10.1080/01 5581.2017.1374418?scroll=top&needAccess=true



Death rate

Recurrence rate

Complications

Distant metastasis

Figure 4: Forest plots of comparison between short-term versus long-term treatments on other outcomes. (a) death rate; (b) recurrence rate; (c) complications; (d) distant metastasis

Optimal Interval to Surgery After Neoadjuvant Chemoradiotherapy in Rectal Cancer: A Systematic Review and Meta-analysis

Donglin Du, Zhourong Su, Dan Wang, Wenwen Liu, Zhengqiang Wei

Clinical Colorectal Cancer

Volume 17, Issue 1, Pages 13-24 (March 2018)

DOI: 10.1016/j.clcc.2017.10.012

pCR with interval to surgery < vs > 8 weeks



pCR was significantly higher with nCRT \rightarrow Sx interval of > 8 weeks

OS

DFS





Local recurrence







Operative time

Post op Complications





Original Article

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Preoperative chemoradiotherapy versus postoperative chemoradiotherapy for stage II–III resectable rectal cancer: a meta-analysis of randomized controlled trials

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pCR

ROJ Radiation Oncology Journal

Chemoradiotherapy timing in rectal cancer



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Fig. 2. Forest plot of comparison: pathologic complete response (ypTONO) between preoperative and postoperative chemoradiotherapy.

A. 5-year locoregional recurrence

	Preop	p-CRT	Postop	D-CRT		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fix	ed, 95% CI		
Park JH et al. 2011	5	107	7	112	9.5%	0.75 [0.24, 2.28]			<u> </u>		
Roh MS et al. 2009	13	123	14	131	18.8%	0.99 [0.48, 2.02]		_	•		
Sauer R et al. 2004	24	405	51	394	71.7%	0.46 [0.29, 0.73]					F I D
Total (95% Cl)		635		637	100.0%	0.59 [0.41, 0.84]					5-yr LR
Total events	42		72								
Heterogeneity : Chi2 =	3.33, df =	2 (P =	0.19); I ² =	40%			·				
Test for overall effect:	Z = 2.89 (F	P = 0.00	004)				0.02	0.5	1 2	5	
							Favour	rs [Preop-CRT]	Favours [Postop-CRT	1	

B. 5-year distant recurrence

	Preop	D-CRT	Postop	-CRT		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	d, 95% CI	
Park JH et al. 2011	25	107	27	112	14.8%	0.97 [0.60, 1.56]				
Roh MS et al. 2009	0	0	0	0		Not estimable				
Sauer R et al. 2004	146	405	150	394	85.2%	0.95 [0.79, 1.13]		-	-	
Total (95% Cl)		512		506	100.0%	0.95 [0.80, 1.13]		-		
Total events	171		177							
Heterogeneity : Chi2 =	0.01, df =	2 (P = (0.93); l ² =	096			-			_
Test for overall effect:	Z = 0.59 (F	= 0.55	5)				0.02	0.5	1 2	5
							Favour	s [Preop-CRT]	Favours [Postop-CRT]	

5-yr DM

C. 5-year relapse-free survival



5-yr RFS

5-yr OS

D. 5-year overall survival



A. sphincter preservation rate



B. conversion rate from APR to LAR

	Preop	-CRT	Postop	-CRT		Risk Ratio		Risk F	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 9596 Cl		M-H, Fixed	d, 95% Cl	
Park JH et al. 2011 Roh MS et al. 2009 Sauer R et al. 2004	42 0 45	62 0 116	22 0 15	52 0 78	57.2% 42.8%	1.60 [1.12, 2.30] Not estimable 2.02 [1.21, 3.36]				
Total (95% CI) Total events Heterogeneity : Chi ² = 0 Test for overall effect: 2	87 0.56, df = 2 = 3.72 (P	178 1 (P = 0 = 0.00	37 0.45); l ² = 02)	130 0%	100.0%	1.78 [1.31, 2.41]	0.02 Favour	0.5 1 rs [Postop-CRT]	2 Favours [Preop-CRT]	5

A. ≥ grade 3 acute complication



B. ≥ grade 3 perioperative or chronic complication



Favours [Preop-CRT]

Favours [Postop-CRT]

conclusions

- Pre-op RT significantly reduces local recurrence
- Pre-op CRT results in higher rates of pCR compared to RT alone
- CRT is associated with higher toxicity c/w RT alone
- Pre-op RT is associated with better local control compared to post op RT
- pCR rates are higher when interval from CRT to Sx is more than 8 weeks
- Longer interval to surgery did not compromise outcomes and was not associated with difference in toxicity rates
- Hypofractionation with doses >5Gy appears to increase perioperative mortality and post op morbidity in some reports
- Pre-op CRT results in better local control compared to post op CRT with no difference in DFS, OS or DM rates
- Pre-op CRT resulted in significantly fewer complications and higher rates of conversion from APR to LAR

Surgical approach

T Meta-analysis of the impact of surgical approach on the grade of mesorectal excision in rectal cancer. BJS 2017; 104: 1609-1619.

Published: 17th October 2017

Authors: B. Creavin, M. E. Kelly, E. Ryan, D. C. Winter

iginal Investigation

ONLINE ONLY FREE

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athologic Outcomes of Laparoscopic vs pen Mesorectal Excision for Rectal ancer Systematic Review and Meta-analysis

x Martínez-Pérez, MD^{1,2}; Maria Clotilde Carra, PhD³; Francesco Brunetti, MD¹; <u>et al</u>

uthor Affiliations | Article Information

A Surg. 2017;152(4):e165665. doi:10.1001/jamasurg.2016.5665

Journal of Laparoendoscopic & Advanced Surgical Techniques, Vol. 28, No. 5 | Full Reports

Laparoscopic Versus Conventional Open Abdominoperineal Resection for Rectal Canc An Updated Systematic Review and Meta-Analysis

Xubing Zhang, Qingbin Wu, Tao Hu, Chaoyang Gu, Liang Bi, and Ziqiang Wang 🖂

Published Online: 1 May 2018 | https://doi.org/10.1089/lap.2017.0593

A Circumferential resection margin involvement

		LRR		ORR					
Source	No. of Events	Participants	No. of Events	Participants	RR (95% CI)				
Guillou et al, ¹⁵ 2005	30	193	14	97	1.08 (0.60-1.93)				
Ng et al, ³⁵ 2008	3	51	2	48	1.41 (0.25-8.09)				
Ng et al, ³³ 2009	2	76	1	77	2.03 (0.19-21.88)				
Luján et al, ³⁴ 2009	4	101	3	103	1.36 (0.31-5.92)				
Kang et al, ¹⁴ 2010	5	170	7	170	0.71 (0.23-2.21)				
van der Pas et al, ¹³ 2013	43	588	26	300	0.84 (0.53-1.35)				
Ng et al, ³⁰ 2014	3	40	2	40	1.50 (0.26-8.50)				
Stevenson et al, ²¹ 2015	16	238	7	235	2.26 (0.95-5.39)				
Fleshman et al, ²⁰ 2015	29	240	17	222	1.58 (0.89-2.79)				
Total	135	1697	79	1292	1.17 (0.89-1.53)				
Heterogeneity τ ² = 0.00, χ ₈ ² = 6.32 (<i>P</i> = .61), <i>I</i> ² = 0% Test for overall effect: <i>Z</i> = 1.13 (<i>P</i> = .26)									



Involvement of CR

B Noncomplete mesorectal excision

		LRR		ORR	-		
Source	No. of Events	Participants	No. of Events	Participants	RR (95% CI)		
Kang et al, ¹⁴ 2010	47	170	43	170	1.09 (0.77-1.56)		
van der Pas al, ¹³ 2013	77	666	28	331	1.37 (0.91-2.06)		
Ng et al, ³⁰ 2014	4	40	3	40	1.33 (0.32-5.58)		
Fleshman et al, ²⁰ 2015	19	240	11	222	1.60 (0.78-3.28)		
Stevenson et al, ²¹ 2015	32	238	19	235	1.66 (0.97-2.85)		
Total	179	1354	104	998	1.31 (1.05-1.64)		
11-1	2 2 1 1 /		,				

Heterogeneity $\tau^2 = 0.00$, $\chi_4^2 = 2.11$ (*P* = .71), $I^2 = 0\%$ Test for overall effect: *Z* = 2.36 (*P* = .02)



Incomplete TME

JAMA Surg. 2017;152(4):e1656

A Distal resection		LRR		ORR	
margin involvement Source	No. of Events	Participants	No. of Events	Participants	RR (95% CI)
Braga et al, ³⁷ 2007	0	83	0	85	Not estimable
Fleshman et al, ²⁰ 2015	4	240	4	222	0.93 (0.23 to 3.65)
Luján et al, ³⁴ 2009	0	101	0	103	Not estimable
Stevenson et al, ²¹ 2015	2	238	1	235	1.97 (0.18 to 21.63)
Total	6	662	5	645	1.12 (0.34 to 3.67)

Heterogeneity $\tau^2 = 0.00$, $\chi_1^2 = 0.29$ (P = .59), $I^2 = 0\%$ Test for overall effect: Z = 0.18 (P = .86)



Favors ORR Favors LRR

Weight,

22.4 21.4 100

Weight,

9.6

34.2

23.3

13.7 10.4

8.8

100

2

%

% 27.8 28.3

10

5

Distal resection margin involvement

B Distance to radial margin Distance, mm

		LRR			ORR		Mean Difference (95% CI)	
Source	Mean	(SD)	Total	Mean	(SD)	Total		
Kang et al, ¹⁴ 2010	9	(5.92)	170	8	(5.92)	170	1.00 (-0.26 to 2.26)	
van der Pas et al, ¹³ 2013	10	(9.62)	588	10	(8.14)	300	0.00 (-1.21 to 1.21)	
Fleshman et al, ²⁰ 2015	10.5	(9.2)	240	12.8	(11.2)	222	-2.30 (-4.18 to -0.42)	
Stevenson et al, ²¹ 2015	10	(10.37)	211	12	(10.37)	201	-2.00 (-4.00 to 0.00)	
Total			1209			893	-0.67 (-2.16 to 0.83)	
			-					

1452

Heterogeneity $\tau^2 = 1.69$, $\chi^2_2 = 11.46$ (P = .009), $I^2 = 74\%$ Test for ove

Heterogeneity $\tau^2 = 0.01$, $\chi^2_{\pm} = 7.82$ (P = .17), $I^2 = 36\%$

Test for overall effect: Z = 0.16 (P = .87)

Total

C Distance to distal margin		1	Distan	ce, cm			Mean Difference	
		LRR			ORR			
Source	Mean	(SD)	Total	Mean	(SD)	Total	(95% CI)	
Kang et al, ¹⁴ 2010	2	(1.85)	170	2	(1.85)	170	0.00 (-0.39 to 0.39)	
Liu et al, ³² 2010	3	(0.375)	98	2	(0.5)	88	0.00 (-0.13 to 0.13)	
Liang et al, ³¹ 2011	3.22	(0.738)	86	3.03	(0.684)	104	0.19 (-0.01 to 0.39)	
van der Pas et al, ¹³ 2013	3	(2.07)	618	3	(2.37)	310	0.00 (-0.31 to 0.31)	
Stevenson et al, ²¹ 2015	2.6	(2.22)	240	3	(1.77)	201	-0.40 (-0.77 to -0.03)	
Fleshman et al. ²⁰ 2015	3.2	(2.6)	240	3.1	(1.9)	222	0.10 (-0.31 to 0.51)	

Favors ORR Favors LRR -2 -1 0 Mean Difference (95% CI)

Mean Difference (95% CI)

-5

Distance to radial margin

Distance to distal margin

D Lymph nodes harvested No. of Lymph Nodes LRR ORR Mean Difference Source Mean (SD) Total Mean (SD) Total (95% CI) Araujo et al, 38 2003 5.5 (7.81) 13 11.9 (7.81) 15 -6.40 (-12.20 to -0.60) Braga et al, 37 2007 12.7 (7.3)83 13.6 (6.9) 85 -0.90 (-3.05 to 1.25) Pechlivanides et al, 36 2007 19.2 (5.5)34 19.2 (6.66) 39 0.00 (-2.79 to 2.79) Ng et al,³⁵ 2008 12.4 (6.7)51 13 (7) 48 -0.60 (-3.30 to 2.10) Ng et al,³³ 2009 (7.9)77 -0.50 (-2.87 to 1.87) 11.5 76 12 (7) Luján et al,³⁴ 2009 13.63 101 11.57 (6.26)(5.1)103 2.06 (0.49 to 3.63) Kang et al.¹⁴ 2010 17 (7.29) 170 18 (6.66) 170 -1.00 (-2.48 to 0.48) Liu et al,³² 2010 16 (5) 98 15 (4.9) 98 1.00 (-0.39 to 2.39) Liang et al.³¹ 2011 7.05 (5.05) 169 7.44 (4.89) 174 -0.39 (-1.44 to 0.66) van der Pas et al.¹³ 2013 13 (5.92) 683 14 (6.66) 341 -1.00 (-1.83 to -0.17) Ng et al,³⁰ 2014 17.7 (8.4)40 14.8 (5.6) 40 2.90 (-0.23 to 6.03) Fleshman et al,²⁰ 2015 17.9 (10.1) 240 16.5 (8.4) 222 1.40 (-0.29 to 3.09) 1412 0.05 (-0.77 to 0.86) Total 1758

1095 0.01 (-0.12 to 0.15)

Heterogeneity $\tau^2 = 1.07$, $\chi^2_{11} = 27.72$ (P = .004), $I^2 = 60\%$ Test for overall effect: Z = 0.11 (P = .91)



Lymph nodes harvested

JAMA Surg. 2017;152(4):e165665.

Adjuvant chemotherapy

Cochrane Database of Systematic Reviews

Postoperative adjuvant chemotherapy in rectal cancer operated for

cure.

Cochrane Systematic Review - Intervention Version published: 14 March 2012 see what's new

Am score 3 View article information

Sune Høirup Petersen | Henrik Harling | Lene Tschemerinsky Kirkeby | Peer Wille-Jørgensen | Simone Mocellin

				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Grage 1981	-0.892	0.366	1.4%	0.41 [0.20, 0.84]	1981	
Thomas 1988 (GTSG)	-0.288	0.215	3.5%	0.75 [0.49, 1.14]	1988	
Fisher 1988 (NSABP)	-0.236	0.134	6.8%	0.79 [0.61, 1.03]	1988	
Hafström 1990	-0.342	0.255	2.6%	0.71 [0.43, 1.17]	1990	
Krook 1991 (NCCTG)	-0.342	0.134	6.8%	0.71 [0.55, 0.92]	1991	
Matsuda 1991 (SGACCS)	-0.03	0.119	7.8%	0.97 [0.77, 1.23]	1991	+
Bosset 2006 (EORTC)	-0.163	0.105	8.9%	0.85 [0.69, 1.04]	1993	
QUASAR 2007	-0.261	0.13	7.0%	0.77 [0.60, 0.99]	1994	
CCCSGJ 1995	-0.416	0.122	7.6%	0.66 [0.52, 0.84]	1995	
Kornek 1996	-0.868	0.464	0.9%	0.42 [0.17, 1.04]	1996	
Ito 1996 (TSGHCFU)	0.285	0.341	1.6%	1.33 [0.68, 2.59]	1996	
Yasutomi 1997 (JFMTC 7-2)	-0.051	0.133	6.9%	0.95 [0.73, 1.23]	1997	-
Kodaira 1998 (JFMTC 7-1)	-0.073	0.125	7.4%	0.93 [0.73, 1.19]	1998	
Taal 2001 (NACCP)	-0.051	0.184	4.4%	0.95 [0.66, 1.36]	2001	
Kato 2002 (TACSG)	-0.416	0.327	1.7%	0.66 [0.35, 1.25]	2002	
Cafiero 2003	0.285	0.198	4.0%	1.33 [0.90, 1.96]	2003	+
Watanabe 2004 (JFMTC15-2)	-0.128	0.222	3.3%	0.88 [0.57, 1.36]	2004	
Glimelius 2005 (NGTATG)	-0.1	0.101	9.2%	0.90 [0.74, 1.10]	2005	
Sakamoto 2007 (JFMTC15-1)	-0.094	0.165	5.2%	0.91 [0.66, 1.26]	2007	
Koda 2009	-1.309	0.845	0.3%	0.27 [0.05, 1.42]	2009	←
Hamaguchi 2011	-0.511	0.239	2.9%	0.60 (0.38, 0.96)	2011	
Total (95% CI)			100.0%	0.83 [0.76, 0.91]		•
Heterogeneity: Tau ² = 0.01; Chi ²	= 28.73, df = 20 (P =	= 0.09);	I² = 30%			
Test for overall effect: Z = 4.11 (F	P < 0.0001)					0.1 0.2 0.5 1 2 5 10
	,					Favours adjuvant Favours control

Os: larger studies

				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Fisher 1988 (NSABP)	-0.236	0.134	7.7%	0.79 [0.61, 1.03]	1988	
Krook 1991 (NCCTG)	-0.342	0.134	7.7%	0.71 [0.55, 0.92]	1991	
Matsuda 1991 (SGACCS)	-0.03	0.119	9.1%	0.97 [0.77, 1.23]	1991	
Bosset 2006 (EORTC)	-0.163	0.105	10.7%	0.85 [0.69, 1.04]	1993	
QUASAR 2007	-0.261	0.13	8.0%	0.77 [0.60, 0.99]	1994	
CCCSGJ 1995	-0.416	0.122	8.8%	0.66 [0.52, 0.84]	1995	
Yasutomi 1997 (JFMTC 7-2)	-0.051	0.133	7.8%	0.95 [0.73, 1.23]	1997	
Kodaira 1998 (JFMTC 7-1)	-0.073	0.125	8.5%	0.93 [0.73, 1.19]	1998	
Taal 2001 (NACCP)	-0.051	0.184	4.7%	0.95 [0.66, 1.36]	2001	
Cafiero 2003	0.285	0.198	4.1%	1.33 [0.90, 1.96]	2003	
Watanabe 2004 (JFMTC15-2)	-0.128	0.222	3.4%	0.88 [0.57, 1.36]	2004	
Glimelius 2005 (NGTATG)	-0.1	0.101	11.2%	0.90 [0.74, 1.10]	2005	
Sakamoto 2007 (JFMTC15-1)	-0.094	0.165	5.6%	0.91 [0.66, 1.26]	2007	
Hamaguchi 2011	-0.511	0.239	3.0%	0.60 [0.38, 0.96]	2011	
Total (95% CI)			100.0%	0.85 [0.78, 0.93]		•
Heterogeneity: Tau ² = 0.01; Chi ²	= 17.62, df = 13 (P =	: 0.17);	l² = 26%			
Test for overall effect: Z = 3.64 (F	P = 0.0003)					U.Z U.S 1 Z 5
resciol overall ellect. Z = 3.04 (F	- 0.0003)					Favours adjuvant Favours control





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Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data

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	Events/patients (n/n)					HR (95% CI)	p value	Pinteraction
	Chemotherapy	Observation						
(y)pTNM								
(y)pTNM II	66/242	59/199	_	♦		0.90 (0.63-1.27)	0.533	0-566
(y)pTNM III	140/333	150/380			<u> </u>	1-01 (0-80-1-27)	0.938	
Tumour distance				1				
<5-0 cm	82/189	81/181				0.96 (0.70-1.31)	0.801	0.126
5-0-9-9 cm	88/246	76/245				1-14 (0-84-1-54)	0.402	
10-0-15-0 cm	35/136	50/142	•			0-61 (0-40-0-94)	0.025	
(y)pN								
(y)pN0	66/242	59/199	_	•		0.90 (0.63-1.27)	0.533	0.743
(y)pN1	86/235	96/276				0.96 (0.72-1.29)	0.801	
(y)pN2	54/98	54/104				1-03 (0-70-1-51)	0.877	
Surgery								
LAR	111/350	114/349		6		0-91 (0-70-1-17)	0.449	0.677
APR	95/225	95/230				0.99 (0.75-1.32)	0.970	
Preoperative treatment								
25 Gy	57/169	61/179	51	•		0.91 (0.64-1.31)	0.615	0.295
45 Gy	60/133	55/134			•	1.19 (0.83-1.72)	0.351	
45 Gy and chemotherapy	89/273	93/266		•		0-91 (0-64-1-31)	0.192	
Overall	206/575	209/579		-	-	0.94 (0.78-1.14)	0.523	
	0.25		0.5	i		2		
			Favours ch	nemotherapy	Favours observation	*		

	Events/patient	ts (n/n)	HR (95% CI)	p value	Pinteraction
	Chemotherapy	Observation			
A					
(y)pTNM					
(y)pTNM II	89/252	82/207	0.87 (0.65-1.18)	0.384	0.253
(y)pTNM III	138/346	142/391	1.09 (0.86-1.38)	0.464	
Tumour distance			1		
<5-0 cm	93/194	84/187	1.01 (0.75-1.36)	0.957	0.644
5·0–9·9 cm	103/263	102/256	1.01 (0.77-1.33)	0.945	
10-0–15-0 cm	31/137	38/144	0.70 (0.44-1.14)	0.152	
(y)pN					
(y)pN0	89/252	82/207	0.87 (0.65-1.18)	0.384	0-475
(y)pN1	93/248	96/287	1.06 (0.80-1.41)	0.687	
(y)pN2	45/98	46/104	1.10 (0.73-1.68)	0.644	
Surgery					
LAR	113/364	111/362	0.96 (0.74-1.25)	0.782	0.814
APR	114/243	113/236	0.99 (0.77-1.29)	0.133	
Preoperative treatment					
25 Gy	38/169	41/179	0.95 (0.61-1.47)	0.225	0.916
45 Gy	71/133	76/134	1.01 (0.78-1.31)	0.135	
45 Gy and chemotherapy	118/296	107/285	0.93 (0.67-1.29)	0.165	
Overall	227/598	224/598	0.97 (0.81-1.17)	0.775	
В			T		
(y)pTNM			- 1		
(y)pTNM II	104/251	98/204	0.84 (0.64-1.10)	0.198	0.335
(y)pTNM III	181/344	197/385	0.99 (0.81-1.21)	0.910	
Tumour distance					
<5-0 cm	113/194	106/185	0.98 (0.75-1.29)	0.895	0.107
5·0-9·9 cm	125/260	120/250	1.01 (0.79–1.29)	0.961	
10-0–15-0 cm	46/137	67/143	0.59 (0.40-0.85)	0.005	
(y)pN					
(y)pN0	104/251	98/204	0-84 (0-64-1-10)	0.198	0.551
(y)pN1	118/246	128/281	0.96 (0.75-1.23)	0.743	
(y)pN2	63/98	69/104	• 0.98 (0.69-1.39)	0.915	
Surgery					
LAR	153/363	160/356	0.86 (0.69–1.07)	0.183	0-482
APR	132/232	135/233	0.98 (0.69-1.39)	0.915	
Preoperative treatment					
25 Gy	65/169	78/179	0-82 (0-59-1-15)	0.250	0.525
45 Gy	83/133	84/134	1.04 (0.77-1.41)	0.787	
45 Gy and chemotherapy	137/293	133/276	0.87 (0.69–1.10)	0.245	
Overall	285/595	295/589	0-91 (0-77-1-07)	0.230	
	0.25	0			

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A systematic review and meta-analysis of adjuvant chemotherapy after neoadjuvant treatment and surgery for rectal cancer

	Experim	ental	Contr	rol		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
1.1.1 Non randomized t	rials							
Chan 2004	23	99	41	85	11.9%	0.32 [0.17, 0.61]	2004	
Hildebrandt 2006	20	73	9	19	6.7%	0.42 [0.15, 1.18]	2006	
Valentini 2009	15	45	10	33	7.4%	1.15 [0.44, 3.02]	2009	
Huh 2009	2	17	3	24	2.5%	0.93 [0.14, 6.29]	2009	
Kiran 2012	1	58	5	70	2.0%	0.23 [0.03, 2.01]	2012	
You 2013	15	115	13	45	8.8%	0.37 [0.16, 0.86]	2013	
Tiselius 2013	63	183	138	253	16.5%	0.44 [0.30, 0.65]	2013	-
Subtotal (95% CI)		590		529	55.9%	0.44 [0.33, 0.58]		•
Total events	139		219					
Heterogeneity: Tau ² = 0.0	00; Chi ² = 5.	80, df =	6 (P = 0.4	45); l ² =	0%			
Test for overall effect: Z =	= 5.77 (P < 0	0.00001						
1.1.2 Randomized trials								
Valentini 2011	435	1572	410	1209	20.6%	0.75 [0.63, 0.88]	2011	+
Breugom SCRIPT 2013	61	238	56	232	16.0%	1.08 [0.71, 1.65]	2013	+
Glynne-Jones 2014	12	54	9	59	7.5%	1.59 [0.61, 4.13]	2014	
Subtotal (95% CI)		1864		1500	44.1%	0.93 [0.64, 1.34]		•
Total events	508		475					
Heterogeneity: Tau ² = 0.0	06; Chi ² = 4.	70, df =	2 (P = 0.	10); l² =	57%			
Test for overall effect: Z =	= 0.40 (P = 0	0.69)						
Total (95% CI)		2454		2029	100.0%	0.64 [0.46, 0.88]		•
Total events	647		694					
Heterogeneity: Tau ² = 0.1	13; Chi ² = 24	4.03, df =	= 9 (P = 0).004); I	² = 63%			
Test for overall effect: Z =	= 2.73 (P = 0	0.006)						0.05 0.2 1 5 20
Test for subgroup differen	nces: Chi ² =	9.91, df	= 1 (P =	0.002).	² = 89.99	6		Favours adj CT Favours no adj CT

2 Forest plot and meta-analysis of 5-year overall survival

	Experim	ental	Contr	ol		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	Year	M-H, Fixed, 95% CI	
1.3.1 Non randomized trials	1								
Hildebrandt 2006 [23]	22	73	8	19	2.5%	0.59 [0.21, 1.68]	2006		
Valentini 2009 [21]	17	45	17	33	3.5%	0.57 [0.23, 1.42]	2009		
Huh 2009 [20]	3	17	6	24	1.2%	0.64 [0.14, 3.03]	2009		
Govindarajan 2010 [16]	40	283	7	41	3.0%	0.80 [0.33, 1.93]	2010		
Du 2011 [18]	2	19	5	26	1.1%	0.49 [0.09, 2.87]	2011		
Kiran 2012 [15]	12	58	13	70	2.6%	1.14 [0.48, 2.75]	2012		
You 2013 [13]	17	115	15	45	5.2%	0.35 [0.15, 0.78]	2013		
Tiselius 2013 [14]	75	183	148	253	20.8%	0.49 [0.33, 0.73]	2013		
Subtotal (95% CI)		793		511	39.8%	0.56 [0.43, 0.73]		•	
Total events	188		219						
Heterogeneity: Chi ² = 5.02, d	f = 7 (P = 0).66); l ² :	= 0%						
Test for overall effect: Z = 4.2	27 (P < 0.00	001)							
1.3.2 Randomized trials									
Breugom SCRIPT 2013 [6]	90	238	97	232	17.3%	0.85 [0.58, 1.22]	2013		
Bosset RTCT 2014 [3]	104	253	114	253	19.0%	0.85 [0.60, 1.21]	2014		
Glynne-Jones 2014 [4]	12	54	17	59	3.6%	0.71 [0.30, 1.66]	2014		
Bosset RT 2014 [3]	106	253	123	252	20.3%	0.76 [0.53, 1.07]	2014		
Subtotal (95% CI)		798		796	60.2%	0.81 [0.66, 0.99]		◆	
Total events	312		351						
Heterogeneity: Chi ² = 0.38, d	f = 3 (P = 0	.95); l ² :	= 0%						
Test for overall effect: Z = 2.0	7 (P = 0.04	4)							
Total (95% CI)		1591		1307	100.0%	0.71 [0.60, 0.83]		♦	
Total events	500		570						
Heterogeneity: Chi ² = 10.20,	df = 11 (P =	= 0.51);	l² = 0%						
Test for overall effect: Z = 4.2	20 (P < 0.00	001)						Eavours adi CT Eavours no adi CT	
Test for subgroup differences: Chi ² = 4.75, df = 1 (P = 0.03), l ² = 79.0%									

Forest plot and meta-analysis of 5-year disease-free survival

	Experim	ental	Contr	ol		Odds Ratio			C	dds Ra	tio	
tudy or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	Year		M-H	Fixed,	95% CI	
5.2 Non randomized trials	s											
ildebrandt 2006 [23]	9	73	1	19	0.5%	2.53 [0.30, 21.32]	2006		-	-	10	
uh 2009 [20]	1	17	1	24	0.3%	1.44 [0.08, 24.71]	2009			- .		
usters 2010 [19]	14	254	42	351	13.1%	0.43 [0.23, 0.80]	2010		_			
iran 2012 [15]	2	58	3	70	1.0%	0.80 [0.13, 4.94]	2012			-		
iselius 2013 [14]	15	183	35	253	10.6%	0.56 [0.29, 1.05]	2013			•		
ou 2013 [13]	6	115	2	45	1.1%	1.18 [0.23, 6.09]	2013		_			
ubtotal (95% CI)		700		762	26.7%	0.58 [0.39, 0.86]				•		
otal events	47		84									
eterogeneity: Chi ² = 3.97, c	if = 5 (P = 0).55); l ²	= 0%									
est for overall effect: Z = 2.	72 (P = 0.0	07)										
5.3 Randomized trials												
alentini 2011 [17]	170	1572	170	1209	67.4%	0.74 [0.59, 0.93]	2011					
reugom SCRIPT 2013 [6]	17	238	16	232	5.9%	1.04 [0.51, 2.11]	2013			+	-	
ubtotal (95% CI)		1810		1441	73.3%	0.77 [0.62, 0.95]				•		
otal events	187		186									
eterogeneity: Chi ² = 0.79, c	if = 1 (P = 0).37); l ²	= 0%									
est for overall effect: Z = 2.	43 (P = 0.0)	2)										
otal (95% CI)		2510		2203	100.0%	0.72 [0.59, 0.86]				•		
otal events	234		270									
eterogeneity: Chi ² = 6.26, c	if = 7 (P = 0).51); l ²	= 0%					+	+	-		+
est for overall effect: Z = 3.4	47 (P = 0.0	005)						0.05 East	U.Z	CT F		20 adi CT
est for subgroup difference	s: Chi ² = 1.4	48, df =	1 (P = 0.2	2), 2 =	32.3%			ra		01 10	10013110	00,01

031101 31	abgroup anterentee	J. Oli - 1.40, di	
t plot ar	nd meta-analysis	of 5-year local	relapse rate

	Experim	ental	Contr	ol		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	Year	M-H, Fixed, 95% CI
1.4.1 Non randomized tria	ls							
Chan 2004 [24]	23	99	36	85	5.6%	0.41 [0.22, 0.78]	2004	
Hildebrandt 2006 [23]	20	73	9	19	1.9%	0.42 [0.15, 1.18]	2006	
Huh 2009 [20]	1	17	4	24	0.6%	0.31 [0.03, 3.08]	2009	· · · · ·
Kusters 2010 [19]	69	254	109	351	12.5%	0.83 [0.58, 1.18]	2010	-
Govindarajan 2010 [16]	32	282	3	41	0.9%	1.62 [0.47, 5.56]	2010	
Kiran 2012 [15]	7	58	8	70	1.2%	1.06 [0.36, 3.13]	2012	
You 2013 [13]	8	115	9	45	2.3%	0.30 [0.11, 0.83]	2013	
Tiselius 2013 [14]	64	183	85	253	8.7%	1.06 [0.71, 1.59]	2013	+
Subtotal (95% CI)		1081		888	33.6%	0.78 [0.63, 0.97]		•
Total events	224		263					
Heterogeneity: Chi ² = 13.32	, df = 7 (P =	0.06); 1	= 47%					
Test for overall effect: Z = 2	.20 (P = 0.0	3)						
1.4.2 Randomized trials								
Valentini 2011 [17]	472	1572	383	1209	56.7%	0.93 [0.79, 1.09]	2011	
Breugom SCRIPT 2013 [6]	69	238	72	232	9.7%	0.91 [0.61, 1.35]	2013	-
Subtotal (95% CI)		1810		1441	66.4%	0.92 [0.79, 1.07]		•
Total events	541		455					
Heterogeneity: Chi ² = 0.01,	df = 1 (P = 0).93); l ²	= 0%					
Test for overall effect: Z = 1	.05 (P = 0.2	9)						
Total (95% CI)		2891		2329	100.0%	0.88 [0.77, 0.99]		•
Total events	765		718					
Heterogeneity: Chi ² = 14.92	, df = 9 (P =	0.09); 1	= 40%					
Test for overall effect: Z = 2	.11 (P = 0.0	3)						0.05 0.2 1 5 3
Test for subgroup difference	es: Chi ² = 1.	51, df =	1 (P = 0.2	2), 2 =	33.9%			Pavours adj CT Pavours no ad

Forest plot and meta-analysis of 5-year distant metastases rate



Breugom A; lancet Oncol – IPD, RCTs



Petrelli F et al; Int J colorectal Dis – Aggregate data, Incl RCTs, retrospective studies

Adjuvant Chemotherapy Is Associated With Improved Overall Survival in Locally Advanced Rectal Cancer After Achievement of a Pathologic Complete Response to Chemoradiation

Danish Shahab, Emmanuel Gabriel, Kristopher Attwood, Wen Wee Ma, Valerie Francescutti, Steven Nurkin, Patrick M. Boland

Open Access 😽 PlumX Metrics



Figure 3 Forest Plots Showing Adjuvant Chemotherapy Was More Likely for Younger Patients (Aged < 60 Years), Higher Grade, Lo Charlson-Deyo Comorbidity Index (CCI), Positive Carcinoembryonic Antigen (CEA) Status, Higher Clinical T Stage, and Hig Clinical N Stage. A Consistent Trend Toward Benefit Was Maintained Across Multiple Subgroups



ONLINE FIRST

Association Between Time to Initiation of Adjuvant Chemotherapy and Survival in Colorectal Cancer

A Systematic Review and Meta-analysis

JAMA. 2011;305(22):2335-2342 Published online June 4, 2011. doi:10.1001/jama.2011.749 Figure 3. Individual Trial and Overall Hazard Ratios of Relationships Between Waiting Times for Adjuvant Chemotherapy and Overall Survival and Disease-Free Survival



Conclusions: Adjuvant chemotherapy

- Conflicting data on benefit in patients treated with neo-adjuvant CRT (nCRT)
- Clear survival benefit in patients treated with surgery
- Appears to benefit patients with pCR following nCRT
- Delay in initiation of adjuvant chemo appears to compromise outcomes

Wait and watch strategy in rectal cancer

IE LANCET troenterology & Hepatology 2. Issue 7. July 2017, Pages 501-513



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tch-and-wait approach for locally advanced rectal er after a clinical complete response following

djuvant chemoradiation: a systematic review and meta-

Dossa MD ^{a, b, c, d}, Tyler R Chesney MD ^a, Sergio A Acuna MD ^{b, c, d}, Prof Nancy N Baxter PhD ^{a, b,}

Wait-and-see treatment strategies for rectal can patients with clinical complete response after neoadjuva chemoradiotherapy: a systematic review and meta-analysis

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Oncological and Survival Outcomes in Watch and Wait Patients With a Clinical Complete Response After Neoadjuvant Chemoradiotherapy for Rectal Cancer: A Systematic Review and Pooled Analysis

Dattani, Mit, FRCS^{*}; Heald, Richard J., FRCS^{*}; Goussous, Ghaleb, FRCS[†]; Broadhurst, Jack, FRCS[‡]; São Julião, Guilherme P., MD[§]; Habr-Gama, Angelita, MD[§]; Oliva Perez, Rodrigo, PhD[§]; Moran, Brendan J., FRCSI[‡]

Annals of Surgery: May 9, 2018 - Volume Publish Ahead of Print - Issue - p doi: 10.1097/SLA.00000000002761 Meta-Analysis: PDF Only

THE LANCET Gastroenterology & Hepatology



Volume 2, Issue 7, July 2017, Pages 501-513

Articles

A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and metaanalysis

Fahima Dossa MD ^{a, b, c, d}, Tyler R Chesney MD ^a, Sergio A Acuna MD ^{b, c, d}, Prof Nancy N Baxter PhD ^{a, b, c, d} \otimes \otimes

		Local regrowth	Study size	Weight (%)	Estimate (95% C
Appelt et al ³⁸	2015	10	40	5.0	25-0 (12-6-39-7)
Araujo et al ³⁹	2015	4	42	5-1	9-5 (2-1-20-6)
Brooker et alto	2015	5	21	3.7	- 23.8 (7-6-44-7)
Cotti et al#1	2016	1	15	3.0	6-7 (0-26-4)
Dickson-Lowe et al	2015	3	14	2.9	21.4 (3.2-47.3)
Gossedge et al43	2012	1	15	3.0	6-7 (0-26-4)
Habr-Gama et al ²⁰	2013	11	47	5.4	23-4 (12-3-36-7)
Habr-Gama et al ²³	2014	23	90	6-6	25-6 (17-0-35-1)
lseas et al	2015	3	32	4-6	9-4 (1-3-22-4)
Kessler et al ⁴⁵	2013	2	16	3.1	12-5 (0-3-34-1)
Kusters et al ⁴⁶	2016	2	11	2.4	18-2 (0-5-47-4)
Lai et al ¹²	2016	2	18	3.4	11.1 (0.2-30.6)
Li et al48	2015	1	30	4.4 -	3.3 (0-13.8)
Loria et al ⁴⁹	2016	6	68	6-1	8-8 (3-0-16-9)
Martens et al ⁵³	2016	10	85	6-5	11-8 (5-7-19-6)
Perez et al ²⁹	2012	1	16	3.1	6-2 (0-24-9)
Renehan et al ²²	2016	43	129	7-1	33-3 (25-4-41-7)
Seshadri et al ¹²	2013	6	23	3.9	26-1 (9-8-46-2)
Smith et al ⁵⁶	2015	19	73	6-2	26-0 (16-5-36-8)
Smith et al ⁶⁰	2015	1	18	3.4	5-6 (0-22-3)
Torres-Mesa et al ⁶¹	2014	4	19	35	- 21-1 (5-2-42-7)
Vaccaro et al ⁶²	2016	4	23	3.9	17-4 (4-2-36-6)
Vatandoust et al ⁶⁴	2015	2	22	3.8	9.1 (0.2-25-5)
Overall		164	867	100-0	15.7 (11-8-20-1)
^{1²} = 55·9%, p=0·0006					
				0% 20% 409	60% 80%

Figure 2: Pooled proportion of patients with local regrowth in those managed by watch-and-wait

Point estimates are based on 2-year local regrowth rates (where extractable) or crude proportions. Size of solid squares represents statistical weights.

Local regrowth

A Disease-free survival for patients treated by surgery with pCR vs W&W

	W&W		W&W Surgery with pCR			with pCR	Weight (%)	Weight (%)					
	Events	Total	Events	Total			(95% CI)						
Araujo et al (2015)39	23	42	22	69	77-4		0.47 (0.26						
Smith et al (2012)58	N/A	32	N/A	57	10.1	_	0.29 (0.06						
Maas et al (2011)50	1	21	4	20	5.5	_	1.39 (0.15-						
Smith et al (2015) ⁶⁰	2	18	2	30	6.9	e	0.42 (0.06						
Total		113		176	100.0	\bullet	0.47 (0.28						
Heterogeneity: τ ² =0-	00; χ ² =1·3:	1, DF=3 (p:	=0·73); l²=0	%		-							
Test for overall effect	: Z=2·89, p	o=0·004											

$B \;\;$ Overall survival for patients treated by surgery with pCR vs W&W $\;$

	W&W		Surgery with pCR		Weight (%)				HR IV, ra
	Events	Total	Events	Total					(95% CI)
Araujo et al (2015) ³⁹	8	42	10	69	59.6		_		0.62 (0.2
Smith et al (2012)58	N/A	32	N/A	57	23.5				0.61 (0.1
Maas et al (2011) ⁵⁰	0	21	2	20	6.9				5.50 (0.3
Gossedge et al (2012))43 1	15	1	13	6.8 —				0.23 (0.0
Smith et al (2015) ⁶⁰	0	18	1	30	3.3				6.89 (0.1
Total		128		189	100.0				0.73 (0.3
Heterogeneity: τ ² =0.0	01; χ ² =4·0	3, DF=4 (p	=0·40); l²=1	%		•			
Test for overall effect	: Z=0·85, p	=0-40			Г			,	

C Disease-free survival for patients treated by surgery with cCR vs W&W

	W&W		/&W Surgery with cCR			Weight (%)					
	Events	Total	Events	Total			(95% CI)				
Li et al (2015) ⁴⁸	3	30	10	92	65.6		0.65 (0.18				
Lai et al (2016)11	2	18	3	26	34.4	B	0.43 (0.07				
Total	5	48	13	118	100.0		0.56 (0.2				
Heterogeneity: τ ² =	0·00; χ ² =0·1	3, DF=1 (p	=0·71); l²=0	%							
Test for overall effe	ct: Z=1·08, J	o=0·28									

D Overall survival for patients treated by surgery with cCR vs W&W

	W&W		Surgery	orgery with cCR		%)					HR IV, ran
	Events	Total	Events	Total							(95% CI)
Li et al (2015) ⁴⁸	0	30	3	92	53-5		_		-	_	4·50 (0·33·
Lai et al (2016)11	2	18	3	26	46.5					_	3.33 (0.20
Total	2	48	6	118	100.0						3·91 (0·57
Heterogeneity: τ²=	0·00; χ²=0·0	2, DF=1 (p	=0·88); l ² =0	0%							
Test for overall effe	ect: Z=1·39, p	o=0·16				_					
						0.01	0.1	1	10	100	
							Favours surgery		Favours W&W		



Non regrowth

	nonoper	ation	surge	ry		Risk Ratio				Risk	Ratio		
r Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		1	M-H, Fixe	ed, 95% CI		
ama et al 2004	0	71	0	22		Not estimable	2004						
t al 2011	0	21	0	20		Not estimable	2011						
D et al 2012	4	32	0	57	17.7%	15.82 [0.88, 284.71]	2012					-	
et al 2012	0	6	0	6		Not estimable	2012						
fri et al 2013	5	23	0	10	33.5%	5.04 [0.30, 83.38]	2013				•		
RK et al 2015	1	18	0	30	18.6%	4.89 [0.21, 114.14]	2015				•		
2015	0	30	0	92		Not estimable	2015						
al 2015	2	8	0	28	11.6%	16.11 [0.85, 305.62]	2015						
et al 2015	1	42	0	69	18.6%	4.88 [0.20, 117.20]	2015				+ •		
5% CI)		251		334	100.0%	8.18 [2.22, 30.07]							
rents	13		0										
geneity: Chi ² = 0.7	72, df = 4 (F	= 0.95); P = 0%					-	-		<u> </u>	+	
r overall effect: Z =	= 3.16 (P =	0.002)						0.01	0.1 nonor	peration	1 surgery	10	100
	nonoper	ation	surge	ry		Risk Ratio				Risk	Ratio		

or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% C	a
ama et al 2004	0	71	0	22		Not estimable	2004		
t al 2011	1	21	0	20	14.1%	2.86 [0.12, 66.44]	2011		
JD et al 2012	6	32	0	57	10.0%	22.85 [1.33, 392.84]	2012		
et al 2012	0	6	0	6		Not estimable	2012		
dri et al 2013	6	23	0	10	18.9%	5.96 [0.37, 96.67]	2013		•
RK et al 2015	1	18	0	30	10.5%	4.89 [0.21, 114.14]	2015		
al 2015	2	8	1	28	12.2%	7.00 [0.72, 67.64]	2015		
2015	1	30	1	92	13.5%	3.07 [0.20, 47.54]	2015		
et al 2015	4	42	1	69	20.8%	6.57 [0.76, 56.84]	2015		•
95% CI)		251		334	100.0%	6.96 [2.58, 18.80]			
vents	21		3						
geneity: Chi² = 1.3 r overall effect: Z :	38, df = 6 (F = 3.83 (P =	P = 0.97 0.0001)); I ^z = 0%				0.0	1 0.1 1	10 100

3-yr LR

Local Recurrence



2-yr LR

	nonoper	ation	surgery			Risk Ratio			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M-H, F	ixed, 95% CI
Habr-Gama et al 2004	0	71	0	22		Not estimable	2004			
Seshadri et al 2013	7	23	0	10	21.1%	6.88 [0.43, 109.97]	2013		-	
Li et al 2015	2	30	2	92	30.3%	3.07 [0.45, 20.84]	2015		-	-
Lee et al 2015	2	8	1	28	13.7%	7.00 [0.72, 67.64]	2015			
Smith RK et al 2015	1	18	0	30	11.7%	4.89 [0.21, 114.14]	2015			· · ·
Araujo et al 2015	8	42	1	69	23.3%	13.14 [1.70, 101.40]	2015			
Total (95% CI)		192		251	100.0%	6.97 [2.44, 19.93]				-
Total events	20		4							
Heterogeneity: Chi ² = 1.1	12, df = 4 (F	^o = 0.89); I ² = 0%					0.01	01	1 10
Test for overall effect: Z =	= 3.62 (P =	0.0003))					0.01	nonoperati	on surgery

	nonoper	ation	surge	ery		Risk Ratio				Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		1	I-H, Fixe	d, 95% CI	_
Habr-Gama et al 2004	1	71	0	22	21.3%	0.96 [0.04, 22.72]	2004			-		-
Seshadri et al 2013	7	23	0	10	19.2%	6.88 [0.43, 109.97]	2013			-		-
Smith RK et al 2015	1	18	0	30	10.7%	4.89 [0.21, 114.14]	2015					-
Li et al 2015	2	30	2	92	27.6%	3.07 [0.45, 20.84]	2015			-	-	-
Araujo et al 2015	8	42	1	69	21.2%	13.14 [1.70, 101.40]	2015					•
Total (95% CI)		184		223	100.0%	5.69 [1.99, 16.25]					-	-
Total events	19		3									
Heterogeneity: Chi ² = 2.1 Test for overall effect: Z :	29, df = 4 (F = 3.24 (P =	P = 0.68); I ² = 0%					0.01	0.1	1	10)
									nonop	eration	surgery	

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5-yr LR



0.10 [0.01, 0.94] 2004

6.3% 3.56 [0.34, 37.77] 2012

30 10.0% 0.54 [0.02, 12.68] 2015

2 28 10.4% 0.64 [0.03, 12.22] 2015

324 100.0% 0.71 [0.31, 1.62]

Not estimable 2011

Not estimable 2012

Not estimable 2015

0.01

0.1

nonoperation surgery

0.99 [0.25, 3.91] 2015

Distant Metastasis

1-yr DM

2-yr DM

	nonoper	ation	surge	ry		Risk Ratio				Risk Rat	tio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fixed, 95% CI	Year		M	H. Fixed. S	95% CI
Habr-Gama et al 2004	1	71	3	22	39.8%	0.10 [0.01, 0.94]	2004		-		
Araujo et al 2015	6	42	5	69	32.8%	1.97 [0.64, 6.06]	2015				
Lee et al 2015	0	8	3	28	14.4%	0.46 [0.03, 8.10]	2015	-		•	
Li et al 2015	0	30	1	92	6.5%	1.00 [0.04, 23.92]	2015				
Smith RK et al 2015	1	18	1	30	6.5%	1.67 [0.11, 25.04]	2015				
Total (95% CI)		169		241	100.0%	0.93 [0.44, 1.96]				-	
Total events	8		13								
Heterogeneity: Chi# = 5.9	2, df = 4 (F	= 0.20); I= 329	6			1	0.04	-	-	+
Test for overall effect Z =	0.19 (P =	0.85)					'	0.01	nonope	ration su	10 Irgery

	nonoper	ation	surge	ry		Risk Ratio			Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M-H, Fixe	d, 95% Cl	
Habr-Gama et al 2004	2	71	3	22	35.0%	0.21 [0.04, 1.16]	2004		-	-	
Li et al 2015	1	30	5	92	18.8%	0.61 [0.07, 5.04]	2015				
Smith RK et al 2015	1	18	1	30	5.7%	1.67 [0.11, 25.04]	2015			•	
Araujo et al 2015	7	42	7	69	40.5%	1.64 [0.62, 4.36]	2015		-	-	
Total (95% CI)		161		213	100.0%	0.95 [0.47, 1.91]			-		
Total events	11		16								
Heterogeneity: Chi ² = 4.5	55, df = 3 (F	= 0.21); I ² = 349	6				-			+
Test for overall effect: Z =	= 0.15 (P =	0.88)						0.01	nonoperative	surgerv	10

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ma et al 2004

al 2011

al 2012

al 2015

015

2015

% CI)

nts

et al 2012

<et al 2015

71

21

32

6

18

42

30

228

8

0

2

0

0

3

0

0

6 eneity: Chi² = 4.96, df = 4 (P = 0.29); I² = 19%

overall effect: Z = 0.80 (P = 0.42)

3

1

0 6

1

12

0 20

0 92

57

5 69 33.2%

22 40.2%

3-yr DM

5-yr DM

10

100

	nonoper	ation	surge	ry		Risk Ratio			Risk Ratio		
Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M-H, Fixed, 95% C	1	
ma et al 2004	71	71	22	22	14.4%	1.00 [0.94, 1.07]	2004		•		
al 2011	21	21	19	20	8.4%	1.05 [0.92, 1.20]	2011		+		
) et al 2012	28	32	57	57	17.6%	0.87 [0.76, 1.00]	2012		•		
t al 2012	6	6	6	6	2.7%	1.00 [0.75, 1.34]	2012		+		
< et al 2015	17	18	30	30	9.8%	0.94 [0.81, 1.08]	2015		+		
015	30	30	92	92	19.5%	1.00 [0.95, 1.05]	2015		•		
2015	6	8	28	28	5.7%	0.73 [0.49, 1.11]	2015				
t al 2015	40	42	68	69	21.7%	0.97 [0.90, 1.04]	2015		1		
5% CI)		228		324	100.0%	0.95 [0.91, 0.99]					
ents	219		322								
eneity: Chi ² = 11	.71, df = 7	(P = 0.1)	1); $I^2 = 40$	1%				<u> </u>		+	
overall effect Z =	= 2.23 (P =	0.03)						0.01	0.1 1 nonoperation surgery	10	100



3-yr DFS

5-yr DFS

DFS

1-yr DFS

2-yr DFS

	nonoper	ation	surge	ry		Risk Ratio			Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year		IV, Rando	m, 95% CI
Habr-Gama et al 2004	70	71	19	22	22.0%	1.14 [0.96, 1.35]	2004			•
Li et al 2015	28	30	89	92	32.6%	0.96 [0.87, 1.07]	2015		•	
Araujo et al 2015	31	42	63	69	18.8%	0.81 [0.67, 0.98]	2015			
Smith RK et al 2015	16	18	29	30	20.9%	0.92 [0.77, 1.10]	2015		-	
Lee et al 2015	6	8	24	28	5.7%	0.88 [0.57, 1.34]	2015		-	-
Total (95% CI)		169		241	100.0%	0.95 [0.85, 1.06]				
Total events	151		224							
Heterogeneity: Tau* = 0.	01; Chi#= 7	7.49, df	= 4 (P = 0	.11); /*	= 47%					
Test for overall effect: Z	= 0.85 (P =	0.39)						0.01	nonoperation	surgery
						Bist Batta				

	nonoper	ation	surge	ry		Risk Ratio			Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year		IV, Rando	m. 95% C	<u> </u>
Habr-Gama et al 2004	69	71	19	22	23.9%	1.13 [0.95, 1.33]	2004			•	
Araujo et al 2015	30	42	62	69	19.6%	0.79 [0.65, 0.98]	2015			1	
Li et al 2015	28	30	87	92	33.3%	0.99 [0.89, 1.10]	2015			•	
Smith RK et al 2015	16	18	29	30	23.2%	0.92 [0.77, 1.10]	2015			t	
Total (95% CI)		161		213	100.0%	0.96 [0.85, 1.08]				•	
Total events	143		197								
Heterogeneity: Tau ^a = 0.1	01; Chi# = 6	5.91, df	= 3 (P = 0).07); I ^a	= 57%			L	01		10
Test for overall effect: Z =	= 0.65 (P =	0.51)						0.01	nonoperation	surgery	10

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Overall survival ABS



2-yr OS

nonoperation Study or Subgroup Events Total			surge	ry		Risk Ratio			Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year		IV, Rande	om, 95% CI	
Habr-Gama et al 2004	71	71	20	22	8.4%	1.11 [0.96, 1.29]	2004			-	
Li et al 2015	30	30	92	92	76.9%	1.00 [0.95, 1.05]	2015				
Smith RK et al 2015	18	18	29	30	14.7%	1.02 [0.92, 1.14]	2015			†	
Total (95% CI)		119		144	100.0%	1.01 [0.97, 1.06]					
Total events	119		141								
Heterogeneity: Tau ² = 0.1	00; Chi ² = 1	.99, df:	= 2 (P = 0	.37); 12	= 0%					<u> </u>	+
Test for overall effect Z =	= 0.58 (P =	0.56)						0.01	0.1 nononeration	Surgery	10
									nonoperation	ourgory	
	nonoper	ation	surge	ry		Risk Ratio			Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	Year		IV, Rande	om, 95% Cl	
Habr-Gama et al 2004	71	71	20	22	21.4%	1.11 [0.96, 1.29]	2004			•	
Smith RK et al 2015	18	18	29	30	27.8%	1.02 [0.92, 1.14]	2015			•	
Li et al 2015	30	30	88	92	37.2%	1.03 [0.97, 1.10]	2015			•	
Araujo et al 2015	30	42	62	69	13.7%	0.79 [0.65, 0.98]	2015		-	1	
Total (95% CI)		161		213	100.0%	1.01 [0.92, 1.11]				•	
Total events	149		199			-					
Heterogeneity: Tau ² = 0.0	00; Chi ² = 7	7.15, df	= 3 (P = 0	.07); I ^z	= 58%			<u> </u>		-	+
Test for overall effect Z =	= 0.23 (P =	0.82)						0.01	U.1	1	10

nonoperation surgery

3-yr OS

5-yr OS

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W&W conclusions

- Risk of local regrowth with W&W approach is around 15% and is higher than the risk of regrowth in patients with pCR who had surgery
- Wait-and-see strategy with strict selection criteria, an appropriate follow-up schedule, and salvage treatments achieved outcomes (DFS, OS, DM) at least as good as radical surgery
- Robust surveillance with early detection of regrowths allows a high rate of successful salvage surgery, without an increase in the risk of systemic disease, or adverse survival outcomes
- More prospective studies are needed to confirm long term safety