Neoadjuvant treatment of rectal cancer

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Professor of Radiation Oncology

Conflict of interest

- Radiation Oncologist

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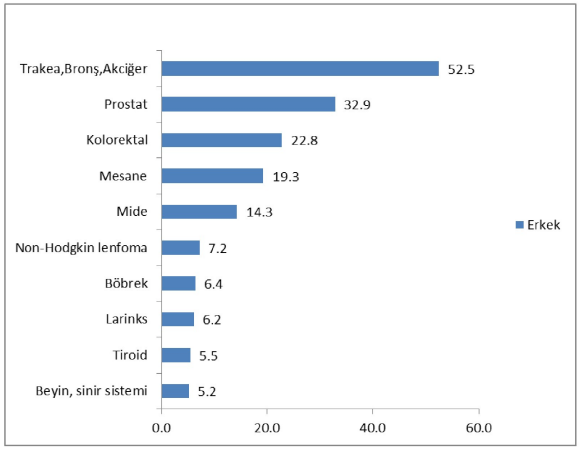
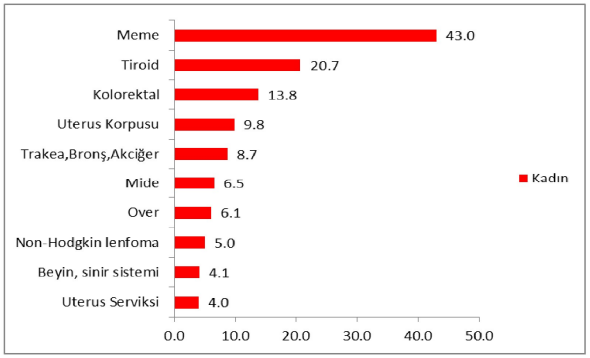
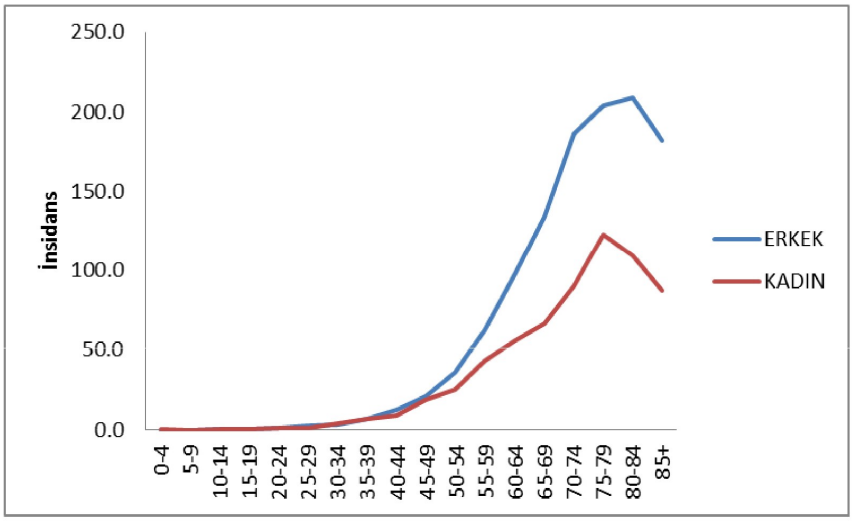
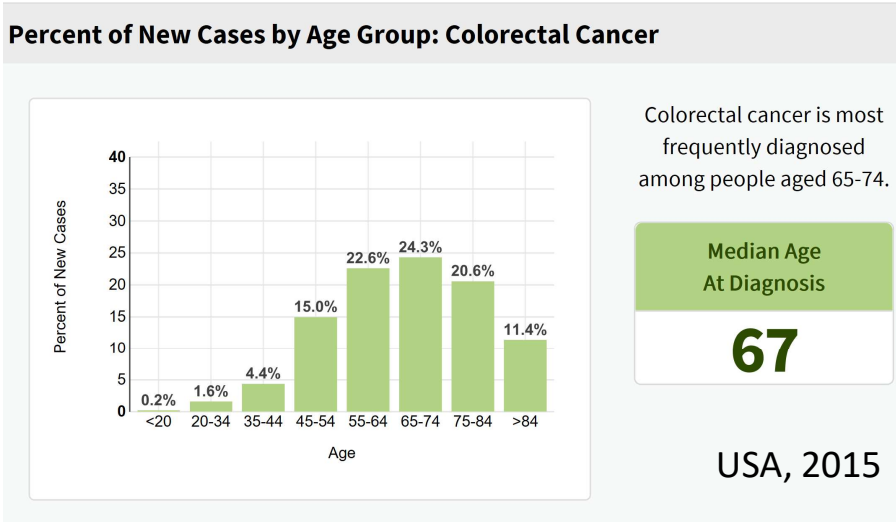


2014 , standardized ratio, every 100.000



2014 , colorectal cancer incidance





http://www.kanser.saglik.gov.tr/

Rectal cancer US stats

- Third leading cause of cancer incidence in US
- Second leading cause of cancer deaths in US
- 140.250 colorectal cancer
  - 97.220 new cases of colon cancer (M/F 1)
  - 43.030 new cases of rectal cancer (M/F 1.43)

50.630 cancer deaths / 2018

- 43 % of rectal ca had localized disease at the presentation.

	Erkek*	Kadın*
Dünya	204,9	165,2
IARC'a üye 24 ülke	235,4	192,1
AB (28 ülke)	311,3	241,4
ABD	347,0	297,4
Türkiye**	220,3	156,8

*Yaşa göre standardize edilmiş hız 100.000 kişide ** Türkiye Birleşik Veri Tabanı, 2014

http://www.kanser.saglik.gov.tr/

25.100 new rectal cancer estimated in Turkey
- 10.793 Localized rectum cancer/year

cancer.org

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Radiotherapy for rectal cancer
According to current guidelines

Stage 1

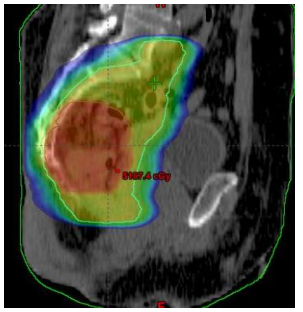
- After Local excision
  - T1 NX with high risk (Margin +, LVI + ,Grade 3, Sm3)

Chemort

Stage 2-3

- After TME
  - T3 N0 (if not well / mod dif, < 2mm mesorectal inv, no LVI, upper rectum)
  - T4 N0
  - Node Positive

Adj. Chemort



- Before TME
  - T3 N (any) Clear CRM
  - T1-2 N 1

Neoadjvant Chemo RT
Or
Short course RT

- Before TME
  - T3 CRM +
  - T4 N 1-2
  - Local Unresectable

Neoadjvant Chemo RT

Stage 4

- Before TME
  - Resectable mets with synhcron local disease

Preop Chemo RT
Or
Preop Short course RT

NCCN, 2018

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Role of Neoadjuvant RT

- Neoadjuvant RT decreased the LRR (even with TME).
  - GERMAN (CAO-ARO-AIO -94), NSABP-R03, MRC CR07&NCIC-CTG CO16
- Neoadjuvant RT increased survival vs surgery only
  - Swedish (Before TME era), Dutch (TME era)
- NRT Increased sphincter preservation
  - GERMAN (CAO-ARO-AIO -94), LYON 96-02

Adjuvant vs. Neoadjuvant radiochemotherapy
German-CAO-ARO-AIO-94 trial

- T3-4 or Node +
- Preop RT+5FU vs. postop RT+5FU
- N=421

	Preop	Postop	
5y local recurrence	6 %	13 %	p=0,006
Sphincter Preserving surgery	39 %	19 %	p=0,004
Acute side effects Gr3/4	27 %	40 %	p=0,001
Long term tox.	14 %	20 %	p=0,01
10y LRR-ITT	7 %	10 %	p=0,048
10y distant mets-ITT	29 %	29 %	

Sauer, JCO , 2012

Table 1. Baseline Characteristics of the 799 Eligible Patients, According to Randomly Assigned Treatment Group.*

Characteristic	Preoperative Chemoradiotherapy (N=405)	Postoperative Chemoradiotherapy (N=394)	P Value
Age — yr			0.35
Median	62	62	
Range	30–76	33–76	
Sex — no. (%)			0.21
Male	286 (71)	262 (66)	
Female	119 (29)	132 (34)	
Clinical tumor category — no. (%)			0.16
T1 or T2	19 (5)	18 (5)	
T3	277 (68)	262 (66)	
T4	23 (6)	10 (3)	
Unknown	86 (21)	104 (26)	
Clinical nodal category — no. (%)			0.88
Node-negative	168 (41)	153 (39)	
Node-positive	217 (54)	202 (51)	
Unknown	20 (5)	39 (10)	
Distance of tumor from anal verge — no. (%)			0.008
<5 cm	157 (39)	117 (30)	
5–10 cm	166 (41)	168 (43)	
>10 cm	47 (12)	69 (18)	
Unknown	35 (9)	40 (10)	

Sauer, NEJM , 2004

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Pts need postop RT
should be neoadjuvant RT candidate

- But what kind of RT
  - Short course Mon-Fri vs. long course chemoRT
    5 x 5 Gy / 1 week 45-50.4 Gy / 25-28 fr
  - Short / long course of RT +/- brachytherapy boost
- Consolidation chemo (i.e. FOLFOX, 5-FU) after RT (total neoadjuvan treatment)

- Neoadjuvant chemo only any indication ?
- Is no Neoadjuvant treatment is possible ?
- Is no surgery possible after effective CRT (WW)
- Quality of RT – Does it matter?

Short vs Long course RT

Polish

- Rezektabl T3-4, digitally reachable
- 25 Gy / 5 fr vs. 50.4 Gy / 28 fr
- No sphincter inv
- Long course has more downsizing but Sph preserv. Equal
- Positive CRM 13 % vs. 4 %
- OS, LRR, DFS same
- Long term more gr 3-4 tox with long c.

Bujko, RO, 2004

Australian

- T3, within 12 cm, sph. inv. ok
- 25 Gy / 5 fr vs. 50.4 Gy / 28 fr
- 6 vs. 4 cycles 5-FU
- 3 y LR 7.5 % vs. 4.4 % NS
- For distal cancers
  - LR : 6/48 (13%) vs. 1/31 (3%) NS
- 5 y DFS, OS NS
- Distant relapses 27 % vs. 30%

Ngan, JCO, 2012

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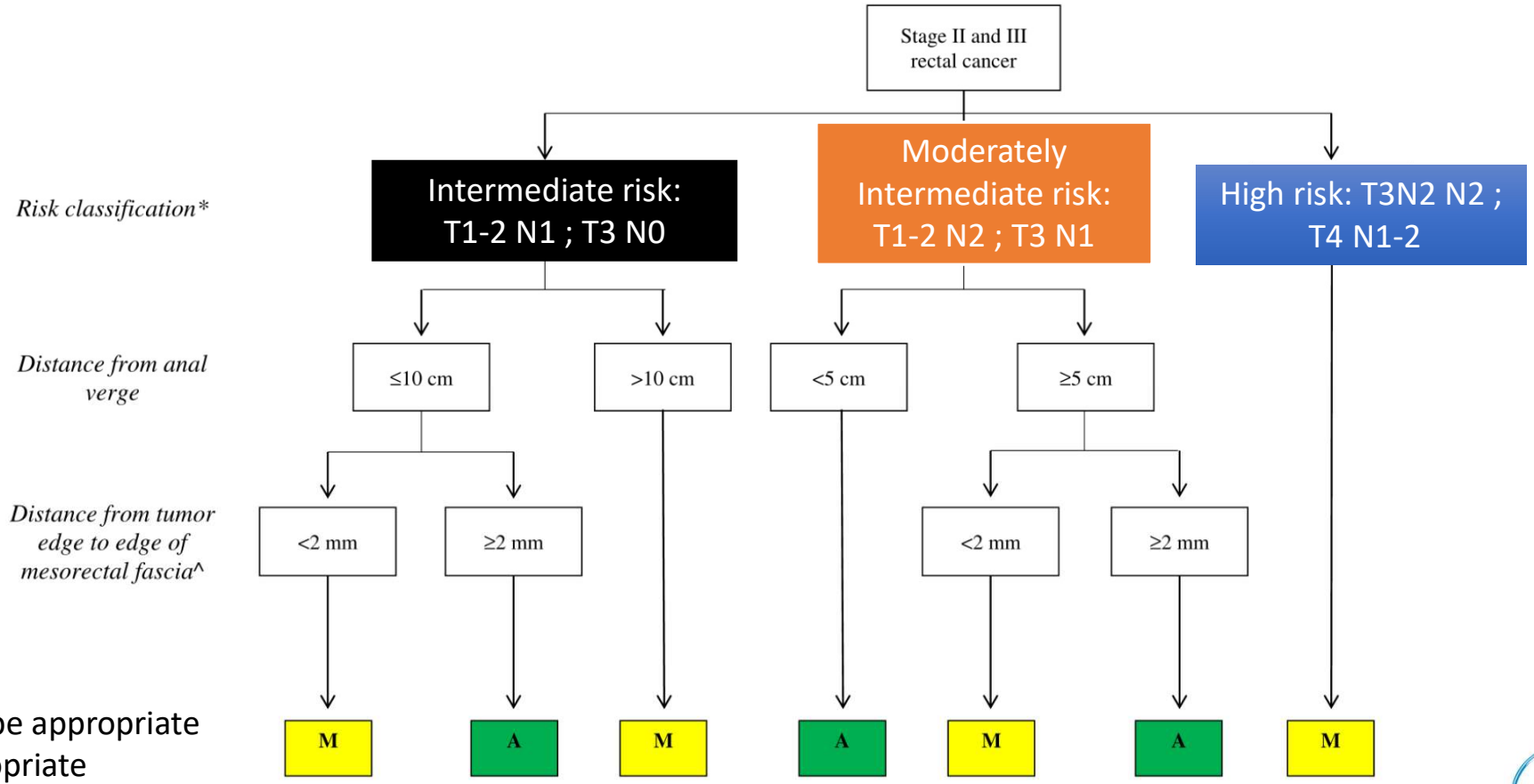
Short course NRT for whom



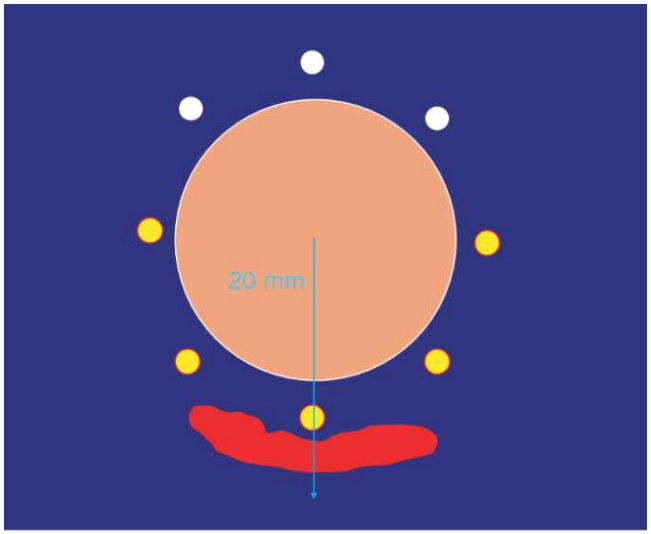
M: Maybe appropriate
A: Appropriate

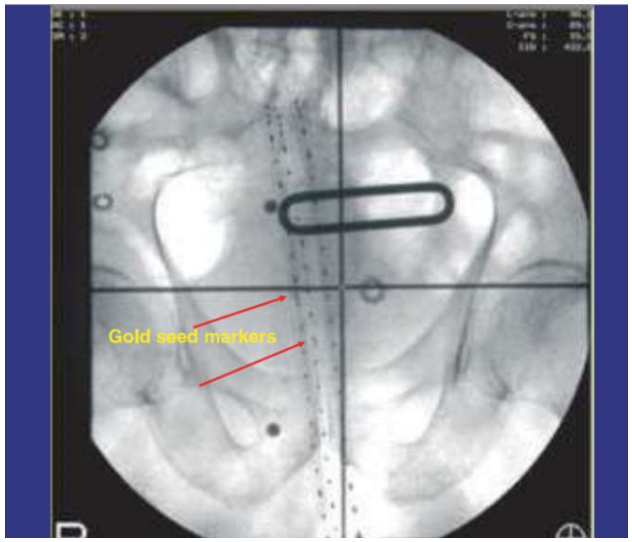
ASTRO expert panel

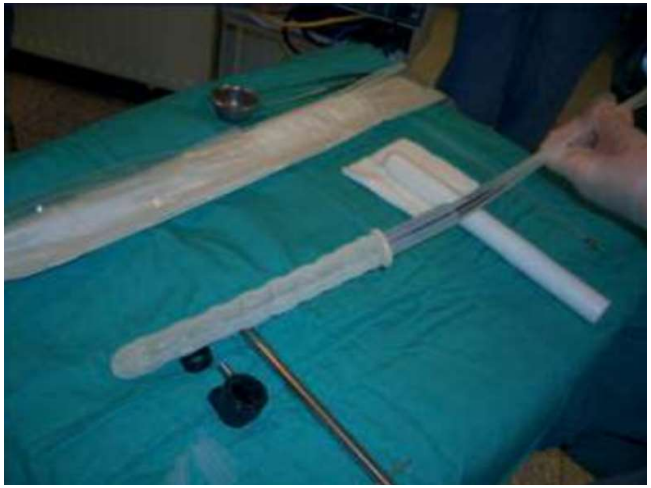
Goodman, PRO, 2016

Brachytherapy boost after chemoRT

- 6-8 weeks after chemoRT
- 10 Gy / 1 fr HDR surface





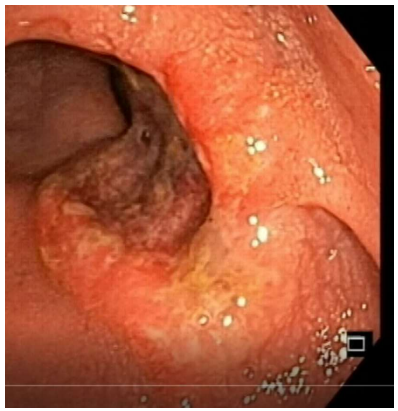


pCR 31 % vs. 12 % (nCRT only)

Myint, Col Disease, 2010

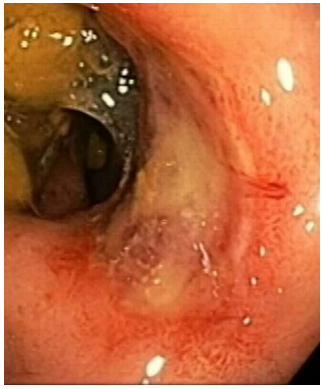
Consolidation chemo after chemoRT (TNT)

- Local relapse rate in TME era is around 10 % .
- NRT further decrease this rate to 5 %
- But almost 30 % of cases has distant mets.
- Needs more effective systemic treatment



Radiotherapy with 2c mFOLFOX6

Total 8 cycles of mFOLFOX6



Fixed T3 or T4 n=79

33 % PCR
21 % yp stage 1

Total 8 cycles of chemo
And surgery > 10 weeks after NRT
pCR 45 %

Deng, ASCO GI 2018

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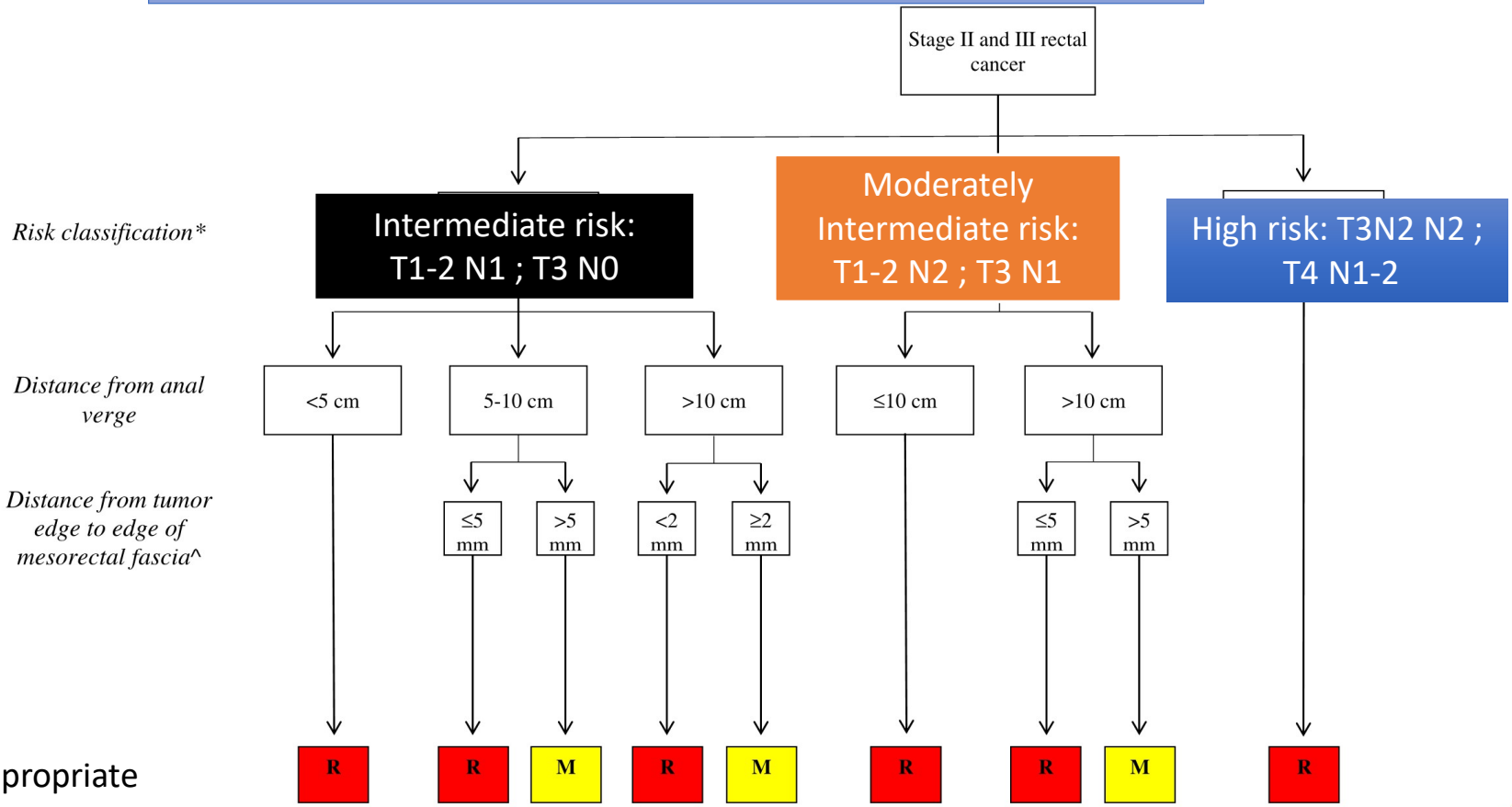
Neoadjuvant chemo only any indication ?

- Current guideline does not support
- Rand studies try to eliminate RT
  - BACCHUS
    - FOLFOX + Beva vs. FOLFOXIRI + Beva
  - FOWARC
    - 5-FU with RT vs. FOLFOX with RT vs. FOLFOX alone
  - PROSPECT
    - 5-FU with RT + surgery + FOLFOX (8) vs. FOLFOX (6 c) if regression > 20 % surgery; if < 20% CRT . IF margins clear FOLFOX 6 cyc IF NOT CRT + FOLFOX 4 cyc

No Neoadjuvan treatment



M: Maybe appropriate
A: Appropriate

ASTRO expert panel

Goodman, PRO, 2016

Is no surgery possible after effective NRT (WW) ?

High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study

Ane L Appelt, John Pløen, Henrik Harling, Frank S Jensen, Lars H Jensen, Jens C R Jørgensen, Jan Lindebjerg, Søren R Rafaelsen, Anders Jakobsen

- T2 / T3 N0-1
- Lower rectum 6 cm
- 60 Gy / 30 fr to tumor
- 50 Gy/ 30 fr to elective nodes (with oral tegafur)
- Than 5 Gy endorectal brachy boost
- Endoscopy and biopsies of the tumor at week 2,4,6 and 6 weeks after tx
- Negative tumor site biopsies and no mets to lymph nodes were disposition to WW others surgery

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Is no surgery possible after effective NRT (WW) ?

- Of 51 patients 40 had path PCR : ww
- Local recurrence at 1 year is 15.5 %
- Grade 3 side effect is rectal mucosal bleeding (8%)
- Sphinkter functions perfect.
- The most common chronic side effect was grade 3 rectal bleeding

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Appelt, Lancet Oncol, 2015

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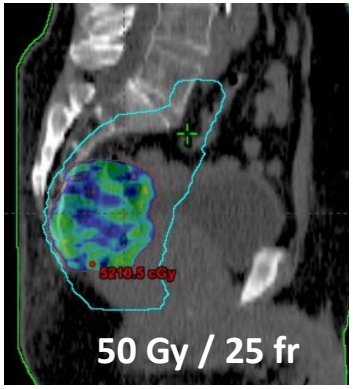
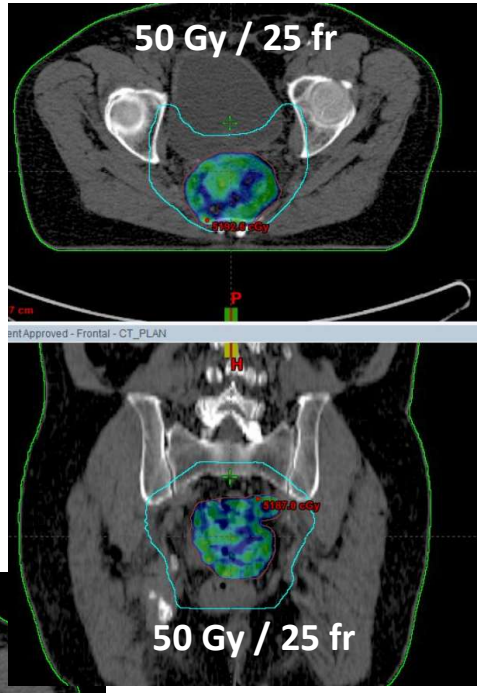
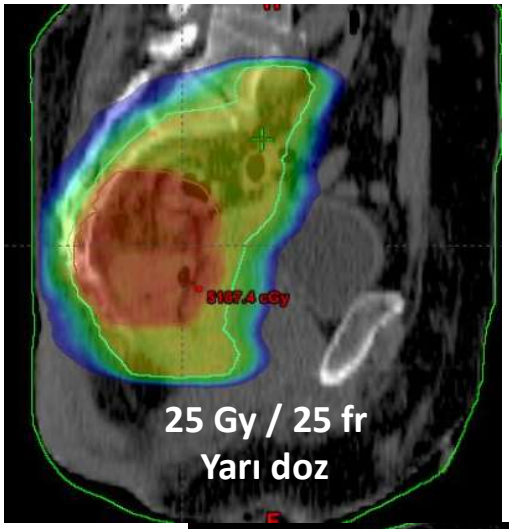
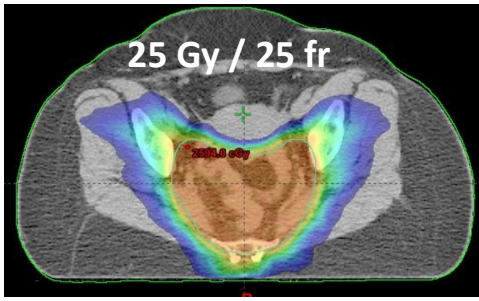
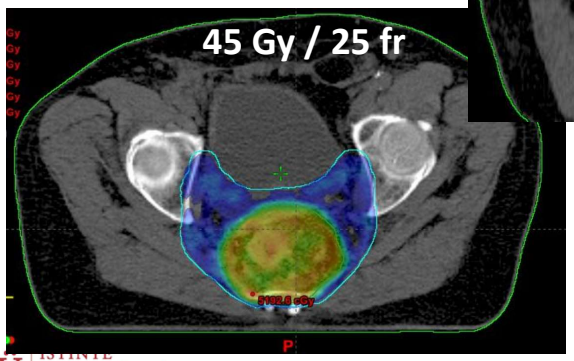
Quality of RT – Does it matter?







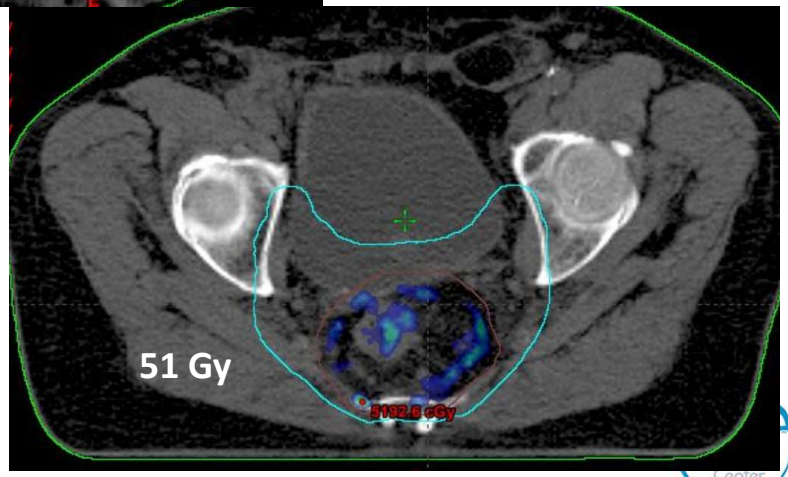




Simultaneous integrated boost IMRT

-- Primary tumor + involved nodes 50 Gy / 25 fr

-- Elective nodes 45 Gy / 25 fr



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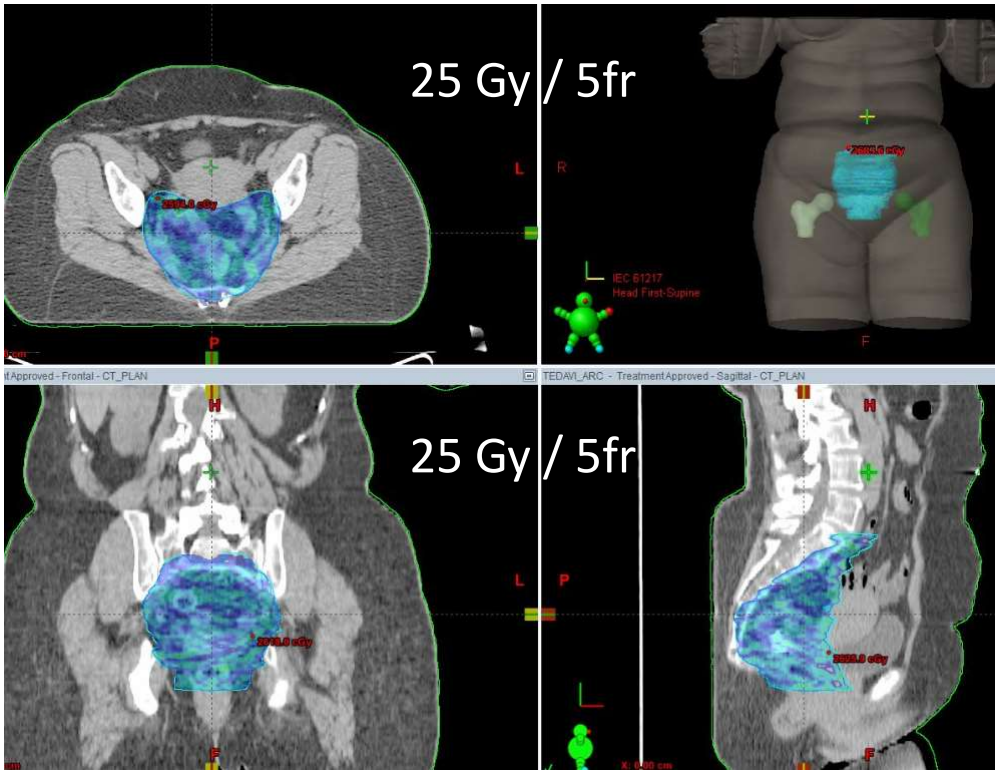
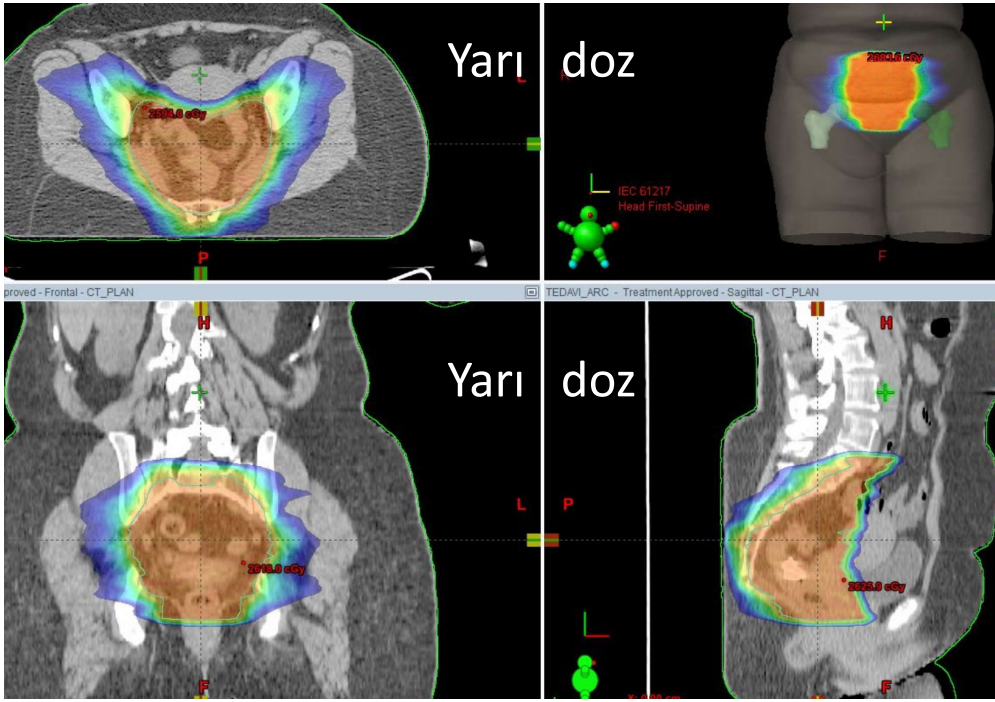
Short course RT (25 Gy / 5 fr IMRT)





Conclusion - 1

- Radiotherapy is an effective treatment for almost every rectal cancer stage.
- Neoadjuvant RT is more effective and less toxic than the adj. RT
- NRT could stregthen surgical «local» outcome even in the TME era
- NRT in combination with systemic chemotherapy help to better oncologic outcome (TNT)

Conclusion - 2

- Dose escalation and also consolidation chemo increase the response rates and could also open window of WW for selected distal rectum cancers.

- The quality of RT is utmost important