



Multi-disciplinary Care of Rectal Carcinoma

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Management of Rectal Cancer 1987-2024

Conclusions

- 1990's-debate over adjuvant treatment vs better surgery then neoadjuvant vs adjuvant
- 2000's-debate settled-preop CRT superior to post op- pCR observed-is organ preservation possible?
- 2010's-more aggressive neoadjuvant therapies leads to organ preservation and NAPRC formed (late)
- 2020's-evaluate better methods of achieving a CR and more organ preservation

Multidisciplinary Care of Rectal Carcinoma

Conclusions

- **The recent advances in care are the most satisfying events of my career**
- **~35% of patients can be successfully managed without surgery**
- **Identifying additional patients who can benefit from organ preservation is being investigated**
- **Improving cCR rates will someday make treatment outcomes of adenocarcinoma of the rectum similar to SCCa of the anal canal**

Historical Perspective: APR results



TABLE 23-5 Abdominoperineal Resection:
5-Year Survival Rate

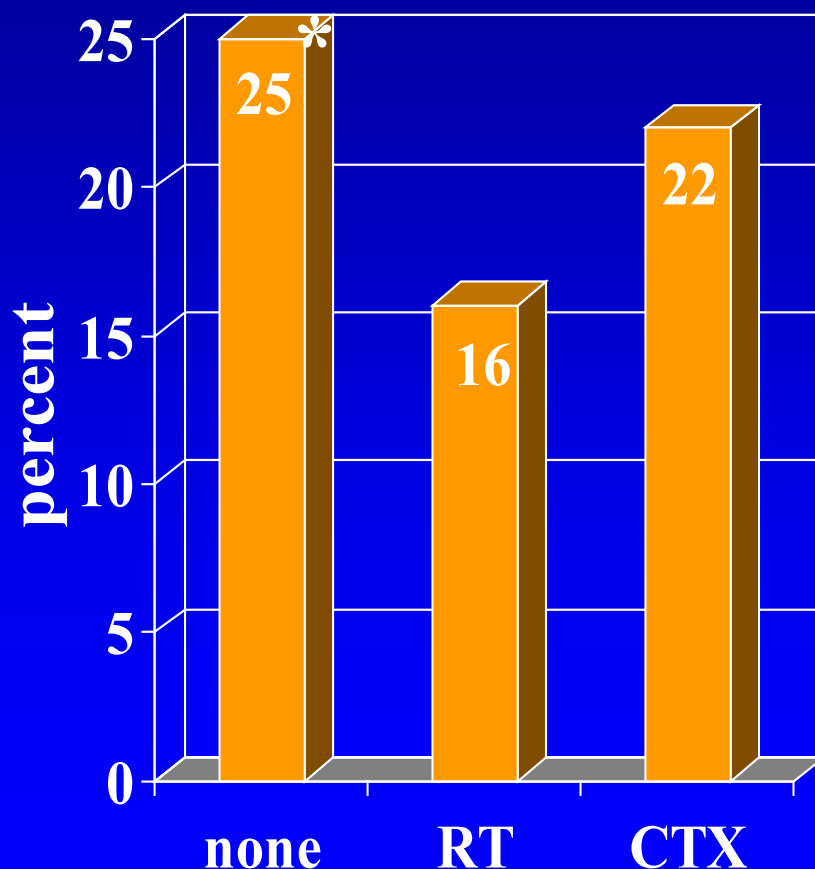
| Author, Year | Dukes' Lesion: | | |
|---------------------------------------|----------------|----|----|
| | A | B | C |
| Dukes, 1940 ¹⁸¹ | 93 | 65 | 23 |
| Gilbertsen, 1960 ²⁵⁴ | 80 | 50 | 23 |
| Slanetz et al., 1972 ⁷⁶⁶ | 81 | 52 | 33 |
| MacLennan et al., 1976 ⁵⁰⁷ | 91 | 59 | 25 |
| Strauss et al., 1978 ⁸⁰⁰ | 82 | 40 | 15 |
| Walz et al., 1977 ⁸⁵³ | 78 | 45 | 22 |

(From Rosen L, Veindenheimer MC, Collier JA, et al. Mortality, morbidity, and patterns of recurrence after abdominoperineal resection for cancer of the rectum. *Dis Colon Rectum* 1982;25:202, with permission.)

NSABP R-01

Impact of Adjuvant Therapy on Local Recurrence After Standard Radical Surgery for Stage II and III Rectal Carcinoma

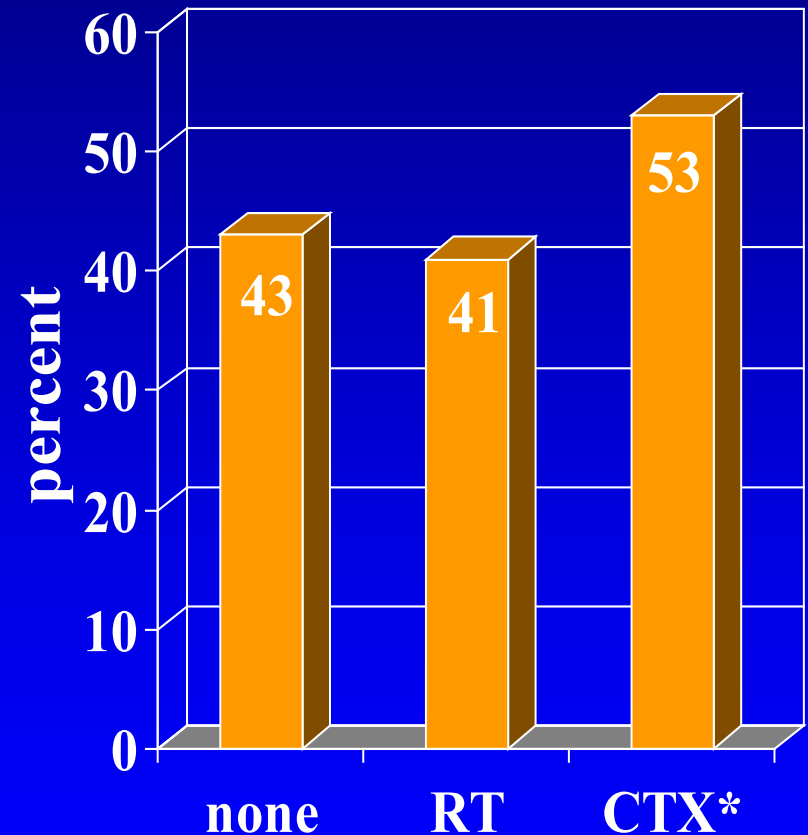
- RT improved LR from 25% in surgery only group to 16% in Surg +RT group ($p=0.05$)
- CTX did not improve local control



NSABP R-01

Impact of Adjuvant Therapy on Survival

- CTX improved survival from 53% to 43% and 41% (p=0.05)
- CTX did NOT improve local control

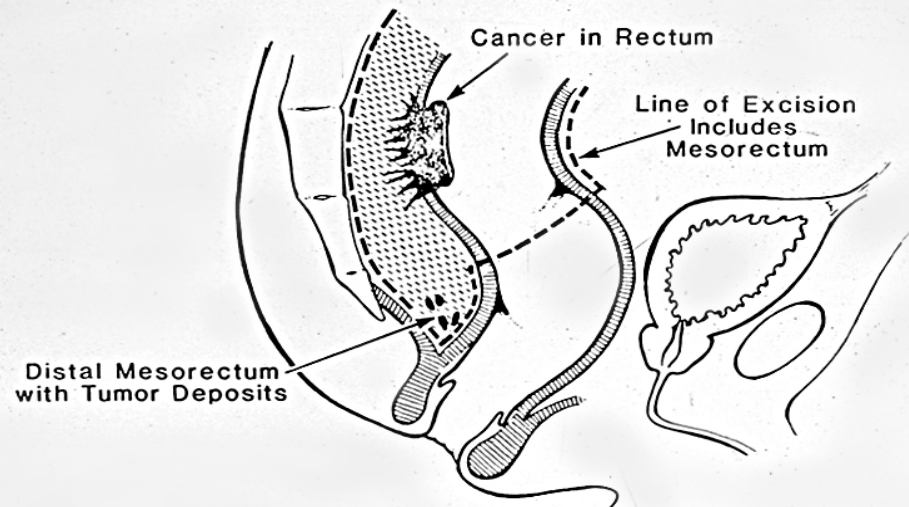




R.J. “Bill” Heald

Popularized TME
(total mesorectal
excision)

Cancer of Mesorectum

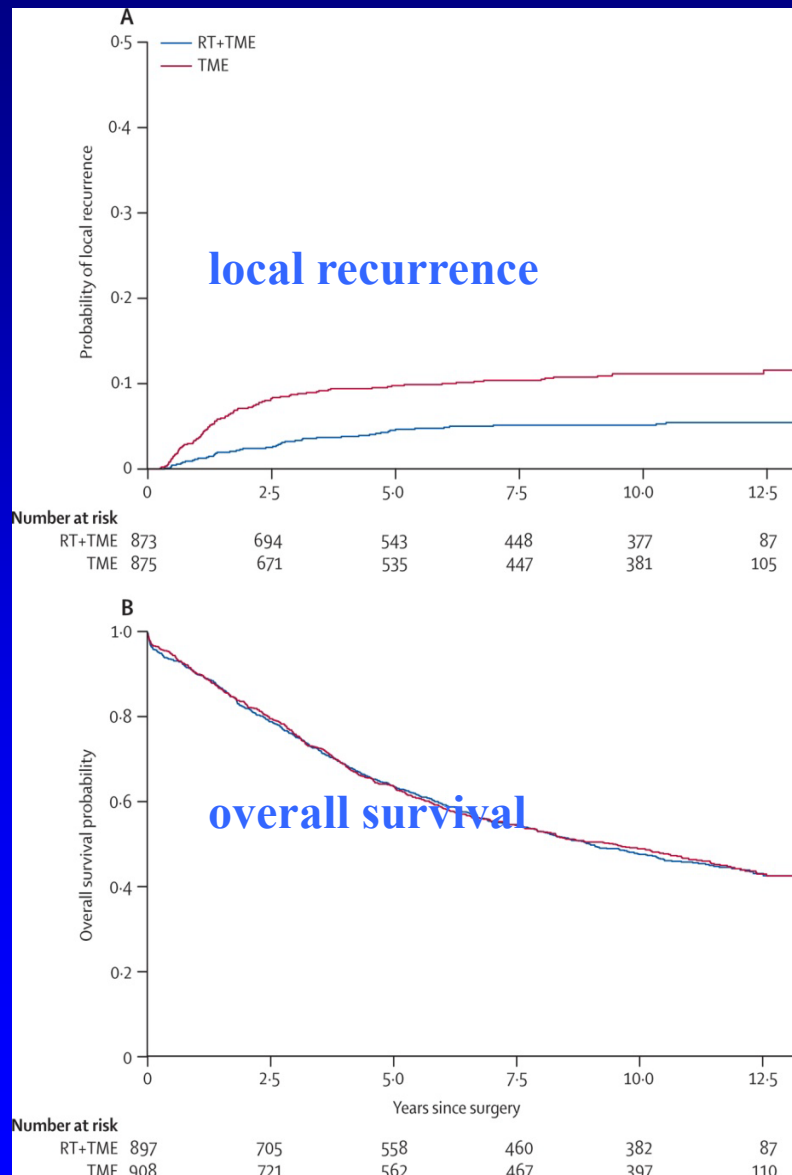


Adapted From: RJ Heald et al, Br J Surg 1982

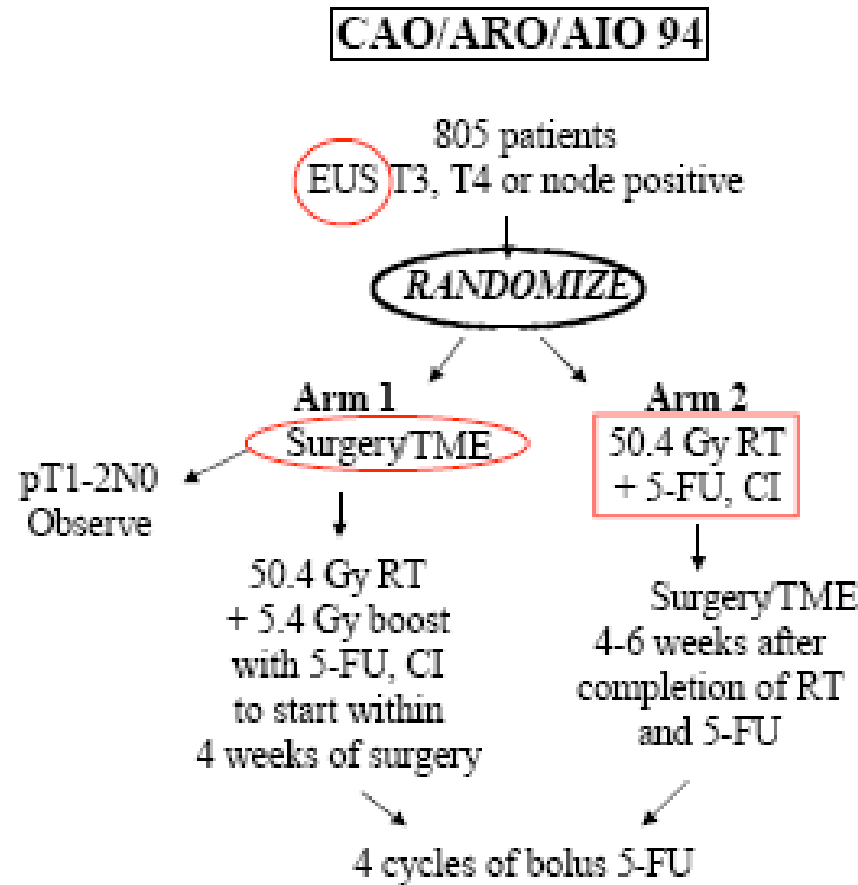
RJ Heald, Br J Surg, 1982

Dutch TME trial -12 year follow up

Compared TME alone vs preop RT then TME



German Rectal Cancer Group



Sauer et al.: N Engl J Med 351, 2004

German Rectal Cancer Trial

Post op CRT

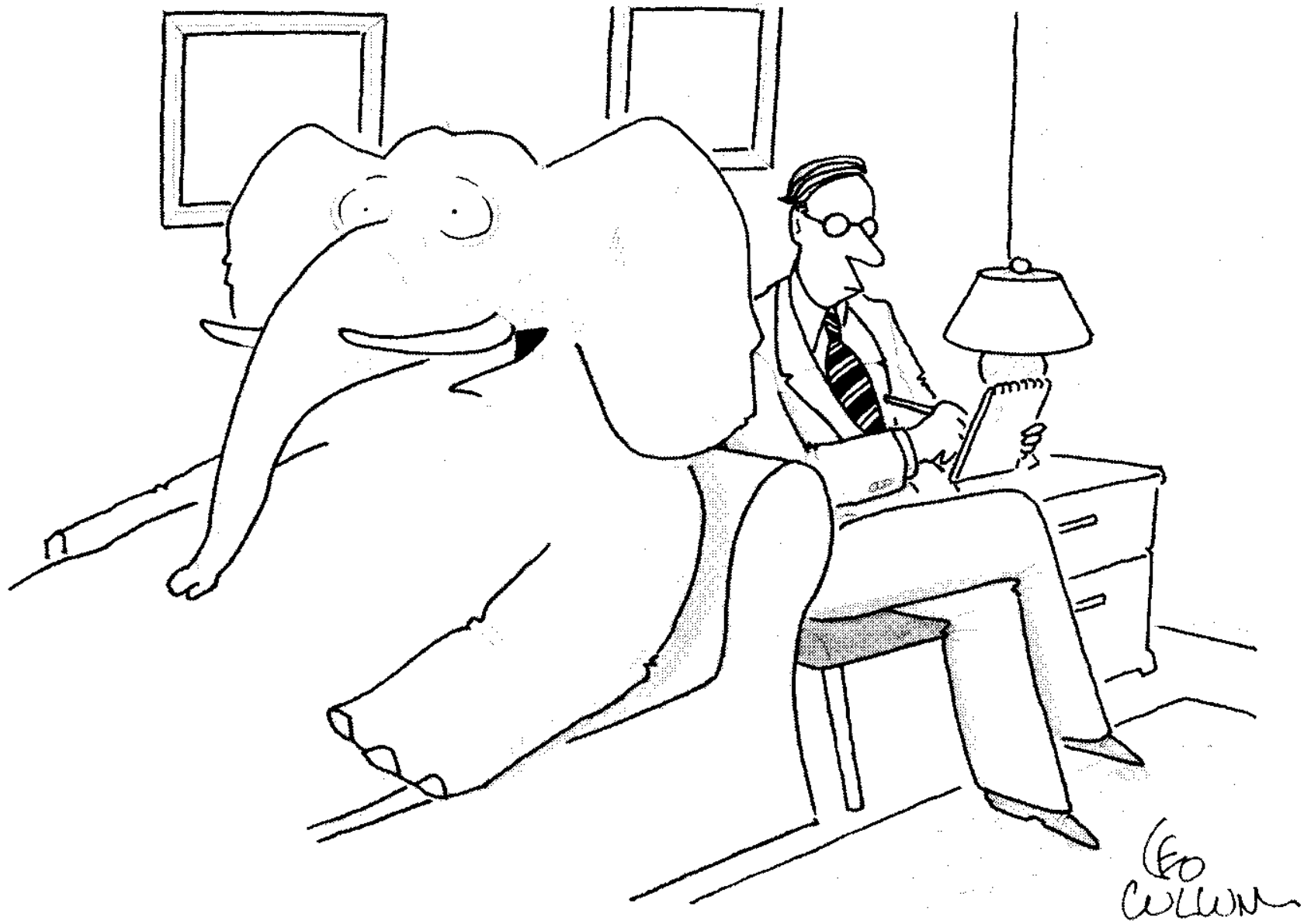
Pre op CRT

5 year

| | | | |
|-----------------------------|------------|------------|------------------|
| Pelvic Recurrence | 13% | 6% | p = .006 |
| Distant Recurrence | 34% | 30% | p = 0.52 |
| DFS | 65% | 68% | p = 0.32 |
| OS | 74% | 76% | p = 0.80 |
| Grade 3+4 toxicity | 40% | 27% | p = .001 |
| Anastomotic Stenosis | 12% | 4% | p = .003 |
| Postop Morbidity | 34% | 36% | p = 0.68 |
| pCR | 0% | 8% | |
| Stage III | 40% | 25% | p = 0.004 |

Surgery for Rectal Carcinoma: Goals/Obligations and Expectations

- Combined modality treatment with preoperative CRT and *standardized surgery* has resulted in very low rates of LR and high rates of sphincter preservation
- Difficult to even mathematically fathom a trial that can be done to improve the local control outcomes as described in the German Rectal Cancer Trial
- Now at a philosophical fork in the road



"I'm right there in the room, and no one even acknowledges me."

German Rectal Cancer Trial

Post op CRT

Pre op CRT

5 year

| | | | |
|-------------------------|-----|-----|-----------|
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| pCR | | 8% | |
| Stage III | 40% | 25% | p = 0.004 |
| Sphincter Preservation* | 19% | 39% | p = 0.004 |
| Rectal preservation* | 0 | 0 | |

Defining cCR

Absence of Residual Disease

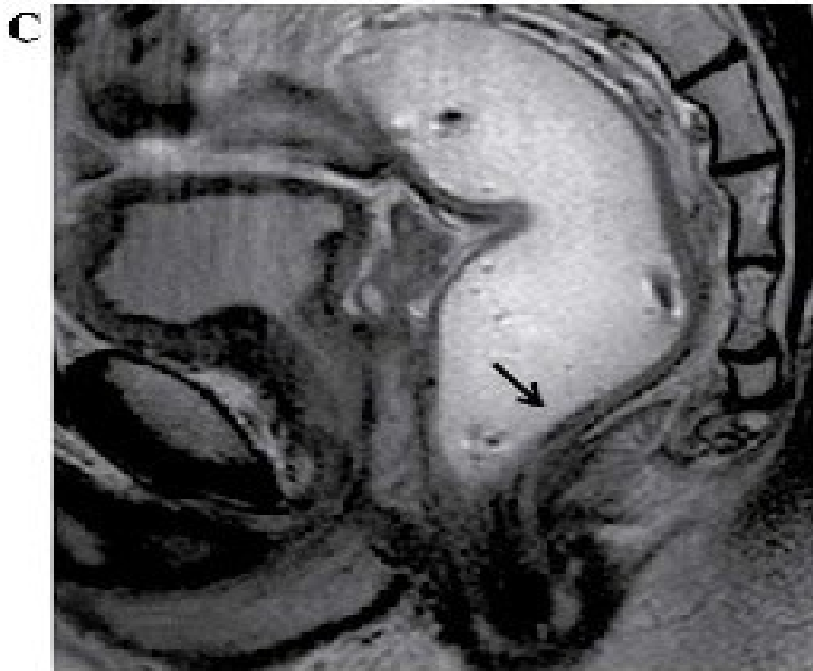
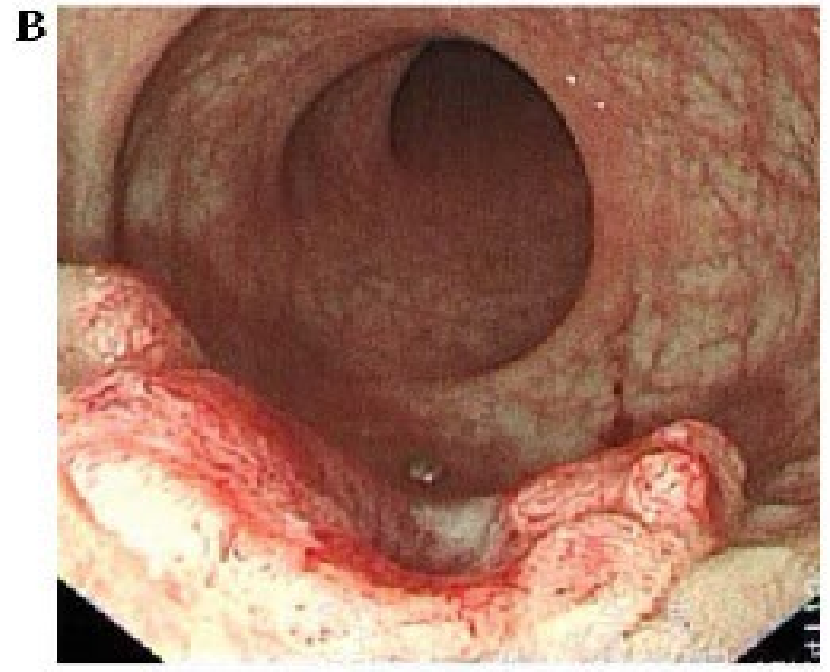
- **Incomplete response**
 - Deep ulceration +/- necrosis
 - Palpable discrete nodule
 - Any non-epithelialized lesion
 - Significant stenosis
- **NOT considered an incomplete response**
 - Whitening of mucosa with reduced pliability
 - Telangiectasia
 - Tumor not felt or seen

Rectal Carcinoma: Goals/Obligations and Expectations of Surgery

- **Goals**
 - Save lives
 - Maintain QOL
- **Enbloc excision of tumor and lymphovascular pedicle and any adjacent structure-R-0**
 - Local control**
 - 1st obligation**
 - Maintain function**
 - 2nd obligation**
 - Manage complications**
 - “first do no harm”**

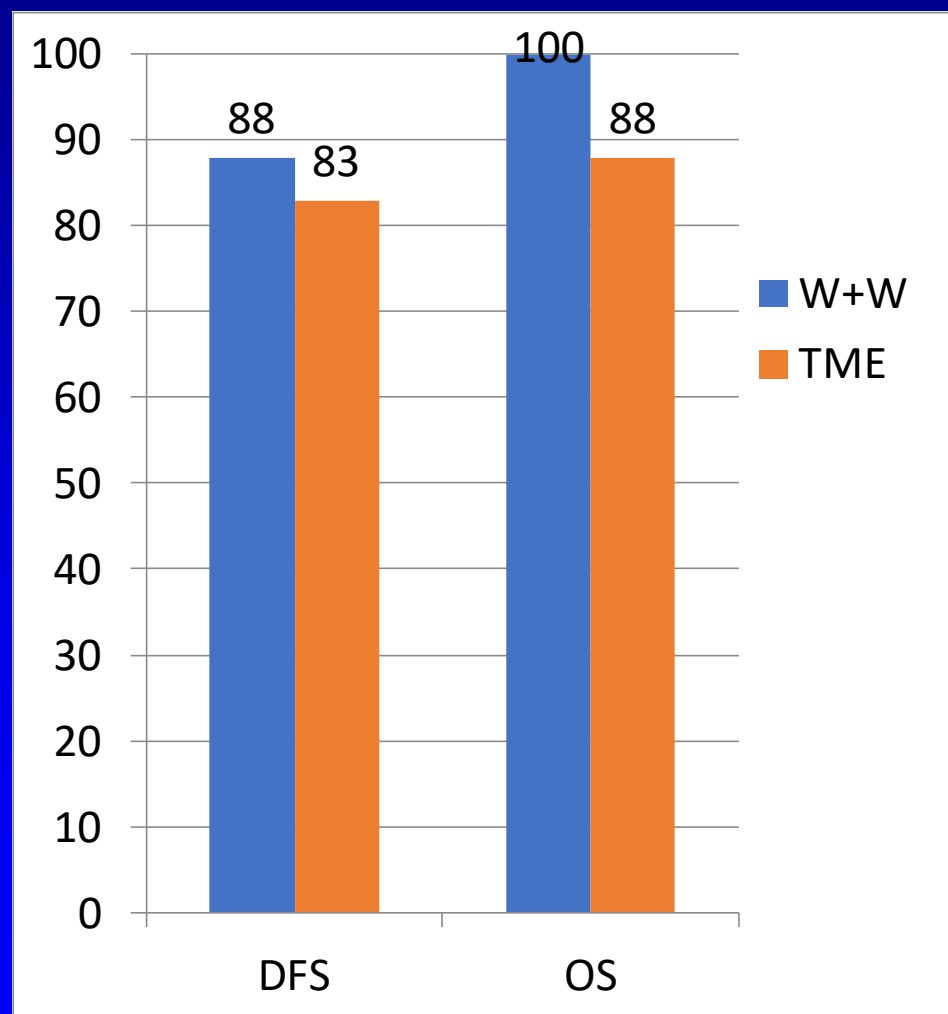
Clinical Complete Response





Operative vs Nonoperative Treatment ypStage 0 Rectal Cancer

- **71/265 (27%) cT2-4** achieved cCR after CRT and observed only; **194/265 (73%)** achieved a cPR and underwent standard TME
- **22/194 PR** found to be ypT0N0M0



Local recurrence after cCR and watch and wait: Impact on salvage

- cCR after CRT+ CTX for cT2-4 distal rectal cancer achieved in 90/183 (49%)
- 28/90 (31%) tumor re-growth in 5 years
 - 17/90 (19%) within one year
 - 11/90 (12%) year 2-5
 - 5 year cCR-pCR=62/183 (34%)
- Salvage after recurrence/re-growth
 - R-0 in 25/28 (93%)
- Cancer specific OS-91%: DFS-68%

Avoiding TME after pCR to CRT

San Paolo Experience Exported

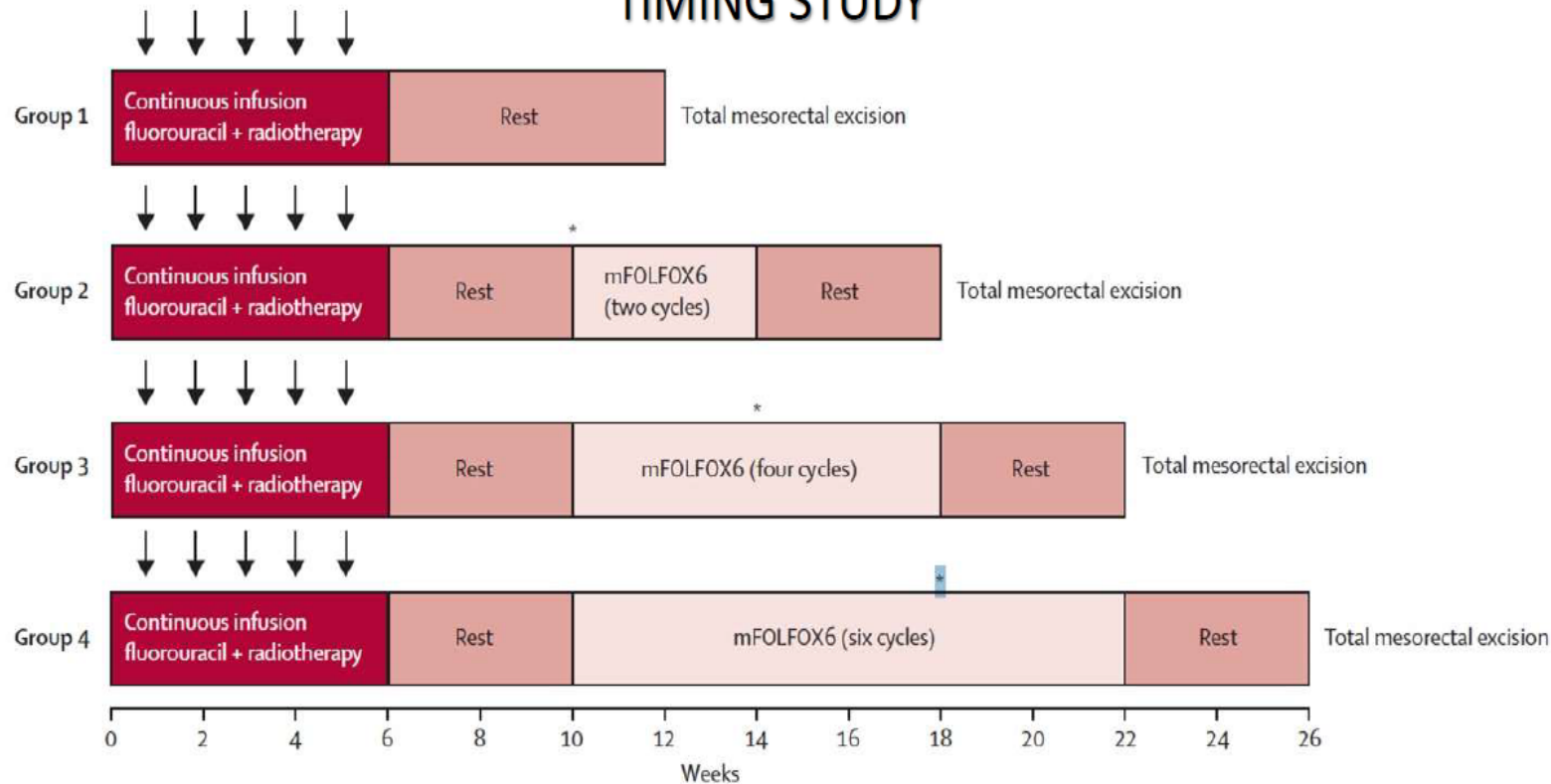
- **Many others have reported their single institution reviews**
 - **MSKCC**
 - **MD Anderson**
 - **Norway national review**
 - **Dutch rectal cancer group**
- **All report local control > 88% (88-98) when pCR observed or proven by local excision**

pCR Rates After CRT-NCDB

- **27,532 cases from 2004-2014 in 1179 hospitals**
- **cStage II-46% cStage III-54%**
- **pCR-13%**
 - **Interval of >60 days between RT+ Surg**
 - **Lower T and N stage, size, grade**
 - **Facility surgical volume**
 - **Insurance class**

Adding Chemotherapy (TNT approach)

“TIMING STUDY”



| Response | Group 1 (n = 60) | Group 2 (n = 67) | Group 3 (n = 67) | Group 4 (n=65) | p value |
|------------------------------------|---------------------|---------------------|---------------------|-------------------|---------|
| Pathologic complete response (pCR) | 11 (18%) | 17 (25%) | 20 (30%) | 25 (38%) | 0.0036 |

MSKCC Adoption of TNT

- 308 patients treated with systemic chemo and CRT then re-assessment
- 235/308 (76%) underwent TME -43/235 (18%) who had pCR
- 73/308 (24%) were entered into watch +wait-67/73 (92%) had sustained CR at 12 months
- pCR+cCR=110/308 (36%)
 - cStage II-53.5%
 - cStage III-32.8%

TNT-initial UPMC approach 2016-17*

(n=31)

- **FOLFOX x 6 cycles + CRT for cStage II-III**
- **DRE, flex sig, and MRI prior to and after treatment-
surgical plan made not at presentation but after all neo-
adjuvant Rx**
- **cCR defined by clinical exam and MRI**
- **Rectal preservation for cCR and all patient with
pretreatment cT2 (CRT only) unless ypT3 or margin+**
- **Favor FTLE* over W+W except in special circumstances
–proceed with TME if residual carcinoma**
- **Among patients who achieve rectal preservation TME
offered for pelvic recurrence**

TNT at UPMC results 2016-2017* (n=31)

Pathology

Watch and Wait-5 (16%)

FTLE-7 (23%)

**6-ypT0-1 patient recurs at 4 months-TME
ypT2N0M0-R-0**

1-ypT1-TME –ypT0N0M0-R-0


TME-19 (61%), PS CAA-15; APR-4

3-ypT0N0 (16%)

5-ypStage I-3 patients ypT1N0+2 ypT2N0

6-ypT3N0

5-ypStage III-2 ypT2N1; 3ypT3N1



TNT at UPMC results 2016-2017*

Surgery

Organ preservation-10 (32%)*

W+W-5

FTLE-5 (of the 7)

Sphincter preservation-27 (87%)

**one patient underwent APR despite cCR as
he refused to commit to f/u-ypT0N0**

NAPRC at UPMC

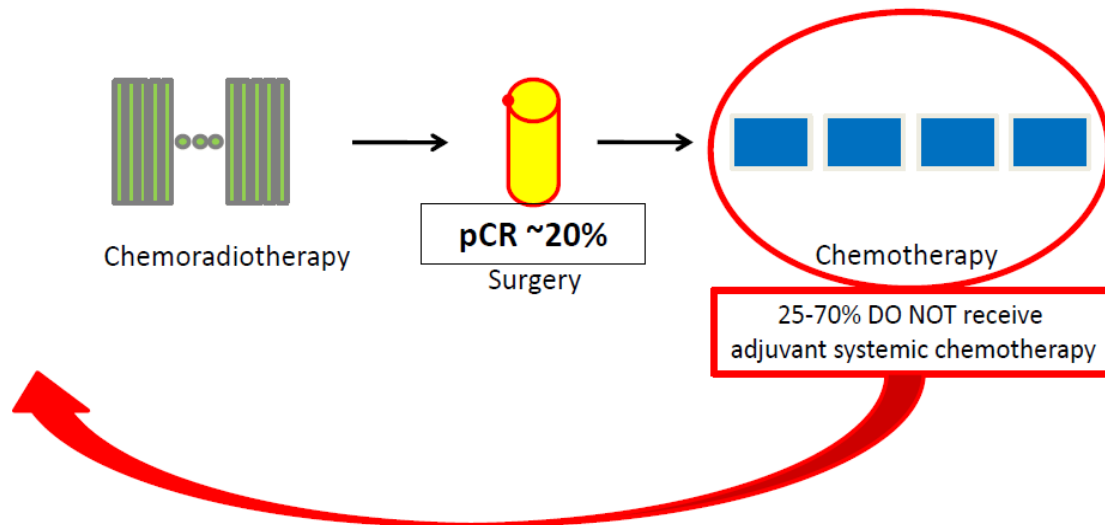
2022-23 snapshot

| | CASES | |
|----------------------------|----------------------|------------|
| TNT | cStage II+III | |
| Outcome presented | 235 | |
| Non-operative (W+W) | 99 | 42% |
| Operative | 136 | 58% |

Why TNT?

Total Neoadjuvant Therapy (TNT)

Current Tri-Modality Paradigm for
T3-4 or Node + Rectal Cancer



O'Connell MJ, et al. *J Clin Oncol* 2014;32(18):1927-34

Khrizman P, et al. *J Clin Oncol* 2013 Jan 1;31(1):30-8

Roh M, et al. *J Clin Oncol* 2009;27:5124-30

Sauer R, et al. *N Engl J Med* 2004;351:1731-40

**TNT-what treatment first?
Induction vs Consolidation
Chemotherapy**

Preliminary results of the organ preservation of rectal adenocarcinoma (OPRA) trial.

| | Induction | | Consolidation | | 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 |

3-year rates with 95% CI.

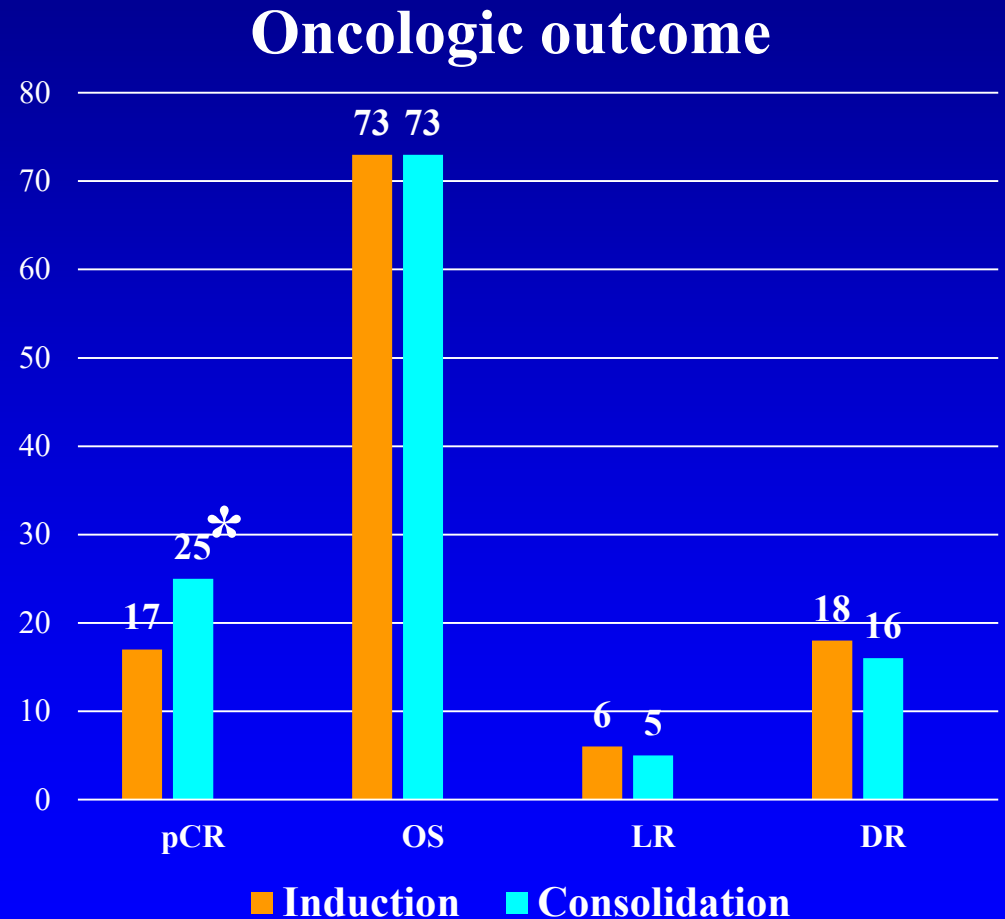
*log-rank test

JCO abstract 2020

German Rectal Cancer Study Group

TNT-Induction vs Consolidation FOLFOX

- 311 patients randomized to induction vs consolidation FOLFOX
- Only 3 cycles
- All patients underwent TME
- Mean F/U-43 mo.(35-60)



Controversies

- Biopsy after TNT
- MRI or clinical exam?
- Is watch and wait safe for cN+ patients?
- How long should we wait before committing to TME
- Can full thickness local excision replace TME? When?

Post TNT Assessment

Role of Biopsy

| | Partial response | Complete response | Total |
|-----------------|------------------|-------------------|-------|
| Positive biopsy | 25 | 0 | 25 |
| Negative biopsy | 11 | 3 | 14 |
| | 36 | 3 | 39 |

Negative biopsy does not equal CR

NPV=21%

Controversies

- Biopsy after TNT
- **MRI or clinical exam?**
- Is watch and wait safe for cN+ patients?
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Post treatment Assessment Predicting Complete Response

| | Clinical exam | T2W MRI –DWI | Both |
|---------------------------|---------------|--------------|------|
| Positive predictive value | 90% | 75% | 98% |
| Negative predictive value | 20% | 26% | 15% |

Controversies

- Biopsy after TNT
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Organ Preservation Among Patients With Clinically Node-Positive Rectal Cancer: Is It Really More Dangerous?

| Variable | cN- (n=135/218-62%) | cN+ (n=62/117-53%) |
|---------------------------|---------------------|--------------------|
| Local regrowth | 40 (29.6%) | 15 (24.2%) |
| Site of regrowth | | |
| endoluminal | 40 (100%) | 14 (93.3%) |
| mesorectal | 0 | 1 (6.7%) |
| Organ preservation at F/U | 96 (71.1%) | 48 (77.4%) |
| Systemic recurrence | 17 (12.6%) | 10 (16.1%) |
| Cancer specific survival | 123 (91.1%) | 58 (93.6%) |
| | | |

Controversies

- Biopsy after TNT
- MRI or clinical exam?
- Is watch and wait safe for cN+ patients?
- **How long should we wait before committing to TME**
- Can full thickness local excision replace TME? When?

66 yom, cT3N0 at Level 0

Tolerated CRT+FOLFOX

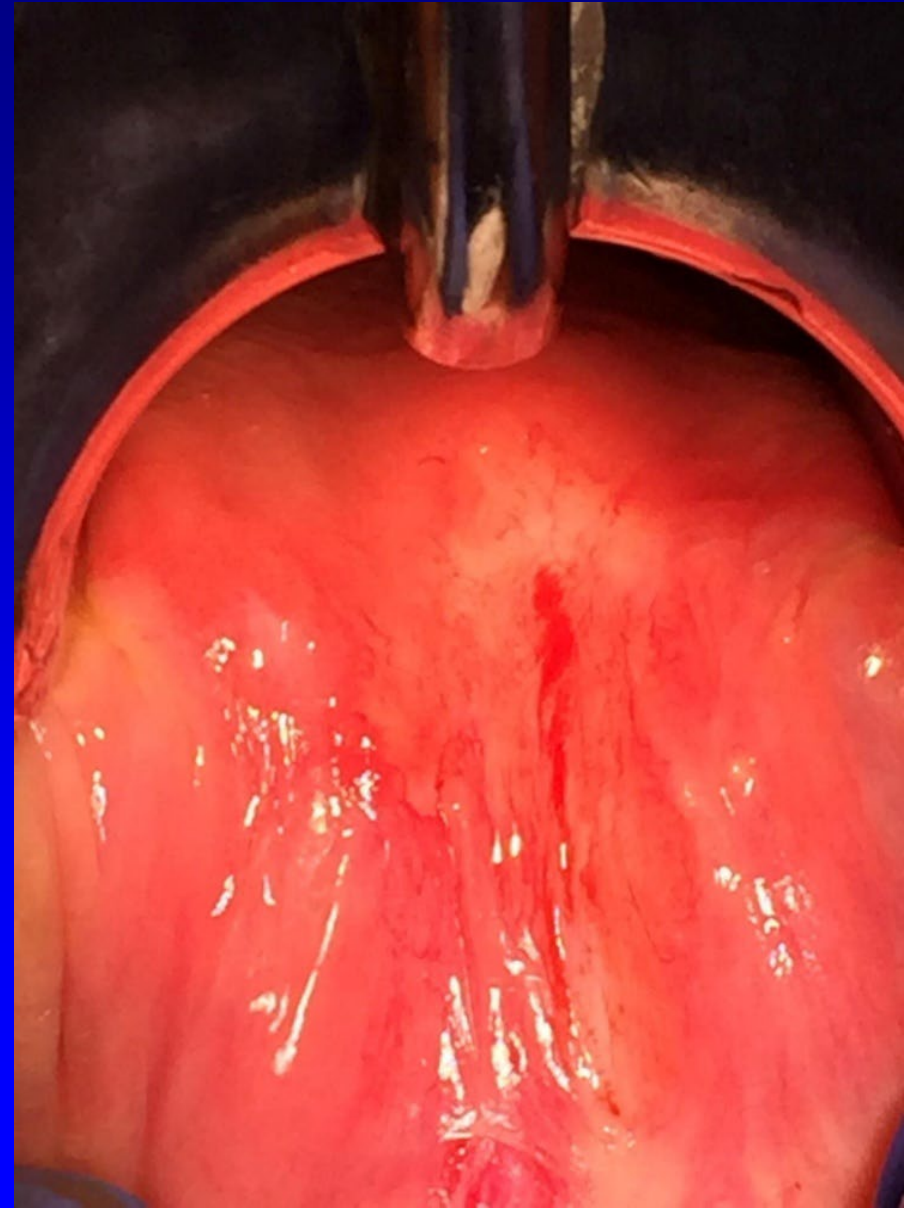
Firm nodularity

MRI-CR

**EUA-core needle biopsy
-persistent adenocarcinoma**

APR deferred 5 months

ypT0N0



Controversies

- Biopsy after TNT
- MRI or clinical exam?
- Is watch and wait safe for cN+ patients?
- How long should we wait before committing to TME
- **Can full thickness local excision replace TME? When?**

44 yof, cT3N0 at 8 weeks after TNT

MRI- CR

FTLE-ypT1

PS-CJAA-ypT0N0



Dutch Experience

Local Excision for Re-growth

- **77** of 591 W+W patients underwent local excision for suspected regrowth (F/U 39-69 months, mean 53)-84/591 TME directly
 - 28/77-ypT0 or adenoma
 - 11/77-ypT1
 - 38/77-ypT2-3; **13/38-TME**
 - 14/64 (77-13) recur-all salvaged with TME
 - 14/36 (64-28)-39% with proven cancer regrowth recur
- Rectal preservation-63%
- OS-96%

Is Watch and Wait Risky?

Dutch experience with extended W+W

Uncertain cCR-68

- 28/68-PR by exam and MRI
- 11/68-PR exam, CR by MRI
- 29/68-CR by exam, PR by MRI

FTLE performed on 19/68

- ypT0-10/19; ypT1-3/19; ypT2-6/19

Extended observation 49/68

- 44/49 sustained CR; 5/49- TME, all R-0

Local regrowth-27%

Not different from 102 patients cCR by both modalities at initial post CRT assessment

International Watch and Wait Database

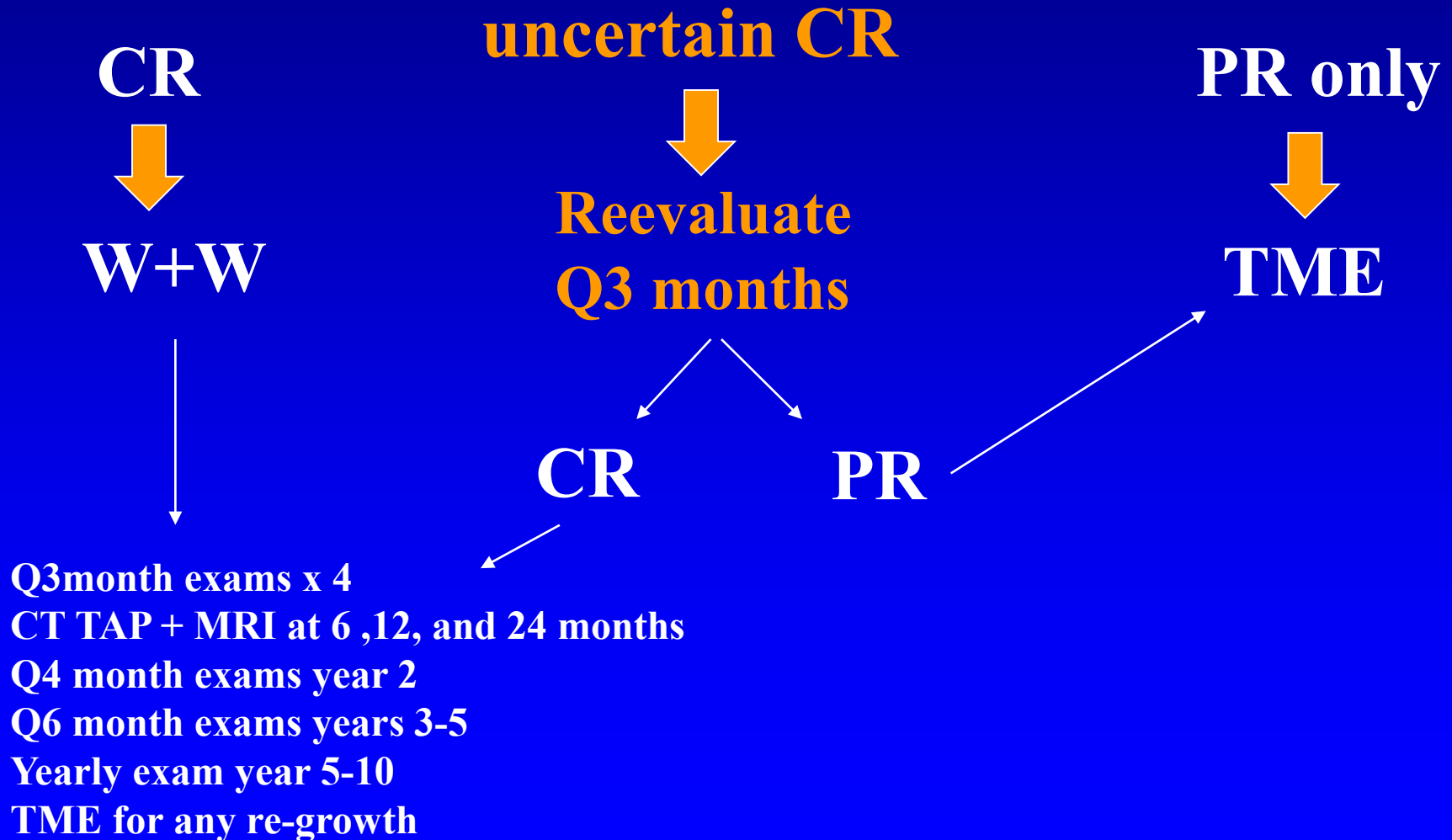
Impact of local regrowth on distant metastasis

- 793 patients entered into W+W; f/u 36-75 months, mean 55)
- 581/793 (73%) no regrowth
 - 34/581 (6%) develop distant metastasis
- 212/793 (27%)-local regrowth
 - 51/212 (24%) develop distant metastasis

Current Standard Treatment at UPMC NAPRC Sites

Prior to and after TNT (consolidation chemo)

Clinical exam + flex sig, MRI-DWI , CT TAP*



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