UNIVERSITÀ CATTOLICA del Sacro Cuore

World Rectal 5 Conference

on Organ Preserving Perspectives

SESSION 7: DO & DON'TS

TEM AS DIAGNOSTIC AFTER CRT?

Gemelli

Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

PROF. CLAUDIO COCO

U.O. CHIRURGIA GENERALE 2
FONDAZIONE POLICLINICO UNIVERSITARIO "A. GEMELLI"
PRESIDIO COLUMBUS
UNIVERSITÀ CATTOLICA S. CUORE - ROMA

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Complete Response after RCT: What Incidence?

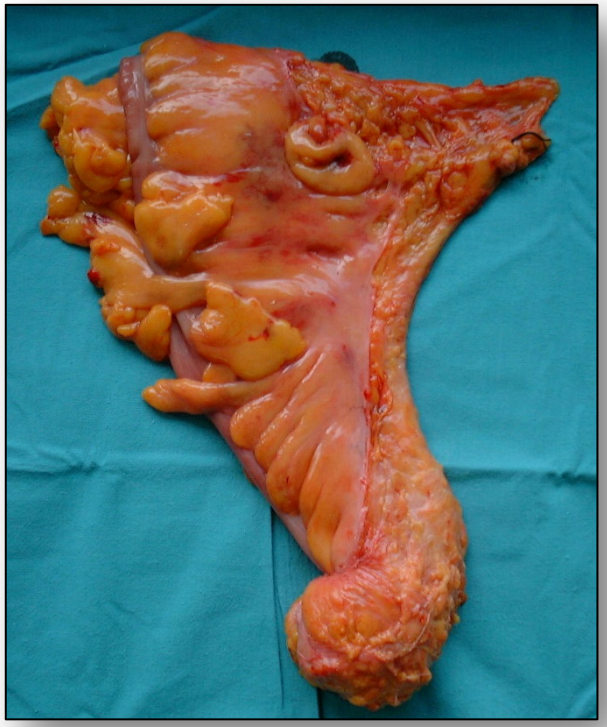
Authors	N. pts	Treatment	% pCR
Hiotis, 2002	488	RT + ChT	**10**
Sauer, 2003	405	RT + ChT	**8**
Bosset, 2004	572	RT + ChT	**13**
Pucciarelli, 2006	235	RT + ChT	**24**
Coco, 2007	272	RT + ChT	**21**
Beddy, 2008	126	RT + ChT	**21**
Belluco, 2011	139	RT + ChT	**30**
Park, 2013	725	RT + ChT	**18**
Vallam, 2015	524	RT + ChT	**21**
Belluco, 2016	226	RT + ChT	**29**
Dinaux, 2017	271	RT + ChT	**19**

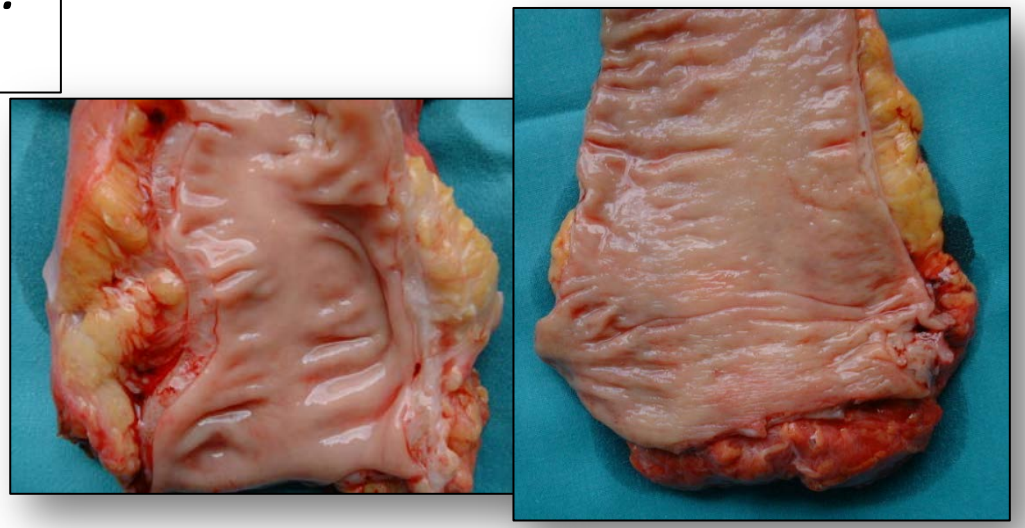
Management of Rectal Cancer after Complete Response to RCT

Br J Surg 1982 Oct; 69(10): 613-6

The mesorectum in rectal cancer surgery - the clue to pelvic recurrence?

Heald RJ, Husband EM, Ryall RD

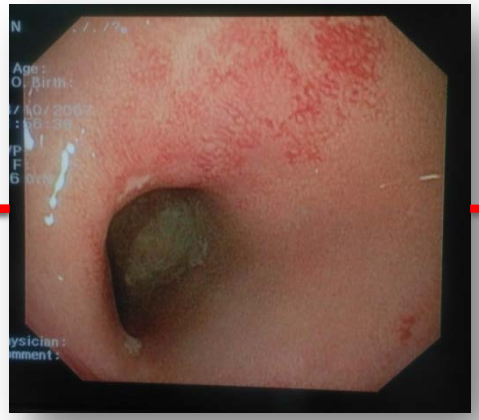




What is the contribution of TME in improving LC, DFS and OS in pCR patients?

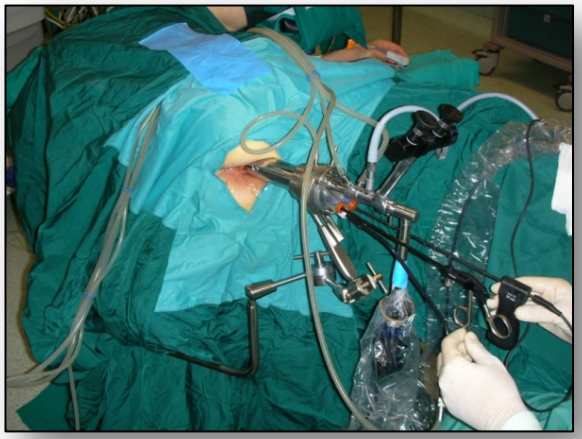
Is it reasonable to imagine to improve the prognosis by removing a healed organ?

Management of Rectal Cancer after Complete Response to RCT

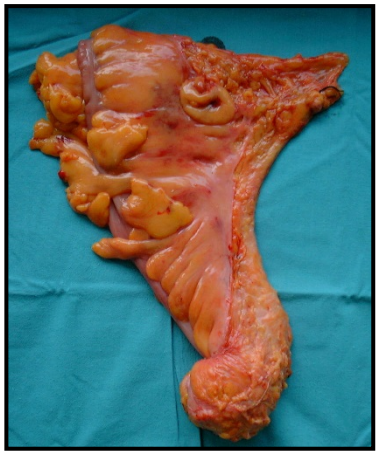


Watch and Wait

Local Excision



TME



Experimental

Standard

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TEM AS DIAGNOSTIC AFTER CRT?

- Why TEM can be an useful diagnostic (and sometimes therapeuthic) tool after CRT?

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CRITICAL ASPECTS
WHAT DEFINITION OF cCR?

HABR-GAMA BRAZILIAN EXPERIENCE

"Patients were considered as having an **initial complete clinical response** (cCR) in the ***absence of residual ulceration, mass, or significant rectal wall irregularity*** as described elsewhere during assessment performed at 10 weeks from RT. Radiological features of a complete response included the presence of ***residual low-signal intensity areas (MRI), absence of restriction to diffusion (diffusion-weighted MRI), or absence of residual FDG uptake within the rectal wall (PET/CT)***. […] Patients were considered as **sustained cCRs** only when assessment **at 12 months from CRT** completion maintained a cCR status".

MAAS NETHERLAND EXPERIENCE

The definition of a **cCR** is: (1) ***substantial downsizing with no residual tumor or residual fibrosis only*** (with low signal on high b-value DWI, if available); (2) ***no suspicious lymph nodes on MRI***; (3) ***no residual tumor at endoscopy or only a small residual erythematous ulcer or scar***; (4) ***negative biopsies*** from the scar, ulcer, or former tumor location; (5) ***no palpable tumor***, when initially palpable with digital rectal examination.

APPELT'S EXPERIENCE

We defined ***clinical complete response on endoscopy as a small, white scar in the rectal wall or a superficial erosion or ulceration without palpable tumour***. If an ulcer or erosion persisted, we took additional biopsies at the edge. We mainly used ***MRI to evaluate the status of regional lymph nodes*** after chemoradiotherapy) and no heterogeneity criteria were used.

RENEHAN'S EXPERIENCE

Clinical complete response: ***absence of residual ulceration, stenosis, or mass within the rectum during digital rectal examination and endoscopic examination 8 weeks or more after chemoradiotherapy completion***. Classification of clinical complete response required normal radiological imaging of the mesorectum and pelvis

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CRITICAL ASPECTS
WHAT DEFINITION OF cCR?

Nonoperative Management or 'Watch and Wait' for Rectal Cancer with Complete Clinical Response After Neoadjuvant Chemoradiotherapy: A Critical Appraisal

Tarik Sammour, MBChB, PhD[1], Brandee A. Price, PhD[1], Kate J. Krause, MLIS[2], and George J. Chang, MD, MS[1,3]

ANALYSIS ON 15 STUDIES - 920 PTS

ASSESSMENT	CRITERIA	N. PAPERS
DRE	**No palpable tumor**	12
	Not defined	3
ENDOSCOPY	**Flat scar without ulceration**	8
	Superficial scar with minimal ulceration	2
	Absence of deep ulceration	1
	Not defined	4
IMAGING	Significant regression with fibrosis and without residual tumor	2
	Regression with no or minimal residual tumor or no extra-disease	5
	Not (well) defined	8
BIOPSY	Negative biopsy	2

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CRITICAL ASPECTS
WHAT ACCURACY OF DIAGNOSTIC TOOLS?

META-ANALYSIS ON 46 STUDIES – 2224 PTS

	SENSITIVITY	SPECIFICITY	PPV	NPV	ACCURACY
MRI					
cCR	95%	31%	83%	47%	75%
cN+	59%	77%	46%	83%	72%
ERUS					
cCR	97%	30%	86%	42%	82%
cN+	53%	80%	55%	79%	72%
CT					
cCR	96%	21%	86%	53%	83%
cN+	60%	66%	34%	85%	65%

DE JONG EA ET AL – SURGERY 2016; 159: 688-699

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Critical Aspects
pCR and iCR ratio?

Rate of Incomplete Response in pCR patients

Autori	N. Pz	pCR	iCR (%)
Hiotis, 2002	488	50	**27/50 (54%)**
Habr Gama 2006	360	123	**24/123(20%)**
Bujko, 2009	44	18	**10/18 (56%)**
Smith, 2014	238	61	**45/61 (74%)**

iCR: incomplete clinical response

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TEM AS DIAGNOSTIC AFTER CRT?

- *Clinical complete response* is no more an absolute requirement for a rectal sparing approach.
- "*Major clinical response*", "*Near clinical complete response*" are terms frequently used in possible candidates to a conservative approach but their exact clinical definition is even more complex
- In many studies "*ypT1 margin free residual tumors*" are generally considered cured by a TEM and conversely would be a failure of a W&W

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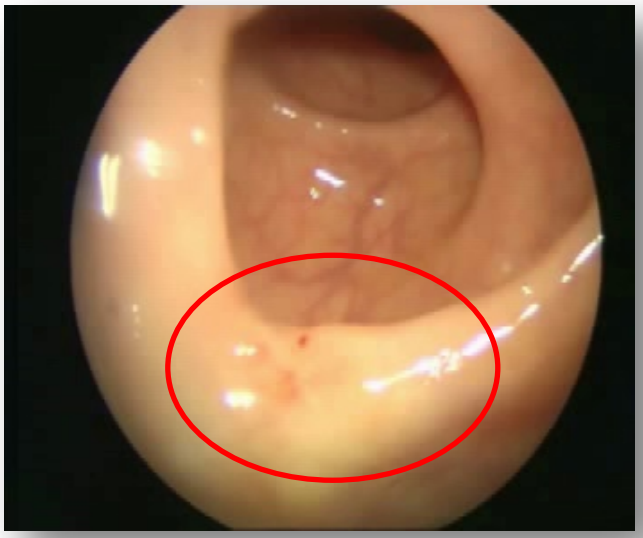
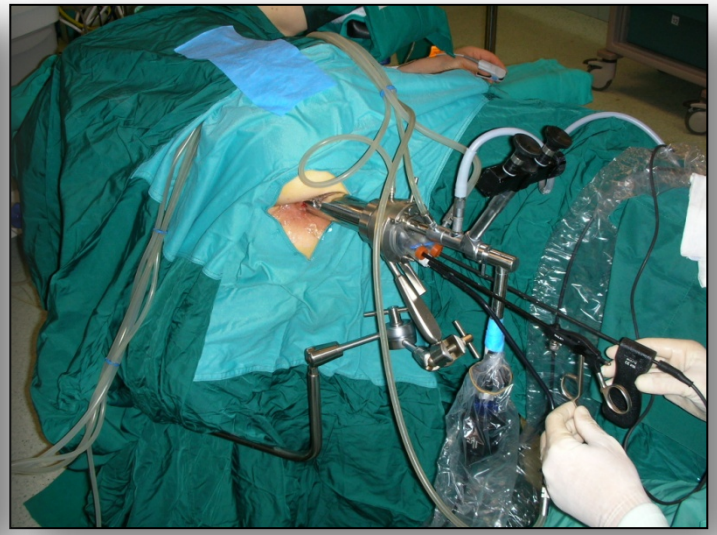
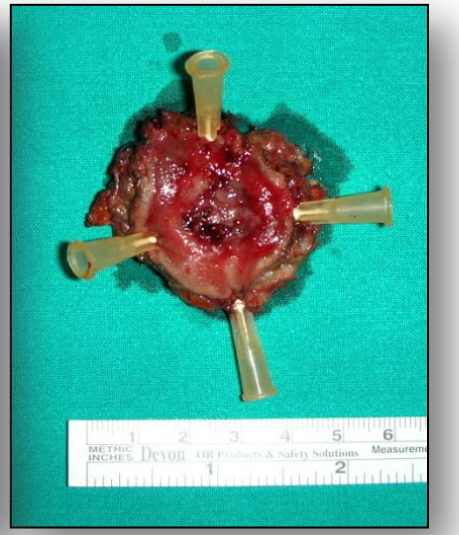
CLINICAL COMPLETE RESPONSE AFTER RCT
ROLE OF LOCAL EXCISION BY TEM

We should consider TEM, as **THE MOST EFFECTIVE DIAGNOSTIC TOOL** to confirm a pathological complete response after neoadjuvant treatment and also **A THERAPEUTIC CHOICE** in ypT1 margin free residual tumor.

The full-thickness excision of the rectal wall disk previously containing the rectal cancer can assess the pathologic response of T with an **ACCURACY OF ~ 99%**.







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TEM AS DIAGNOSTIC TOOL IN cCR AFTER RCT

WHAT INFORMATIONS ABOUT NODES?

AUTHORS	# ypT0	# N+	% N+
CRANE, 2004	84	1	**1.2%**
READ, 2004	42	1	**2.3%**
BEDROSIAN, 2004	45	4	**8.8%**
PUCCIARELLI, 2005	56	1	**1.8%**
COCO, 2007	56	1	**1.8%**
GUILLEM, 2008	37	1	**2.7%**
MAAS, 2010	509	26	**5.1%**
YEO, 2010	333	29	**8.7%**
JANG, 2012	91	6	**6.6%**
PARK, 2013	143	13	**9.1%**
BELLUCO, 2016	40	4	**10%**
TOTAL	**1436**	**87**	**6.06%**

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TEM AS DIAGNOSTIC TOOL IN cCR AFTER RCT

AUTHORS	PTS	ypT>1	TME	RESIDUAL CANCER
LEADER 2013	63	20 (32%)	11 (55%)	**6 (55%)**
POLISH 2013	89	26 (29%)	8 (31%)	**5 (63%)**
CARTS 2015	51	17 (33%)	8 (47%)	**8 (100%)**
GRECCAR II 2017	74	34 (46%)	26 (76%)	**2 (7%)**
OUR EXPERIENCES 2017	36	9 (25%)	6 (67%)	**4 (67%)**

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TEM as diagnostic tool in cCR after RCT

The Rate of Organ-Sparing

Authors	Pts	Organ-Sparing	Stoma-Free Rate
LEADER 2013	63	**85.7%**	**90.5%**
POLISH 2013	89	**91.0%**	**97.7%**
CARTS 2015	51	**82.9%**	**88.2%**
GRECCAR II 2017	74	**65.4%**	**93.8%**
Our Experiences 2017	36	**83.3%**	**100%**

TEM AS DIAGNOSTIC TOOL IN cCR AFTER RCT
COMPLICATIONS

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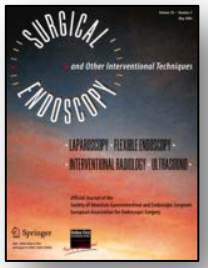


Transanal endoscopic microsurgery after neoadjuvant radiochemotherapy for locally advanced extraperitoneal rectal cancer: short-term morbidity and functional outcome

C. Coco · G. Rizzo · C. Mattana · M. A. Gambacorta · A. Verbo · B. Barbaro · F. M. Vecchio · D. P. Pafundi · M. G. Mastromarino · V. Valentini

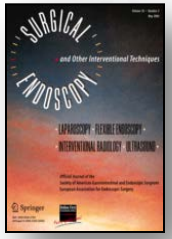
	NAD RCT N (%)	No RCT N (%)	P-VALUE
N. OF PTS.	22	25	-
POST OPERATIVE COMPLICATIONS ALL	8 (36.3)	4 (16%)	0.114
POST OPERATIVE COMPLICATIONS GRADE I *	4 (18.2)	2 (8%)	0.301
POST OPERATIVE COMPLICATIONS GRADE I I*	4 (18.2)	2 (8%)	0.301
POST OPERATIVE COMPLICATIONS GRADE III*	0%	0%	-
SUTURE DEHISCENCE	5 (22.7)	1 (4)	0.068
RE-RICOVERO	0%	0%	-

*: CLAVIEN CLASSIFICATION

COCO C ET AL – SURG END 2013; 27:2860-7

TEM AS DIAGNOSTIC TOOL IN cCR AFTER RCT

FUNCTIONAL OUTCOME



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	TEM POST-RCT (22)	TME POST-RCT (100) (COCO ET AL. INT. J COLORECTAL DIS 2007; 22:903-10)
EVACUATION SCORE (0-28; 28 THE BEST)	**24.1±2.82**	**16.12 ± 5.12**
DAILY EVACUATION>3	3.3%	23%
SENSATION OF INCOMPLETE EVACUATION	10%	58%
NECESSITY TO RETURN TO BATHROOM <15 MIN	0%	37%
INABILITY TO COMPLETELY EVACUATE <15 MIN	0%	35%
URGENCY	10%	31%
CONTINENCE SCORE (0-20; 0 THE BEST)	**1.97±3.02**	**6.30 ± 4.79**
INCONTINENCE TO FLATUS	13.3%	46%
SOILING	3.3%	19%
INCONTINENCE TO SOLID STOOLS	0%	5%
NECESSUTY OF WEARING A PAD	3.3%	14%
MODIFICATION OF LIFESTYLE	3.3%	29%

TEM AS DIAGNOSTIC TOOL IN cCR AFTER RCT

P.O. MORBIDITY

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Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial

Eric Rullier, Philippe Rouanet, Jean-Jacques Tuech, Alain Valverde, Bernard Lelong, Michel Rivoire, Jean-Luc Faucheron, Mehrdad Jafari, Guillaume Portier, Bernard Meunier, Igor Sieznieff, Michel Prudhomme, Frédéric Marchal, Marc Pocard, Denis Pezet, Anne Rullier, Véronique Vendrely, Quentin Denost, Julien Asselineau, Adélaïde Doussau

OUTCOMES FINAL TREATMENT	LE (53 PTS)	TME (61 PTS)	LE + TME (28PTS*)	P-VALUE
MAJOR MORBIDITY (DINDO III-V) AT 2-Y	12%	22%	46%	0.0001
DEFINITIVE STOMA AT 2-Y	4%	9%	25%	0.0178
FAECAL INCONTINENCE AT 2-Y	0%	16%	14%	0.0056
SEXUAL DYSFUNCTION AT 2-Y	13%	17%	41%	0.0113

*** 2/28 pts (7%) had residual tumor or LFN+ in operative specimen**

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LOCAL EXCISION AFTER RCT (MAJOR OR CCR) WHAT ABOUT LYMPH NODE?

Clinicopathological characteristics predict lymph node metastases in ypT0-2 rectal cancer after chemoradiotherapy

Steven L Bosch,[1] Thomas A Vermeer,[2] Nicholas P West,[3] Hendrik A M Swellengrebel,[4] Corrie A M Marijnen,[5] Annemieke Cats,[4] Cornelis Verhoef,[6] Ineke van Lijnschoten,[7] Johannes H W de Wilt,[8] Harm J Rutten[2,9] & Iris D Nagtegaal[1]

675 PTS WITH LOCALLY ADVANCED RECTAL CANCER TREATED BY RCT (45-50 GY PLUS 5-FU OR OXALIPLATIN)

210 PTS WITH **YPT0-2 -> YPN+**: 44 (**21%**)

EVALUATION OF INDIPENDENT FACTORS OF YPN+:

- CLINICAL PRE-TREATMENT YPN+ (**OR: 2.79; P:0.042**)
- HIGH GRADE HISTOPATHOLOGY POST-RCT SPECIMEN (**OR: 6.46; P:0.028**)
- RESIDUAL TUMOUR DIAMETER ≥10 MM (**OR: 2.54; P:0.036**)

BOSCH SL ET AL. – HISTOPATH 2016; EPUB 6 JUNE 2016

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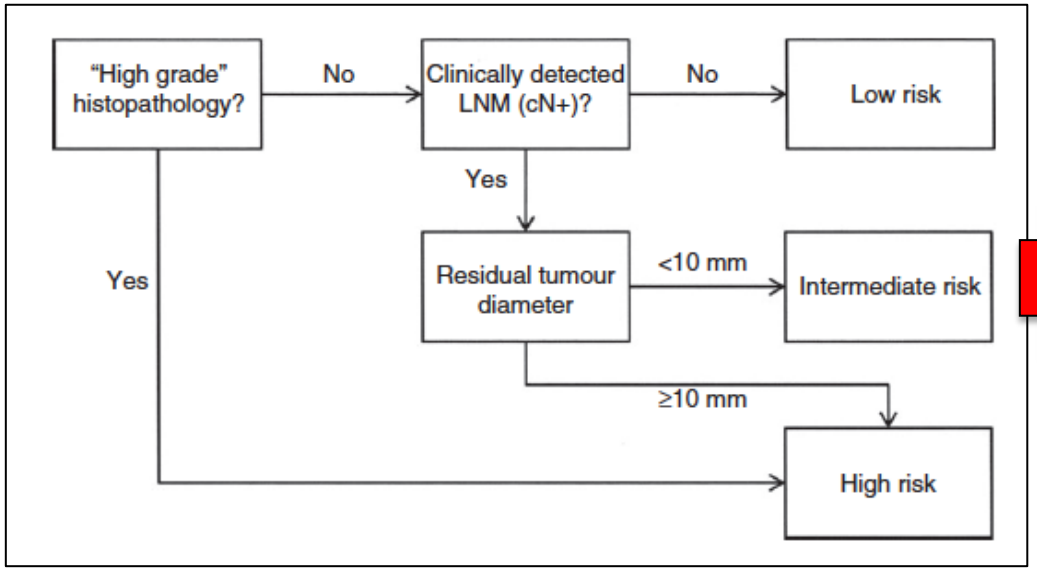
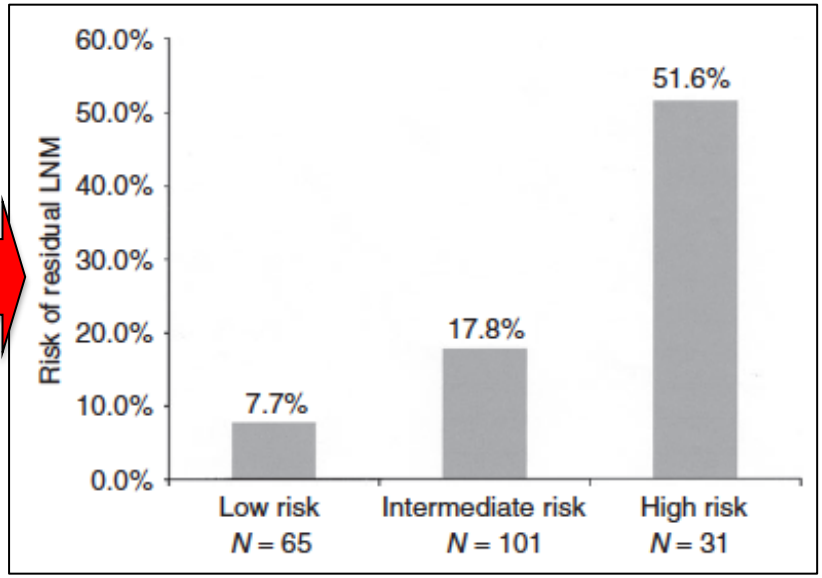
FLOWCHART DEPICTING ALGORITHM FOR RISK STRATIFICATION



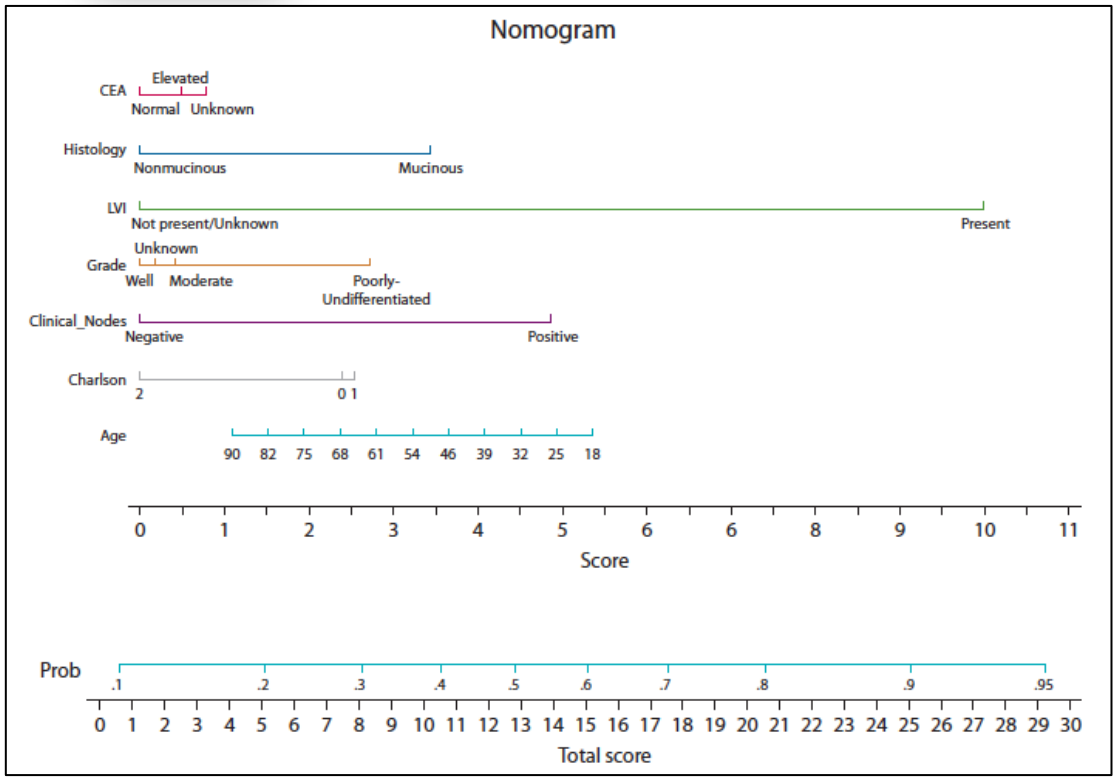
RISK OF RESIDUAL LN METASTASES BASED ON ALGORITHM



W&W Approach – Critical Aspects
What Accuracy of Nomograms?

A Nomogram to Predict Lymph Node Positivity Following Neoadjuvant Chemoradiation in Locally Advanced Rectal Cancer

Andrew D. Newton, M.D.[1] • Jiaqi Li, M.S.[2] • Arjun N. Jeganathan, M.D.[1]
Najjia N. Mahmoud, M.D.[1] • Andrew J. Epstein, Ph.D., M.P.P.[3]
E. Carter Paulson, M.D., M.S.C.E.[1,4]



Predictive Accuracy:

70.9%

$$p(positivity) = \frac{e^{XB}}{1+e^{XB}}$$

Let XB = –0.92 – (0.01 × age) – (0.06 if Charlson score of 1) – (0.42 if Charlson score of 2+) + (0.82 if clinical nodes positive) + (0.04 if moderately differentiated) + (0.55 if poorly/undifferentiated) + (0.16 if unknown grade) + (1.84 × LVI present) + (0.70 if mucinous histology) + (0.11 if CEA elevated) + (0.19 if CEA unknown).

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CONCLUSIONS

WHY TEM AS DIAGNOSTIC AFTER CRT?

- **Sets of noninvasive tests to define a cCR are not uniformly accepted and are subject to change over time.**
- **Criteria adopted in each diagnostic method may vary from study to study**
- **cCR is not truly reliable in predicting pCR (50-75%); a significant part of pCR do not have a cCR (25-75%)**
- **Full-Thickness Local Excision after RCT is the best diagnostic tool we have today to confirm pCR.**
- **It allows an high accuracy in definition of ypT stage and in ypT0 gives possibility to predict a low risk of lymph node involvement.**
- **It allows to know immediately the need to do a TME without the necessity of a close follow-up, not always feasible in all countries and for all patients**
- **TEM is considered curative in ypT1 but in the future we could probably identify also ypT2 tumor at low risk of nodal involvement were close follow-up as in W&W can be considered**

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Thanks for your attention