Adjuvant and neoadjuvant chemotherapy for rectal cancer: Expensive but little gain

Outline

- The problem
- Adjuvant therapy
- Neoadjuvant therapy
- Options
- Conclusion

The problem

- 30 years ago:
  - Local recurrence rates for rectal cancer – 25-30%
  - Local recurrence was a disaster
    - Almost untreatable
    - Unpleasant
    - Long duration
- 25 years ago:
  - Radiotherapy ± chemotherapy for all reduced local recurrence by 50%
  - Minimal effect on survival
  - Number needed to treat: 8:1

The problem

- 20 years ago:
  - Improvements in surgical technique reduced local recurrence to below 10% without chemoradiotherapy
  - Chemoradiotherapy still reduced local recurrence by 50%
  - Number needed to treat 20:1
  - Significant side-effects
  - Minimal change in survival

The problem
Over the last 20 years

- Detection of earlier lesions:
  - Screening programs
  - Awareness campaigns
  - Early lesions increased from - 4% to 20+%
- Concept of threatened margin
- Development of accurate pelvic imaging
- Selective chemoradiotherapy

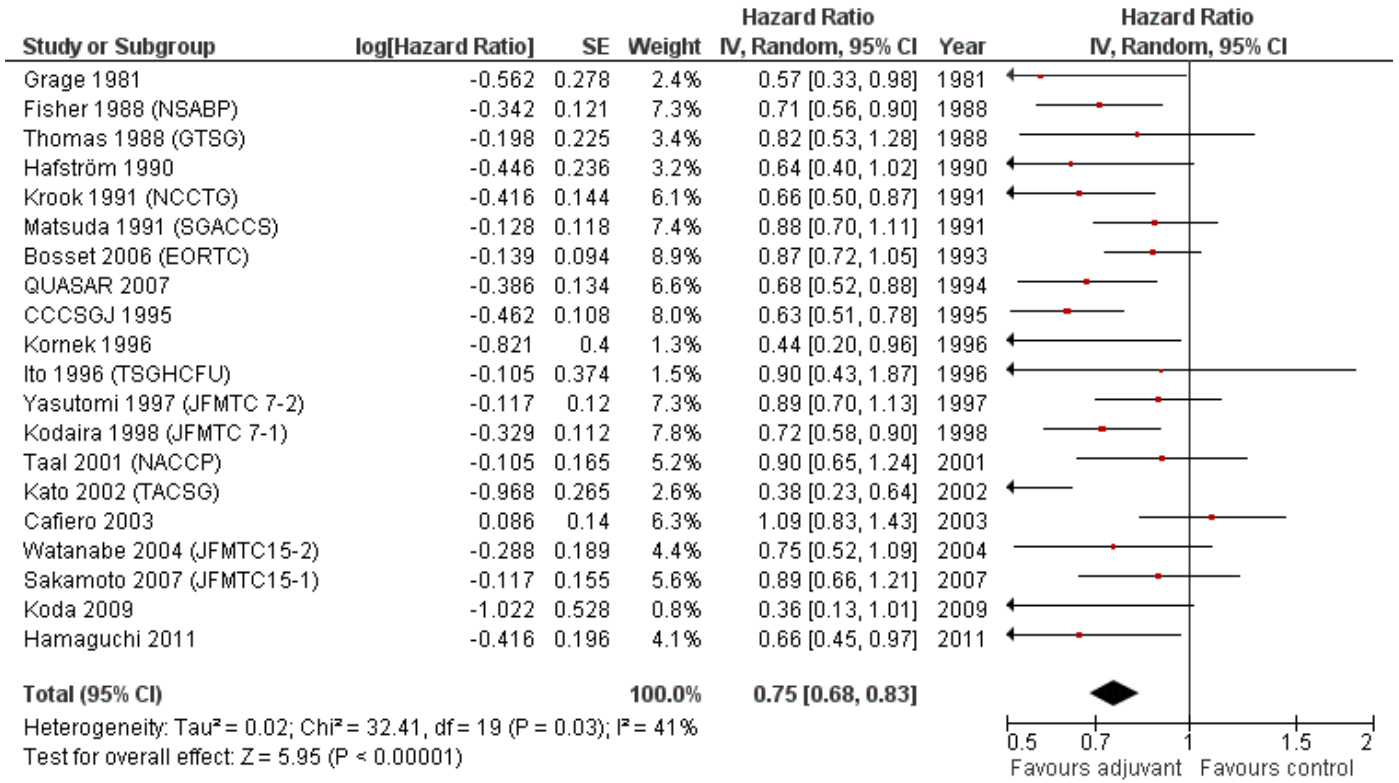
Problems Today

- Improving survival
- Organ preservation

Adjuvant chemotherapy for rectal cancer

- Adjuvant chemotherapy improves survival in colon cancer
- Surely it would work in rectal cancer
- Well does it?

Disease Free Survival: Rectal cancer 5FU based



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Grage 1981	-0.562	0.278	2.4%	0.57 [0.33, 0.98]	1981
Fisher 1988 (NSABP)	-0.342	0.121	7.3%	0.71 [0.56, 0.90]	1988
Thomas 1988 (GTSG)	-0.198	0.225	3.4%	0.82 [0.53, 1.28]	1988
Hafström 1990	-0.446	0.236	3.2%	0.64 [0.40, 1.02]	1990
Krook 1991 (NCCTG)	-0.416	0.144	6.1%	0.66 [0.50, 0.87]	1991
Matsuda 1991 (SGACCS)	-0.128	0.118	7.4%	0.88 [0.70, 1.11]	1991
Bosset 2006 (EORTC)	-0.139	0.094	8.9%	0.87 [0.72, 1.05]	1993
QUASAR 2007	-0.386	0.134	6.6%	0.68 [0.52, 0.88]	1994
CCCSGJ 1995	-0.462	0.108	8.0%	0.63 [0.51, 0.78]	1995
Kornek 1996	-0.821	0.4	1.3%	0.44 [0.20, 0.96]	1996
Ito 1996 (TSGHCFU)	-0.105	0.374	1.5%	0.90 [0.43, 1.87]	1996
Yasutomi 1997 (JFMTC 7-2)	-0.117	0.12	7.3%	0.89 [0.70, 1.13]	1997
Kodaira 1998 (JFMTC 7-1)	-0.329	0.112	7.8%	0.72 [0.58, 0.90]	1998
Taal 2001 (NACCP)	-0.105	0.165	5.2%	0.90 [0.65, 1.24]	2001
Kato 2002 (TACSG)	-0.968	0.265	2.6%	0.38 [0.23, 0.64]	2002
Cafiero 2003	0.086	0.14	6.3%	1.09 [0.83, 1.43]	2003
Watanabe 2004 (JFMTC15-2)	-0.288	0.189	4.4%	0.75 [0.52, 1.09]	2004
Sakamoto 2007 (JFMTC15-1)	-0.117	0.155	5.6%	0.89 [0.66, 1.21]	2007
Koda 2009	-1.022	0.528	0.8%	0.36 [0.13, 1.01]	2009
Hamaguchi 2011	-0.416	0.196	4.1%	0.66 [0.45, 0.97]	2011
Total (95% CI)			**100.0%**	**0.75 [0.68, 0.83]**	

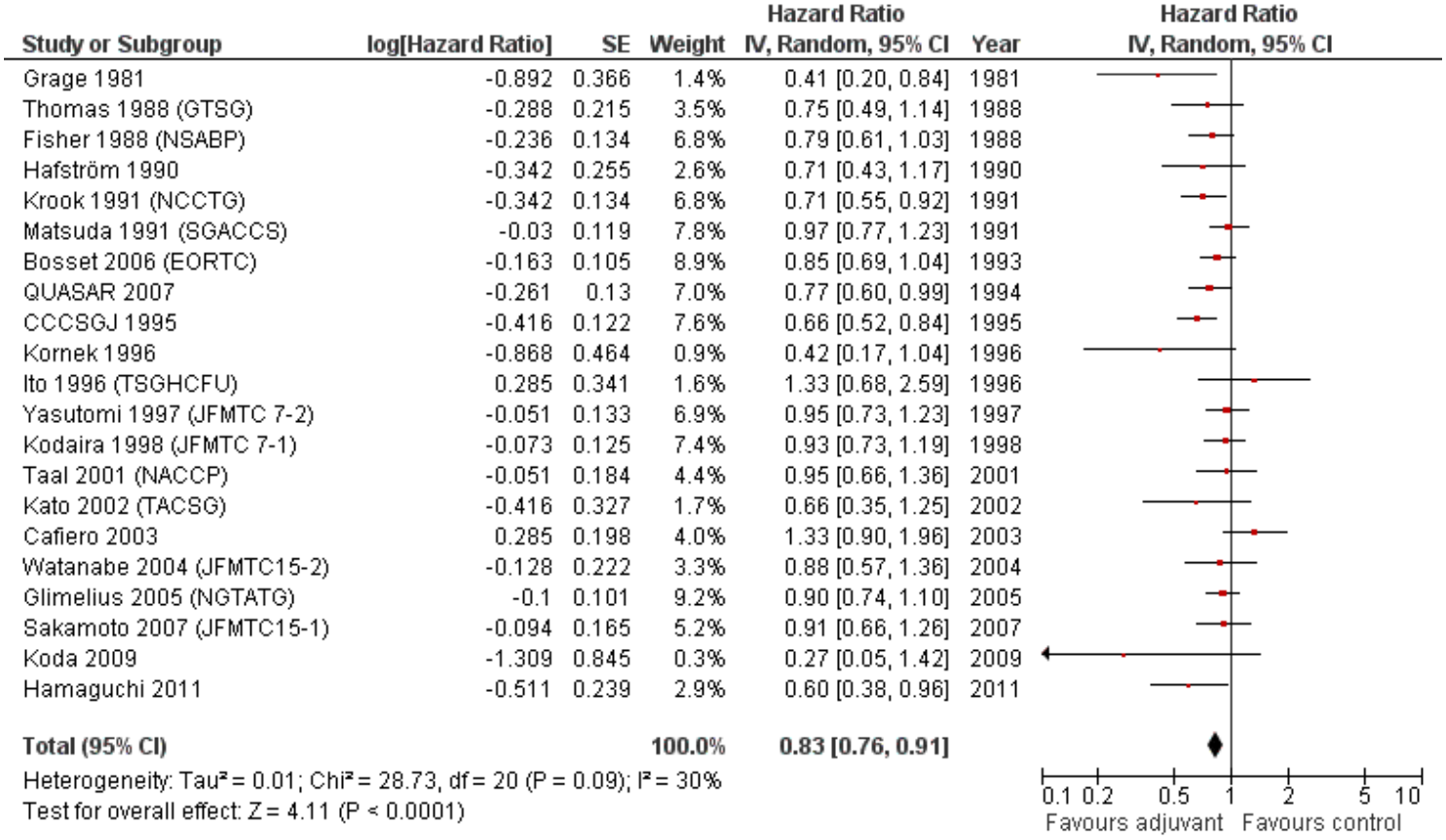
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 32.41$, df = 19 (P = 0.03); $I^2 = 41\%$

Test for overall effect: Z = 5.95 (P < 0.00001)

8. Forest plot of comparison: 1 Adjuvant vs No Adjuvant_ALL, outcome: 1.2 Disease Free Survival (DFS).

Petersen SH, Harling H, Kirkeby LT, Wille-Jørgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure.. Cochrane Database of Systematic Reviews 2012, 3. Art. No.: CD004078. DOI: http://dx.doi.org/10.1002/14651858.CD004078.pub2

Overall Survival: Rectal cancer 5FU based



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
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); $I^2 = 30\%$

Test for overall effect: Z = 4.11 (P < 0.0001)

1. Forest plot of comparison: 1 Adjuvant vs No Adjuvant_ALL, outcome: 1.1 Overall Survival (OS).

Petersen SH, Harling H, Kirkeby LT, Wille-Jørgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure.. Cochrane Database of Systematic Reviews 2012, 3. Art. No.: CD004078. DOI: http://dx.doi.org/10.1002/14651858.CD004078.pub2

Concerns

- Data extracted from studies of rectal and colon carcinoma
- Inadequate staging modalities
- Out-dated chemotherapeutic regimens
- Differing surgical approaches
- Small sample sizes
- Will adjuvant therapy work after preoperative chemotherapy?

Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study

- 10 years of follow-up
- Randomised
- Clinical T3 or T4 rectal carcinoma
- No benefit of postoperative adjuvant chemotherapy after preoperative chemoradiotherapy

2014 Lancet Oncology Bosset JF et.al

Potential problems with adjuvant chemotherapy

- Long delay from diagnosis to starting therapy
  - May be up to 6 months
- Neoadjuvant therapy may selectively kill sensitive cells before adjuvant therapy is given
- Pre-operative radiotherapy alters staging
  - Who should get adjuvant therapy?

Adjuvant therapy

- Some guidelines still recommend adjuvant therapy for:
- Node positive
- Anyone who has had preoperative radiotherapy
- Less than 15 nodes in specimen
- No level 1 evidence

Ongoing trials

- NCT01941979: phase Ⅲ trial
  - FOLFOX vs observation in patients with T3-4, N1, M0 who were treated with preoperative chemo-radiotherapy and showed poor response
- Biomarkers

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REVIEW

Adjuvant chemotherapy for rectal cancer: Is it needed?

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Neoadjuvant chemotherapy

- Options:
  - Chemotherapy alone
  - With radiotherapy
    - As a sensitiser
    - As full dose therapy after chemoradiotherapy
  - Short course radiotherapy and delay to surgery

Neoadjuvant Chemotherapy alone

Table 1 Studies of neoadjuvant chemotherapy alone in rectal cancer

Study	Key inclusion criteria	#pts	Treatment	pCR rate	Outcomes
Ishii, *et al.* (35)	T3 or T4	26	Irinotecan, 5-FU, Leucovorin ×8 weeks	3.8%	5-year DFS—74% 5-year OS—84%
Uehara, *et al.* (36)	MRI-defined poor risk: T4, N2, CRM ≤1 mm, extramural invasion >5 mm	32	CAPOX, bevacizumab ×12 weeks	13%	R0 resection rate—90%
Hasegawa, *et al.* (37)	T4 or N+	25	CAPOX, bevacizumab ×12 weeks	4%	R0 resection rate—92% DFS at 31 months—68%
Cercek, *et al.* (38)	No radiation, resected primary	20	FOLFOX +/– bevacizumab	35%	N/A
Schrag, *et al.* (39)	T3	32	FOLFOX + bevacizumab ×8 weeks	25%	R0 resection rate—100% 4-year LR—0% 4-year DFS—84%

pCR, pathologic complete response; DFS, disease free survival; OS, overall survival; CRM, circumferential resection margin; LR, local recurrence.

- Very small numbers
- Not randomised

Neoadjuvant chemoradiotherapy followed by chemotherapy

Table 3 Studies of neoadjuvant chemoradiation followed by chemotherapy

Study	Key inclusion criteria	# pts	Treatment	pCR rate	Outcomes
Zampino, *et al.* (54)	T3, T4 or N+	51	ChemoRT with capecitabine → capecitabine ×6 weeks	18% (9/50)	R0 resection—100% 5-year DFS—85.4%
Gao, *et al.* (55)	T4, bulky (>5 cm), <6 cm from anal verge, N+, elevated CEA	36	ChemoRT with CAPOX → CAPOX ×3 weeks	36%	R0 resection—100% Downstaged—81%
van DijK, *et al.* (56)	Metastatic rectal cancer	50	Short course radiation → CAPOX + bevacizumab for up to 18 weeks	26% (11/43)	R0 resection of primary—91% (39/43) 2-year OS—80% LR rate after R0 resection—6% (2/36)
Garcia-Aguilar, *et al.* (51)	T3, T4 or N+	144	Chemoradiation with 5-FU	18%	R0 resection—97%
			Chemoradiation with 5-FU → FOLFOX ×4 weeks	25%	R0 resection—96%

pCR, pathologic complete response; DFS, disease free survival; CEA, carcino-embryonic antigen; LR, local recurrence.

Very small numbers

Not randomised

Conclusion

- Current management has little impact on survival
- Local recurrence has been reduced
- Radiotherapy results in significant long term side-effects
- Early neoadjuvant chemotherapy may improve survival but data is currently not available.