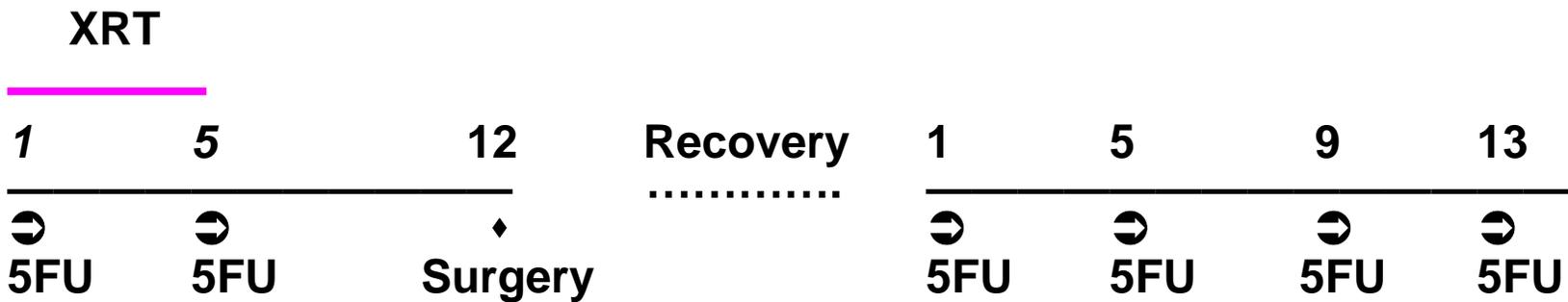
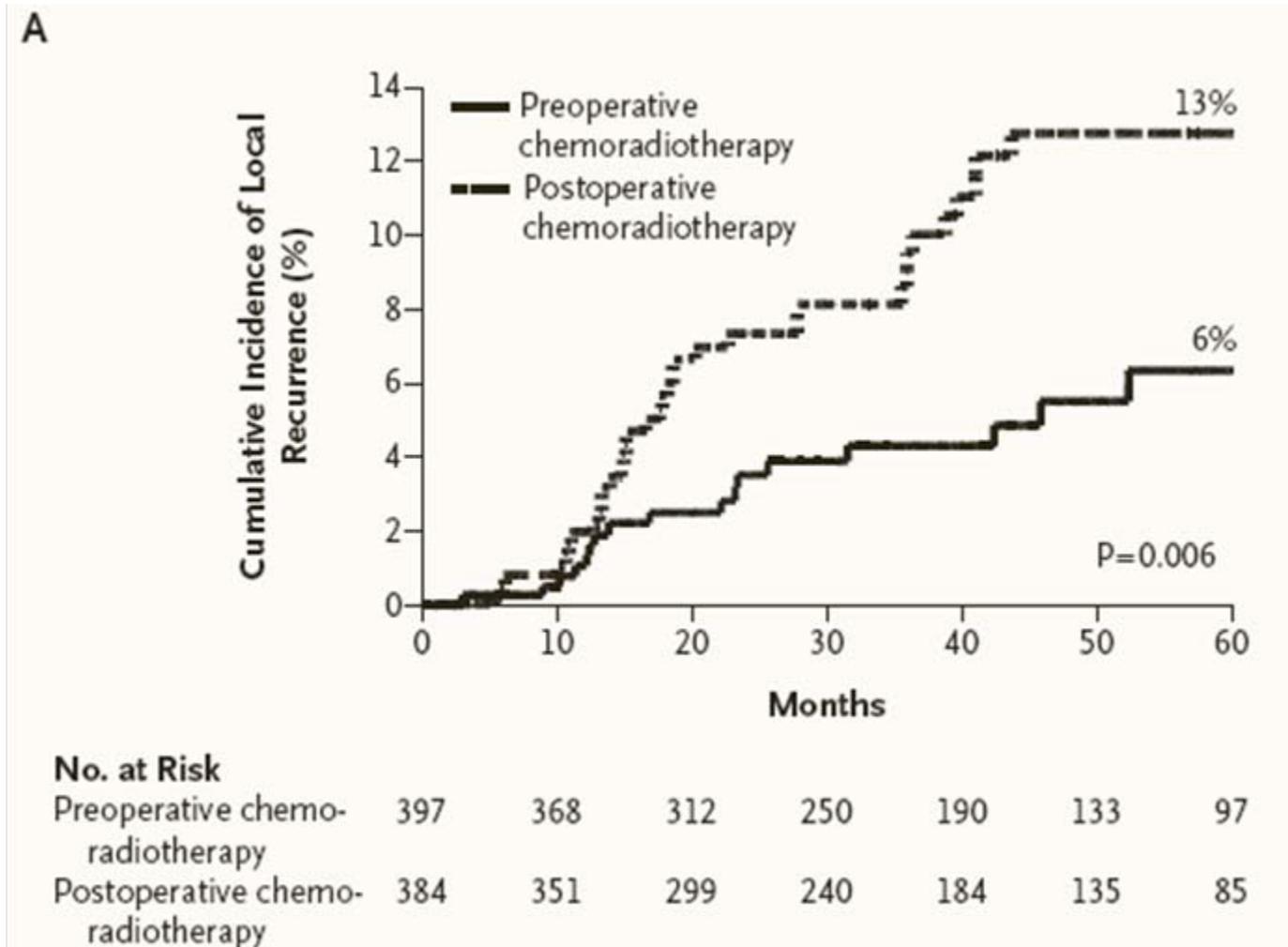


The standard of Care In Stage II and III Rectal Cancer

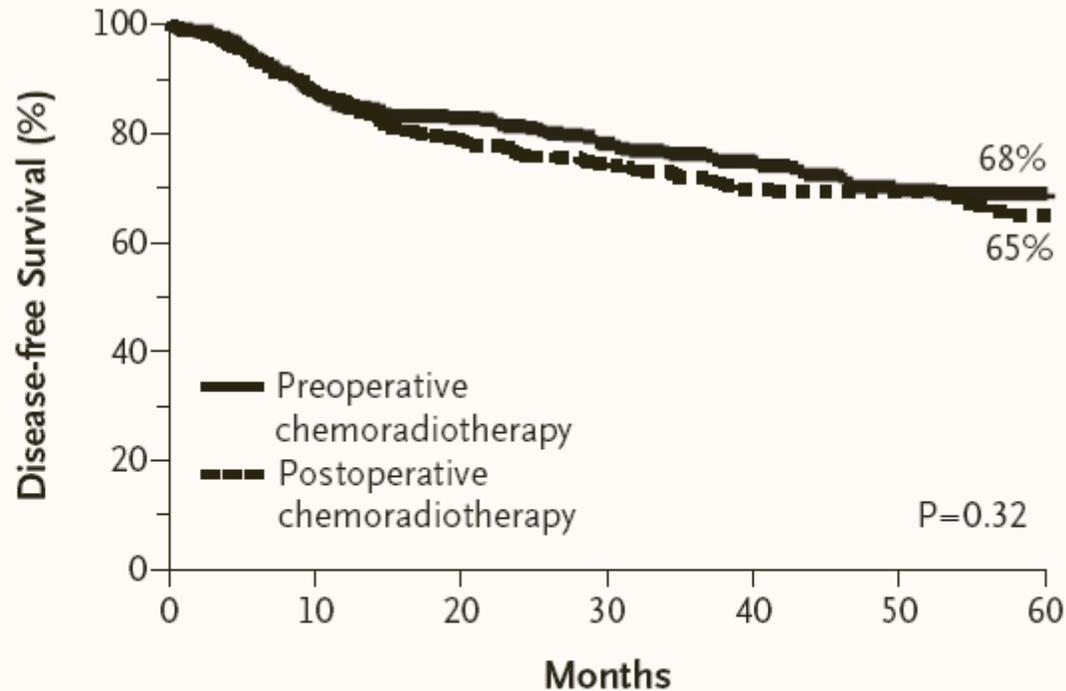
Neoadjuvant Therapy and TME



The German Trial: Local Recurrence



The German Trial: Disease-free Survival



No. at Risk

Preoperative chemo-radiotherapy	397	331	280	224	169	115	85
Postoperative chemo-radiotherapy	384	314	259	209	159	117	73

Side Effects of the Treatment of Rectal Cancer

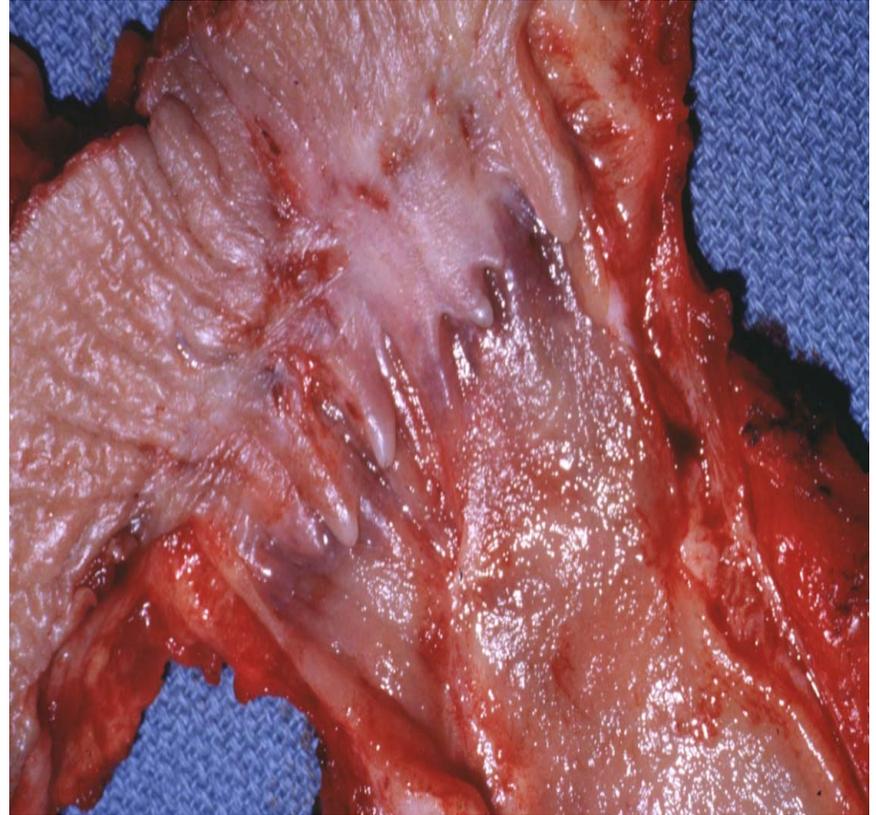
- Mortality 2.3% to 3.2%
- Morbidity 30% to 46%
- Urinary dysfunction 10-17%
- Sexual dysfunction 5-69%
- Colostomy 10% to 40%
- Bowel dysfunction 13-80%

Tumor Response to Neoadjuvant Therapy

Before



After

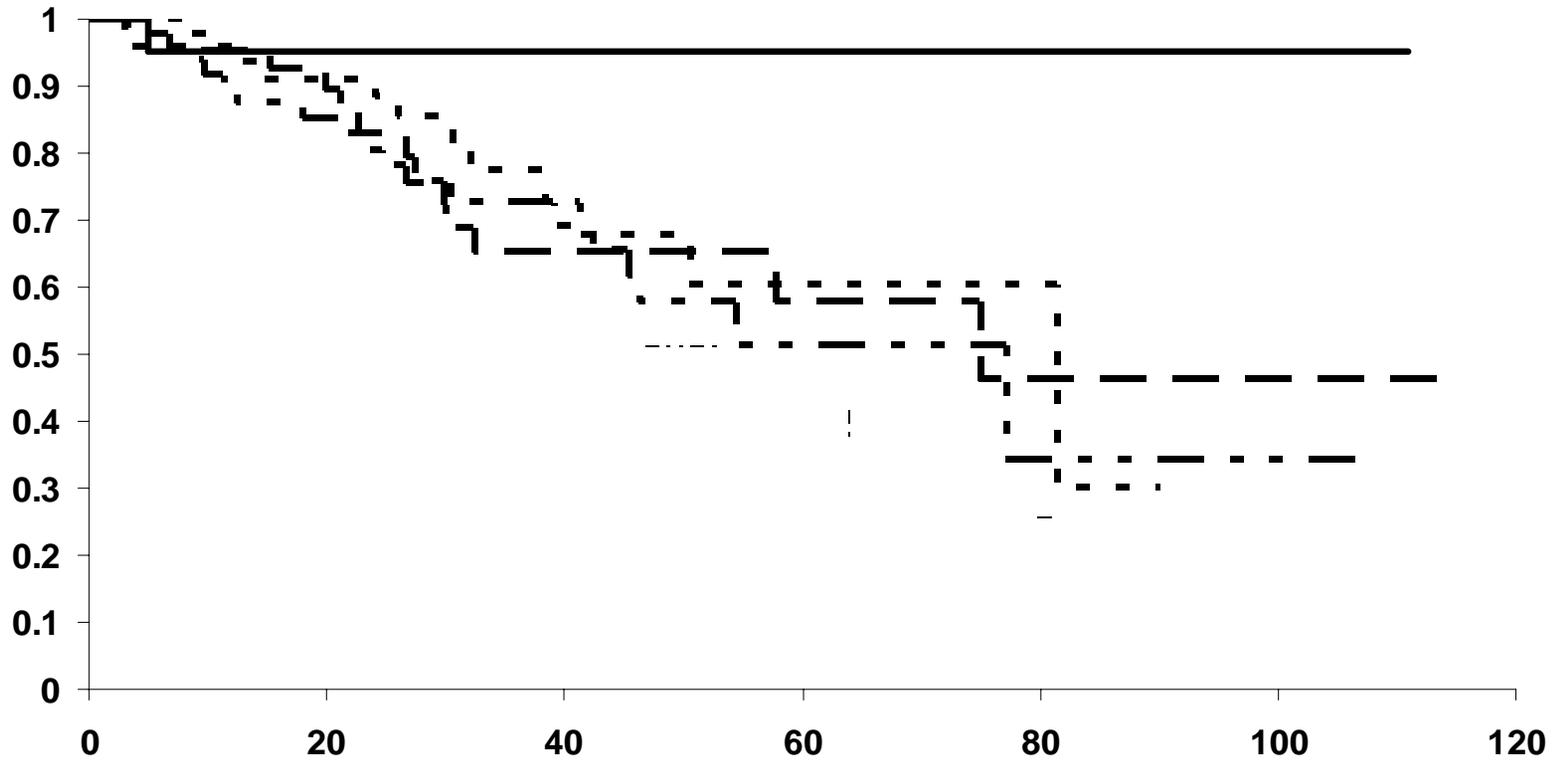


Response to Neoadjuvant Therapy

- Many rectal cancers respond to neoadjuvant therapy
 - 10-30% pathologic complete response
 - 30-55% pathologic partial response
- Pathologic response is a prognosticator of favorable outcome
 - 78-100% disease-free survival in responders
 - 40-75% disease-free survival in non-responders

Stage II-III rectal cancer patients treated with neoadjuvant therapy and TME

Survival by yPT stage



— pstage = 0 - - - pstage = 1 - - - pstage = 2 - . - pstage = 3

The question of the day...

Should we change our treatment plan in patients with tumors that respond to neoadjuvant therapy?

1. Reduce the scope of the surgery?
2. No surgery at all?

Opportunity.....

- 36,400 new cases of rectal cancer a year in USA
- 50% are stage II or III tumors receiving neoadjuvant therapy
- Rate of response ranges from 9% to 56%
- Assuming a 25% rate of pCR, almost 5,000 patients could be spared a radical resection every year

Anecdotal Evidence

- Kodner et al., St Louis, MO
 - » Surgery, 1993
- Wang et al., Prince Margaret Hospital, Toronto, Canada
 - » Radiother Oncol, 2005
- Habra-Gamma et al., Sao Paulo, Brazil
 - » Ann Surg 2004

Kodner et al., St Louis, MO, Surgery, 1993

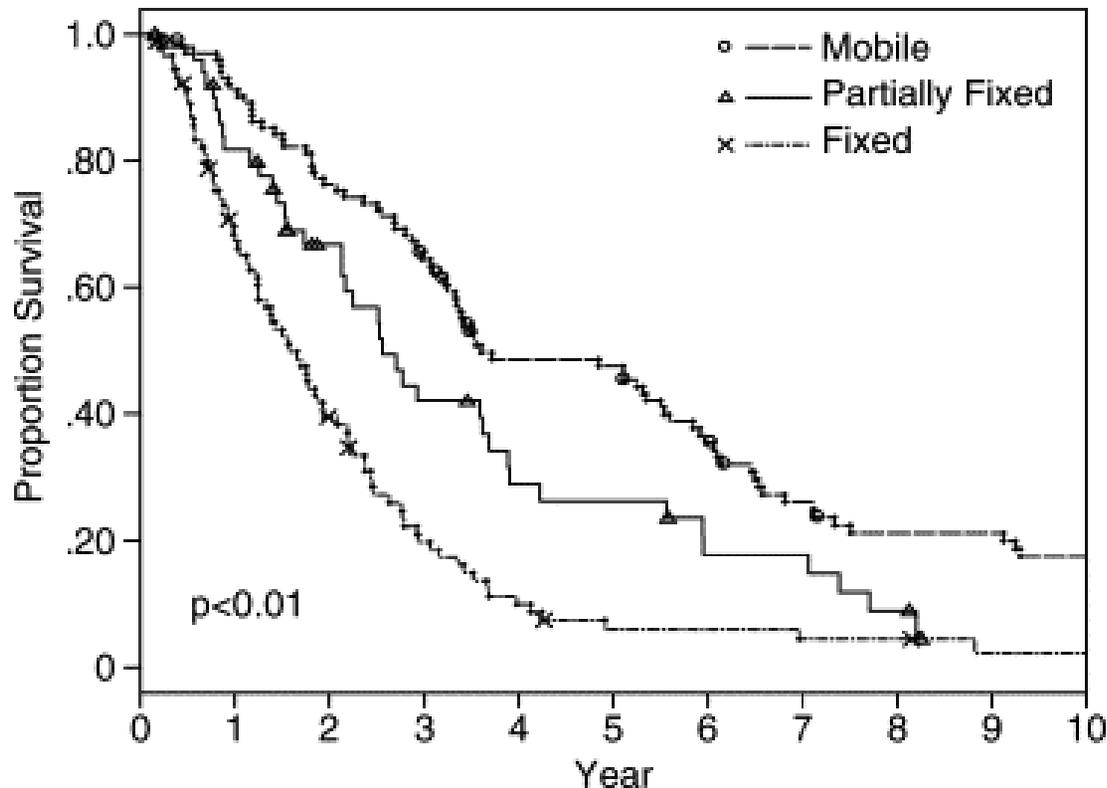
84 patients with rectal cancer treated with external beam and intracavitary radiation

	local control	survival
Ideal Cancer	93%	75%
Curable Tumors	100%	87%
Aggressive Cancers	14%	
50%*		

(*) survivors had salvage APR

Wang et al, Radiother Oncol 2005

- 271 patients treated with radiation as the primary form of treatment
- 80 (30%) had a complete clinical response
 - **78% of them latter recurred**
- 253 failed radiation (no response or relapse after response) – 78 salvage surgery



Habr-Gama et al., Ann Surg 2004

- 265 patients with resectable rectal cancer received neoadjuvant therapy
- 71 patients had complete clinical response – Observation Group
- 194 patients incomplete clinical response
 - 22 pathologic complete response – Resection Group

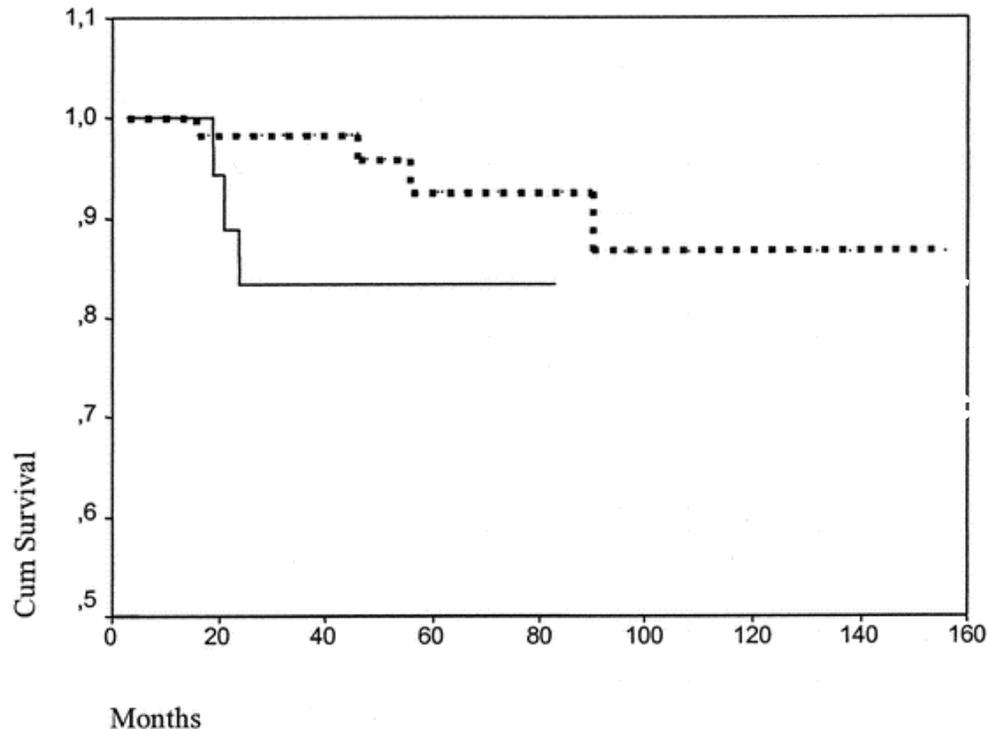
TABLE 3. Pretreatment Clinical Characteristics

	(OB) Observation Group	(R) Resection Group	<i>P</i>
Gender (M:F)	1.05	1.2	ns
Mean age	58.1 (35–92)	53.6 (25–73)	ns
Pre-CRT tumor size (mean)	3.6 cm (1–7)	4.2cm (2.5–7)	ns
Distance from AV (cm)	3.6 (0–7)	3.8 (2–7)	ns
T2	14 (19.7%)	1 (4.5%)	ns
T3	49 (69%)	19 (86.5%)	ns
T4	8 (11.3%)	2 (9%)	ns
N+	16 (22.5%)	6 (27.2%)	ns
Total	71	22	

AV, anal verge; F, female; M, male; ns, not significant.

Habr-Gama et al., Ann Surg 2004

- **Observation group**
 - two patients developed local recurrence
 - three patients developed distant recurrence
- **Resection group**
 - no local recurrence
 - three distant recurrence



Nakagawa et al, Ann Surg Oncol 2002

**52 rectal cancer patients treated with neoadjuvant therapy
10 patients had complete clinical response - Observed
8 developed recurrence between 4 and 9 months**

TABLE 1. Clinical characteristics, treatment, and follow-up of the 10 patients with CR after CRT

Patient No.	Age (y)	Rectal lumen involvement (%)	Tumor mobility	CT (cycles)	RT (cGy)	Local recurrence after CRT	Surgery	Status
1	46	50	Tethered	2	4500	Yes	No (metastatic disease)	Local/distant disease
2	45	50	Tethered	2	5040	No	No (complete response)	Without disease
3	69	25	Mobile	2	5040	Yes	APR	Dead with metastases
4	23	25	Tethered	2	5040	Yes	No (refuse)	With local and distant disease
5	55	50	Tethered	2	5040	Yes	APR	Dead with metastases
6	30	50	Tethered	2	5040	No	No (complete response)	Without disease
7	61	50	Tethered	1	5040	Yes	Anterior resection	Without disease
8	70	50	Tethered	2	5040	Yes	APR	Without disease
9	44	25	Tethered	2	5040	Yes	APR	Without disease
10	63	25	Tethered	2	5040	Yes	APR	Without disease

CR, complete response; CRT, chemoradiation; CT, chemotherapy; RT, radiotherapy; APR, abdominoperineal resection.

Hindrances to Watchful Waiting

- Time to assess response chosen arbitrarily
- No standard criteria to define clinical response
- Clinical response does not correlate with pathologic response
- Imaging studies not accurate at predicting pathologic complete response
- Pathologic complete response in the bowel wall does not predict tumor sterilization of the regional lymph nodes

Accuracy of Diagnostic Tests Predicting pCR

Endorectal Ultrasoun: 48-72%

Gavioli Dis Colon Rectum 2000

Vanagunas Am J Gastr 2004

TAC: < 50%

Guillen J. Dis Colon Rectum 2000

MRI: < 60%

Suppiah Colorectal Dis. 2008

Kulkarni Colorectal Dis. 2008

G Jon JG Chir. 2007

PET Scan: 60%

Guillen J. Dis Colon Rectum 2000

Recommendations

- Tumor response to neoadjuvant therapy is an important marker of favorable biological tumor behavior
- Tumor response could be exploited to avoid over-treatment of some rectal cancer patients
- Uncertainties about predictors, timing of assessment, and diagnosis of response
- Deviation to standard protocol only considered in the context of well designed clinical trials (Royal Marsden Hospital and Pelican Cancer Foundation, UK, and ACOSOG, USA)