Predicting Response to Neoadjuvant Chemoradiation in Rectal Cancer: Is It Still Out of Reach?

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Background

- The standard treatment of locally advanced RC is nCXRT followed by TME
- LR and toxicity were ↓ after nCXRT Vs. postop CXRT

Sauer et al, N. Engl. J. Med. 2004

- OS wasn't significantly different

Sauer et al, J. Am. Soc. Clin. Oncol. 2012

Rational of Neoadjuvant CXRT

- Treat local micrometastatic disease
- Downstage tumor, increase probability of curative resection
- Decrease tumor cell dissemination during resection
- Patients more likely to complete prescribed treatment in preoperative period

Oncological effect

- When local recurrence was 15- 30%, old meta-analyses have shown nCXRT reduces LR by almost 50 %
- Dutch TME trial in rectal cancer reported a 10-year local recurrence cumulative incidence of 5 % in the group assigned to short course RT versus 11 % in the surgery alone

  van Gijn W,et al (2011) Dutch Colorectal Cancer Group. Lancet Oncol
- Didn't take into account the quality of the mesorectal excision
- None of the trials of RT alone (Peeters et al. 2007; Sebag-Montefiore et al. 2009) or nCXRT in the last decade had impacted on DFS or OS (Sauer et al. 2004; Bosset et al. 2006, Gerard et al. 2006; Roh et al. 2009)

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

*Phil Quirke, Robert Steele, John Monson, Robert Grieve, Subhash Khanna, Jean Couture, Chris O'Callaghan, Arthur Sun Myint, Eric Bessell, Lindsay C Thompson, Mahesh Parmar, Richard J Stephens, David Sebag-Montefiore, on behalf of the MRC CR07/NCIC-CTG CO16 trial investigators and the NCRI colorectal cancer study group**

- With short course RT or post op CRT
- Node positive patients with defects in the mesorectum are likely to be at high risk of local recurrence
- Complete mesorectal excision ……7-8% local recurrence

(Quirke et al. 2009)

Late Effects of Radiotherapy

- Pelvic radiotherapy
  - 5–10 % of experiencing grade 3 or 4 late morbidity
- Effects on sexual functioning (Marijnen et al. 2005)

Marijnen CA, et al. J Clin Oncol 2005

- Urinary incontinence (45 vs 27%)

Pollack J,et al. Dis Colon Rectum 2006

- FI have been documented (61 vs 39% without RT)

Lange MM, et al. Br J Surg 2007

Late Effects of Radiotherapy

- Swedish Rectal Cancer Trial
  - Bowel obstruction
  - Chronic abdominal pain

Birgisson H, et al (2006).J Clin Oncol

- There are also unexplained late cardiac effects (35 vs. 19%)

Pollack J, et al. Dis Colon Rectum 2006

- Insufficiency fractures in the pelvis

Herman MP, et al (2009) Int J Radiat Oncol Biol Phys

- Dutch TME trial
  - Second malignancy in the RT arm Vs. TME arm alone (13.7 % versus 9.4 %)

van Gijn et al. 2011. Lancet Oncol

- Findings were seen after only 11.6 years of follow up

Can Radiotherapy be Omitted?

- Several groups have explored omitting radiotherapy when MRI suggests the tumour is easily resectable
- This omission does not appear to increase the local recurrence rate

(Taylor et al. 2011, Frasson et al. 2011, Mathis et al. 2012)

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original research

Routine preoperative restaging CTs after neoadjuvant chemoradiation for locally advanced rectal cancer are low yield: A retrospective case study

Jennifer S. Davids, Karim Alavi, J. Andres Cervera-Servin, Christine S. Choi, Paul R. Sturrock, W. Brian Sweeney, Justin A. Maykel*

University of Massachusetts Medical School, Division of Colon and Rectal Surgery, Department of Surgery, Worcester, MA 01602, USA

- 96 patients,
- 91 patients (95%) completed neoadjuvant chemoradiation
- 83/91 patients (91%) had restaging CTs
- Four patients (5%) had new lesions suspicious for distant metastasis (2 lung, 2 liver)

Original Article

Restaging after neoadjuvant chemoradiation in rectal cancers: is histology the key in patient selection?

Nitin Singhal[1], Karthik Vallam[1], Reena Engineer[2], Vikas Ostwal[3], Supreeta Arya[4], Avanish Saklani[5]

- PD tumors had a significantly higher:
  - Local progression (32.1% *vs.* 5.6% %, P=0.0011)
  - Systemic progression (35.7% *vs.* 6.9%, P=0.0008) as compared to WMD tumors

International Journal of Surgery 23 (2015) 120–127

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original research

Is it safe to omit neoadjuvant chemo-radiation in mucinous rectal carcinoma?

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- 102 patients with mucinous AC
- nCXRT in 61 patients
- 48% partial response
- 42% no response
- 10% tumor progression

Is Neoadjuvant Chemotherapy an Alternative?

Chemotherapy alone

Table 1 Studies of neoadjuvant chemotherapy alone in rectal cancer

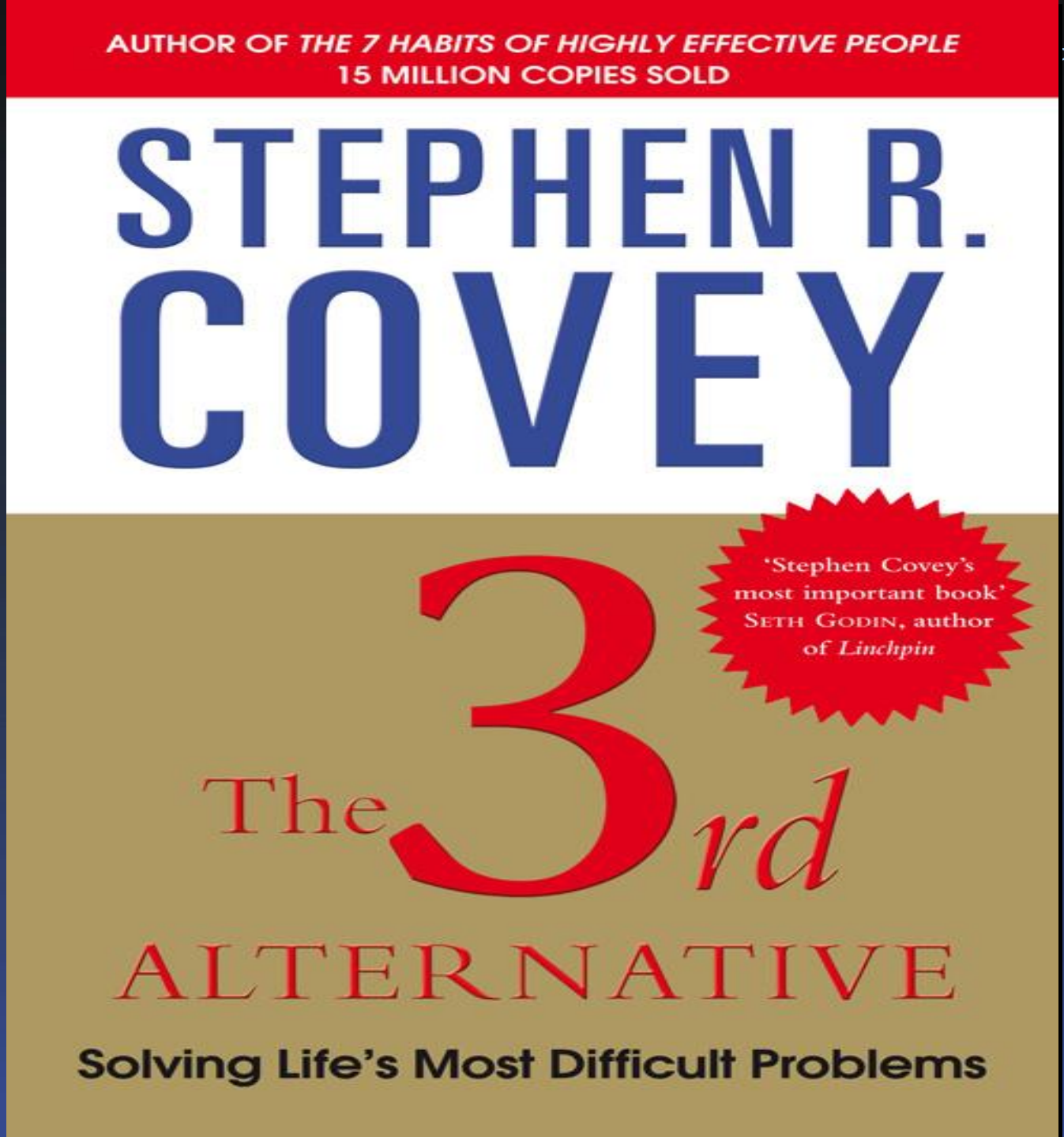
Study	Key inclusion criteria	#pts	Treatment	pCR rate	Outcomes
Ishii, *et al.* (35)	T3 or T4	26	Irinotecan, 5-FU, Leucovorin ×8 weeks	3.8%	5-year DFS—74% 5-year OS—84%
Uehara, *et al.* (36)	MRI-defined poor risk: T4, N2, CRM ≤1 mm, extramural invasion >5 mm	32	CAPOX, bevacizumab ×12 weeks	13%	R0 resection 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.

Journal of Gastrointestinal Oncology, Vol 5, No 5 October 2014


We must all suffer one of two things:
the pain of discipline
or the pain of regret or disappointment
JIM ROHN
SUNWARRIOR


You always have two choices: your commitment versus your fear.
Sammy Davis, Jr.
BrainyQuote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Is there anyway to predict response to nCXRT?

Potential Predictive Factors of the Response of Rectal Cancer to nCXRT

- Diffusion-Weighted 3 Tesla MR Imaging
- Molecular Biomarkers in Tumor Tissues
  - DNA Mutation and DNA Methylation
  - Gene Expression Profiles
  - Proteins and Metabolites
  - Tumor Immune Microenvironment
  - MicroRNA
- Biomarkers in Blood
  - Protein and Metabolites
  - MicroRNA
  - Circulating Tumor Cells (CTCs)
  - Circulating Cell-Free Nucleic Acids
  - Host Immune Response
  - Single Nucleotide Polymorphisms (SNPs)

MRI- DWI

- The apparent diffusion coefficient (ADC) value of tissue water content acquired by diffusion-weighted MR imaging (DWI) provides information related to tumor cellularity and the integrity of cell membranes

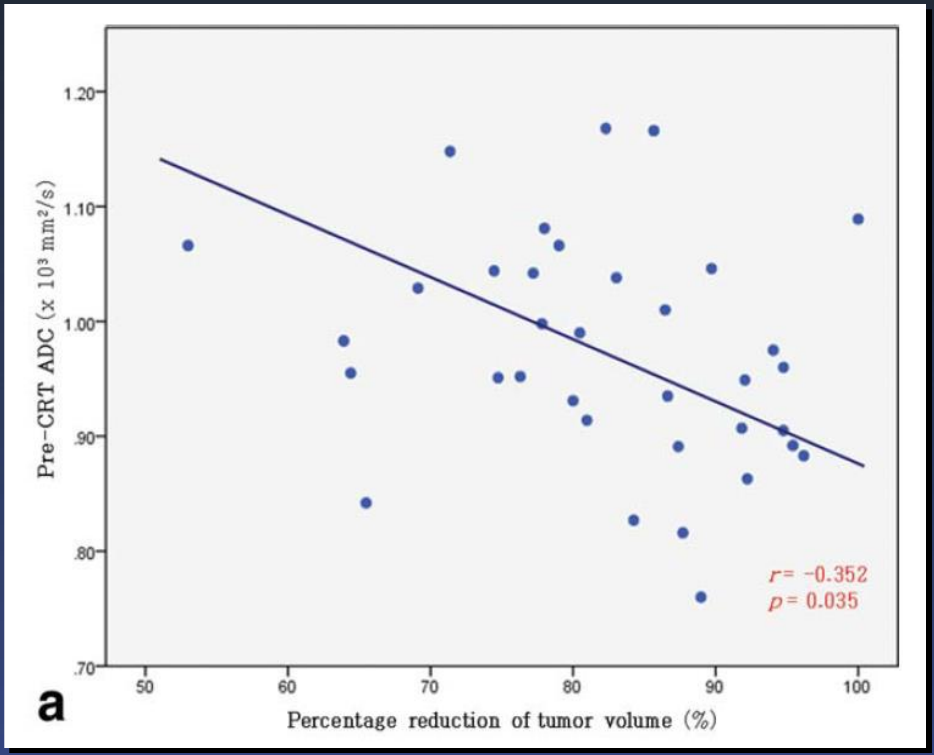
JOURNAL OF MAGNETIC RESONANCE IMAGING 35:110–116 (2012)

XRT

Original Research

Predicting Response to Neoadjuvant Chemoradiation Therapy in Locally Advanced Rectal Cancer: Diffusion-Weighted 3 Tesla MR Imaging

Se Hee Jung, MD,[1] Suk Hee Heo, MD,[2] Jin Woong Kim, MD,[2]
Yong Yeon Jeong, MD,[2*] Sang Soo Shin, MD,[3] Min-Gyu Soung, PhD,[4]
Heong Rok Kim, MD,[5] and Heoung Keun Kang, MD[2]



- There is weak negative correlation between the mean ADC before neoadjuvant CRT and the percentage of tumor volume reduction

MRI- DWI

- Pretreatment ADC in locally advanced rectal cancer can help predict a successful response to nCXRT
- DWI on 3T MR imaging may help to predict and monitor the treatment response to nCXRT in patients with locally advanced RC

Curr Colorectal Cancer Rep (2017) 13:276–283
DOI 10.1007/s11888-017-0376-3

RADIATION THERAPY AND RADIATION THERAPY INNOVATIONS IN COLORECTAL CANCER (JY WO, SECTION EDITOR)

Biomarkers that Predict Response to Neoadjuvant Chemoradiation in Locally Advanced Rectal Cancer

Philmo Oh[1] · Kevin L. Du[1]

- p53 protein mediates cell cycle arrest and cell death
- Inactivation of the p53 leads to survival of cells with damaged DNA
- p53 plays key roles in apoptosis, tumorigenesis and sensitivity to chemotherapeutic agents
- Malignant cells with wild-type p53 are sensitive, whereas mutated p53 malignant cells are resistant to radiotherapy and chemotherapeutic agents

p53

Author	Pts. n.	Method	Treatment	Endpoint	Comment
Chang [32]	130	IHC	50.4 Gy 5-FU + LV	TRG	No correlation
Sturm [31]	66	IHC	45 Gy Heat shock hyperthermia 5-FU + LV	TNM downstaging	No correlation
Lin [39]	70	IHC	45 Gy ± 5-FU	TNM downstaging	Lack of p53 expression associated with poor response
Bertolini [33]	91	IHC	50 Gy 5-FU	TRG TNM downstaging DFS/OS	No correlation
Kudrimoti [38]	17	IHC	50.4–59.4 Gy 5-FU	pCR *vs.* PR	No correlation
Jakob [36]	22	IHC	50.4 Gy 5-FU	TRG	No correlation
Terzi [30]	37	IHC	45 Gy 5-FU	TRG TNM downstaging	No correlation
Negri [34]	57	IHC	40–45 Gy ± 5-FU + Oxa	pCR	No correlation
Moral [35]	39	IHC	42 Gy 5-FU + LV	TNM downstaging	No correlation
Huerta [37]	38	IHC	50.4 G Capecitabine	Tumor size	No correlation

p53

- The majority of studies did not find any association between p53 expression and treatment response
- Lin et al. showed that absence of p53 protein in biopsy specimens obtained before radiation was a good predictor of poor response

Lin et al. Surg. Oncol. 2006

- it seems unlikely that it could be used as a marker of response

EGFR

- EGFR mediates signaling by activating KRAS
- It is involved in many cellular pathways, such as proliferation, apoptosis and differentiation

EGFR

Author	Pts. n.	Method	Treatment	Endpoint	Comment
Giralt [55]	87	IHC	45–50.4 Gy ± 5-FU + LV or UFT + LV	pCR DFS/OS Metastasis-free survival	EGFR expression associated with decreased pCR rate
Kim [54]	183	IHC	50 Gy 5-FU + LV	TRG TNM downstaging	Low EGFR expression associated with TNM downstaging
Spindler [48]	77	PCR/DNA	65 Gy UFT + LV	TRG	EGFR Sp1-216 associated with tumor response
Spindler [49]	60	PCR/DNA	65 Gy UFT + LV	TRG	Combination of TS 2R/2R and EGF 61A/G or EGFR Sp1-216T associated with tumor regression
Bertolini [33]	91	IHC	50 Gy 5-FU	TRG TNM downstaging DFS/OS	No correlation
Toiyama [56]	40	PCR/RNA	20 Gy 5-FU + UFT	TNM Grading	Low EGFR expression associated with high response rate
Bengala [58]	39	IHC, FISH PCR/DNA	50.4 Gy 5-FU + Cetuximab	TRG	High EGFR GCN and wild-type KRAS associated with response to treatment
Debucquoy [57]	41	IHC	50.4 Gy FU + LV	TNM downstaging TRG	No correlation
Bengala [59]	146	ICH, FISH PCR/DNA	50 Gy 5-FU ± Oxa + Capecitabine	TRG DFS/OS	No association of EGFR GCN and KRAS with TRG and OS

EGFR

- Conflicting results!!!
- Level of EGFR expression may be useful in the prediction of pathological response to CRT
- Additional studies are needed to clarify the role of EGFR in response CRT

Thymidylate Synthase

- TS is the primary intracellular target of 5-FU
- TS is involved in DNA synthesis
- In CRC, the overexpression of TS is associated with 5-FU resistance

Kuremsky, J.G et al. Int. J. Radiat. Oncol. Biol. Phys. 2009

TS

- TS expression and TRG:
  - Negri et al. demonstrated that a high TS level is predictive of a higher pathological response
  - Carlomagno et al. showed that rectal tumors with low TS expression associated with not obtaining a pCR
  - Jakob et al found low TS associated with good response
  - Many studies found no correlation between TS protein expression and response to CXRT

TS expression and prediction of response to neoadjuvant radiochemotherapy in locally advanced rectal cancer patients.

Author	Pts. n.	Method	Treatment	Endpoint	Comment
Terrazzino [52]	125	PCR/DNA	45–50.4 Gy5-FU or FU + LV or FU + Oxa or FU + Carboplatin	TRG	No correlation
Bertolini [33]	91	IHC	50 Gy 5-FU	TRG TNM downstaging OS/DFS	No correlation
Spindler [49]	60	PCR/DNA	65 Gy UFT + LV	TRG	TS 2R/2R associated with tumor regression
Jakob [36]	22	PCR/RNA	50.4 Gy 5-FU	TRG	Low TS expression associated with tumor regression
Stoehlmacher [47]	40	PCR/DNA PCR/RNA	50.4 Gy 5-FU	TRG	TS 3'-UTR 6 bp deletion slightly associated with tumor response
Negri [34]	57	IHC	40-45 Gy ± 5-FU + Oxa	pCR	High TS expression associated with higher rate of response
Kikuchi [43]	60	IHC	45 Gy Irinotecan	TRG	Higher TS expression associated with better response
Carlomagno [42]	46	IHC	45 Gy Capecitabine + Oxa	TRG	Low TS expression associated with low response

CEA

Author (Reference)	Year	Number of Samples	Blood Collection	Cut off Values for CEA (ng/mL)	*p*-Value
Das et al. [92]	2007	562	pre-nCRT	≤2.5	$p = 0.015$
Yoon et al. [93]	2007	351	pre-nCRT	≤5	$p = 0.004$
Moreno Garcia et al. [94]	2009	148	pre-nCRT and post-surgery	≤2.5	$p = 0.05$
Kalady et al. [95]	2009	242	Not Reported	≤2.5	$p = 0.19$
Park et al. [96]	2009	352	pre and post-nCRT	≤3	$p < 0.001$
Lee et al. [97]	2009	490	pre-nCRT	≤5	$p = 0.004$
Kang et al. [98]	2010	84	pre and post-nCRT	≤3	$p = 0.01$
Aldulaymi et al. [99]	2010	33	pre-nCRT	≤5	$p = 0.002$
Yan et al. [100]	2011	98	pre-nCRT	≤3	$p = 0.002$
Hur et al. [101]	2011	37	pre-nCRT	≤3	$p = 0.54$
Moureau-Zabotto et al. [102]	2011	168	pre-nCRT	≤5	$p = 0.019$
Wallin et al. [103]	2013	267	pre-nCRT	≤3.4	$p = 0.008$
Restivo et al. [104]	2013	260	pre-nCRT	≤5	$p = 0.001$
Lee et al. [105]	2013	345	pre-nCRT	≤5	$p = 0.002$
Huh et al. [22]	2013	391	pre-nCRT	≤5	$p = 0.002$
Yeo et al. [106]	2013	609	pre-nCRT	≤5	$p < 0.001$
Yang et al. [107]	2013	138	pre-nCRT	≤6	$p = 0.152$
Wang et al. [108]	2014	240	pre-nCRT	≤5	$p = 0.047$
Zeng et al. [21]	2015	323	pre-nCRT	≤5	$p = 0.007$
Kim et al. [90]	2015	419	pre-nCRT	Not Reported	
Kleiman et al. [109]	2015	141	pre and post-nCRT	Not Reported	$p = 0.003$
Song et al. [91]	2016	1782	pre-nCRT	Not Reported	
Probst et al. [89]	2016	18,113	pre-nCRT	Not Reported	$p < 0.001$

International Journal of *Molecular Sciences*

MDPI

Review

Predictive and Prognostic Molecular Biomarkers for Response to Neoadjuvant Chemoradiation in Rectal Cancer

Delphine Dayde, Ichidai Tanaka, Rekha Jain, Mei Chee Tai and Ayumu Taguchi *

Table 1. Tissue-based protein biomarkers for nCRT response in rectal cancer.

Author (Reference)	Year	Number of Samples	Specimens Collection	Biomarker Name	*p*-Value
Croner et al. [71]	2016	20	pre-nCRT	PLEC1, HADHA, TKT and TAGLN	Not Reported
Qin et al. [58]	2015	67	pre-nCRT	XRCC2	$p < 0.001$
Voboril et al. [67]	2016	50	pre-nCRT and post-surgery	NF-κB	Not Significant
Lee et al. [74]	2015	172	pre-nCRT	HSD17B2 and HMGCS2	$p < 0.001$
Chai et al. [73]	2016	172	pre-nCRT	VNN1	$p = 0.001$
Chao et al. [72]	2016	46	pre-nCRT	DSG3	$p = 0.001$
Ho et al. [59]	2016	54	post-surgery	ATM and MRE11	$p = 0.011$
Cebrian et al. [61]	2016	75	pre-nCRT	PLK1	$p = 0.049$
Zhu et al. [64]	2016	148	pre-nCRT	GOLPH3	$p = 0.026$
Yan et al. [60]	2016	105	pre-nCRT	PAF15	Not Reported
Zaanan et al. [70]	2015	96	pre-nCRT	Beclin 1	$p = 0.02$
del Puerto-Nevado et al. [62]	2016	67	pre-nCRT	VRK1 and VRK2	$p = 0.004$
Gomez del Pulgar et al. [65]	2016	73	pre-nCRT	FAK	$p = 0.007$
Ahmed et al. [66]	2016	43	pre-nCRT	FGFR4	$p = 0.03$
Peng et al. [69]	2016	82	pre-nCRT and post-surgery	APAF-1 and COX-2	$p = 0.05$
Li et al. [63]	2016	329	pre-nCRT	c-Myc, PCNA and TIMP1	Not Reported
Yu et al. [68]	2016	116	post-surgery	Survivin	Not Reported

Proteomics? !!!

Any hope!!!

- Modest progress in identification of factors that may predict response to CXRT, whether it was molecular, serologic, immunologic, or radiologic features
- Examination of pre-operative characteristics lacked the sensitivity and specificity to be used in clinical practice
- All studies are limited by small sample sizes, and biologic heterogeneity of rectal tumors
  - range of reported pCR rates despite similar neoadjuvant therapy

Conclusions

- None of the investigated biomarkers, pathologic or radiological features can be useful in clinical practice
- New technologies and approaches, such as microarrays, miRNA analyses and searches for circulating molecules, might provide new potential markers
- It is important that old and new biomarkers will be studied in larger, prospective trials that have the same staging, treatment and response criteria


Unless you try to do something
beyond what you have already
mastered, you will never grow.
Ralph Waldo Emerson
quotefancy


Thank You