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Is (neo)adjuvant therapy necessary in T3 Rectal Cancer?
A Surgeon's View

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Colorectal Cancer Genomic Health Service
Personalized Care Through Scientific Discoveries

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SingHealth

A colorectal surgeon’s view

- T3N0 Rectal Ca need not receive CRT in specialized centres with LR <10% after ‘optimal’ TME
- CRT given only in cases with ‘suboptimal’ TME performed
- N1 & N2 disease should receive Chemotherapy to reduce risks of distant mets

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Introduction

- Surgery remains the only potentially curative option in CRC
- Challenges in rectal cancer:
  - narrow confines of pelvis, technical challenges
  - higher risks of local failure
- Understand the evolution of rectal cancer management in the context of 2 time periods: the era before & after introduction of TME (Total Mesorectal Excision)

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TME (Total Mesorectal Excision)

- With TME (Havenga, Eur J Surg Oncol. 1999; 25:368-374)
  - cancer cure rates increased from 45% to 75%
  - rate of pelvic recurrence decreased from 38%-40% to 5%-10%
  - sphincter-preservation in mid rectal Ca increased from 45% to 95%
- Quirke et al (*Lancet* 1986; 1:996-999):
  - local recurrence due to inadequate resection
  - 27% of “curative” resection specimens revealed violated mesorectum.

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Background

- Risk of LR highest in T3 ± N1:
  - In the era before TME (prior to 1990s): LR ~ 20% for T3N0 or T2N1, ~ 50% LR for T3N1 or T4 with surgery alone. (Rich et al. *Cancer* 1983;52:1317-29)
  - In the TME era (after mid 1990s): TME alone substantially superior to the best

	TME alone	Conv surgery + RT	Conv surg +CRT
LR (5 yrs)	5%	25%	13.5%
Overall Recurrence	22%	62.7%	41.5%

(MacFarlane, Ryall, Heald. *Lancet* 1993; 341: 457-60.)

- Risk of distant mets ~24% to 50%.
- Systemic chemo to reduce systemic failure in N+ disease ✓
- ChemoRT to reduce local failure ?

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Table 1
Randomized trials of postoperative radiation therapy vs. surgery alone for resectable rectal cancer

Study	Year	Median follow-up (yr)	Therapy	*N*	Local recurrence		Distant metastases	5-yr Overall survival	
					%	*p*	%	%	*p*
Danish [8]	1986	NA[a]	Surgery	250	18		24	NA	
			Surgery + 50 Gy, 2 weeks	244	16	NS	26	NA	
GITSG 7175 [5,9]	1985–1988	6.7	Surgery	58	24		34	46	
			Surgery + 40–48 Gy, 4 weeks	50	20	NS	30	52	NS
NSABP R-01 [10]	1988	5.3	Surgery	184	25		26	43	
			Surgery + 46.5 Gy, 5 weeks	184	16	0.06	31	41	NS
			Surgery + MOF	187	21	NS	24	53	0.05
Netherlands [11]	1991	3.2	Surgery	84	33		26	57	
			Surgery + 50 Gy, 5 weeks	88	24	NS	39	45	NS
MRC III [12]	1996	5.0[b]	Surgery	235	34		35	38	
			Surgery + 40 Gy, 4 weeks	234	21	0.001	32	41	NS
EORTC [13]	1997	7.1	Surgery	88	34		31	40[c]	
			Surgery + 46 Gy, 4–5 weeks	84	30	NS	42	45[c]	NS

EBRT, external beam radiation therapy; GITSG, Gastrointestinal Tumor Study Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; MRC, Medial Research Council; EORTC, European Organization for Research and Treatment of Cancer; NS, not significant; NA, data not available; MOF, 5-FU, semustine, vincristine.

[a] Results reported from first 5 yr of study.

[b] Min follow-up was 5 yr.

[c] Plotted from Kaplan–Meier curve.

Table 2
Randomized trials of postoperative chemoradiation for resectable rectal cancer

Study	Year	Median follow-up (yr)	Therapy		Local recurrence		Distant metastases	Overall survival	
				N	%	p^a	%	%	p^a
GITSG 7175 [5,9]	1986	7.8	Surgery alone	58	24		34	46 (5-yr)	
			EBRT	50	20	0.08[b]	30	52 (5-yr)	NS
			5-FU/MeCCNU	48	27	NS	27	56 (5-yr)	NS
			EBRT + 5-FU/MeCCNU	46	11	0.08[b]	26	59 (5-yr)	0.005
NCCTG 794751 [14]	1991	7.0	EBRT	100	25		46	48 (5-yr)	
			EBRT + 5-FU/MeCCNU	104	13.5	0.04	29	58 (5-yr)	0.025
GITSG 7180 [15]	1992	5.8	EBRT + 5-FU	104	16		26	75 (3-yr)	
			EBRT + 5-FU/MeCCNU	95	17	NS	40	66 (3-yr)	NS
NCCTG 864751 [16]	1994	3.8	Bolus 5-FU/EBRT + 5-FU ± MeCCNU	332	12		40	60 (4-yr)	
			CI 5-FU/EBRT + 5-FU ± MeCCNU	328	8	NS	31	70 (4-yr)	0.005
Norwegian [17]	1995	3.5–7.8[c]	Surgery alone	70	30		NA	49 (5-yr)	
			EBRT + 5-FU	66	12	0.01	NA	64 (5-yr)	0.05
INT 0114 [18]	1997	4.0	EBRT + 5-FU	421	12		31	78 (3-yr)	
			EBRT + 5-FU/leucovorin	425	9	NS	28	80 (3-yr)	NS
			EBRT + 5-FU/levamisole	426	13	NS	33	79 (3-yr)	NS
			EBRT + 5-FU/ leucovorin/levamisole	424	9	NS	32	79 (3-yr)	NS

GITSG, Gastrointestinal Tumor Study Group; NCCTG, North Central Cancer Treatment Group; INT, Intergroup; EBRT, external beam radiation therapy; CI, continuous infusion; NS, not significant; NA, data not available.

[a]Treatment arm vs. control arm.

[b]EBRT vs. no EBRT, $p = 0.08$.

[c]Range for follow-up.

Table 4
Randomized trials of preoperative radiation therapy (> 20 Gy) for resectable rectal cancer

Study	Year	Median follow-up (yr)	*N*	Therapy	Local recurrence		5-yr Overall survival	
					%	*p*	%	*p*
VASOG II [32]	1986	5.0	181	Surgery	NA		47	
			180	31.5 Gy, 3.5 weeks + Surgery	NA	NA	43	NA
Norwegian [33]	1990	4.5	145	Surgery	21		58	
			155	31.5 Gy, 3.5 weeks + Surgery	15	NS	57	NS
EORTC II [34]	1988	5.0	175	Surgery	30		49	
			166	34.5 Gy, 3 weeks + Surgery	15	0.003	52	NS
Stockholm I [6]	1995	8.9	425	Surgery	28		36	
			424	25 Gy, 5 fractions + Surgery	14	< 0.01	36	NS
MRC II [35]	1996	5.0[a]	140	Surgery	46		19	
			139	40 Gy, 4 weeks + Surgery	36	0.04	26	NS
Swedish [7]	1997	5.0	585	Surgery	27		48	
			583	25 Gy, 5 fractions + Surgery	11	< 0.001	58	0.004

VASOG, Veterans Administration Surgical Oncology Group, second trial; EORTC, European Organization on Research and Treatment of Cancer; MRC, Medical Research Council; NS, not significant; NA, data not available.

[a]Minimal follow-up of 5.0 years.

Swedish Trial

- Surgery was not standardized.
- Since surgical technique is a key factor in LR, standardization and quality control are critical for evaluating the effects of adjuvant Rx.
- Dutch Rectal Cancer Trial to investigate the efficacy of preop-RT in combination with standardized TME in rectal cancer.

N Engl J Med 2001;345:638-46.

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PREOPERATIVE RADIOTHERAPY COMBINED WITH TOTAL MESORECTAL EXCISION FOR RESECTABLE RECTAL CANCER

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N Engl J Med 2001;345:638-46.

- 1996 - 1999: 1861 patients from 84 Dutch, 13 Swedish, 11 European/Canadian centres
- prospective RCT to investigate the efficacy of [preop-RT + TME] *vs* [TME-alone].
- median follow-up 2 years

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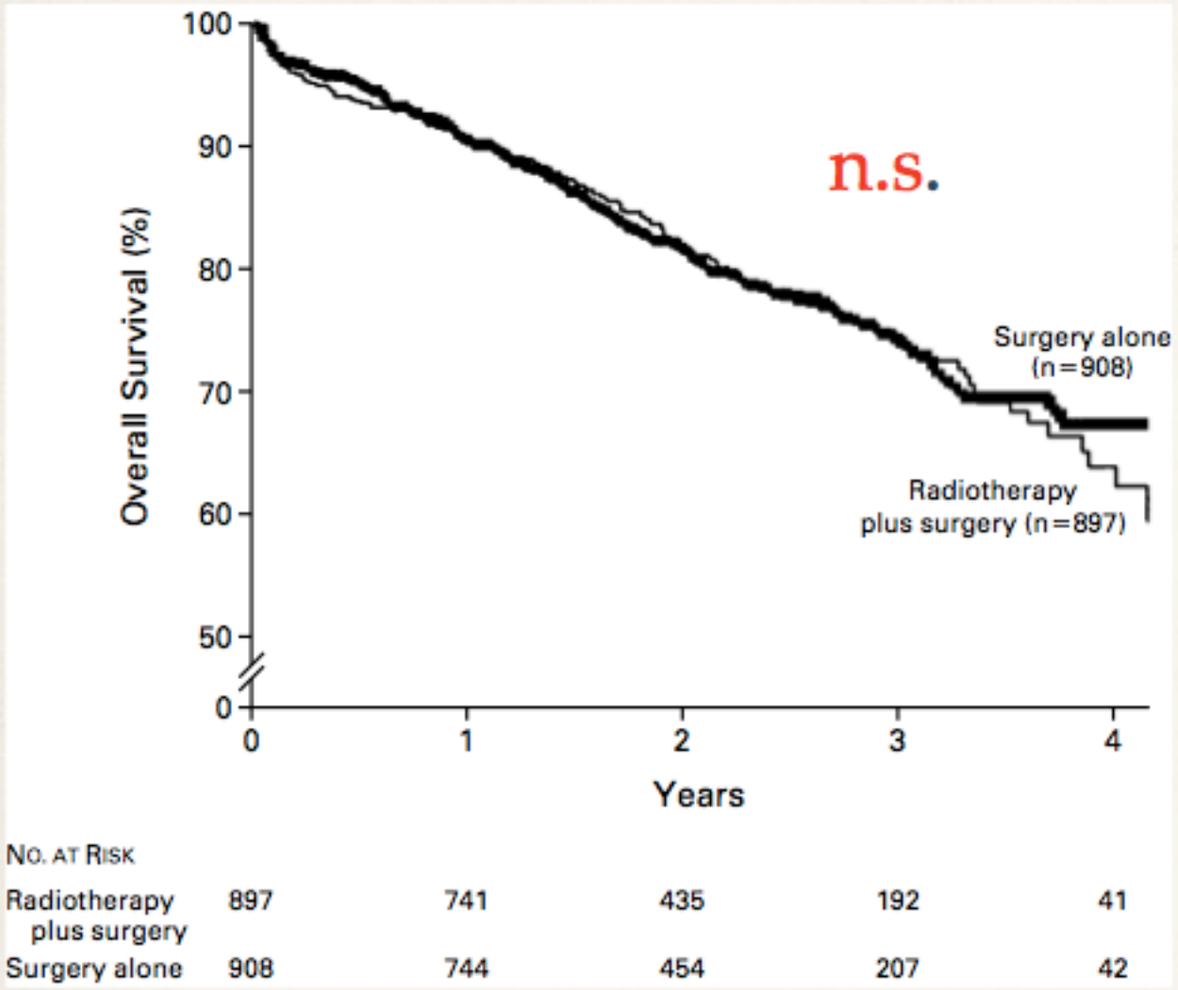
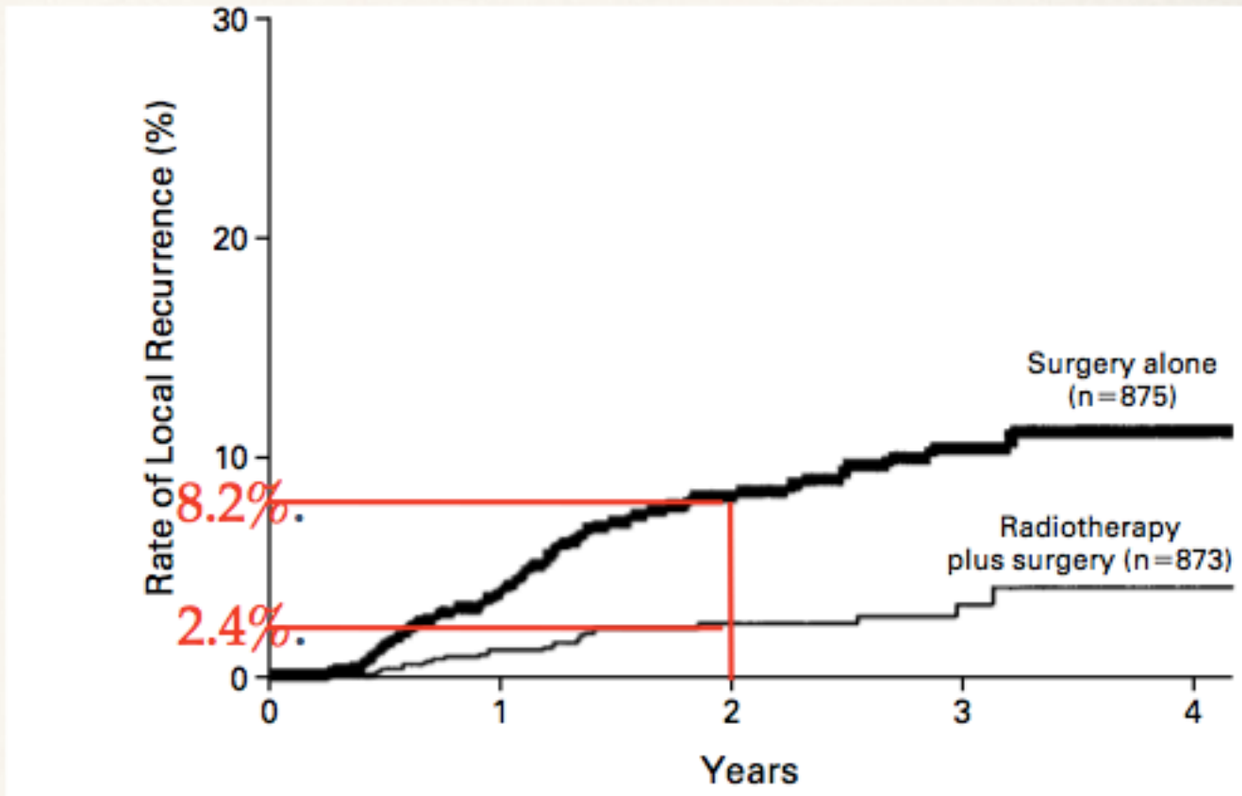
Figure 1. Rates of Overall Survival in the Population of 1805 Eligible Patients, According to Treatment Group.

At two years, the rate of overall survival was 82.0 percent in the group assigned to radiotherapy and surgery and 81.8 percent in the group assigned to surgery alone (P=0.84).



No. at Risk

Radiotherapy plus surgery	897	741	435	192	41
Surgery alone	908	744	454	207	42



No. at Risk

Radiotherapy plus surgery	873	691	407	170	30
Surgery alone	875	688	406	173	37

Figure 2. Rates of Local Recurrence in the Population of 1748 Eligible Patients Who Underwent Macroscopically Complete Local Resection, According to Treatment Group.

At two years, the rate of local recurrence was 2.4 percent in the group assigned to radiotherapy and surgery and 8.2 percent in the group assigned to surgery alone (P<0.001).

N Engl J Med 2001;345:638-46.

Pre-operative radiotherapy for rectal carcinoma? Has the case really been made for short course pre-operative radiotherapy if surgical standards for rectal carcinoma are optimal?

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P. Hermanek & R. J. Heald. *Colorectal Disease* 2004; 6: 10–14.

- Problems with Dutch TME Trial:
  - reported 'rate of LR at 2 yrs' based on a median follow up time of 24.9 mths (range 1.1–56.0 mths), not the rate after a follow up of a least 2 yrs.
    - 87% were followed for at least 1 yr
    - only 56% for at least 2 yrs
    - 5% for at least 4 yrs
  - even with 27.9% (244/875) stage I tumors, early recurrence rate of 8.2% corresponds to 12.1% after 5 years (present standard of LR should be <10%).
  - 23.3% microscopically involved margin cases or 23.9% of macroscopically 'poor' cases
    - 139 surgeons from 84 Dutch Hospitals contributing 1530 cases over 4 years = 4.75 cases/yr/hospital
    - Ave # of cases = 2.75/surgeon/yr, (substantial minority performing < 2/yr)

P. Hermanek & R. J. Heald. *Colorectal Disease* 2004; 6: 10–14.

- macroscopic evaluation of the TME by pathologist was reported only in ~20% of non-irradiated patients and showed incomplete TME in 23.9% of these.

- Hence, Dutch data suggested that:
  - short-term pre-op RT for resectable tumors not effective in CRM+
  - Benefit was seen only in CRM-
  - Such benefit must therefore result from RT destruction of only very small residues – probably cells shed during surgery or the smallest of residual micro- metastases.

Lancet 1993; 341: 457–60
Ann Med 1997; 29: 127–33

- TME by specialist colorectal surgeons: 5-year LR rates < 10%.

- Thus, at the end of the 1990s, 2 questions remained:
  - did preop-RT add anything to optimal TME?
  - can we better identify the few patients at high risk postoperatively for RT (e.g. those with CRM+, rather than postop CRT for *all* stage II or III disease)?

RADIOTHERAPY DOES NOT COMPENSATE FOR POSITIVE RESECTION MARGINS IN RECTAL CANCER PATIENTS: REPORT OF A MULTICENTER RANDOMIZED TRIAL

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Int. J. Radiation Oncology Biol. Phys., Vol. 55, No. 5, pp. 1311–1320, 2003

- 1996 - 1999, 1861 patients
- Multi-centre RCT: pre-op RT vs TME-alone (given post-op RT if CRM+)
- ‘Standardized TME’, Quirke protocol for CRM review
- Pre-op RT: 5 x 5Gy (25Gy) over 5 - 7 days, then TME within 10 days (i.e no ‘down-staging’)
- Post-op RT if CRM+: 28 x 1.8Gy (50.4Gy), 5x/week
- median followup 33.6 mths (range 1-63)

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Int J Rad Oncology Biol Phys 2003; vol 55(5): 1311-20

Table 2. Relationship between circumferential margin involvement and local recurrences over treatment arms

	TME		RT + TME		Total		
	n	LR (%)	*n*	LR (%)	*n*	LR (%)	*p* value
>2 mm	483	5.8	504	0.9	987	3.3	<0.0001
1–2 mm	53	14.9	47	0	100	8.5	0.02
≤1 mm	120	16.4	107	9.3	227	13.1	0.08
Postoperative RT	56	17.3	—		—		
No postoperative RT	64	15.7	—		—		
Total	656	8.4	662	2.1	1318	5.2	<0.0001

Local recurrence rates after 2 years follow-up are given. Log–rank testing is used to compare differences.
Abbreviations: TME = total mesorectal excision; RT = radiotherapy; LR = local recurrence.

- Although RT appears to be useful for those with CRM > 2mm & 1-2mm, RT did not work when CRM+(<1mm): 2yr LR 17.3% vs 15.7% (p=0.08)

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Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial

Lancet 2009; 373: 821–28

	Muscularis propria	Intramesorectal HR (95%CI)*	Mesorectal HR (95% CI)*
Overall	13%	7%, 0·48 (0·25–0·93)	4%, 0·32 (0·16–0·64)
Treatment			
Preoperative radiotherapy	10%	4%, 0·52 (0·15–1·79)	1%, 0·09 (0·02–0·49)
Selective postoperative chemoradiotherapy	16%	10%, 0·49 (0·23–1·06)	7%, 0·48 (0·23–1·00)
Sex			
Male	12%	9%, 0·57 (0·27–1·22)	4%, 0·28 (0·12–0·67)
Female	18%	5%, 0·36 (0·10–1·23)	4%, 0·35 (0·10–1·19)
Age			
≤54	18%	9%, 0·22 (0·04–1·16)	4%, 0·17 (0·03–0·93)
55–64	13%	9%, 0·51 (0·15–1·73)	5%, 0·22 (0·05–0·92)
65–74	15%	7%,0·56 (0·20–1·59)	4%, 0·40 (0·13–1·18)
≥75	7%	4%, 0·37 (0·06–2·29)	5%, 0·63 (0·13–3·11)
Operation			
Anterior resection	11%	7%, 0·62 (0·21–1·79)	5%, 0·58 (0·20–1·65)
Abdominoperineal excision	18%	10%, 0·41 (0·18–0·93)	3%, 0·18 (0·07–0·47)
CRM			
Positive	21%	13%, 0·67 (0·19–2·38)	12%, 0·46 (0·12–1·76)
Negative	12%	7%, 0·50 (0·24–1·06)	4%, 0·33 (0·15–0·74)
TNM stage			
I	8%	2%, 0·33 (0·07–1·59)	0%, 0·01 (0·00–0·10)
II	6%	2%, 0·11 (0·01–0·94)	5%, 0·78 (0·20–3·08)
III	20%	14%, 0·72 (0·33–1·56)	6%, 0·37 (0·15–0·89)

*Compared with muscularis propria. CRM=circumferential resection margin. HR=hazard ratio.

Table 2: **3-year local recurrence rates for the plane of surgery achieved**

- Preop RT reduced the LR, generally by ≥ 50% in each of these categories.
- If LR 25%→ 12% after RT; If LR 5% → 3% after RT
- best outcomes occurred when preop RT was followed by optimum surgery.
- preop RT can mitigate but not eliminate the adverse effects of imperfect surgery.

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Read TE, DCR 2002; 45(7): 904 - 14

	Colorectal Surgeon	Non-colorectal Surgeon	*p* value (Tarone-Ware)
5 yr actuarial disease-free survival	77%	68%	< 0.005
5 yr actuarial local control rates	93%	84%	< 0.005

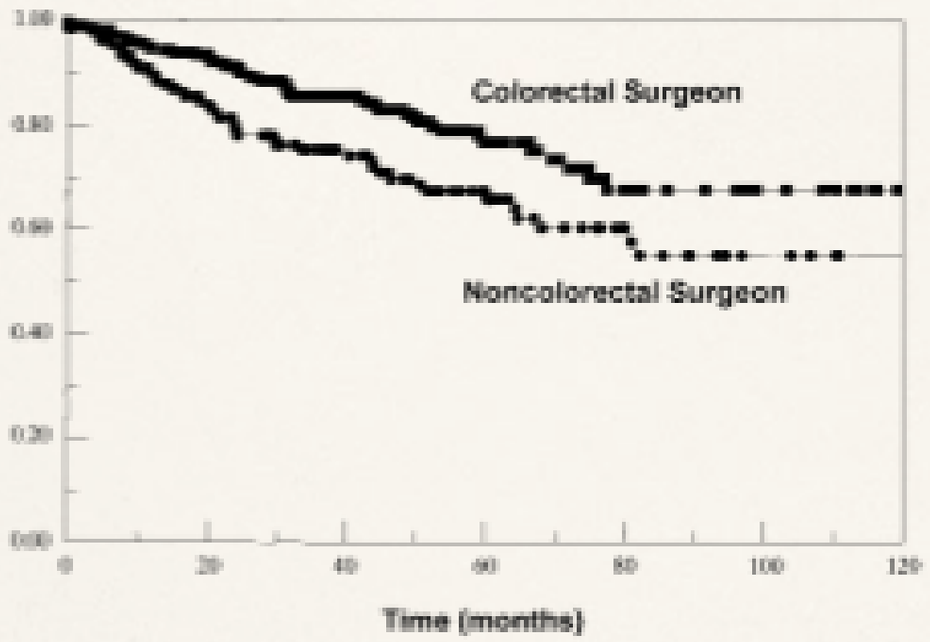

Figure 2. Actuarial (Kaplan-Meier) freedom from relapse in 384 patients with rectal cancer undergoing neoadjuvant radiotherapy and proctectomy by colorectal surgeons (*n* = 251) and noncolorectal surgeons (*n* = 133). *P* = 0.004, Tarone-Ware.

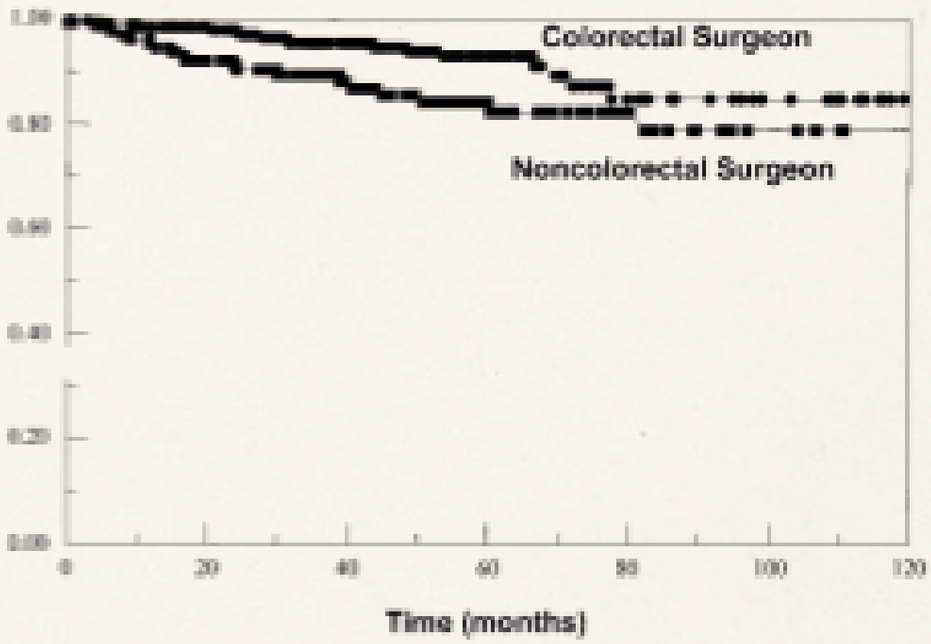

Figure 3. Actuarial (Kaplan-Meier) local pelvic control in 384 patients with rectal cancer undergoing neoadjuvant radiotherapy and proctectomy by colorectal surgeons (*n* = 251) and noncolorectal surgeons (*n* = 133). *P* = 0.005, Tarone-Ware.

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ANZ J. Surg. 2006; 76: 286–287 doi: 10.1111/j.1445-2197.2006.03709.x

PERSONAL VIEW

MULTICENTRE PROSPECTIVE RANDOMIZED TRIALS ARE NOT ALWAYS RELEVANT TO SURGEONS

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- An operation of the same name, may not necessary be of the ‘same’ quality
- Although the “science” of surgery forms the basis of clinical decision making, it is the “art” of surgery that delivers the intervention to achieve the intended outcome.
- Surgical techniques are not homogeneous like pharmacological products.
- In multi-centre studies
  - surgical standards are diverse
  - difficult to determine if the surgery was identical in both the control and experimental groups

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Conclusions

- the role of short-course RT in patients who have undergone “optimal TME surgery” remains to be conclusively proven
- +CRM cases should receive “optimal” RT – short course RT would not be enough.
- RT ‘fails’ to improve Overall Survival when we need it most: +CRM
- Even with RT, poor surgical techniques will affect survival outcomes
- When do we need RT (long-course)?
  - Neoadjuvant setting:
    - to downstage large bulky tumor to achieve sphincter preservation
    - threatened CRM on MRI
  - Adjuvant setting:
    - poor TME, CRM+, ?perforation/spillage
    - ? T3,T4 in centres/surgeons with high LR rates
    - “close-shave” distal margins
    - T2 after local excision?

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The way forward?

- Know our own outcome data, National Audits of surgical outcomes
- ‘standardized’ TME surgery techniques
- standardized pathology assessment of TME specimens
- stratify outcome analysis according to hospital/surgeon volume

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The road ahead.....

THANK YOU!

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