Normalization of Carcinoembryonic Antigen levels post-neoadjuvant therapy is a strong predictor of pathologic complete response in rectal carcinoma

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Disclosures

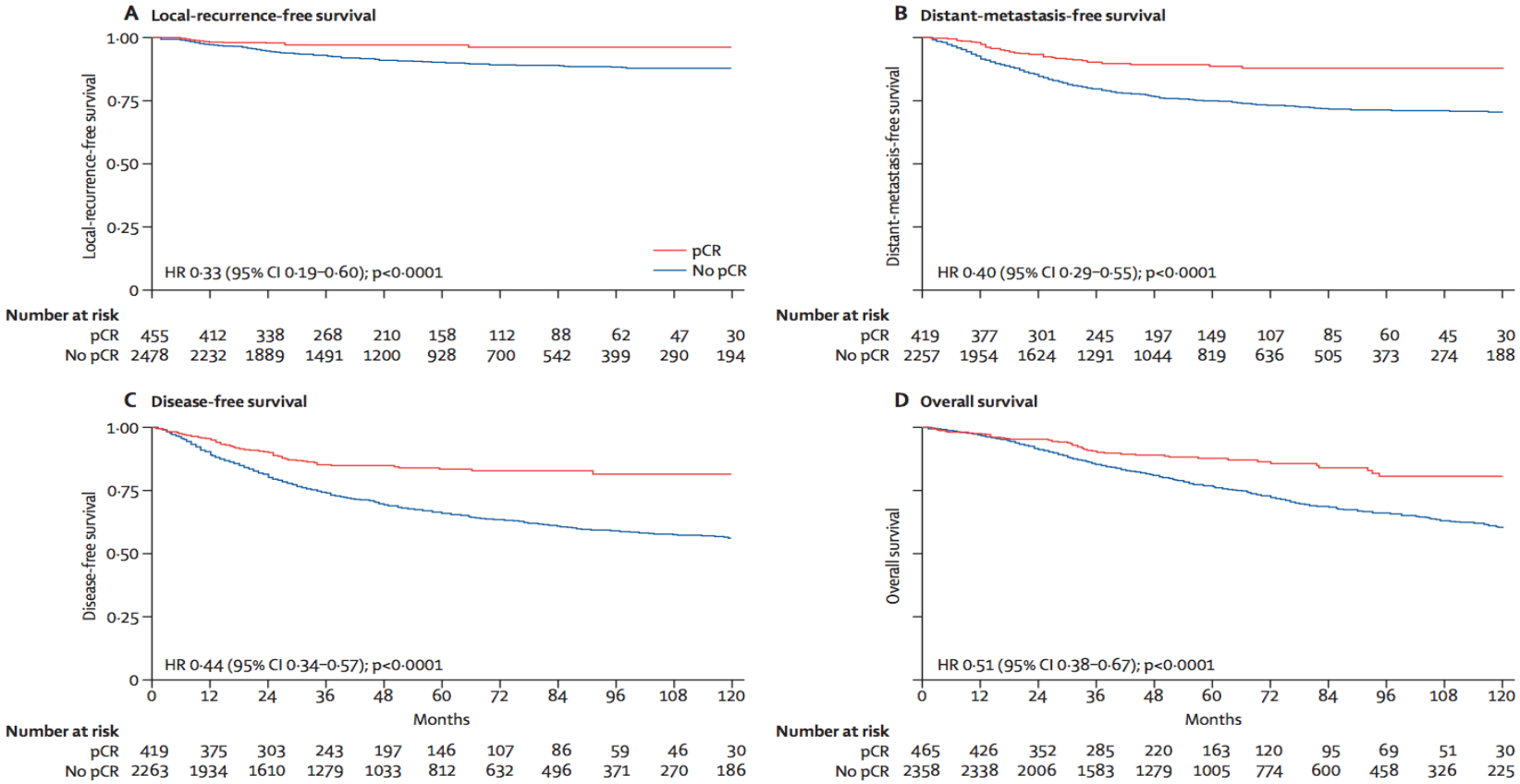
- No relevant disclosures

Background

- Neoadjuvant chemoradiation therapy (nCRT) for rectal cancer results in pathologic complete response (pCR) in 10-30% of patients[1]
- pCR is associated with decreased local recurrence and improved survival[2]

1. Wallin et al. *Dis Colon Rectum 2013*
2. Yeo et al. *Ann Surg. 2010*

Survival curves for patients with and without pathological complete response[1]



1. Meas M et al. Lancet Oncol 2010

Background

- Predictors of pCR remain incompletely defined
- Accurate means of assessing pCR may impact treatment decisions

Clinical assessment after nCRT

- EUS: US T and N stage matched with pathology 54% and 75% respectively[1]
- PET scan correlation with pathology in complete responders around 71%[2]
- MRI 67% sensitivity (95% CI, 24-94%) and 95% specificity compared to MRI (95% CI, 71-99%) [3]

1. Pastor C et al. *Dis Colon Rectum. 2011*
2. *Mak D et al. Radiother Oncol. 2010*
3. *Koh DM et al. Int J Radiat Oncol Biol Phys. 2008*

Predictive factors of pCR	Author (year)
Low pretreatment CEA levels	Wallin et al 2013 Huh et al. 2013 Restivo et al. 2013 Lin et al. 2009
Normalization of CEA post nCRT	Yang et al. 2013
Early T stage	Huh et al. 2013
Early N stage	Huh et al. 2013
Well differentiated tumors	Huh et al. 2013
Distance from anal verge >5cm	Das et al. 2007 Restivo et al. 2013
Interval length between nCRT and surgery (>8wks)	Kaladay et al. 2009

Negative predictors of pCR	Author (year)
Interruption in nCRT	Wallin et al. 2013
Macroscopic ulceration	Huh et al. 2013
Circumferential tumor	Huh et al. 2013 Das et al. 2007 Steinhagen et al. 2013 Jayanand et al. 2011
Low lying tumor (<5cm from anal verge)	Restivo et al. 2013
High pretreatment CEA	Restivo et al. 2013
Adverse pathologic features	Steinhagen et al. 2013
Signet ring cell histology	Jayanand et al. 2011

Study Objectives

- Examine the association between CEA levels and pCR

Methods

- 2007 – 2013
- Retrospective chart review of a prospectively maintained database
- Inclusion criteria: Patients who completed a course of nCRT prior to primary resection of rectal cancer
- Exclusion criteria: IBD, recurrent disease, familial colon cancer syndromes, previous transanal excision, information regarding pre or post treatment T stage missing

Methods

- **Primary endpoint**
  - Pathologic Complete Response (T0N0 in operative specimen)
- **Definitions for CEA levels**
  - Pretreatment: at initial visit
  - Post-treatment: after nCRT, prior to surgery

Methods

- **Statistical Analysis**
  - Univariate analyses were conducted using Fisher exact, Student's *t* and Wilcoxon rank sum tests for categorical, continuous normally distributed and non-normally distributed data, respectively.
  - Multivariate logistic regression was performed

Results

- 141 patients underwent primary resection for rectal cancer post nCRT

- pCR: 13.5% (N=19)

Demographic & Clinical Characteristics

Variable	pCR N = 19 Mean [SD] or %	No pCR N = 122 Mean [SD] or %	*p* value
Age	63.5[12.3]	63.4[11.1]	0.99
Male	73.7%	57.9%	0.22
Smoker	11.1%	23.5%	0.36
Statin use	42.1%	25.4%	0.17
Diabetes on Metformin	26.3%	10.7%	0.07

Demographic & Clinical Characteristics

Variable	pCR N = 19 Mean [SD] or %	No pCR N = 122 Mean [SD] or %	*p* value
ASA			0.79
1	5.3%	13.3%	
2	57.9%	47.8%	
3	36.8%	36.3%	
4	0	1.8%	
ECOG			0.51
0	87.5%	74.3%	
1	12.5%	24.3%	
2	0	1.4%	

Tumor Characteristics

Variable	pCR N = 19 Mean [SD] or %	No pCR N = 122 Mean [SD] or %	*p* value
Pre-op T			0.73
1	0	0.83(1)	
2	10.5%	6.7(8)	
3	84.2%	80.0%	
4	5.3%	12.5%	
Pre-op N			0.14
0	31.6%	39.3%	
1	63.2%	41%	
2	5.3%	19.7%	

Tumor Characteristics

Variable	pCR N = 19 Mean [SD] or %	No pCR N = 122 Mean [SD] or %	*p* value
Poor differentiation	7.7%	24.8%	0.30
Circumferential tumor	25%	31.4%	0.75
Distance from anal verge (cm)	6[2.9]	6.3[3.2]	0.70
Anal canal involvement	12.5(2)	22.5(22)	0.52
Tethered/fixed	16.7(1)	29.4(10)	0.99

Treatment Characteristics

Variable	pCR N = 19 Median [IQR] or %	No pCR N = 122 Median [IQR] or %	*p* value
Restorative proctectomy	63.2%	71.1%	0.59
External beam	52.9%	56.5%	0.79
Delay between nCRT and surgery (weeks)	8[5.5-10.1]	8[6.5-11]	0.41

CEA levels

Variable	pCR N = 19 Median [IQR] or %(n)	No pCR N = 122 Median [IQR] or %(n)	*p* value
Pre-nCRT CEA (ug/L)	2.75[1.98,6.75]	4.5[2.38,8.05]	0.65
Post-nCRT CEA (ug/L)	1.7 [0.875, 2.55]	2.4 [1.3, 4.4]	0.003

CEA levels

Variable	pCR N = 19 Median [IQR] or %	No pCR N = 122 Median [IQR] or %	*p* value
Pre-nCRT CEA (ug/L)	2.75[1.98,6.75]	4.5[2.38,8.05]	0.65
Post-nCRT CEA (ug/L)	1.7 [0.875, 2.55]	2.4 [1.3, 4.4]	0.003
Normal pre-nCRT CEA	55.6%	35.6%	0.11
Normal post-nCRT CEA	90.0% * 83.3%	59.4% 50.9%	0.083 0.11

* Excluding patients with normal pre-nCRT CEA

Multivariate model for pCR

Variable	OR	Confidence interval
Age	1.04	[0.96, 1.11]
Diabetes on MTF	1.23	[0.197, 11.32]
Pre-nCRT N stage	0.43	[0.056, 2.11]
Post-nCRT CEA level	**1.74**	**[1.06, 3.81]**

Multivariate model for pCR

Variable	OR	Confidence interval
Age	1.03	[0.96, 1.11]
Diabetes on MTF	1.27	[0.131, 9.15]
Pre-nCRT N stage	0.43	[0.056, 2.11]
Post-nCRT CEA level	**1.74**	**[1.06, 3.81]**

1 unit decrease in CEA results in a 74% increased likelihood of achieving pCR

Multivariate model for PCR

Excluding patients with normal pre-treatment CEA (N=84)

Variable	OR	Confidence Interval
Age	1.65	[1.16, 3.18]
Diabetes on MTF	9.36	[0.44,617.4]
Pre-nCRT N stage	0.17	[0.0035,3.21]
Normalization of post-nCRT CEA	**64.8**	**[2.53,18371]**

Conclusions

- Low post-neoadjuvant treatment CEA is an independent predictor of pCR
- Normalization of CEA post neoadjuvant CRT is a strong predictor of pCR
- CEA may be used in conjunction with other predictors of pCR to guide treatment strategies

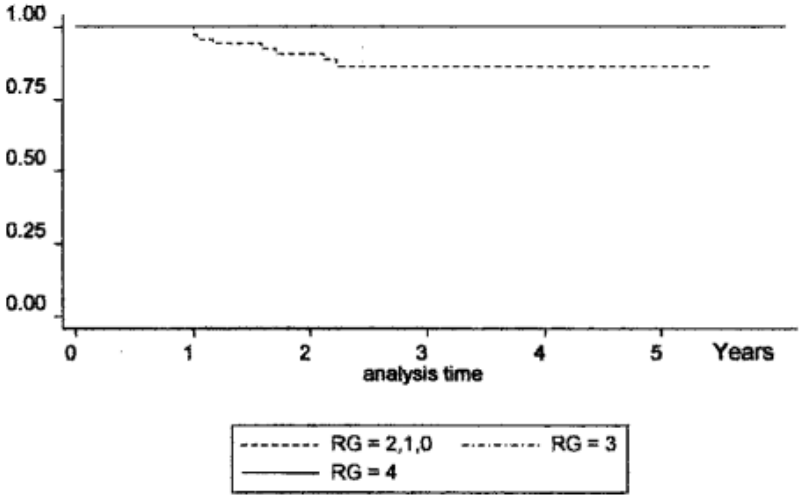
Thank you!

Multivariate model for pCR (smoking)

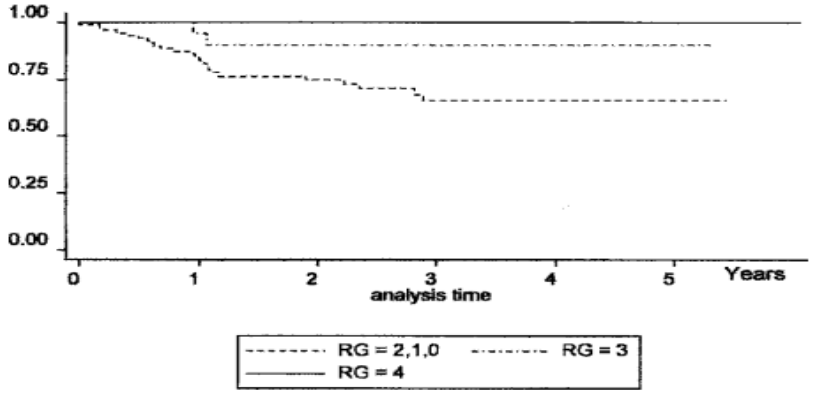
Variable	OR	Confidence interval
Smoking	0.57	[0.27, 4.77]
Diabetes on MTF	2.65	[0.32,59.29]
Pre-nCRT N stage	4.60	[0.62,96.71]
Post-nCRT CEA	**1.84**	**[1.06, 4.99]**

1 unit decrease in CEA results in a 84% increased likelihood of achieving pCR

Outcome of Surgery following PCR



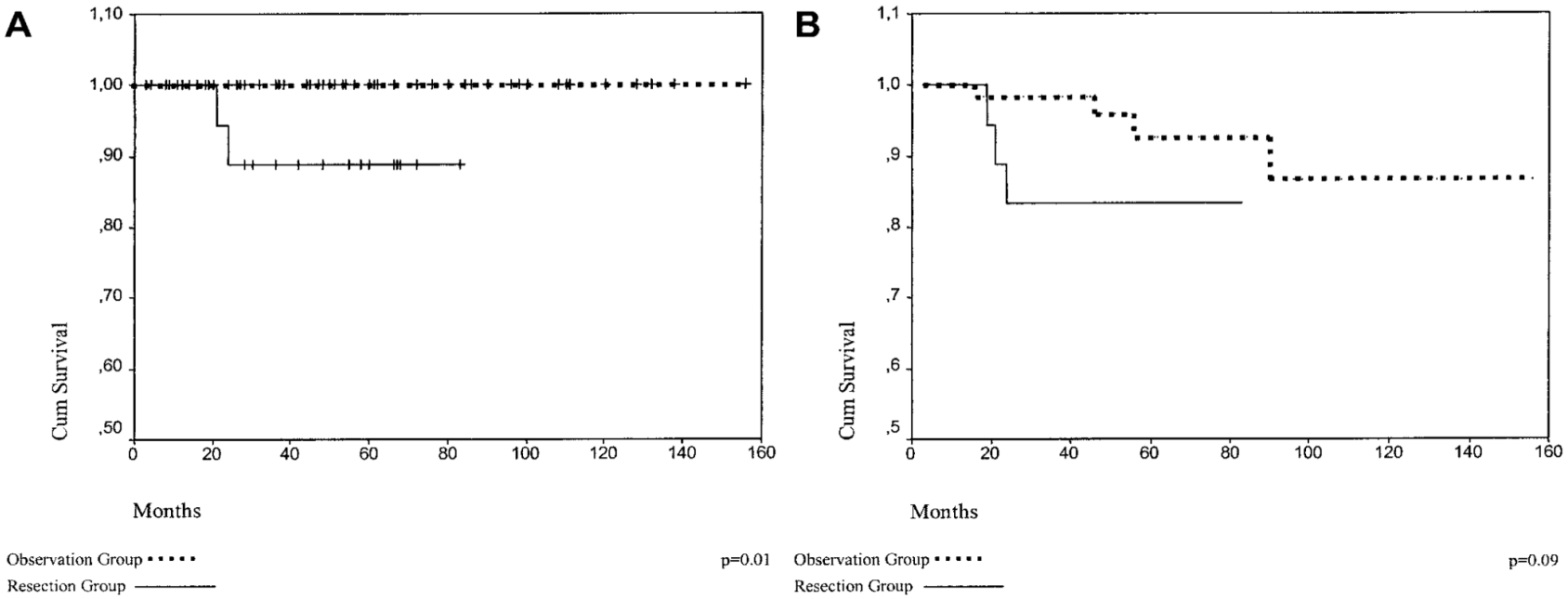
- Kaplan-Meier survival estimates by regression grade (RG): local recurrence-free survival ($p<0.02$)



- Kaplan-Meier survival estimates by regression grade (RG): distant recurrence-free survival ($p<0.004$)

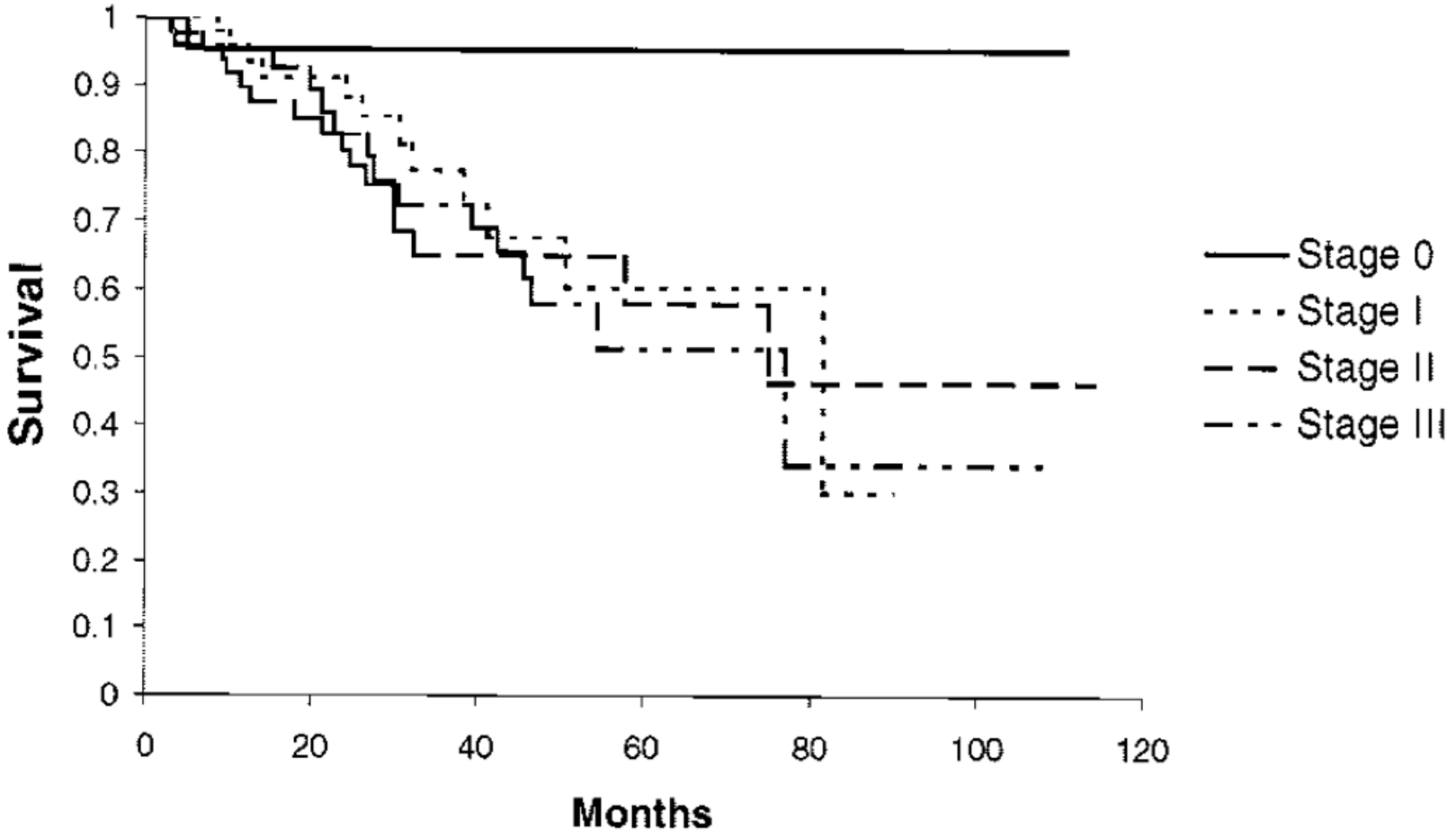
1. *Gavioli M. et al. Dis Colon Rectum. 2005*

Outcome following PCR in observation group



1. *Habr-Gama A et al. Annals of Surgery 2004*

Overall survival by pathologic stage of rectal cancer patients treated by preoperative chemoradiation therapy and radical surgery



(1) Garcia-Aguilar et al Dis Colon Rectum 2003

Treatment for Patients with Rectal Cancer and a Clinical Complete Response to Neoadjuvant Therapy: A Decision Analysis

- In the base-case analysis, the quality-adjusted life expectancy with surgery exceeded observation (5.63 vs. 5.34 quality-adjusted life-years). Sensitivity analysis demonstrated that observation was preferred to surgery if the ability to correctly identify patients with true complete responses exceeded 58 percent, if quality-of-life after surgery was poor (utility G0.81), or if the relative reduction in recurrence risk with surgery was G43 percent when compared with observation.
- CONCLUSIONS: Our model outlines the issues associated with surgery vs. observation, and suggests that surgery is beneficial for the average patient with rectal cancer with a clinical complete response after neoadjuvant therapy.
- Although perioperative mortality for patients with rectal cancer has decreased and rates of sphincter preservation have increased in recent years, surgery still results in stomas and/or alterations in bowel, bladder, and sexual function and may impair quality of life (QOL). The question has been raised: Is it necessary for patients with a clinical complete response (cCR) to preoperative CRT to undergo surgery?
- The largest study describes outcomes for patients with no evidence of disease 12 months after CRT, reporting a 5-year disease-free survival rate of 92 percent (mean follow-up, 57.3 months).19 Although these results are provocative- and appear to raise the possibility that more patients might be spared the morbidity of surgery with good oncologic outcome-they have not been duplicated elsewhere.

- Critics of observation alone cite the limitations of clinical assessment of response, as well as poor correlation be-tween clinical assessment and final pathology. Furthermore, residual mesorectal disease is observed in as many as 20 percent of patients with pT0 tumors after neoadjuvant therapy. Finally, the feasibility of surgical salvage in patients whose cancer locally re- curs after observation is uncertain.