Is Neoadjuvant Radiotherapy always Necessary for locally advanced Mid-High Rectal Cancers?

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Rectal Cancer

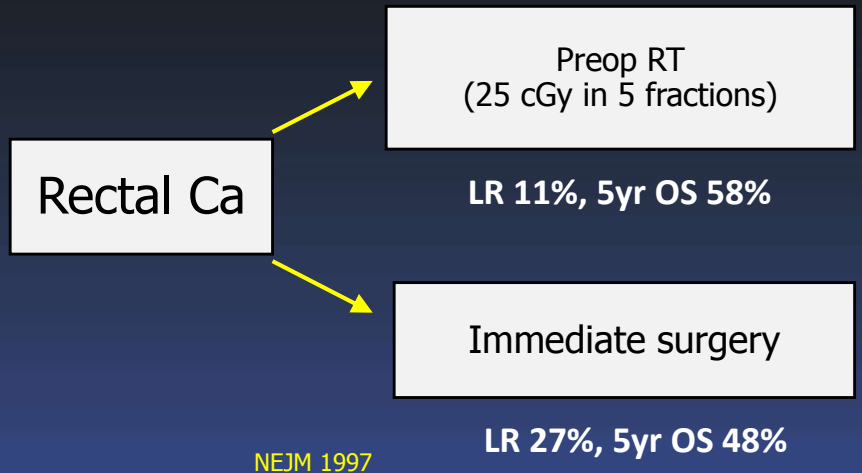
- Historically, high both local recurrence and requirement for a permanent stoma
- Now, within specialized rectal cancer teams, recurrence < 10%. With CXRT
- The desire to avoid local recurrence and a permanent stoma drove the initial swing for preoperative RT

Kennedy ED et al, Cancer 2011;117:2853–62

Short-course XRT?

- 25 cGy in 5 fractions
- Northern Europe approach
- No concurrent chemo(5FU) radio-sensitizer
- Surgery within a 1-2 weeks
- No down-staging (not for T4 or concern re CRM)

Swedish Rectal Cancer Study



NEJM 1997

Dutch Colorectal Group (NEJM 2001)

Rectal Ca

Preop RT + TME
(25 cGy in 5 fractions)

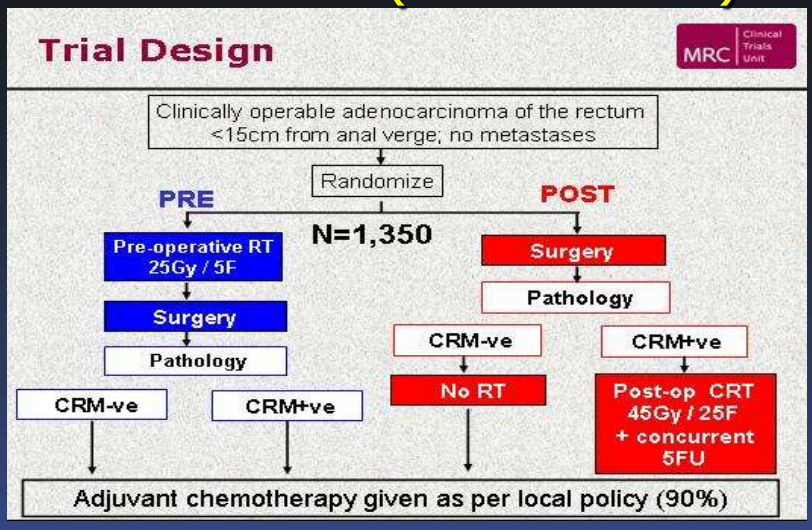
LR 5.6%

TME alone

LR 10.9%

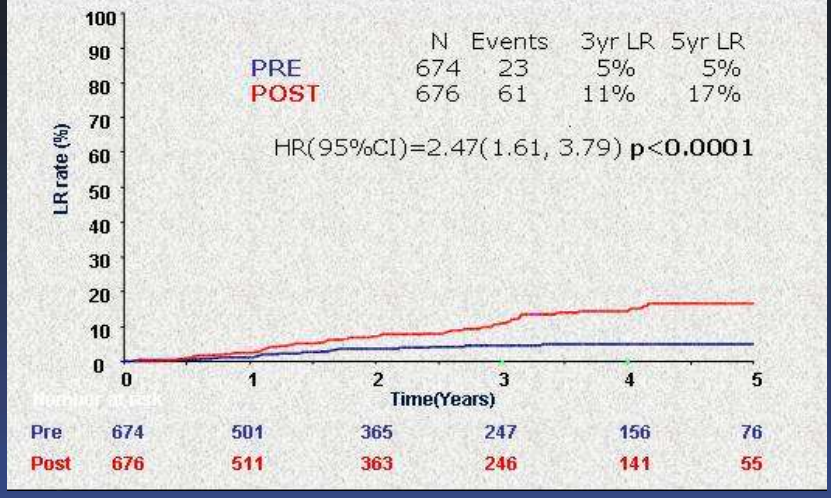
Kapiteijn NEJM 2001

MRC CR-07 (NCIC CO-16)



Lancet 2009; 373: 821–28

LR by treatment (ITT)



Lancet 2009; 373: 821–28

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Randomized Phase III Trials of Preoperative Radiotherapy vs Surgery Alone as initial therapy for Resectable Rectal Cancer

	CONTROL		PREOPERATIVE RADIATION			
	No.	Local Relapse Rate at 5 y	No.	Local Relapse Rate at 5 y	Hazard Ratio	CI at 95%
SWEDISH (1997)	585	26%	583	9% p<0.001	NR	NR
DUTCH (2001)	924	11.4%	937	5.8% p<0.001	3.42	2.05-5.71
MRC CR07 (2006)	676	17%	674	5% P<0.0001	2.47	1.61-3.79
TOTAL	2185	17.3%	2194	6.9%		

PREOPERATIVE RADIATION REDUCES SIGNIFICANTLY LOCAL RELAPSES EVEN IN TME RESECTED PATIENTS

Preoperative Chemoradiotherapy

- North American/Southern Europe approach
- For patients with locally advanced disease
  -T3/T4 or N+
- More protracted RT course 5-6 weeks(45-50.4 cGy)
- Concurrent 5FU based chemotherapy
- Followed by Surgery 6 - 11 weeks later

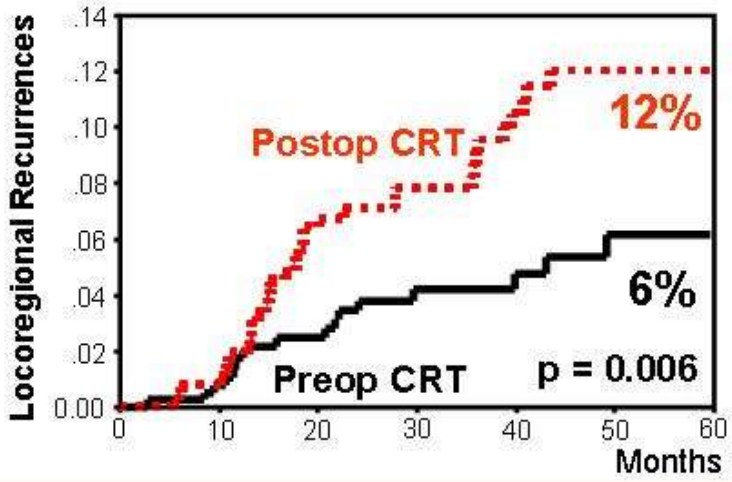
The NEW ENGLAND JOURNAL of MEDICINE

Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer

Rolf Sauer, M.D., Heinz Becker, M.D., et al. for the German Rectal Cancer Study Group 2004

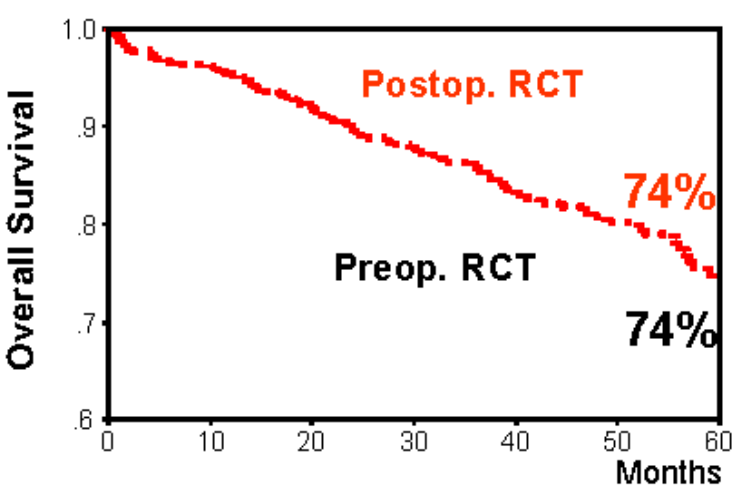
- 421 receive preoperative and 402 receive postoperative CXRT
- The overall 5 year **survival** rates were 76% and 74% **(P=0.80)**
- The 5 year incidence of **local relapse** 6% for preoperative and 12% in the postoperative group **(P=0.006)**
- Grade 3 or 4 acute **toxicity** occurred in 27 % of the patients in the preoperative-treatment group, as compared with 40 %of the patients in the postoperative-treatment group **(P=0.001)**

Cumulative Incidence of Local Relapses
Intent-to-treat Analysis (Med. F/up: 40 mos)



Sauer NEJM 2004

Overall Survival
Intent-to-Treat Analysis (Med. Follow-up: 40 mts)



Sauer NEJM 2004

German Rectal Study Conclusions

- Preop CXRT significantly improves local control
- Preop CXRT improves sphincter preservation in low-lying tumors
- Preop CXRT reduced acute and chronic toxicity
- Preop CRT should be the standard treatment in cT3/4 or cN+ rectal cancer

????

- 10% getting benefit
- What about the 90% who are radiated without benefit ? any harm?

RT Late effects

- Bregendahl S et al Colorectal Dis. 2015 Jan
  - 516 patient
  - 6 years follow up
  - Voiding difficulties (OR = 1.63, 95% CI 1.09-2.44)
  - Reduced vaginal dimensions (OR = 4.77, 95% CI 1.97-11.55)
  - Dyspareunia (OR = 2.76, 95% CI 1.12-6.79)
  - Lack of desire (OR = 2.22, 95% CI 1.09-4.53)
  - Reduced sexual activity (OR = 0.55, 95% CI 0.30-0.98).

RT Late effects

- Sexual dysfunction (Marijnen et al 2005)
  - 990 patients without recurrence
  - RT had a negative effect on sexual functioning in males (P.004) and females (P .001)
  - Irradiated males had more ejaculation disorders (P .002) and erectile functioning deteriorated over time (P .001)
- Second malignancy (13.7% vs. 9.4) in Dutch trial (van gijn et al 2011)
- Unexplained late cardiac effects
- Higher % of SBO

Fecal incontinence

Reference	No. of patients	Therapy strategy	Follow-up (yrs; median)	Fecal incontinence (%)	P value
Peeters 2005	177 vs. 185	5x5 Gy versus TME	5.1	62 vs. 38*	<0.001
Pollack 2006	21 vs. 43	5x5 Gy versus conventional surgery	14	57 vs. 26	0.013
Brændengen 2006	18 vs. 19	Preop. RTX versus RCTX	4-12	58 vs. 38° 75 vs. 56 ♣	
Coco 2007	100	50.4Gy	12	46 ♣ 14 ♥	
Urso † 2006	12	Pre- and postoperative	19 mths	75 ♥	
Bruheim † 2010	69 vs. 240	Pre- and postoperative versus TME	4.8	71 vs. 58♣ 52 vs. 13 ♥	0.01 <0.001

You will get rid of your cancer but you won't be able to urinate, defecate or have sex!! Is that ok with you?

Surgeon & Patient Priorities

- The desire to avoid local recurrence and a permanent stoma overrode concerns regarding long-term bowel, urinary and sexual function Surgeon view
- Surgeon vs. patient desires
  - These priorities are not currently shared by patients. Patients may be keen to avoid a permanent stoma, but value good functional outcomes, and are prepared to trade off and accept a higher risk of local recurrence to achieve that!

Why Question Use of Neoadjuvant XRT?

- Current standard of care for all Stage II-III rectal cancer is tri-modality therapy—has been so since 1990
- Only ± 10% get real benefit from nXRT
- Neoadjuvant XRT may be overtreatment in some cases (due to inaccurate pre treatment staging)
- Pelvic radiation causes short and long-term morbidity
- Landmark TME trials showed that XRT marginally improves LR rates, but not survival

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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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HIGHLIGHTS

- We are studying the oncologic outcome of patients having mucinous rectal carcinoma with or without Neoadjuvant chemoradiation.
- Partial tumor regression occurred in limited percentage of patients.
- A considerable percentage of patients developed tumor progression during chemoradiation and became unresectable.
- No difference between groups in the disease free survival and overall survival after total mesorectal excision.

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INTERNATIONAL JOURNAL OF SURGERY

Volume 23 :120-127October 2015

Is It Safe to Omit Using Neo-adjuvant chemoradiation in mucinous Rectal Carcinoma

Khaled Madbouly, M.D., Abd rabbo Mashhour et al.

- 102 patients of mucinous rectal carcinoma
- 61 receive preoperative CXRT
- 29 had partial response, 26 no response and 6 disease progression
- No difference in the overall five-year **survival** rates ,69% and 67% **(P=0.39)**
- The five-year incidence of **local relapse** 21% for preoperative and 23%in the postoperative group **(P=0.29)**

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Conclusions

- In most MRC , tumor regression is not significant after nCXRT and there is considerable possibility of tumor progression during nCXRT
- So, nCXRT should be used with close follow- up in MRC for early detection of possible tumor progression
- If the patient can't tolerate nCXRT, it is possibly safe to do surgery followed by pCXRT

New concepts after MDT

- Rectal cancer should no longer be considered a single monolithic disease entity, with a simple unifying management strategy
- Outcome depends on
  - Tumor location, CRM status, whether it is exophytic (polypoid or sessile) or ulcerated, mobile or fixed as well as its (TNM) staging
  - Histopathological parameters are also important as mucinous/signet ring tumors
  - Lack of data about factors affecting response to XRT

How to solve problems of RT complications and the wide spectrum of response?

Theoretical solutions

- Neoadjuvant chemotherapy alone
- Tailored protocols
- Study predictors for good response to RT
- Change size of radiation field and/or dose

Neoadjuvant Chemotherapy Pilot Study

- Phase II pilot at MSKCC administered 6 cycles of induction FOLFOX+Bev to patients with clinical T2N1, T3N0, T3N1 RC who were candidates for LAR
- XRT planned if no response or any positive margin
- 30 participants, none required preoperative XRT
- With more than 4 years median follow up:
  - 1 post-op death, 2 cancer deaths
  - No local recurrences
  - 4 recurrences, all with metastases to lung

JCO Jan 2014

Challenging routine CXRT PROSPECT

N1048-CALGB81001-ACOSOGZ6052

An NCI Cooperative Group Phase II/III Trial of Neoadjuvant FOLFOX with
Selective Use of Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision

PROSPECT: N1048

- Objective:
  - To determine if selective use of neoadjuvant XRT is a safe alternative strategy to routine use of XRT for management of locally advanced rectal cancer that is amenable to sphincter sparing TME

PROSPECT: Study Design

- A phase II/III NCI Cooperative Group study:
  - Randomized phase II of 366 patients with early stopping rule if failure to complete R0 resections or if an unacceptably high rate of Local recurrences
  - Phase III will include 644 additional patients if stopping criteria are not met

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Study Endpoints

Primary Outcomes:

- Randomized Phase II Component
  - R0 Resection Rate
  - Time to local recurrence (TLR)
- Phase III Component:
  - Time to local recurrence (TLR)
  - Disease free survival (DFS)

Secondary Outcomes:

- Pathologic complete response rate (Pcr)
- Overall survival (OS)
- Quality of life (QOL)
- Rates of receiving 5FUCMT

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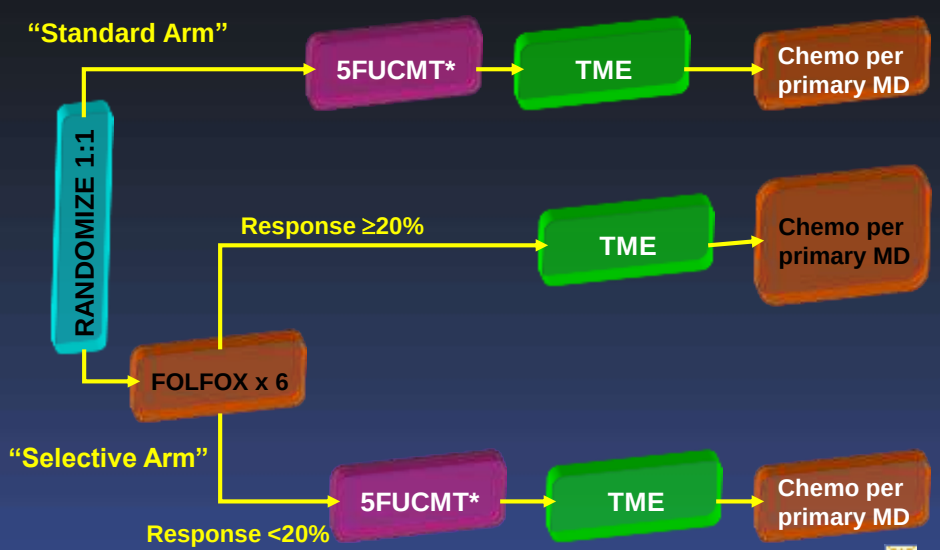
PROSPECT: **Study Schema**



*5FUCMT = infusional or oral 5FU + radiation therapy

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Radiation in the Intervention Arm is Used Selectively

- Preoperative 5FUCMT is to be administered if:
  - Evidence of clinical progression during pre-op FOLFOX
  - Restaging reveals rectal tumor response is an estimated <20%
  - Unable to tolerate FOLFOXx6 at or above dose level-2
  - Patient withdraws consent
- Postoperative 5FUCMT is recommended if:
  - TME pathology is T4
  - TME pathology has any positive margin (R1 or R2 resection)
  - Surgeon's self assessment is that TME was incomplete
  - Surgical/Path QA report indicates incomplete TME

Preliminary Conclusions

- Neoadjuvant chemotherapy strategies are an investigational approach for patients with resectable rectal CA amenable to sphincter sparing TME
- XRT is a mainstay of Rx for a curable cancer 5-12 cm from the anal verge: selective approach appropriate on a trial
- Patients with threatened margins are inappropriate candidates for selective use of XRT
- Induction FOLFOX for pts
  - who can't have XRT due to prior therapy
  - with stage IV disease amenable to R0 resection
  - With suspected metastatic disease

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EJSO
EJSO 42 (2016) 829–835
www.ejso.com

Early results of multicenter phase II trial of perioperative oxaliplatin and capecitabine without radiotherapy for high-risk rectal cancer: CORONA I study

T. Kamiya [a], K. Uehara [a,*], G. Nakayama [b], K. Ishigure [c], S. Kobayashi [d], K. Hiramatsu [e], H. Nakayama [f], K. Yamashita [g], E. Sakamoto [h], Y. Tojima [i], S. Kawai [j], Y. Kodera [b], M. Nagino [a], the Nagoya Surgical Oncology Group and the Chubu Clinical Oncology Group

- 41 patients. The completion rate of the preoperative XELOX was 90.3%
- 4 Major complications occurred in 6 /40 patients (15.0%)
- Pathological complete response (pCR) rate was 12.2%
- Good tumor regression was exhibited in 31.7%
- N down-staging (cN1 to ypN0) and T down-staging were detected in 56.7% and 52.5%, respectively
- Clinical T4 tumor was a predictor of poor pathological response ($p < 0.001$)

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- Conclusions: We could show the favorable pCR rate after preoperative XELOX alone.
- T and N down-staging rate was likely to be insufficient
- When tumor regression is essential for curative resection, the use of preoperative CRT is likely to be recommended

On going Trials

STUDY (reference)	Pre-operative treatment	Entry criteria	Status	RT/CRT	Comments
Phase III trials					
GEMCAD (Fernández-Martos et al. 2010b) 41 patients	Capecitabine/oxaliplatin + bevacizumab 3 cycles then capox = total 4 cycles	MRI defined entry	Recruiting	Selective CRT according to response	Primary endpoint: Response rate (RECIST)
RAPIDO Phase III EudraCT number 2010-023957-12 885 patients	SCPRT (5x5 Gy) followed by Oxaliplatin/ capecitabine 6 cycles vs Control Capecitabine +CRT	MRI defined entry	Yet to open	CRT 50.4 Gy/28# with capecitabine	Primary endpoint: 3 year DFS
Polish Study EGERJ 0109 NCT00833131 540 patients	SCPRT (5 X 5 Gy) followed by FOLFOX (3 cycles) then surgery versus Versus 5FU/capecitabine CRT (50 Gy) as control	Unresectable rectal cancer	Recruiting	SCPRT versus CRT	Primary endpoint: the rate of R0 resection
Randomized Phase II trials					
BACCHUS NCRI Randomised phase II 60 patients	FOLFOX +bevacizumab for 5 courses,then final FOLFOX then surgery versus FOLFOXIRI bevacizumab for 5 courses,then final FOLFOXIRI then surgery	MRI defined entry	Yet to open	SCPRT or CRT only for progression/lack of response	Primary endpoint: pCR
randomised phase II GRECCAR 4 150 patients	FOLFIRINOX 6-8 weeks then reassess/randomised according to response. If good cap 50 Gy vs surgery. If poor cap 50 Gy vs cap 60 Gy	MRI defined entry	?started	If good cap 50 Gy vs surgery. If poor cap 50 Gy vs cap 60 Gy	Primary endpoint: %R0
French phase II NCT00865189 91 patients	FOLFOX +bevacizumab for 6 courses then CRT(with bevacizumab/5FU) versus CRT alone	Not MRI	Ongoing not recruiting		Primary endpoint: pCR
Chinese Randomised phase II NCT01211210 495 patients	FOLFOX (4 cycles) then surgery versus FOLFOX CRT Versus 5FU CRT (control)	Not MRI	Recruiting		Primary endpoint: 3 year DFS
SWOG study NCT00070434 Up to 65 patients	Multiple regimens	T4 rectal cancer	Ongoing not recruiting	CRT with cape	Primary endpoint: Response

- 130 patients with locally advanced mid and low rectal cancer
- Long-course nCXRT followed by radical surgical resection were included in the study
- Paraffin-embedded sections obtained in diagnostic biopsies were assessed by immunohistochemical staining for molecular markers and classified using a semi-quantitative method
- Results were related with T-downstaging and tumor regression grade using Mandard scoring system on surgical specimens

Predictors for response to nCXRT

- Predictive markers of response in univariate analysis:
  - Expression of B-cell lymphoma 2 (anti-apoptotic protein)
  - B-catenin
  - VEGF
  - Apoptotic protease activating factor 1 ($P = 0.03$)
  - Tumor differentiation grade ($P < 0.001$)
- Multivariate analysis
  - Tumor differentiation grade
  - Bcl-2 expression

Still a lot to go….proteomics!!! Genetic!!

What else?

- Expanding options for more effective & individualized combinations of chemotherapy and biological treatments which may improve radiotherapy effectiveness
- Potentially more effective systemic chemotherapy may avoid the need for radiotherapy all together and this is currently under investigation in many trials
- Predictors for good response to RT are being studied

Challenges

- Which patient do not need to receive preoperative RT?
- Is neoadjuvant chemotherapy an alternative?
- How do we select the most appropriate treatment between chemotherapy, CXRT?
- What is the optimal chemotherapy regime alone or to combine with RT?
- What is the optimal RT dose?
- What are the optimal radiotherapy fields?
- Should we use standard or tailored protocols?

Thank you