PARIS 2022 ESMO congress

Role, timing and duration of neo-adjuvant (chemo)radiotherapy

Plenty of choices in rectal cancer

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DECLARATION OF INTERESTS

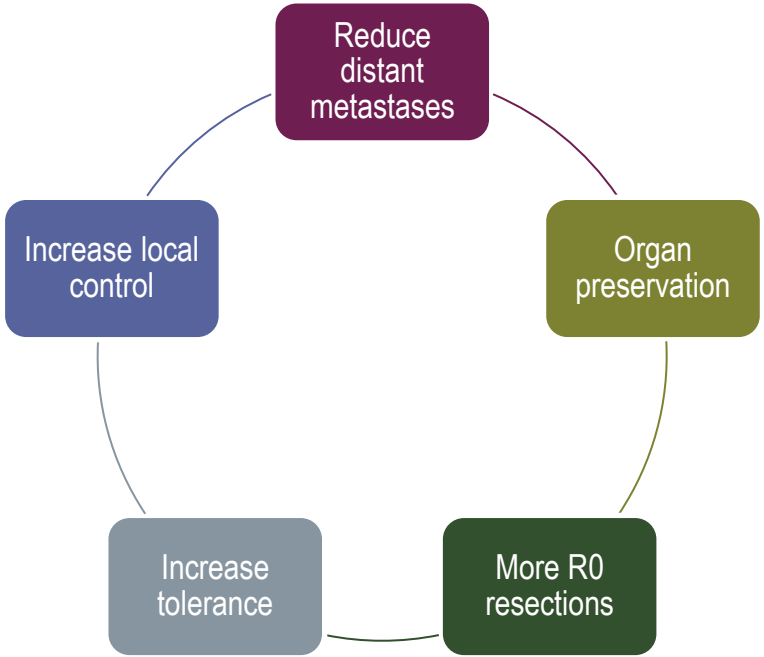
Nothing to declare

Karin Haustermans

Role of neo-adjuvant (C)RT in rectal cancer

What we hope to achieve by combining RT and chemo in the pre-operative setting

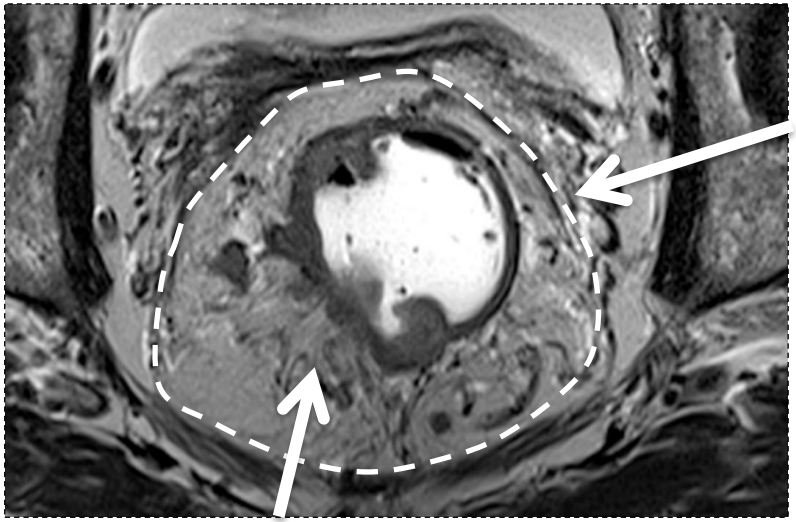
RADIOTHERAPY	CHEMOTHERAPY
Reduces the number of viable tumor clonogens available for metastasis	Local radiosensitization + decrease DM directly



Role of neo-adjuvant (C)RT in rectal cancer

To increase local control

Increase local control



Mesorectal facia (MRF)

Target to reduce pelvic recurrences =

Tissues beyond the future surgical margins containing subclinical deposits

Infiltration of perirectal fat (in mm, cT3a-d)

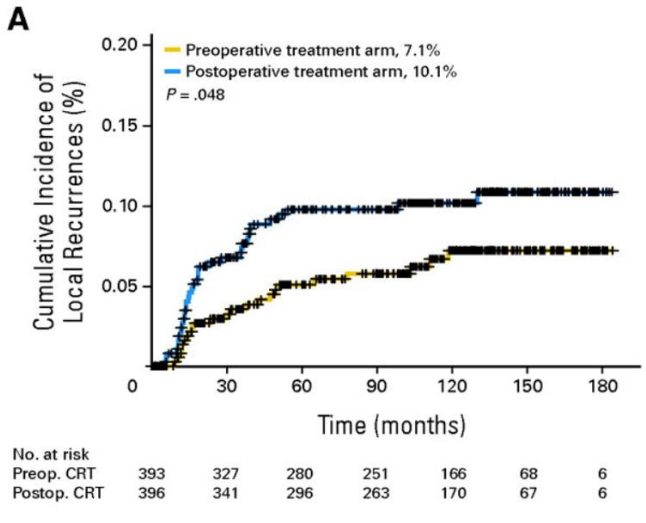
Withers et al. IJROBP 2004

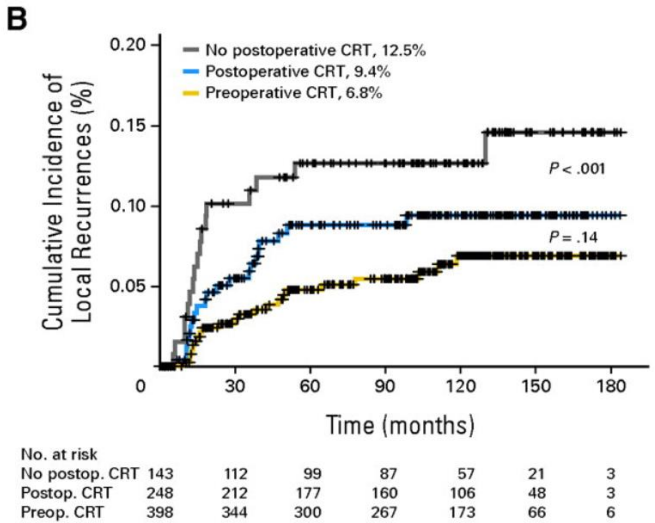
Role of neo-adjuvant (C)RT in rectal cancer

To increase local control

Increase local control

CAO/ARO/AIO-94 phase III RCT (10 years): significant LC improvement of pre- vs postop CRT for LARC





Sauer et al JCO 2012

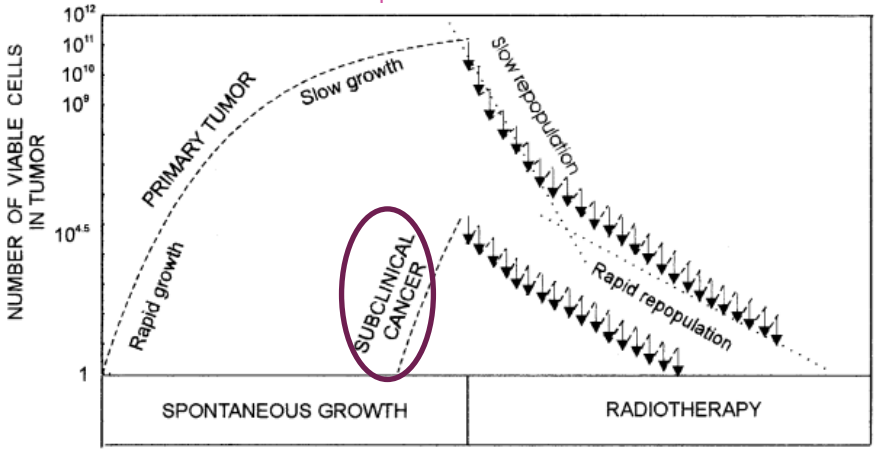
Role of neo-adjuvant (C)RT in rectal cancer

Reduce distant metastases

To reduce distant metastases

- Probability that metastases will develop, increases with increase in size of the primary tumor
- It requires on average a tumor mass of 10^9-10^{10} malignant cells before metastatic dissemination becomes a clinical problem
- Subclinical disease beyond future surgical margins grows faster than the primary tumor

Average doubling time of 4-14 days
for microscopic foci of metastatic rectal cancer!



→ Treatment should be AS FAST and AS INTENSE as tolerable!

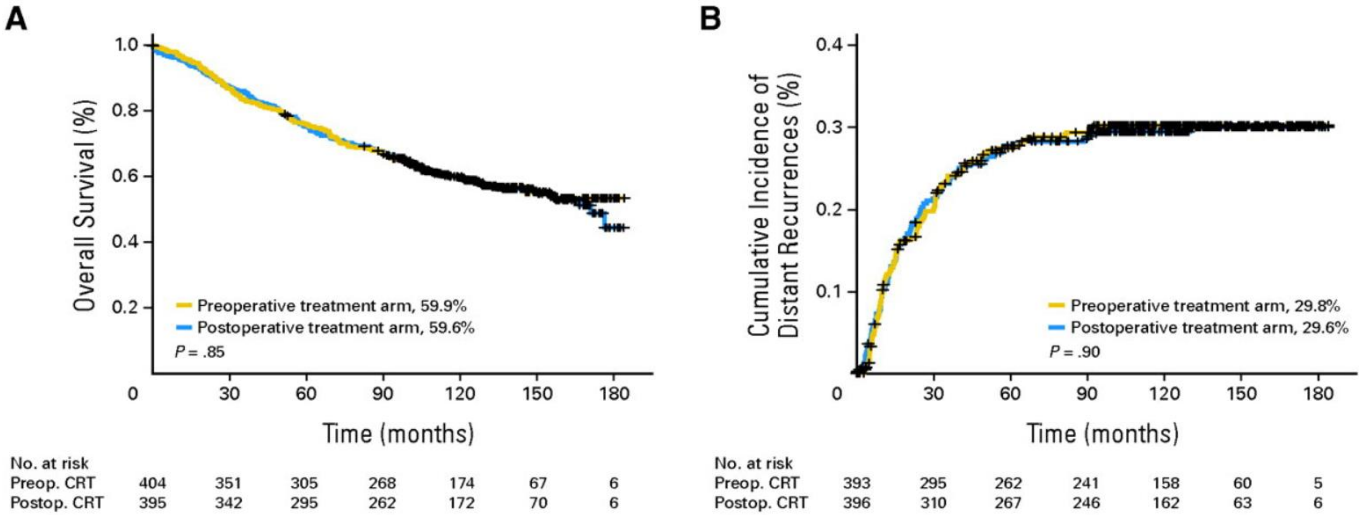
Withers et al. IJROBP 2004; Suwinski et al IJROBP 1998

Role of neo-adjuvant (C)RT in rectal cancer

To reduce distant metastases

Reduce distant metastases

- However…preop CRT had no effect on OS or DM (compared to post-op CRT)



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Sauer et al JCO 2012

Role of neo-adjuvant (C)RT in rectal cancer

Reduce distant metastases

To reduce distant metastases

- Intensify neo-adjuvant CRT → Total Neoadjuvant Treatment (TNT)
  - Rationale: earlier systemic therapy would
    - immediately address risk of DM
    - maximize compliance
    - allow assessment of chemosensitivity
  - Timing?
    - Most common approach = chemo first
    - However, (C)RT first might be beneficial because
      - earlier treament primary tumor and regional nodes
      - longer interval for response → increased ypCR?
      - consolidation effect subsequent chemo

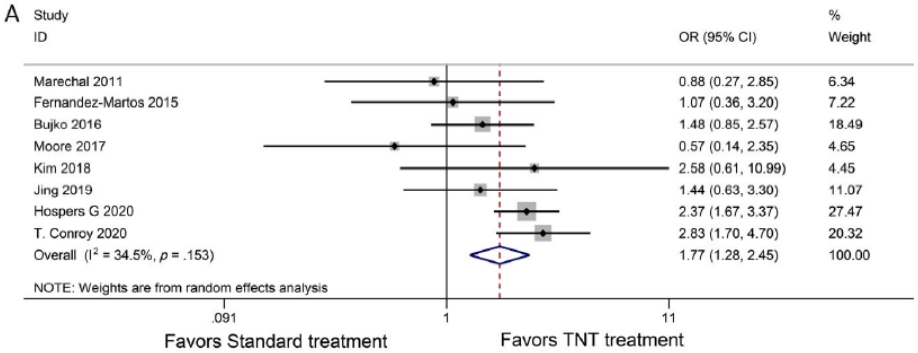
Role of neo-adjuvant (C)RT in rectal cancer

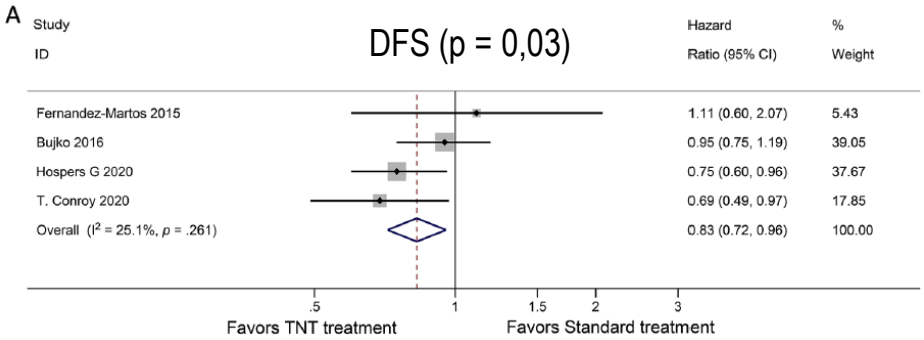
To reduce distant metastases

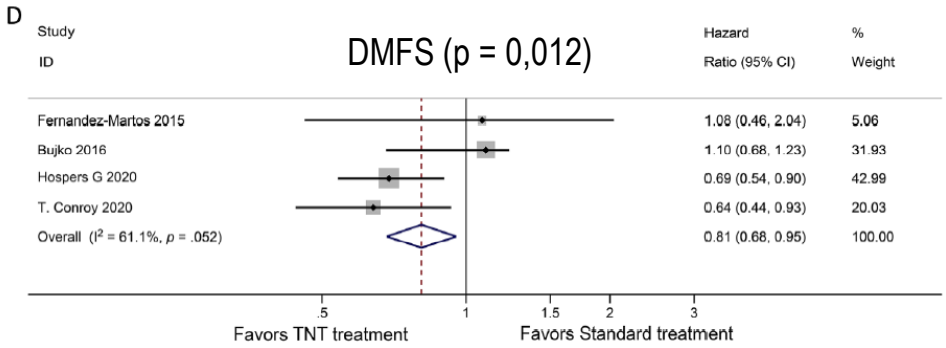
Reduce distant metastases

- TNT meta-analysis

ypCR (p = 0.0005)







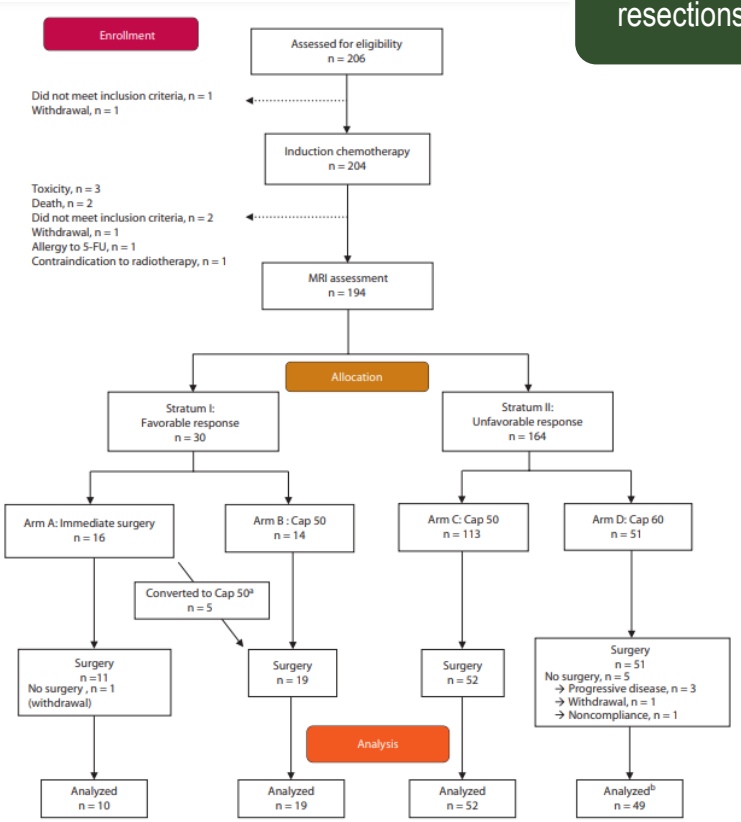
Shuang et al The Oncologist 2021

Role of neo-adjuvant (C)RT in rectal cancer

More R0 resections

To obtain more R0 resections

- GRECCAR 4 study:
  - Assess feasibility of CRT tailored based on tumor response to induction chemo to obtain a minimum R0 resection rate of 90% in the 4 arms of the study
  - Preop chemo vs chemo + CRT for responders to chemo, followed by surgery
  - Good responders ≥ 75% tumor shrinkage: n = 30 (15%) vs Bad responders < 75 % tumor shrinkage: n = 164 (85%)! (PROSPECT trial: good responder ≥ 20%)



Rouanet et al Dis Colon Rectum 2022

Role of neo-adjuvant (C)RT in rectal cancer

To obtain more R0 resections

More R0 resections

- GRECCAR 4 study:

	Immediate surgery	Standard CRT + surgery	Standard CRT + surgery	Intensive CRT + surgery
	Arm A: CT + S Good responders	**Arm B: CT + CRT (50 Gy) + S Good responders**	**Arm C: CT + CRT (50 Gy) + S Bad responders**	**Arm D: CT + CRT (60 Gy) + S Bad responders**
R0 resection rates	100%	100%	83%	88.2%
ypCR rates	10%	58%	13.5%	20%
Positive distal margins	0%	0%	11%	2%
Metastasis rate	20%	10.5%	18%	18.8%
5y OS	90%	93.3%	84.3%	86.1%
5y DFS	80%	89.5%	72.9%	72.8%
	Difficult to draw conclusions on efficacy CT alone	Highest OS and DFS	Prognosis bad responders worse compared to good responders; not clear if RT dose escalation was beneficial	

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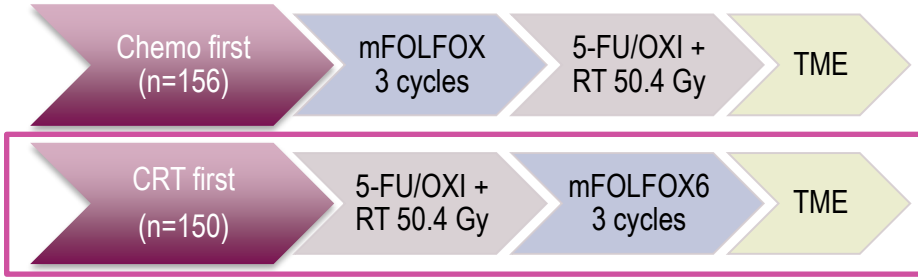
Timing of neo-adjuvant (C)RT in rectal cancer

Chemo first or CRT first in TNT?

- CAO/ARO/AIO-12 phase II RCT : CRT + induction or consolidation CT as TNT for LARC?

'Pick the winner' design:
ypCR 25% after TNT compared with standard 15% after preop CRT



	ypCR	CRT-related grade 3-4 toxicity	Compliance with CRT	Compliance with chemo	Median interval between end CRT - surgery
Chemo first (n=156)	17%	37%	91% RT 78% FU 76% OXI	92%	45
CRT first (n=150)	25%	27%	97% RT 87% FU 93% OXI	85%	90

Fokas et al JCO 2019

Timing of neo-adjuvant (C)RT in rectal cancer

Chemo first or CRT first in TNT?

- CAO/ARO/AIO-12 phase II RCT : CRT + induction or consolidation CT as TNT for LARC?

  Long-term results – median FUP 43 months (35 – 60 months)

POPULATION

206 Men, 100 Women

Patients with cT3-4 and/or node-positive rectal adenocarcinoma

Median age, 61 y

SETTINGS / LOCATIONS

18 Academic and private clinics in Germany

INTERVENTION

306 Patients randomized

156 Induction chemotherapy

Induction chemotherapy (fluoro-uracil, leucovorin, oxaliplatin) followed by chemoradiotherapy (fluorouracil/ oxaliplatin, radiation 50.4 Gy)

Chemo first

150 Consolidation chemotherapy

Chemoradiotherapy followed by consolidation chemotherapy

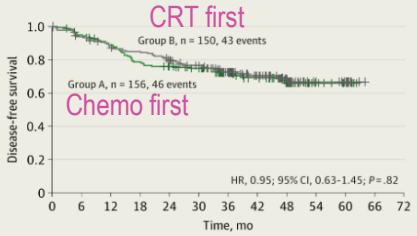
CRT first

PRIMARY OUTCOME

Disease-free survival (DFS) defined as the time from randomization and either R2 resection, no resection (tumor progression), locoregional recurrence, distant metastases, or death from any cause, whichever occurred first

FINDINGS

After a median follow-up of 43 mo, there was no significant difference in 3-y DFS between the 2 groups (HR, 0.95; 95% CI, 0.63-1.45; *P* = .82)



3-y DFS

73% In induction chemotherapy group — Chemo first

73% In consolidation chemotherapy group — CRT first

Also no significant differences for:

3y cumulative incidence of
LR: chemo first 6% vs CRT first 5%
DM: chemo first 18% vs 16%

Chronic toxicity grade 3-4:
Chemo first 11.8 % vs 9.9% CRT first

Global health status/QoL
Stool incontinence

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Fokas et al JAMA Oncol 2022

Timing of neo-adjuvant (C)RT in rectal cancer

Chemo first or CRT first in TNT?

Organ preservation

- CAO/ARO/AIO-12 phase II RCT : CRT + induction or consolidation CT as TNT for LARC?

CRT followed by chemotherapy
resulted in higher ypCR
without compromising DFS, toxicity, QoL, or stool incontinence

and is thus proposed as the preferred TNT sequence
if organ preservation is a priority

Fokas et al JAMA Oncol 2022

Timing of neo-adjuvant (C)RT in rectal cancer

Chemo first or CRT first in TNT?

- OPRA trial
  - Confirms results CAO/ARO/AIO-12 phase II RCT : CRT + consolidation CT as TNT for LARC

RT dose **54.0 Gy** in both arms

3-year rates with 95% CI.

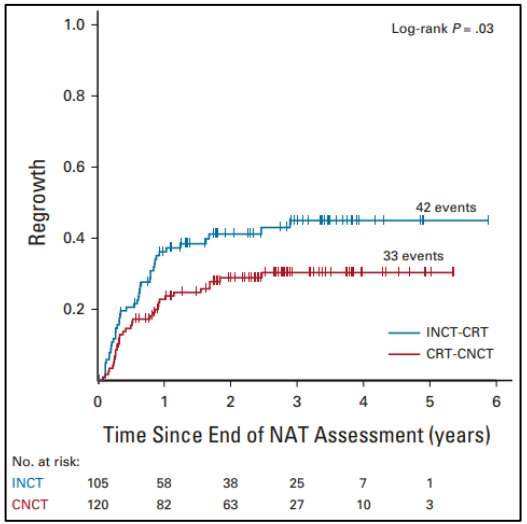
	Induction N = 152		Consolidation N = 155		p*
DFS	78%	(70%,87%)	77%	(69%,86%)	0.90
DMFS	81%	(74%,90%)	83%	(76%,91%)	0.86
OP	43%	(35%,54%)	58%	(49%,69%)	0.01

*log-rank test

Garcia-Aguilar et al Meeting Abstract ASCO 2020;

	Induction		Consolidation	
DFS	76%	(69-84%)	76%	(69-83%)
TME-free survival	41%	(33-50%)	53%	(45-62%)

Garcia-Aquilar et al JCO 2022



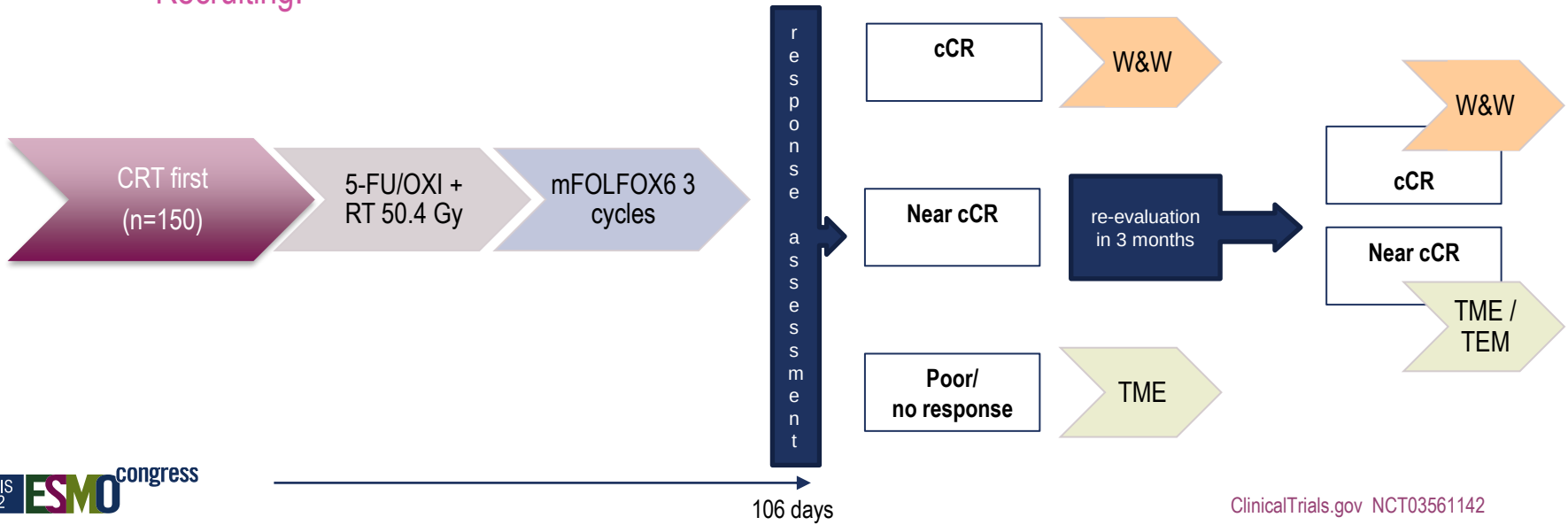
Garcia-Aquilar et al JCO 2022

Timing of neo-adjuvant (C)RT in rectal cancer

Chemo first or CRT first in TNT?

- CAO/ARO/AIO-16 phase II RCT : CRT + consolidation CT as TNT for organ preservation in LARC

  Recruiting!



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ClinicalTrials.gov NCT03561142

Timing of neo-adjuvant (C)RT in rectal cancer

The best surgical interval?

- Meta-analysis
  - 3085 patients from 7 RCTs (Accord12/0405, EORTC22921, FFCD9203, CAO/ARO/AIO-94, CAO-ARO-AIO-04, INTERACT, TROG01.04)
  - Age ≥ 18, cT3-T4 and cN0-2, no clinical evidence of DM at diagnosis, neo-adjuvant CRT + surgery
  - Median delivered RT dose: 50.4 Gy (range 44 – 59.4 Gy)
  - Median SI 6 weeks – 14% pCR

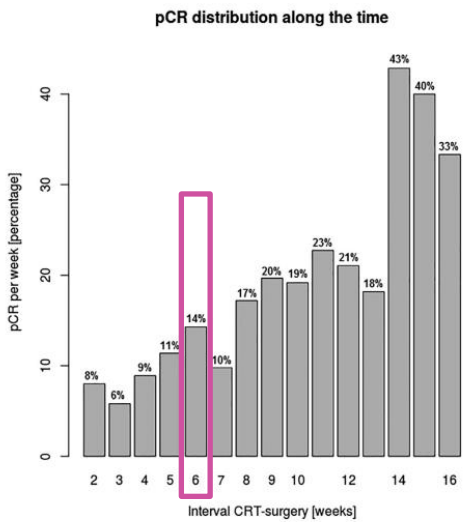


Fig. 2. pCR percentage per week. pCR: pathological complete response; CRT: chemoradiotherapy.

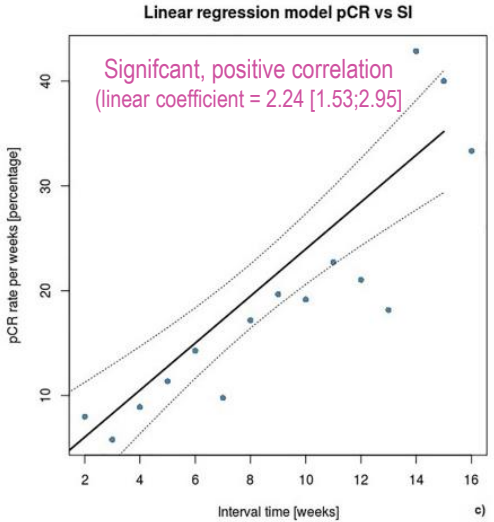


Fig. 3. Linear regression model correlation between pCR rate per week and SI. pCR: pathological complete response; SI: surgical interval.

Gambacorta et al Radiother Oncol 2021

Timing of neo-adjuvant (C)RT in rectal cancer

The best surgical interval?

Best time to achieve pCR in LARC = 10 weeks

- Meta-analysis

Early SI (< 6 weeks):
cumulative pCR = 11.6%

vs (p < 0.01)

Late SI (≥ 6 weeks):
cumulative pCR = 18.8%

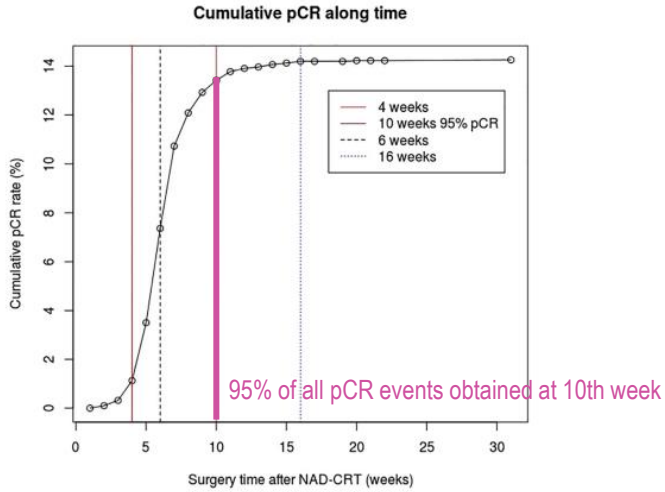


Fig. 4. Cumulative pCR rate. pCR: pathological complete response; NAD-CRT: neoadjuvant chemo-radiotherapy.

ypCR Variable name	Multivariate analysis Coefficient	p-value
SI (as continuous variable)	0.131	**p < 0.01**
RT dose	-	-
OXI based-chemo	0.366	**p < 0.01**
Tumor distance	-	-
cT	-0.49	**p = 0.04**
cN	-	-

Gambacorta et al Radiother Oncol 2021

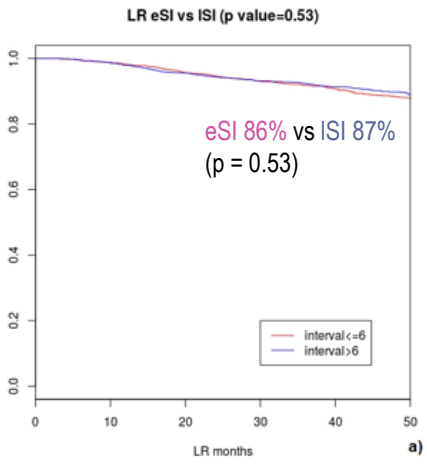
Timing of neo-adjuvant (C)RT in rectal cancer

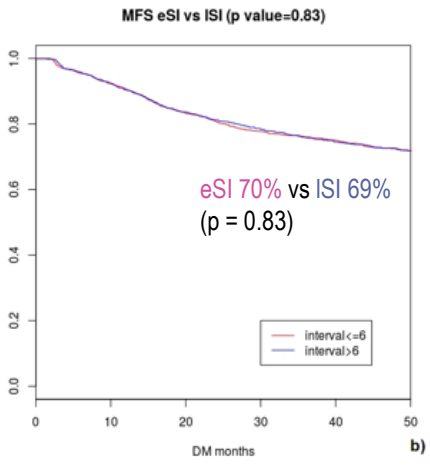
The best surgical interval?

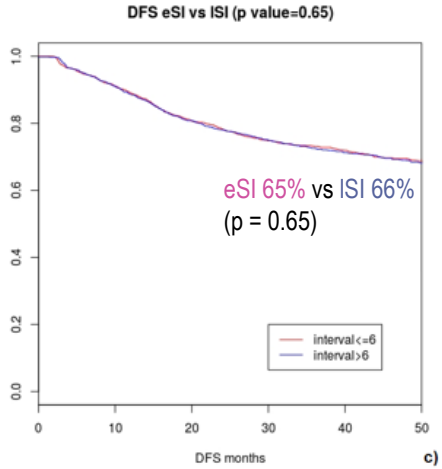
- Meta-analysis

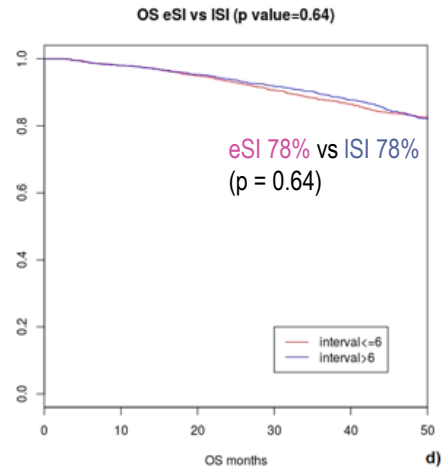
Best time to achieve pCR in LARC = 10 weeks

considering that lengthening of SI is not detrimental for survival outcomes









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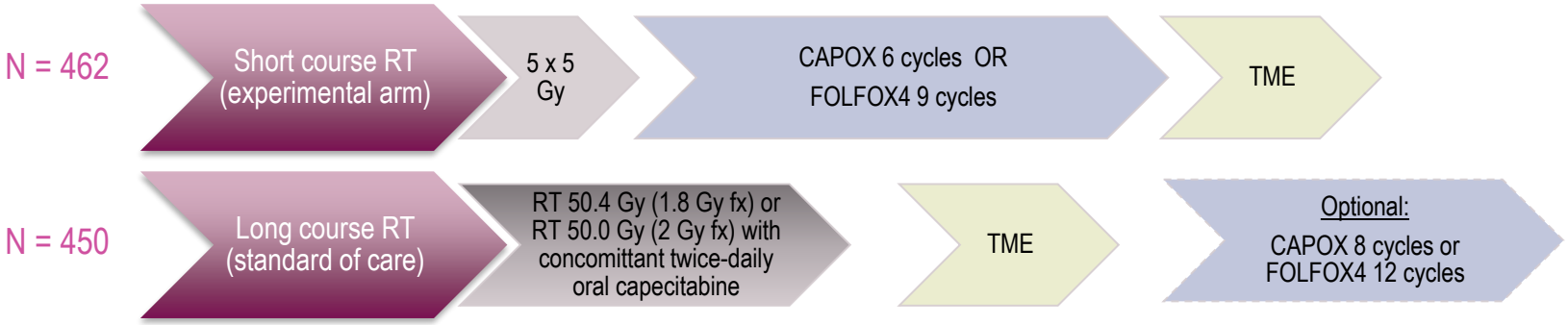
Duration of neo-adjuvant (C)RT in rectal cancer

Optimal duration?

- RAPIDO phase III RCT: short-course RT vs long-course RT aimed to reduce DM without compromising LC

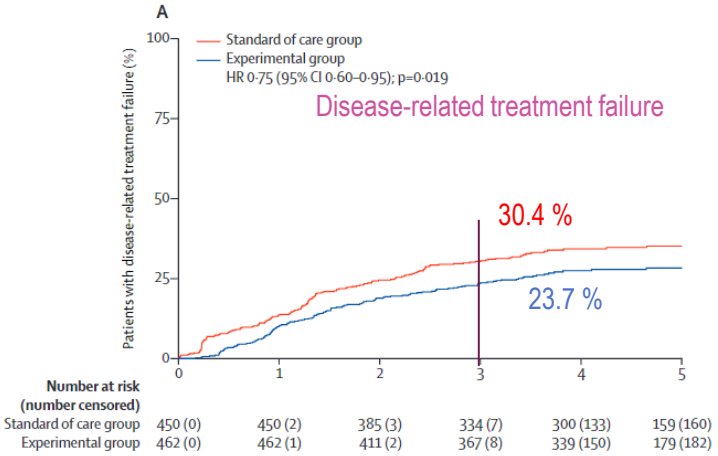


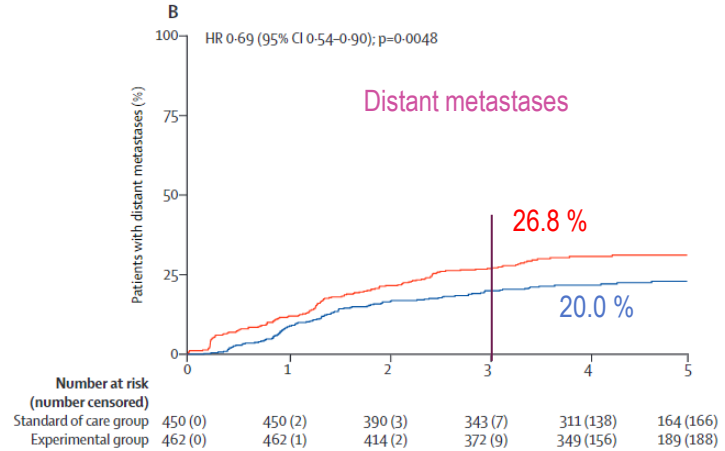
Bahadoer et al al Lancet Oncol 2020

Duration of neo-adjuvant (C)RT in rectal cancer

Optimal duration?

- RAPIDO phase III RCT: short-course RT vs long-course RT aimed to reduce DM without compromising LC
  - Primary endpoint: 3y disease-related treatment failure lower in short course RT group





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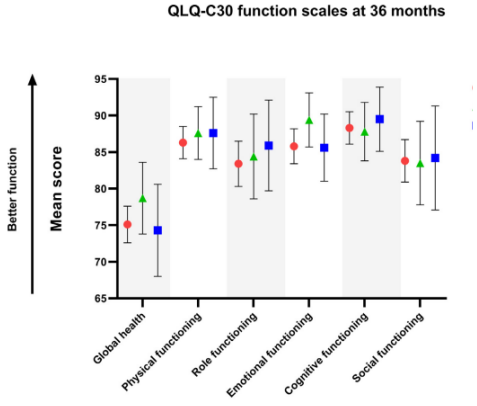
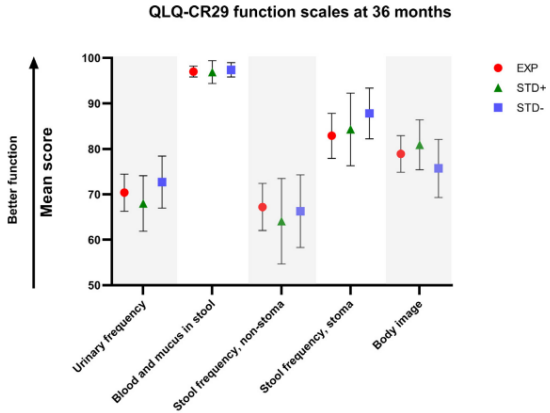
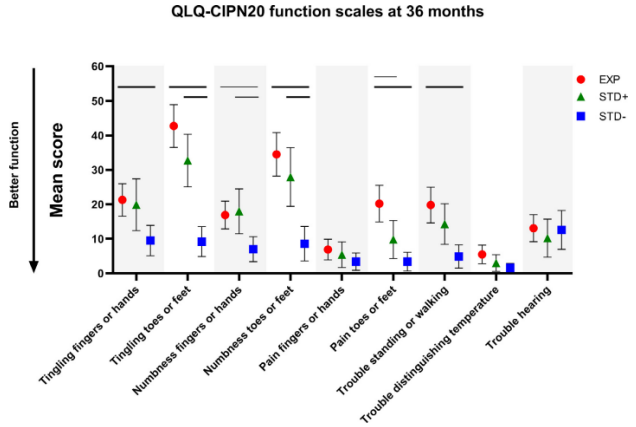
Duration of neo-adjuvant (C)RT in rectal cancer

Optimal duration?

- RAPIDO phase III RCT: short-course RT vs long-course RT aimed to reduce DM without compromising LC
  - Short-course RT followed by preop-CT, does not compromise HRQL, bowel function or results in more grade 3 toxicity compared to standard long-course CRT at 3 yrs after surgery in DrTF patients







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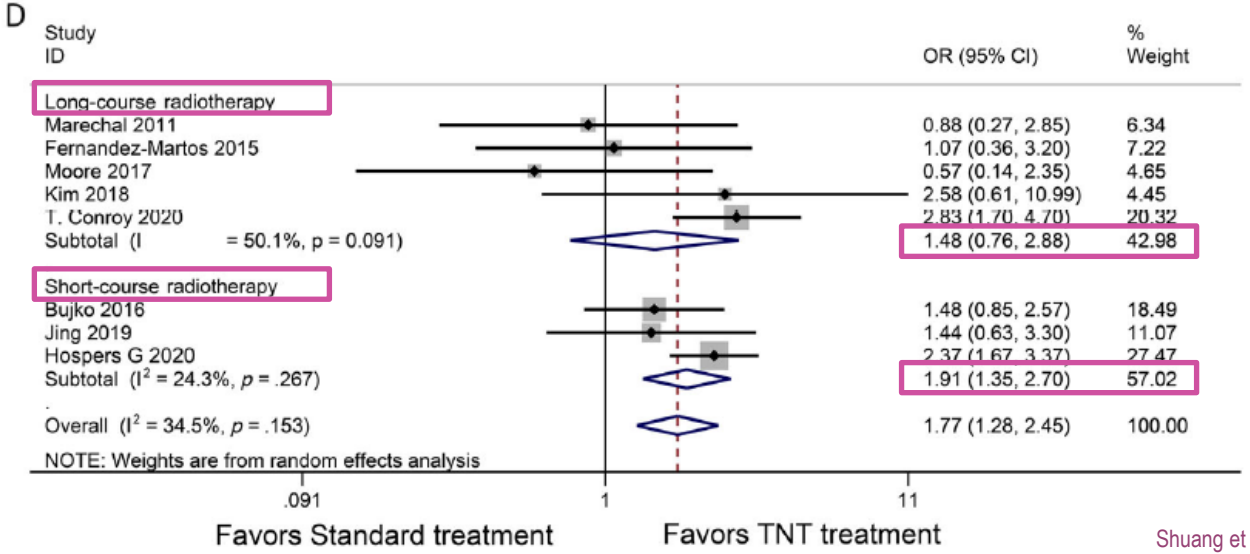
Duration of neo-adjuvant (C)RT in rectal cancer

Optimal duration?

- TNT meta-analysis: subgroup analysis short-course RT vs long-course RT

Higher ypCR rate in short-course RT



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Duration of neo-adjuvant (C)RT in rectal cancer

Optimal duration?

- TNT meta-analysis: subgroup analysis long-course RT vs short-course RT

Higher ypCR rate in short-course RT groups

Considerations

- *Short-course RT studies all consolidation chemo TNT (vs. induction chemo TNT in long-course RT studies)*
- *Longer intervals between RT and surgery in short-course RT studies*
- *Promising, but no consensus on the optimal time interval between RT and chemo, duration of consolidation chemo, or the ideal modes*

Trial	Chemo	Timing
POLISH II trial	FOLFOX; 6w; 3 cycles	After 1 week of RT
RAPIDO trial	CAPOX; 12w; 4 cycles	11-18 days after RT
STELLAR trial	CAPOX; 18w; 6 cycles	1 week after RT

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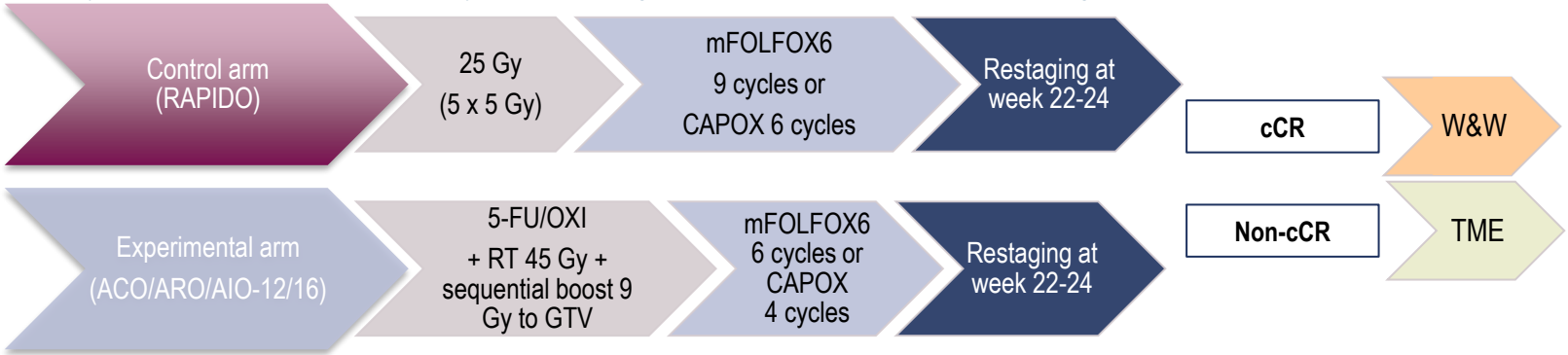
Duration of neo-adjuvant (C)RT in rectal cancer

Optimal duration?

- ACO/ARO/AIO-18.1 phase III RCT (recruiting!)
  - CRT (CAO/ARO/AIO-12 phase II RCT) vs short-course RT (RAPIDO), followed by consolidation chemo and surgery or W&W (for pts with cCR)
  - Primary endpoint: 3y DFS
  - Hypothesis: CRT + chemo may increase organ preservation while maintaining DFS



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ClinicalTrials.gov NCT04246684

Take home message

Lessons learnt?

- Significant LC improvement of pre- vs postop CRT for LARC
- Pre-op treatment should be AS FAST and AS INTENSE as tolerable → TNT
- CRT + consolidation chemo is the preferred TNT for LARC
  - Higher ypCR
  - Organ preservation (higher TME-free survival)
- Surgical interval: best time to achieve ypCR following TNT in LARC is 10 weeks
- Short-course RT seems more promising compared to long-course RT
- More research needed since no consensus on the optimal time interval between RT and chemo, duration of consolidation chemo, or the ideal modes…