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# 17th ESO-ESMO-EONS Masterclass
# Management of rectal cancer

David Sebag-Montefiore

Audrey and Stanley Burton Professor of Clinical Oncology

Leeds Cancer Centre UK

@MontefioreD

+ Razvan Popescu


TUMOR ZENTRUM AARAU TZA

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# Summary of topics

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- Quality of imaging, surgery and pathology
- Effectiveness of pre-operative radiotherapy
- ESMO treatment guidelines
- Evidence for (C)RT from clinical trials
- Future directions

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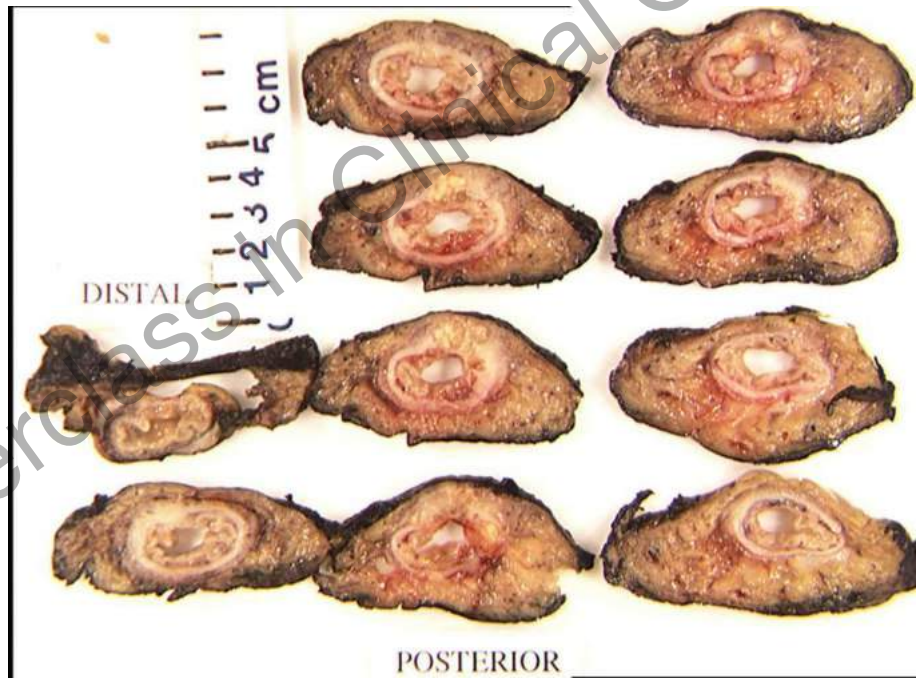
# Histopathology




+ve CRM = microscopic tumour
<=1mm from the painted margin

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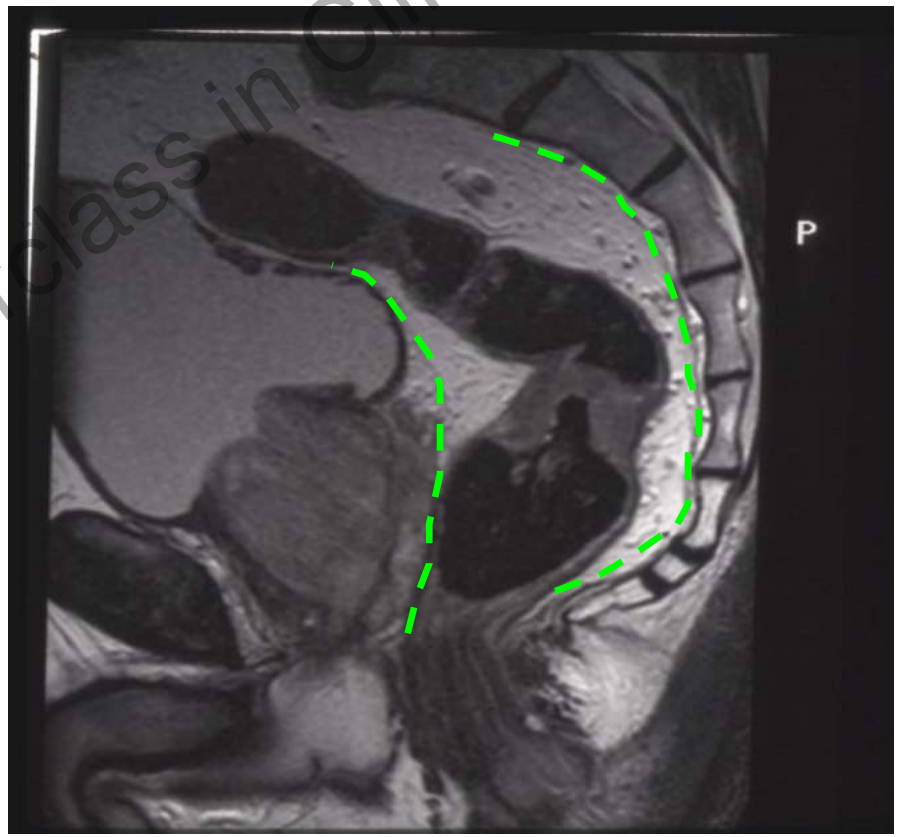
# MRI – mesorectal fascia

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# Role of circumferential margin involvement in the local recurrence of rectal cancer

Adam et al Lancet 1994;344;707-711

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- All patients n=190 LR 29%
- "Curative resections" n=141 LR 23%
  - CRM+ve (25%) n=35 LR 66%
  - CRM -ve (75%) n=106 LR 8%

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# CR07 – Plane of surgical specimen

## Quirke et al 2009

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Mesorectal

n=596

53%

Intra-mesorectal

n=382

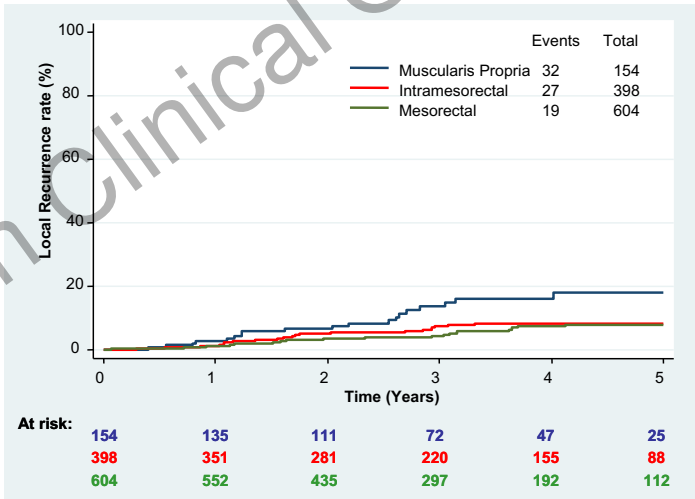
34%

Muscularis propria

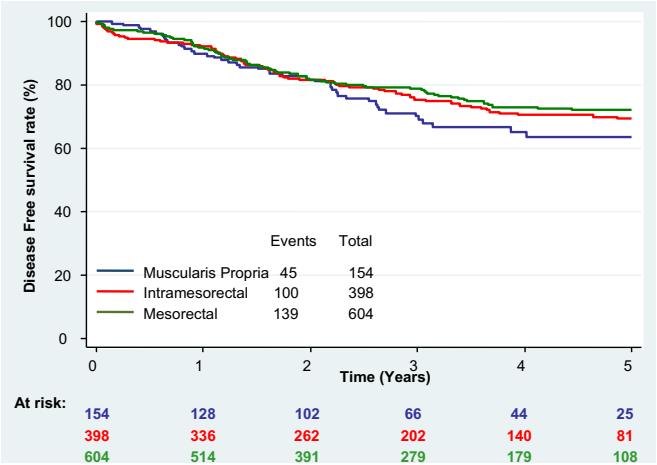
n=141

13%

Local recurrence




Disease free survival

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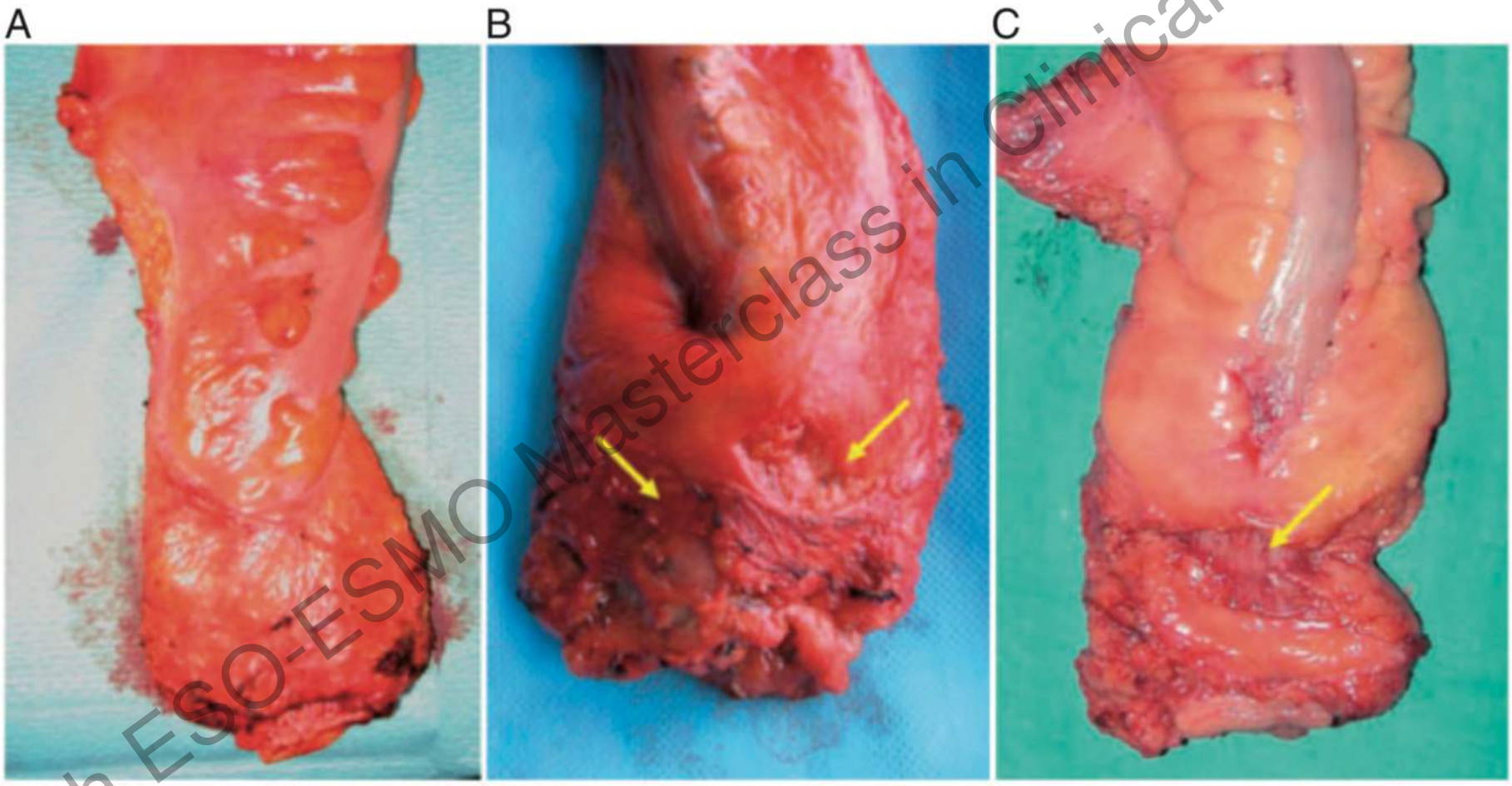


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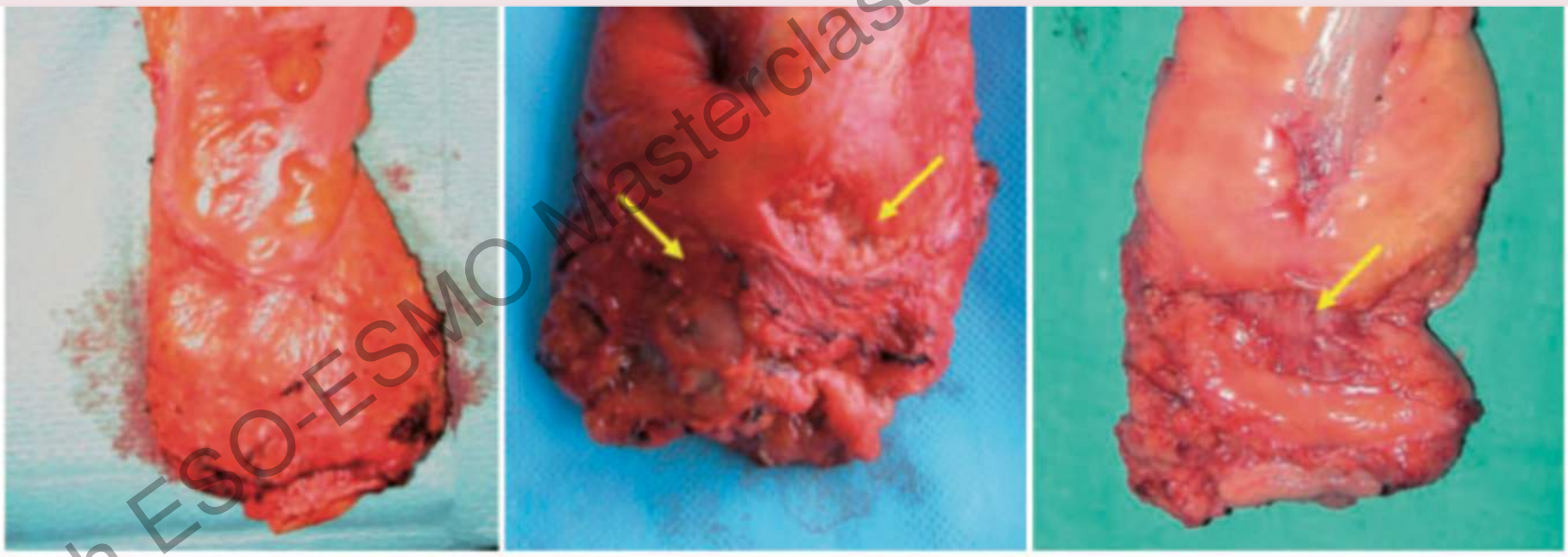
**Table 5. Grading of quality and completeness of the mesorectum in a total mesorectal excision specimen according to the plane of surgical excision [27]**

| | |
|---|---|
| Mesorectal plane (good plane of surgery achieved) | Intact mesorectum with only minor irregularities of a smooth mesorectal surface; no defect deeper than 5 mm; no coning; and smooth circumferential resection margin on slicing |
| Intramesorectal plane (moderate plane of surgery achieved) | Moderate bulk to mesorectum, with irregularities of the mesorectal surface; moderate distal coning; muscularis propria not visible with the exception of levator insertion; and moderate irregularities of circumferential resection margin |
| Muscularis propria plane (poor plane of surgery achieved) | Little bulk to mesorectum with defects down onto muscularis propria; very irregular circumferential resection margin; or both |

The specimen is examined as a whole (fresh) and as cross-sectional slices (fixed) to make an adequate interpretation. A TME specimen ideally should have a smooth surface, without incisions, defects or cracks, as an indication of successful surgical excision of all mesorectal tissue. 'Coning' represents the tendency for the surgeon to cut inwards towards the central tube of the rectum during distal dissection, rather than staying outside the visceral mesorectal fascia. The specimen then shows a tapered, conical appearance representing suboptimal surgical quality.
TME, total mesorectal excision.



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# Radiotherapy reduces LR for all planes of surgical excision Quirke et al Lancet 2009

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| | Muscularis propria | Intramesorectal % HR (95% CI) | Mesorectal % HR (95% CI) |
|---|---|---|---|
| All patients | 13% | 7% 0.48 (0.25-0.93) | 4% 0.32 (0.16-0.64) |
| | | | |
| Selective post | 16% | 10% 0.49 (0.23-1.06) | 7% 0.48 (0.23-1.00) |
| Pre-op RT | 10% | 4% 0.52 (0.15-1.79) | 1% 0.09 (0.02-0.49) |

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# Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma – Wong et al Cochrane review 2007

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- 19 trials >8000patients

**Total (95% CI)** 100.0 % 0.93 [ 0.87, 1.00 ]

Heterogeneity: $Chi^2$ = 18.29, df = 13 (P = 0.15); $I^2$ =29%

Test for overall effect: Z = 2.06 (P = 0.039)

Test for subgroup differences: Not applicable

Overall mortality

0.1 0.2 0.5 1 2 5 10

**Total (95% CI)** 100.0 % 0.87 [ 0.78, 0.98 ]

Heterogeneity: $Chi^2$ = 8.70, df = 4 (P = 0.07); $I^2$ =54%

Test for overall effect: Z = 2.40 (P = 0.016)

Test for subgroup differences: Not applicable

Cause specific mortality

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

**Total (95% CI)** 100.0 % 0.71 [ 0.64, 0.78 ]

Heterogeneity: $Chi^2$ = 68.71, df = 11 (P<0.00001); $I^2$ =84%

Test for overall effect: Z = 6.76 (P < 0.00001)

Test for subgroup differences: Not applicable

Local recurrence

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

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# Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer- Caluwe Cochrane review 2012

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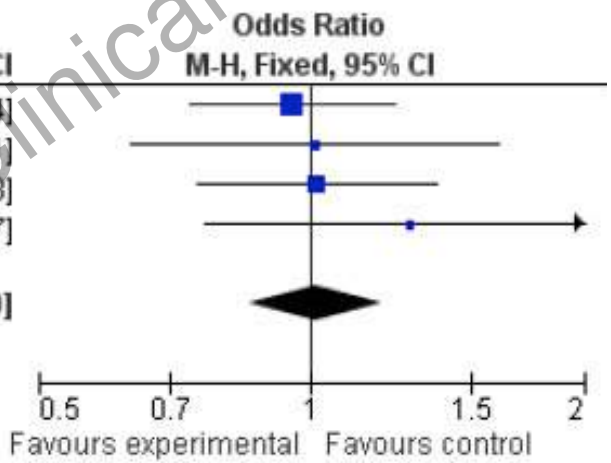
- 5 trials >2000 patients

## Overall Survival

| Study or Subgroup | Chemoradiation Events | Chemoradiation Total | Radiotherapy Events | Radiotherapy Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bosset 2006 | 173 | 506 | 178 | 505 | 45.2% | 0.95 [0.74, 1.24] |
| Bujko 2006 | 53 | 157 | 52 | 155 | 13.4% | 1.01 [0.63, 1.61] |
| Gerard 2006 | 128 | 375 | 124 | 367 | 31.8% | 1.02 [0.75, 1.38] |
| Boulis-Wassif 1984 | 49 | 126 | 40 | 121 | 9.6% | 1.29 [0.77, 2.17] |
| **Total (95% CI)** | | **1164** | | **1148** | **100.0%** | **1.01 [0.85, 1.20]** |
| Total events | 403 | | 394 | | | |

Heterogeneity: Chi² = 1.02, df = 3 (P = 0.80); I² = 0%

Test for overall effect: Z = 0.15 (P = 0.88)

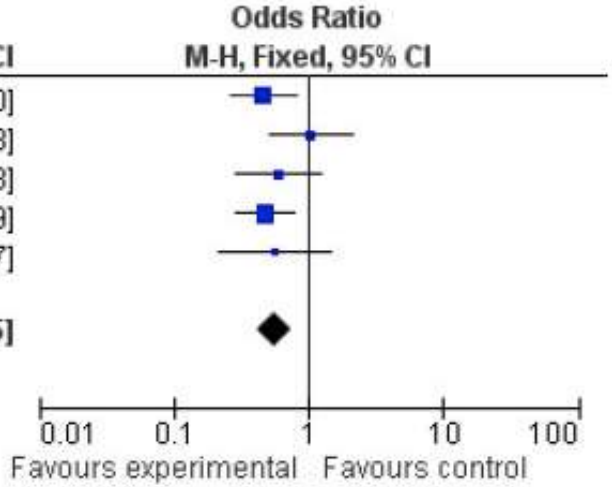



## Local Recurrence

| Study or Subgroup | Chemoradiation Events | Chemoradiation Total | Radiotherapy Events | Radiotherapy Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bosset 2006 | 22 | 253 | 43 | 252 | 30.0% | 0.46 [0.27, 0.80] |
| Boulis-Wassif 1984 | 19 | 124 | 18 | 121 | 11.8% | 1.04 [0.51, 2.08] |
| Bujko 2006 | 13 | 155 | 21 | 157 | 14.6% | 0.59 [0.29, 1.23] |
| Gerard 2006 | 25 | 375 | 49 | 375 | 34.9% | 0.48 [0.29, 0.79] |
| Ngan 2010 | 7 | 163 | 12 | 163 | 8.8% | 0.56 [0.22, 1.47] |
| **Total (95% CI)** | | **1070** | | **1068** | **100.0%** | **0.56 [0.42, 0.75]** |
| Total events | 86 | | 143 | | | |

Heterogeneity: Chi² = 3.86, df = 4 (P = 0.43); I² = 0%

Test for overall effect: Z = 3.98 (P < 0.0001)

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# Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer-
## Caluwe Cochrane review 2012

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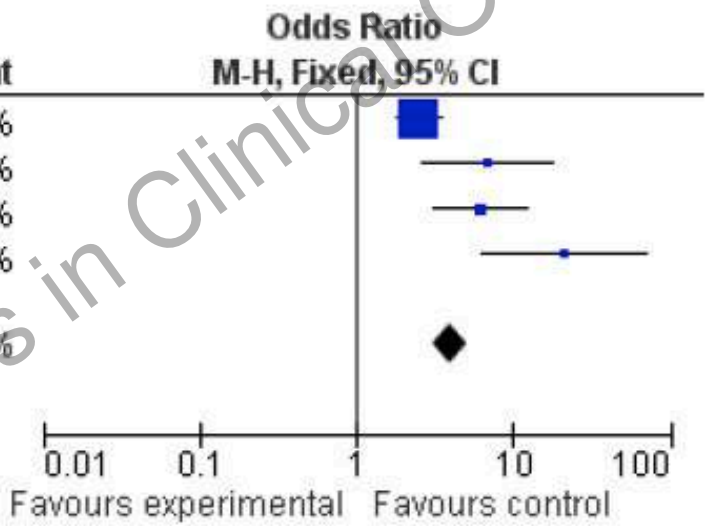
### Acute Toxicity

| Study or Subgroup | Chemoradiation Events | Chemoradiation Total | Radiotherapy Events | Radiotherapy Total | Weight |
|---|---|---|---|---|---|
| Bosset 2004 | 137 | 400 | 69 | 398 | 75.3% |
| Bujko 2006 | 29 | 157 | 5 | 155 | 6.8% |
| Gerard 2006 | 55 | 375 | 10 | 367 | 14.3% |
| Ngan 2007 | 46 | 163 | 3 | 163 | 3.6% |
| **Total (95% CI)** | | **1095** | | **1083** | **100.0%** |
| Total events | 267 | | 87 | | |

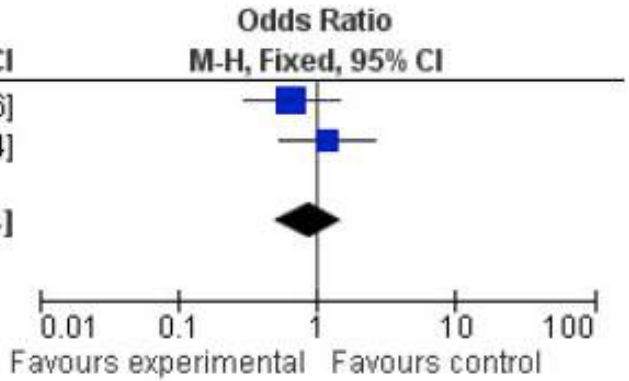
Heterogeneity: Chi² = 17.82, df = 3 (P = 0.0005); I² = 83%
Test for overall effect: Z = 10.06 (P < 0.00001)




### Late Toxicity

| Study or Subgroup | Chemoradiation Events | Chemoradiation Total | Radiotherapy Events | Radiotherapy Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bujko 2006 | 11 | 157 | 16 | 155 | 57.7% | 0.65 [0.29, 1.46] |
| Ngan 2010 | 14 | 163 | 12 | 163 | 42.3% | 1.18 [0.53, 2.64] |
| **Total (95% CI)** | | **320** | | **318** | **100.0%** | **0.88 [0.50, 1.54]** |
| Total events | 25 | | 28 | | | |

Heterogeneity: Chi² = 1.04, df = 1 (P = 0.31); I² = 4%
Test for overall effect: Z = 0.45 (P = 0.65)

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# MERCURY Trial - Primary end point

Radiology 2007 243: 132-139;
BMJ 2006 333:779-783

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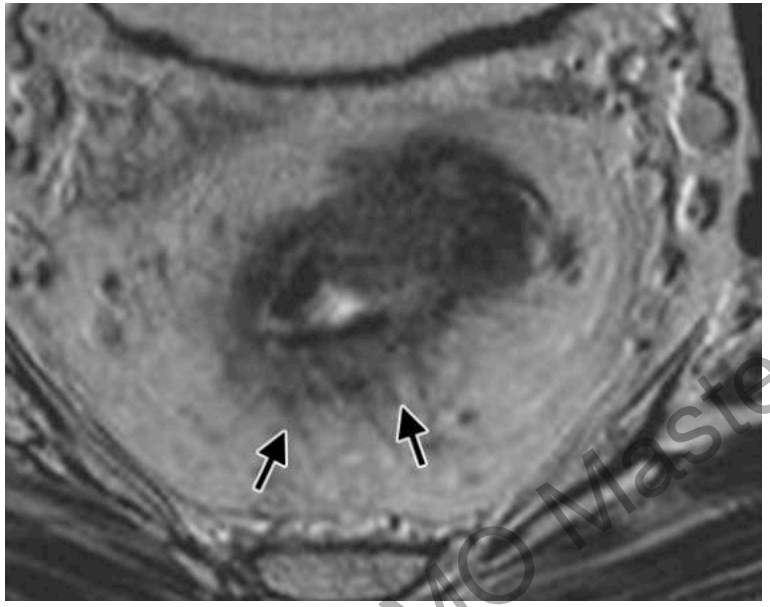

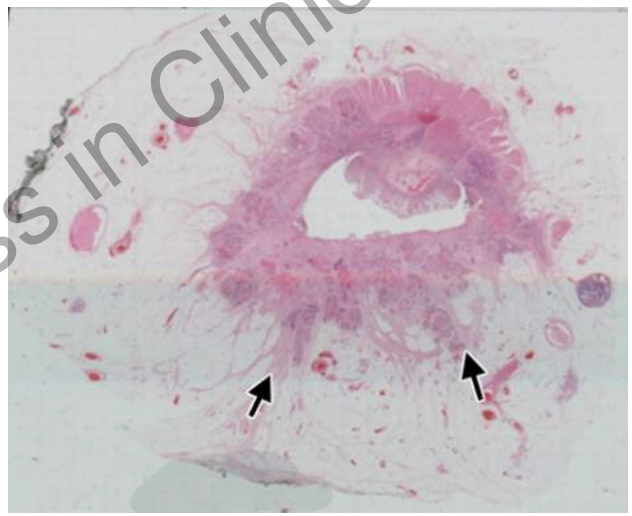

Mean extramural spread MRI 2.8mm = Mean extramural spread path 2.81mm

- ESMO Guidelines statement

"…….. rectal MRI for all tumours, including the earliest ones, is required in order to select patients for preoperative treatment and extent of surgery."

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# MERCURY results

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- MRI assessment of the CRM predicts DFS and LR
  - Taylor FG et al, J *Clin Oncol.2014 Jan 1;32(1):34-43*
- Comparison of MR and Histopath response to CRT
  - Patel UB et al *Ann Surg 2012*
- MRI detected tumour response for locally advanced rectal cancer predicts survival outcomes
  - Patel U, *Journal Of Clinical Oncology* 2011*;* 29:3753-60
- Preop High-resolution MRI Can Identify Good Prognosis Stage I, II, and III Rectal Cancer Best Managed by Surgery Alone
  - Taylor FG et al *Annals of Surgery* 2011 253:711-719

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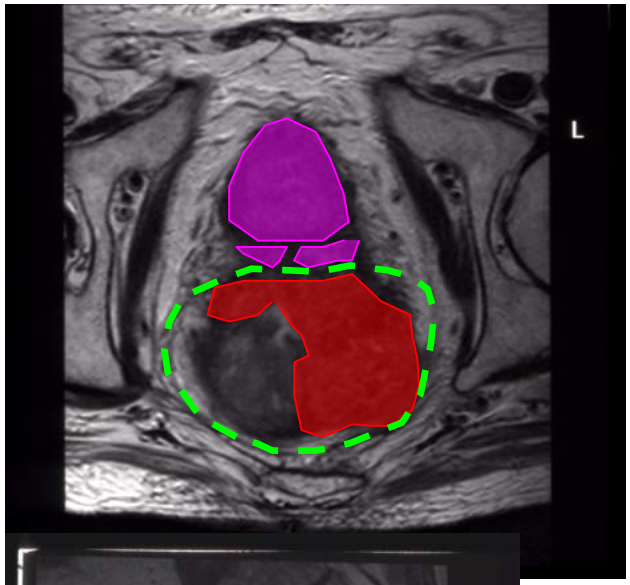
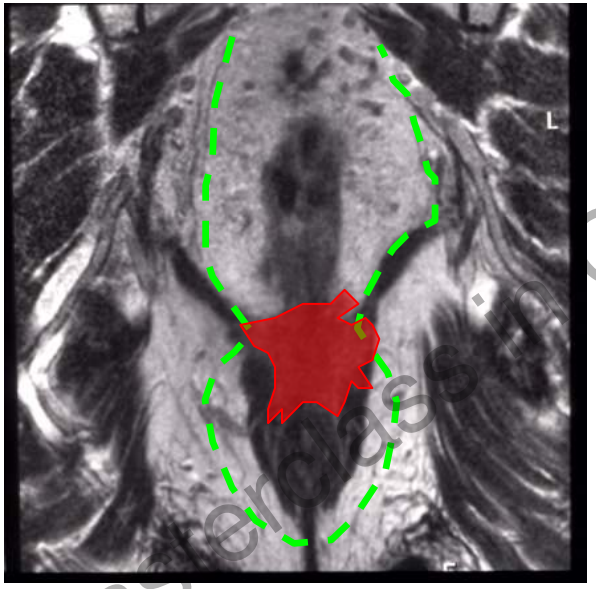
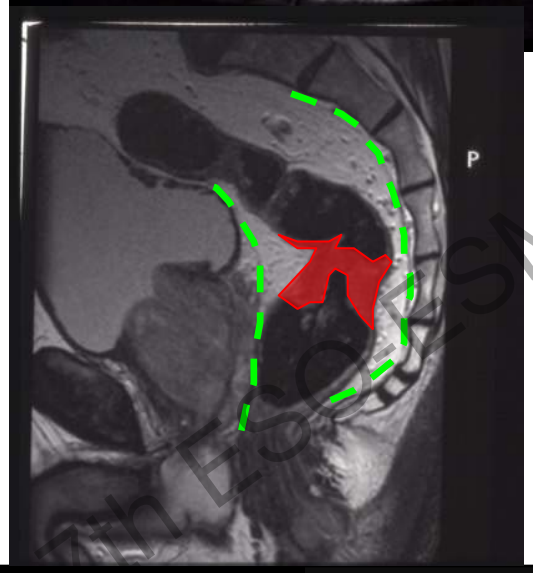
# MRI – Selection for pre-op (C)RT






Margin at risk =
Pre-op CRT

**Options**

- Surgery alone
- Surgery then post-op CRT
- Pre-op SCPRT then surgery

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# Local recurrence by T3 substage

Sebag-Montefiore et al ESTRO 2012

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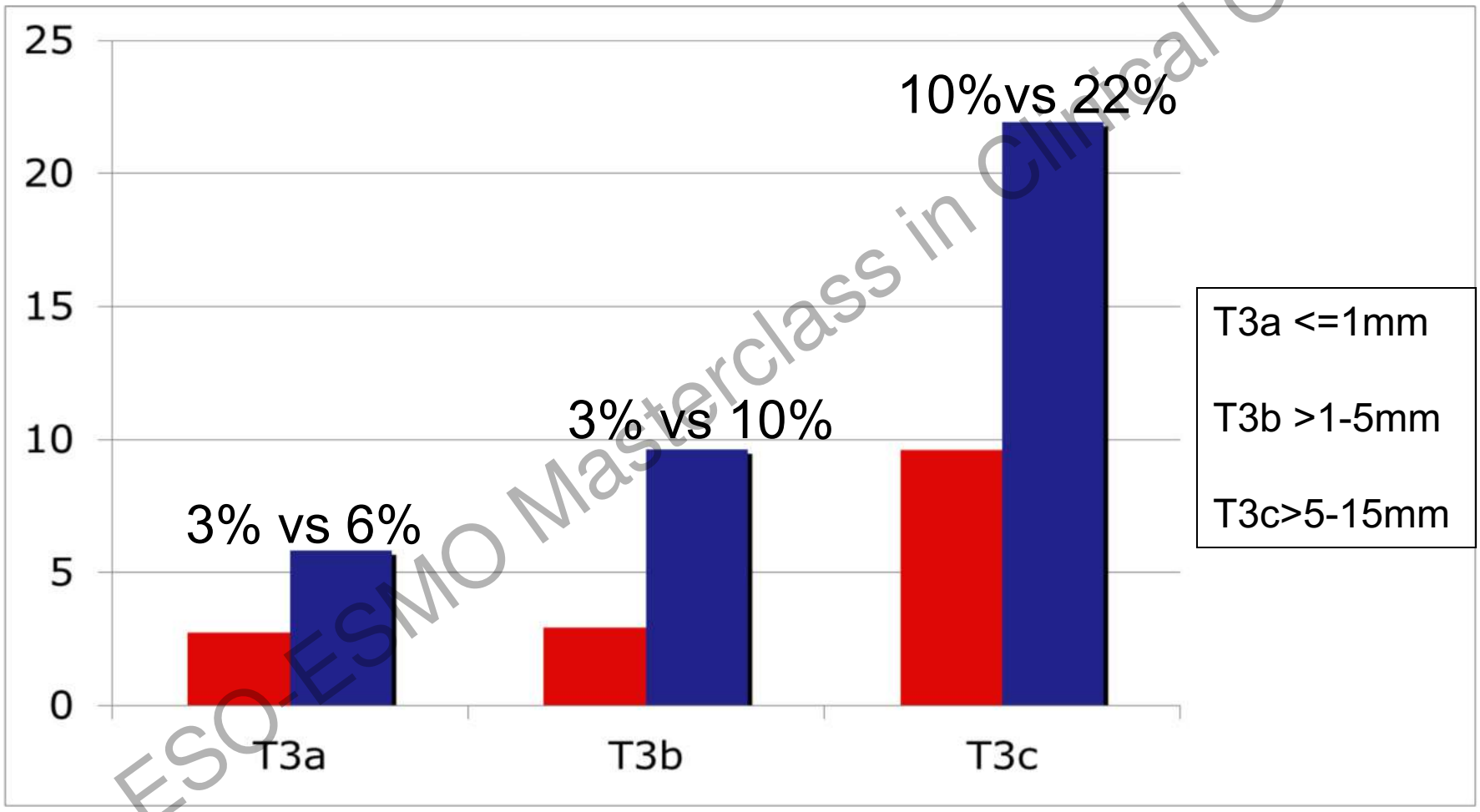


N=184 N=309 N=150

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# NICE guidelines 2011 - Risk of locoregional failure

NHS National Institute for Health and Clinical Excellence

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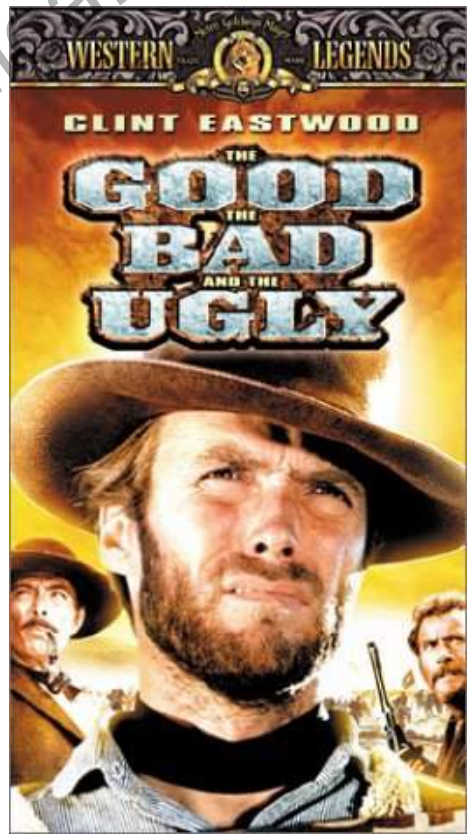
| | MRI findings |
|---|---|
| High risk | A threatened (<1 mm) or breached resection margin or low tumours encroaching onto the inter-sphincteric plane or with levator involvement |
| Moderate risk | Any cT3b or greater, in which the potential surgical margin is not threatened **or** any suspicious lymph node not threatening the surgical resection margin **or** the presence of extramural vascular invasion |
| Low risk | T1 or cT2 or cT3a and **no lymph node involvement** |

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# Rectal Cancer: ESMO Clinical Practice Guidelines

## Annals of Oncology 2017

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| Early (good) | Intermediate / bad | Advanced (ugly) |
| --- | --- | --- |
| cT1-2; cT3a<br>T3 (b) if mid or high<br>N0 (or cN1 if high)<br>MRF –ve; EMVI –ve | cT2 very low,<br>cT3 mrf –ve (unless cT3a(b) and mid or high rectum,<br>N1-2, EMVI +ve,<br>limited cT4aN0 | cT3 MRF +ve<br>cT4a,b<br>Lateral node +ve |

Surgery (TME alone)

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# "Good prognosis" rectal cancer best managed by surgery alone Taylor et al Annals of Surgery 2011

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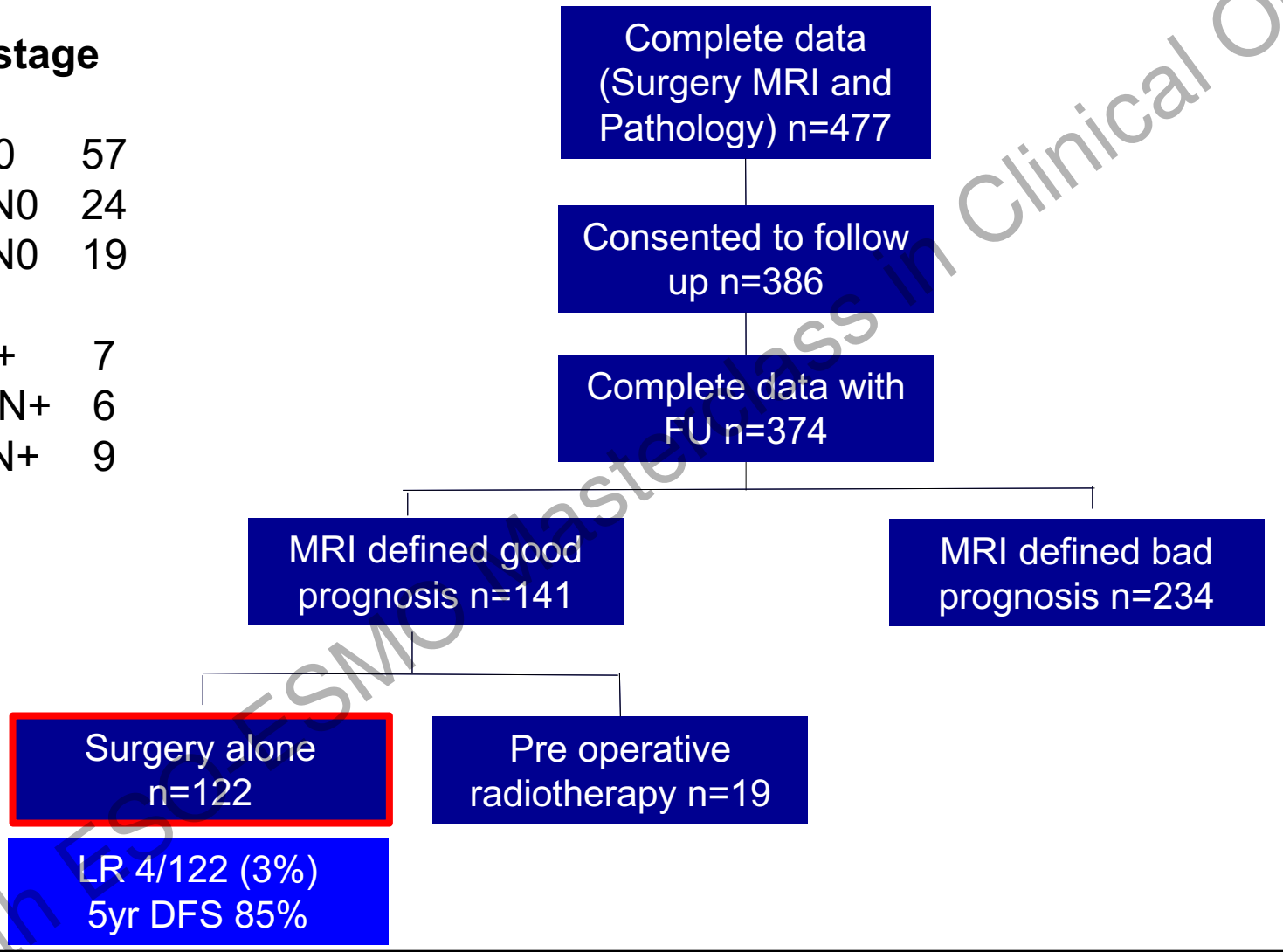
**MR stage**

| | |
|---|---|
| T2N0 | 57 |
| T3aN0 | 24 |
| T3bN0 | 19 |
| T2N+ | 7 |
| T3a N+ | 6 |
| T3bN+ | 9 |

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# Side effects of Preop RT

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## Rectal and sexual function is worse after preoperative radiotherapy and TME compared with TME alone: Results from many randomised studies

- Peeters K, J Clin Oncol 2015;25:6199
- Dahlberg M, Dis Colon Rectum 1998;41:543
- Stephens RJ, J Clin Oncol 2010;28:4233
- Marijnen CAM, J Clin Oncol 2005;23:1847
- Lundby L, Lancet 1997;350:564
- Lange MM, Br J Surg 2007;94:1278

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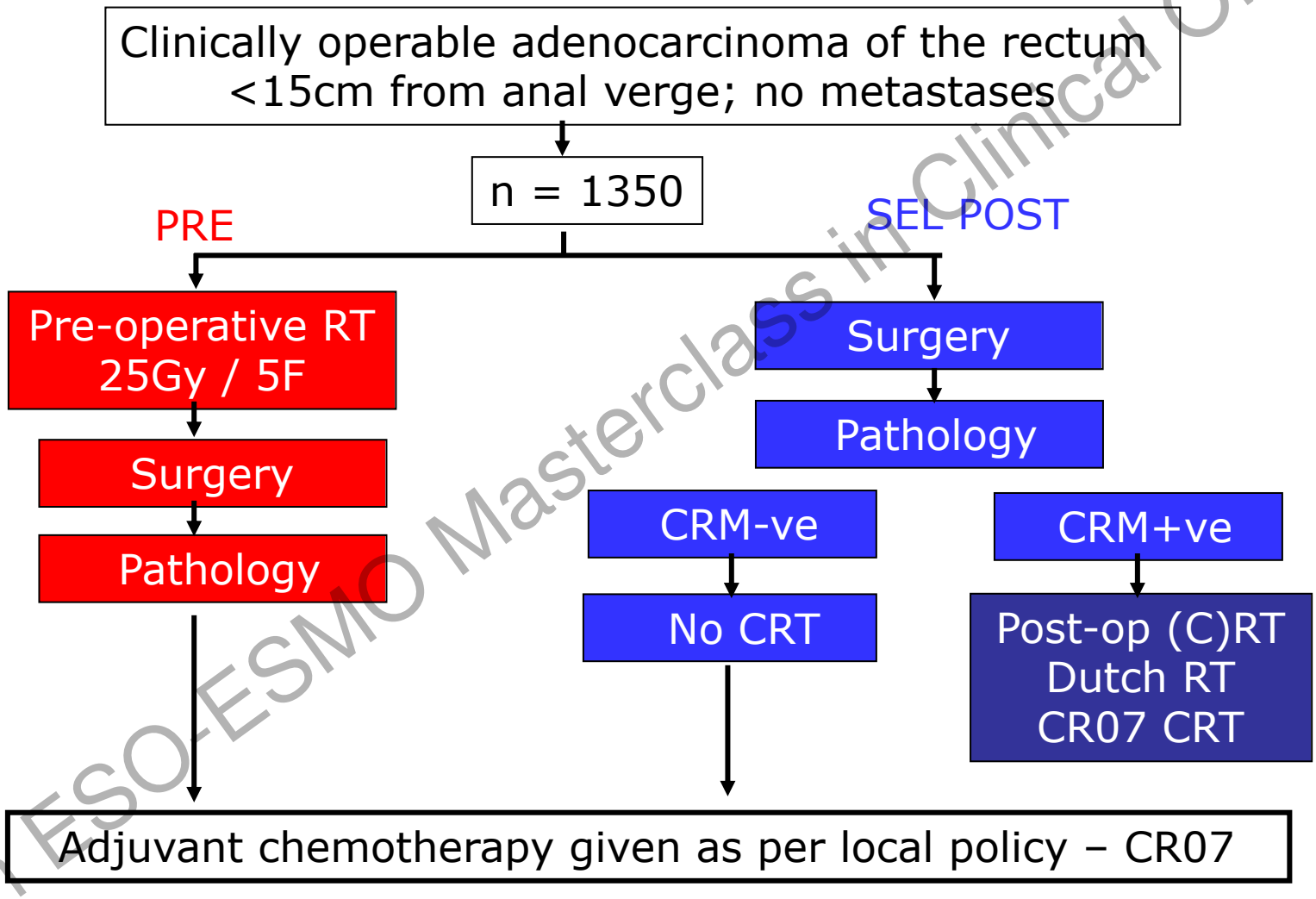
# Dutch TME and MRC CR07 trial design



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# CR07 and Dutch TME trial data

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| | PRE | SEL POST | | NNT |
|---|---|---|---|---|
| Dutch TME trial Lancet Oncology 2011 | | | | |
| Stage I | <1% | 3% | 10 yr eligible | 50 |
| MRC CR07 ESTRO 2012 | | | | |
| Stage I | 3% | 5% | 5 yr ITT | 50 |
| T2 or less | 5% | 7% | 5yr ITT | 50 |
| T3a | 3% | 6% | 5 yr ITT | 33 |

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# Dutch TME and MRC CR07 trials

Van Gijn et al Lancet Oncology 2011

Sebag-Montefiore et al Lancet 2009

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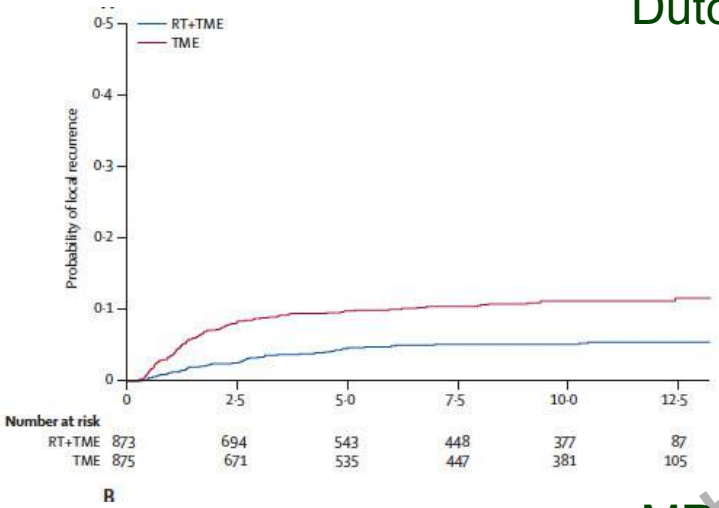
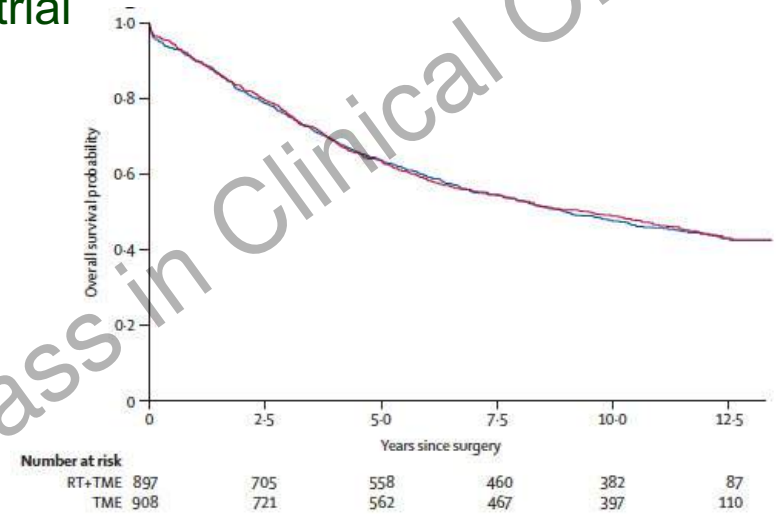
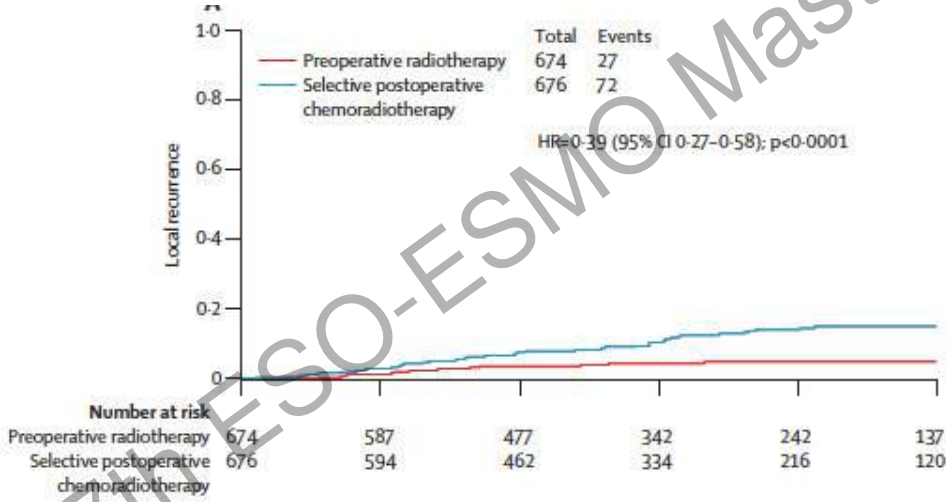
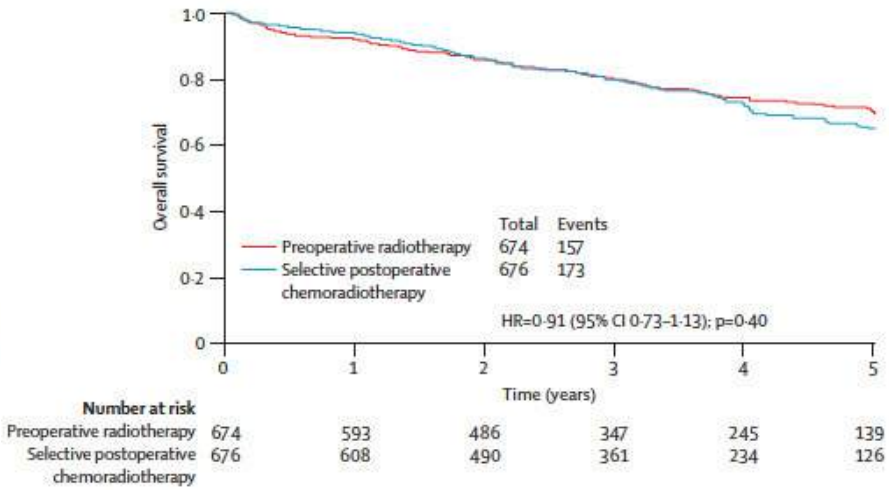
## Dutch TME trial




## MRC CR07

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# TROG AGIT LSSANZ RACS trial

Ngan et al JCO 2012

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N=326

Short course

Pre op (25Gy in 5F)

S

5FU/LV x 6

CRT – 5FU 225mg/m2 cont

50.4Gy CRT

S

5FU/LV x4

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# TROG AGIT LSSANZ RACS trial

Ngan et al JCO 2012

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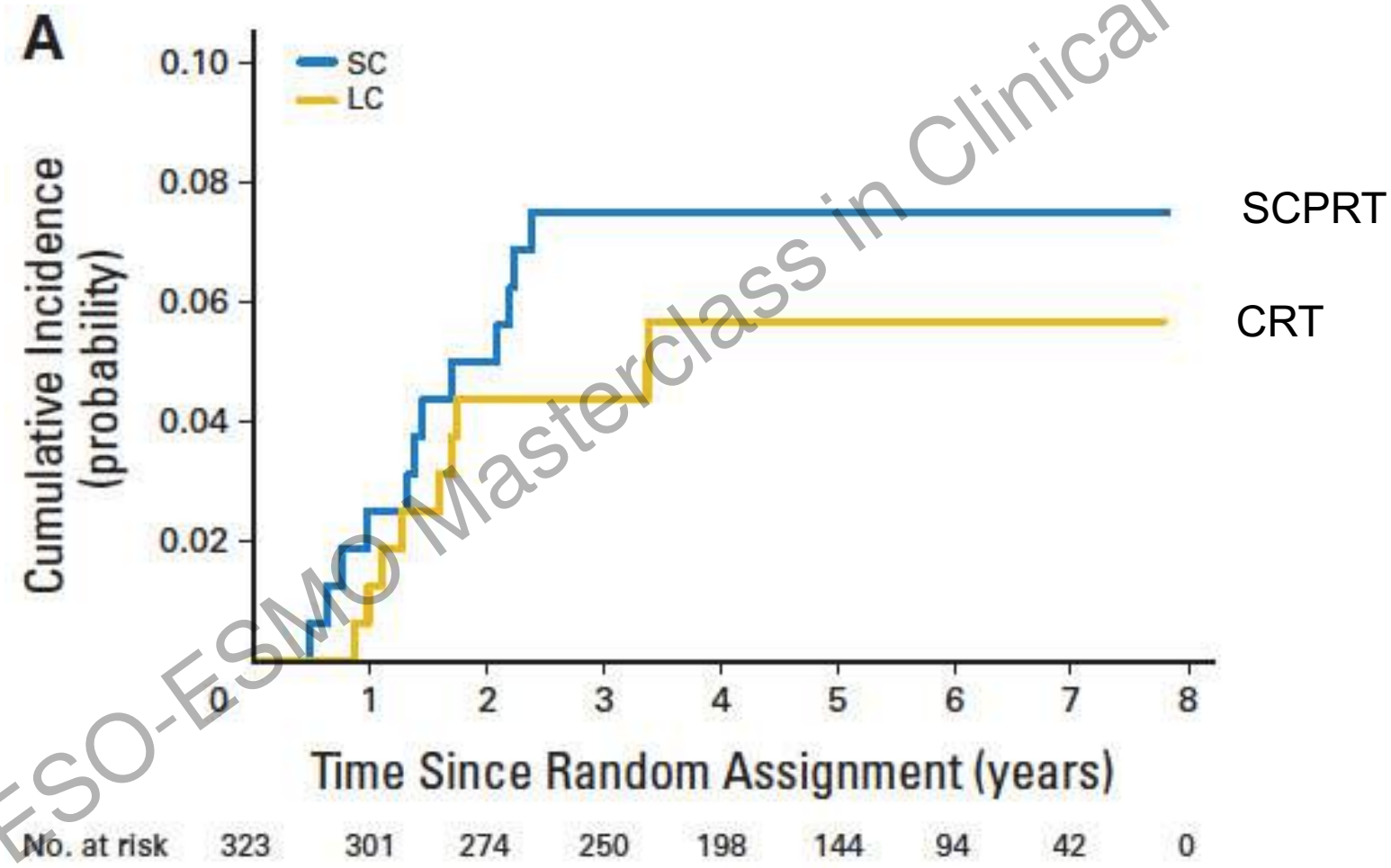


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# Rectal Cancer: ESMO Clinical Practice Guidelines

## Annals of Oncology 2017

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| Surgery (TME alone) | 25Gy in 5F<br>or<br>CRT<br>Followed by TME | |

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# Rectal Cancer: ESMO Clinical Practice Guidelines Annals of Oncology 2017

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| Surgery (TME alone) | 25Gy in 5F<br>or<br>CRT<br>Followed by TME | CRT<br>? Neoadjuvant Chemo<br>Followed by TME |

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# ESMO 2017 Guidelines Risk Groups

| Risk group | TN substage | Possible therapeutic options | Further considerations |
|---|---|---|---|
| Very early | cT1 sm1 N0 (on ERUS and MRI) | Local excision (TEM)<br>If pT1 and no adverse features, TEM is sufficient<br>If adverse histopathology (sm ≥ 2, G3, V1, L1), requires radical resection (TME) as standard | Alternatively, in the case of adverse features on pathology, TEM plus salvage (or adjuvant) CRT in perioperative high-risk patients (but unproven benefit—with high risk of local recurrence for pT2) |
| Early (Good) | cT1-cT2; cT3a/b if middle or high, N0 (or also cN1 if high), MRF clear, no EMVI | Surgery (TME) alone is standard. If unexpected poor prognostic signs on histopathology (CRM+, extranodal/N2), consider postoperative CRT/CT (see postoperative recommendations in Table 7) | For fragile, high-risk patients or those rejecting radical surgery (CRT with evaluation, local excision or if achieving cCR, 'watch-and-wait', organ preservation) |
| Intermediate | cT3a/b very low, levators clear, MRF clear or cT3a/b in mid- or high rectum, cN1-2 (not extranodal), no EMVI | Surgery (TME) alone is a standard only if good-quality mesorectal resection assured (and local recurrence ≤0.5% or, if not, preoperative SCPRT (5×5 Gy) or CRT followed by TME | If CRT is given and cCR is achieved, 'watch-and-wait' in high-risk patients for surgery may be considered |
| Bad | cT3c/d or very low localisation levators threatened, MRF clear cT3c/d mid-rectum, cN1–N2 (extranodal), EMVI+, limited cT4aN0 | Preoperative SCPRT (5×5cGy) or CRT followed by TME, depending on need for regression | If CRT and cCR achieved, 'watch-and-wait' in high-risk patients may be considered |
| Advanced (Ugly) | cT3 with any MRF involved, any cT4a/b, lateral node+ | Preoperative CRT followed by surgery (TME and more extended surgery if needed due to tumour overgrowth), or preoperative SCPRT (5×5 Gy) plus FOLFOX and delay to surgery | Alternatively, 5×5 Gy alone with a delay to surgery in fragile/elderly or in patients with severe comorbidity who cannot tolerate CRT |

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# Pre-operative Chemoradiotherapy regimen

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- Fluorpyrimidine
  - 5FU bolus or as continuous infusion
  - Oral Capecitabine
- Radiotherapy dose
  - ESMO guidelines
    - 45-50.4Gy intermediate risk
    - 50.4Gy advanced
- Radiotherapy target volume
  - External iliac nodes not routinely included
  - In intermediate risk superior limit can be lowered to S2/3
  - Low level evidence for the role of boost in advanced

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# Intensification of CRT

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- Addition of drug or targeted therapy to CRT
  - Disappointing (0xaliplatin ph III, VEGF/EGFR ph II)
  - Clinical trials
- Neoadjuvant chemotherapy + pre-op CRT
  - More evidence (encouraging ph II eg EXPERT)
- Short course radiotherapy + neoadjuvant chemotherapy
  - RAPIDO trial ongoing
- Neoadjuvant chemotherapy
  - PROSPECT trial ongoing
- Radiotherapy dose escalation
  - Clinical trials

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# Summary of doublet and triplet CRT

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- Oxaliplatin
  - Phase III disappointing
- Irinotecan
  - ARISTOTLE trial recruiting
- EGFR
  - Single arm phase II – inferior early pathological end points
- Vascular targeted
  - Limited data

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# RAPIDO Ph III Trial n=940

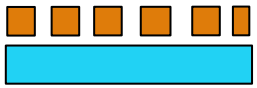
Hospers et al ECCO 2017

Standard of care control arm

MRI defined Locally advanced

MRI defined cT4a,cT4 b,cN2, EMVI+, Lat LN+

**RT+CAPE**



5.5 weeks 6-8 weeks

**CAPE + OXALIPLATIN**

6-8 weeks 24 weeks

14 weeks

Overall ypT0 = 23%

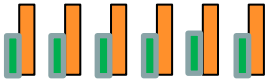
Variable use by country
Differing Standards of Care

24 weeks

**5x5**

1 week

**CAPE + OXALIPLATIN**



1 week 18 weeks

2-4 weeks

Use of 5x5

18 weeks NAC

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# Intensification of treatment using neoadjuvant chemo separate from RT

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## SELECTION FOR NEOADJUVANT CHEMOTHERAPY

- Extensive EMVI
- Disease breaching/outside the mesorectal fascia

- NEO-ADJUVANT BEFORE CRT
- IN THE INTERVAL BETWEEN CRT AND TME OP

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# Intensification of treatment using neoadjuvant chemo separate from RT

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NEO-ADJUVANT CHEMO BEFORE CRT

EXPERT, EXPERT-C Trials

| Clinical Response after NACT | ITT population n=269 | % |
|---|---|---|
| Complete response | 11 | 4.1 |
| Partial response | 157 | 58.4 |
| Stable disease | 76 | 28.3 |
| Progressive disease | 3 | 1.1 |
| Unassessable/not known | 22 | 8.2 |

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# Intensification of treatment using neoadjuvant chemo separate from RT

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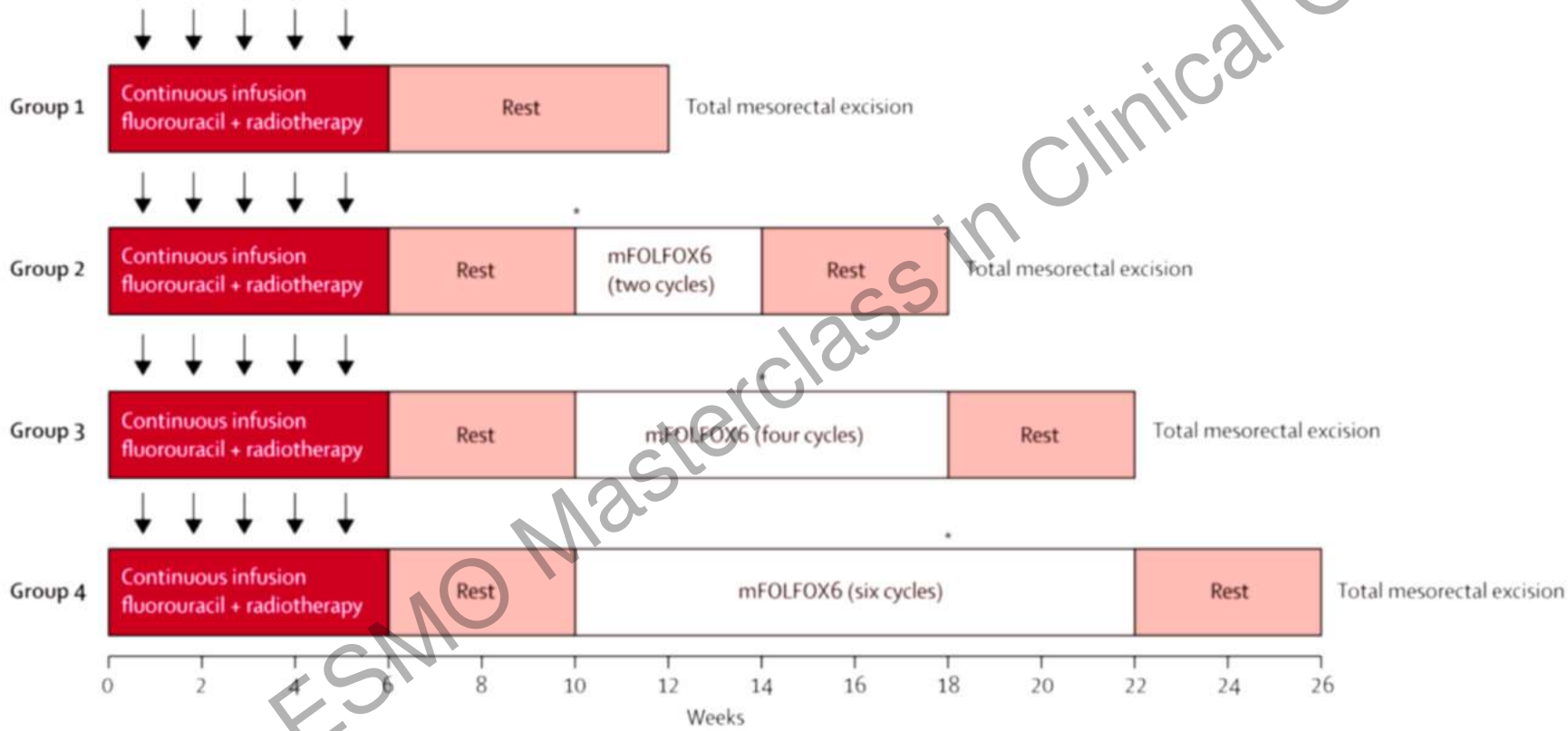


Radiotherapy was given 5 days per week for 5 weeks for a total of 45 Gy with a minimum boost of 5.4 Gy.
Fluorouracil was given as a 225 mg/m$^2$ per day continuous infusion for 7 days/week during radiation therapy for 5-6 weeks, depending on the number of radiation boosts given.
mFOLFOX6 was given in 2-week cycles of leucovorin 200 mg/m$^2$ or 400 mg/m$^2$ and oxaliplatin 85 mg/m$^2$ in a 2-h infusion, bolus fluorouracil 400 mg/m$^2$ on Day 1, and a 46-h infusion of fluorouracil 2400 mg/m$^2$.
*Interim assessments were done by proctoscopic examination; total mesorectal excision was done if the patient had stable or progressive disease.

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| | Cohort 1 (60) SG1 | Cohort 2 (67) SG2 | Cohort 3 (67) SG3 | Cohort 4 (65) SG3 |
|---|---|---|---|---|
| pCR | 11 (18%) | 17 (25%) | 20 (30%) | 25 (38%) |
| Post CRT Chemo | None | 2 cycles FOLFOX | 4 cycles FOLFOX | 6 cycles FOLFOX |
| Interval to surgery | 8 weeks | 11 weeks | 15 weeks | 19 weeks |
| N0/N+ | 75%/25% | 75%/25% | ? | ? |

## Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial

*Julio Garcia-Aguilar, Oliver S Chow, David D Smith, Jorge E Marcet, Peter A Cataldo, Madhulika G Varma, Anjali S Kumar, Samuel Oommen, Theodore Coutsoftides, Steven R Hunt, Michael J Stamos, Charles A Ternent, Daniel O Herzig, Alessandro Fichera, Blase N Polite, David W Dietz, Sujata Patil, Karin Avila, for the Timing of Rectal Cancer Response to Chemoradiation Consortium*

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| | Cohort 1 (60) SG1 | Cohort 2 (67) SG2 | Cohort 3 (67) SG3 | Cohort 4 (65) SG3 |
|---|---|---|---|---|
| **Post CRT Chemo** | None | 2 cycles FOLFOX | 4 cycles FOLFOX | 6 cycles FOLFOX |
| **Interval to surgery** | 8 weeks | 11 weeks | 15 weeks | 19 weeks |
| **Pelvic Fibrosis (1-10)** | 2.4 | 3.4 | 4.4 | 3.9 p=0.0001 |
| **Technical difficulty (1-10)** | 4.6 | 4.9 | 5.1 | 4.8 (p=0.8) |

## Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial

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# SUMMARY

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- Preoperative CRT better than postop
- SCPRT=CRT for resectable cancers
- SCPRT/CRT improves local recurrence but not DFS or OS
- If CRM threatened on MRI needs response so CRT
- Low rectal cancers (below the levators) often have threat to CRM and may have LPLN

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GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

European Society for Medical Oncology

# ESMO Rectal Cancer Guidelines

Annals of Oncology 28 (Supplement 4): iv22–iv40, 2017

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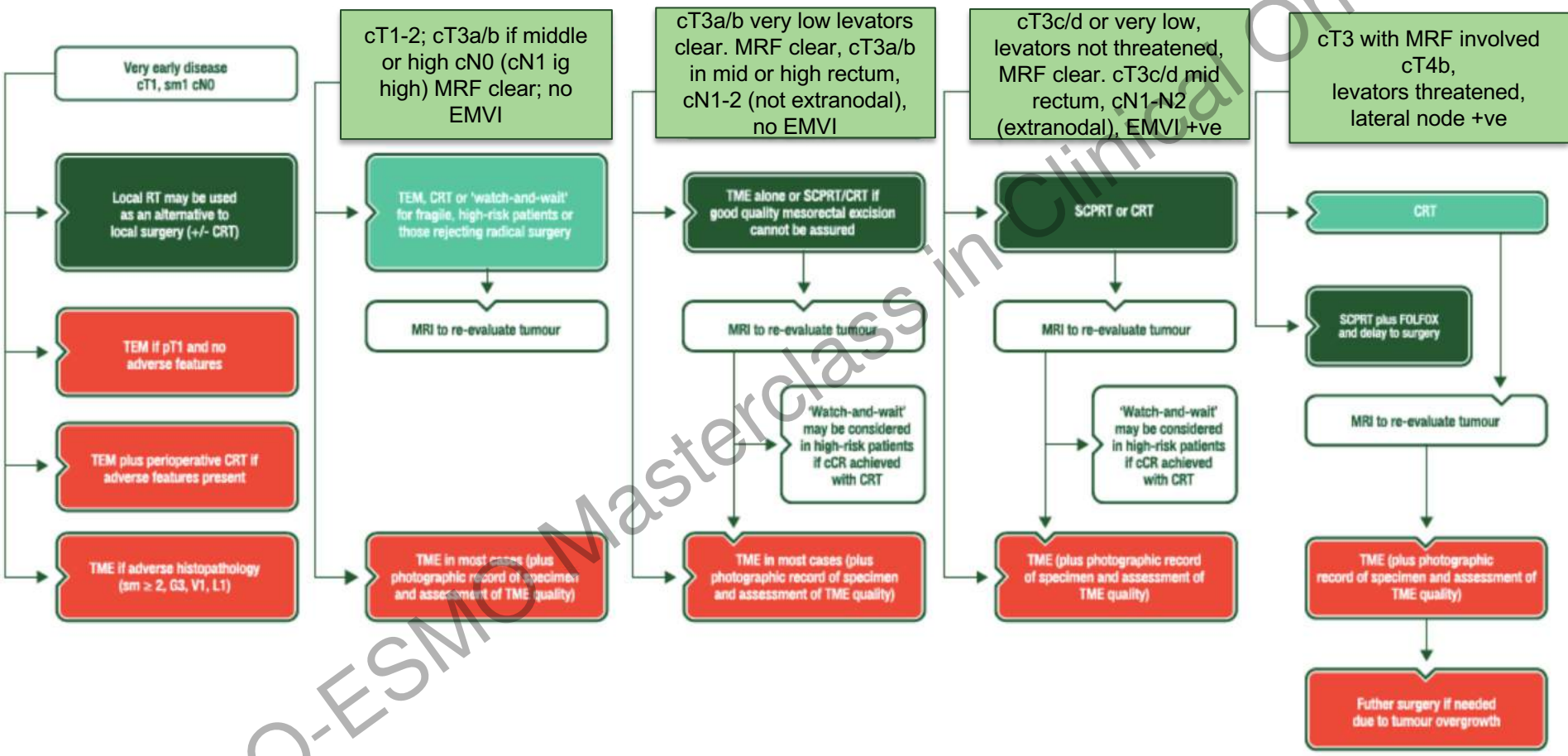


**Key Messages**

SoC
TME alone
AVOID RT

TME alone if high quality or plus SCPRT/CRT

SCPRT or CRT Then TME

CRT or SCPRT + FOLFOX then TME

# Organ Preservation

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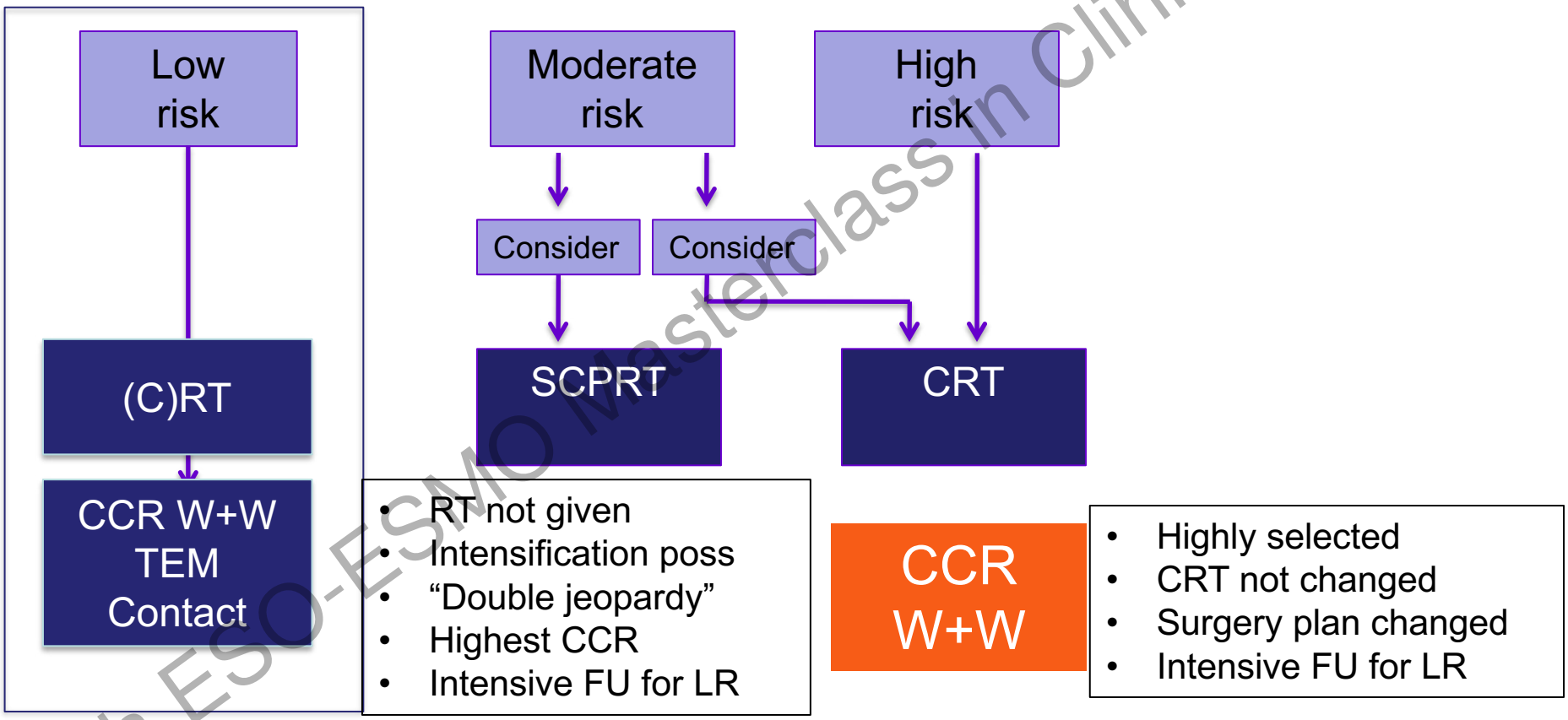
Organ preservation trials
Allows intensification

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# Habr Gama data

IJROBP 2014 88:822-8

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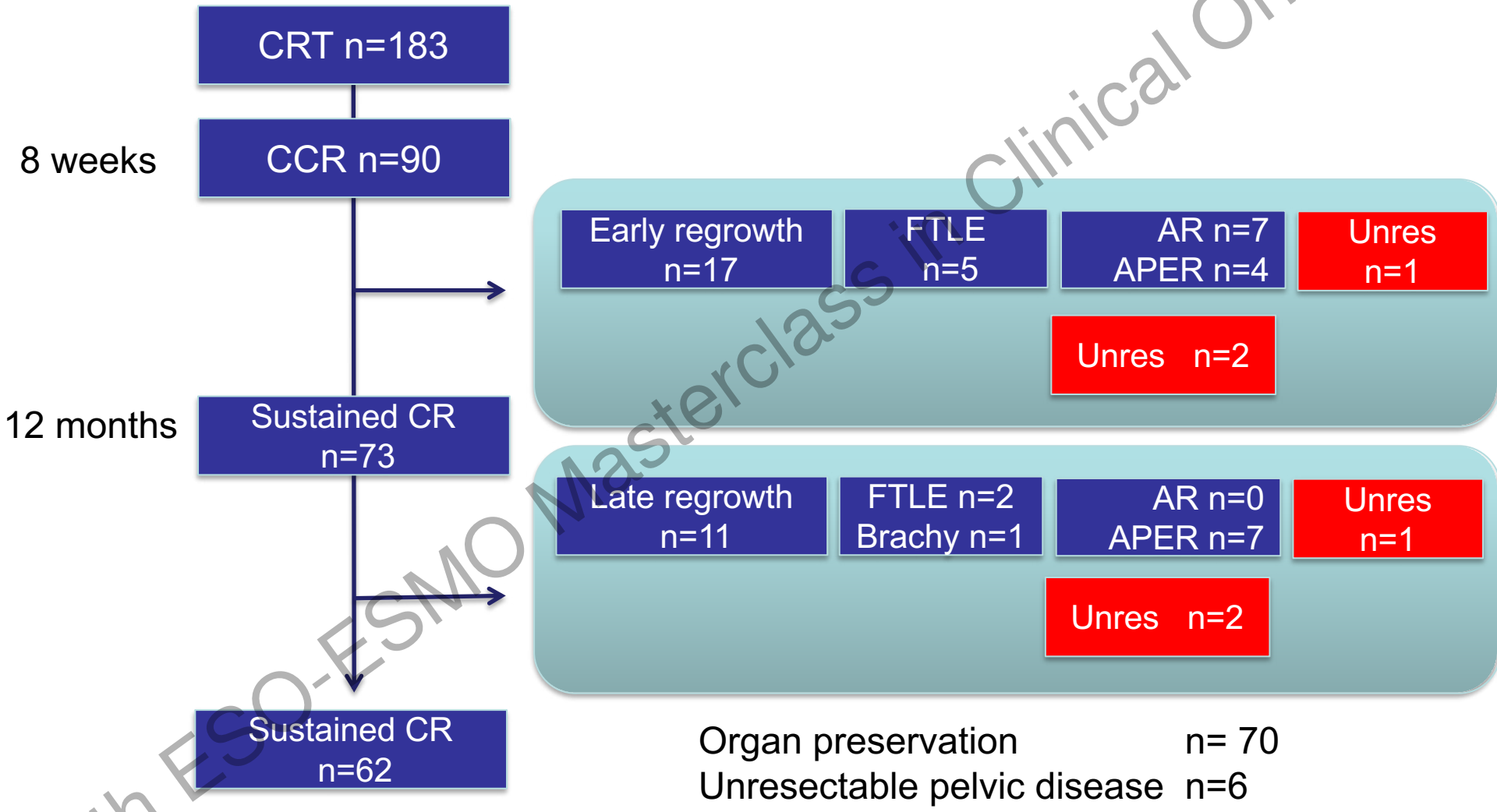


Organ preservation n= 70

Unresectable pelvic disease n=6

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

# Organ Preservation – Key publications

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

## Wait-and-See Policy for Clinical Complete Responders After Chemoradiation for Rectal Cancer

*Monique Maas, Regina G.H. Beets-Tan, Doenja M.J. Lambregts, Guido Lammering, Patty J. Nelemans, Sanne M.E. Engelen, Ronald M. van Dam, Rob L.H. Jansen, Meindert Sosef, Jeroen W.A. Leijtens, Karel W.E. Hulsewé, Jeroen Buijsen, and Geerard L. Beets*

See accompanying editorial doi: 10.1200/JCO.2011.38.1335; listen to the podcast by Dr Kachnic at www.jco.org/podcast

## Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis

*Andrew G Renehan, Lee Malcomson, Richard Emsley, Simon Gollins, Andrew Maw, Arthur Sun Myint, Paul S Rooney, Shabbir Susnerwala, Anthony Blower, Mark P Saunders, Malcolm S Wilson, Nigel Scott, Sarah T O'Dwyer*

*Lancet Oncol* 2015
Published Online
December 16, 2015
http://dx.doi.org/10.1016/S1470-2045(15)00467-2

## 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 Silezniefff, Michel Prudhomme, Frédéric Marchal, Marc Pocard, Denis Pezet, Anne Rullier, Véronique Vendrely, Quentin Denost, Julien Asselineau, Adélaïde Doussau*

*Lancet* 2017; 390: 469–79
Published Online
June 7, 2017
http://dx.doi.org/10.1016/S0140-6736(17)31056-5

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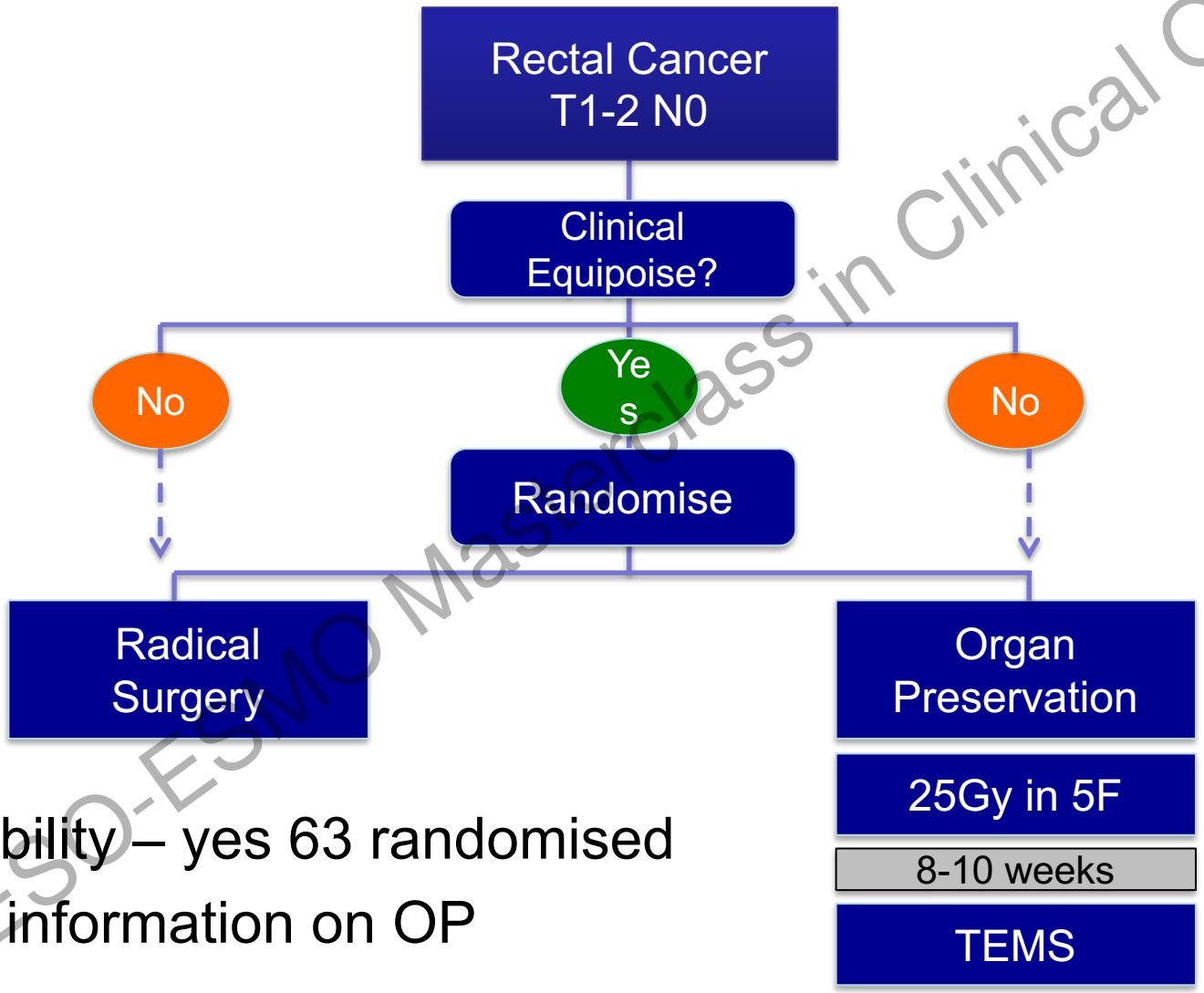
# TREC - Study Design






- Feasibility – yes 63 randomised
- Early information on OP

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# Deferral of rectal surgery study

Royal Marsden Study – gina.brown@rmh.nhs.uk

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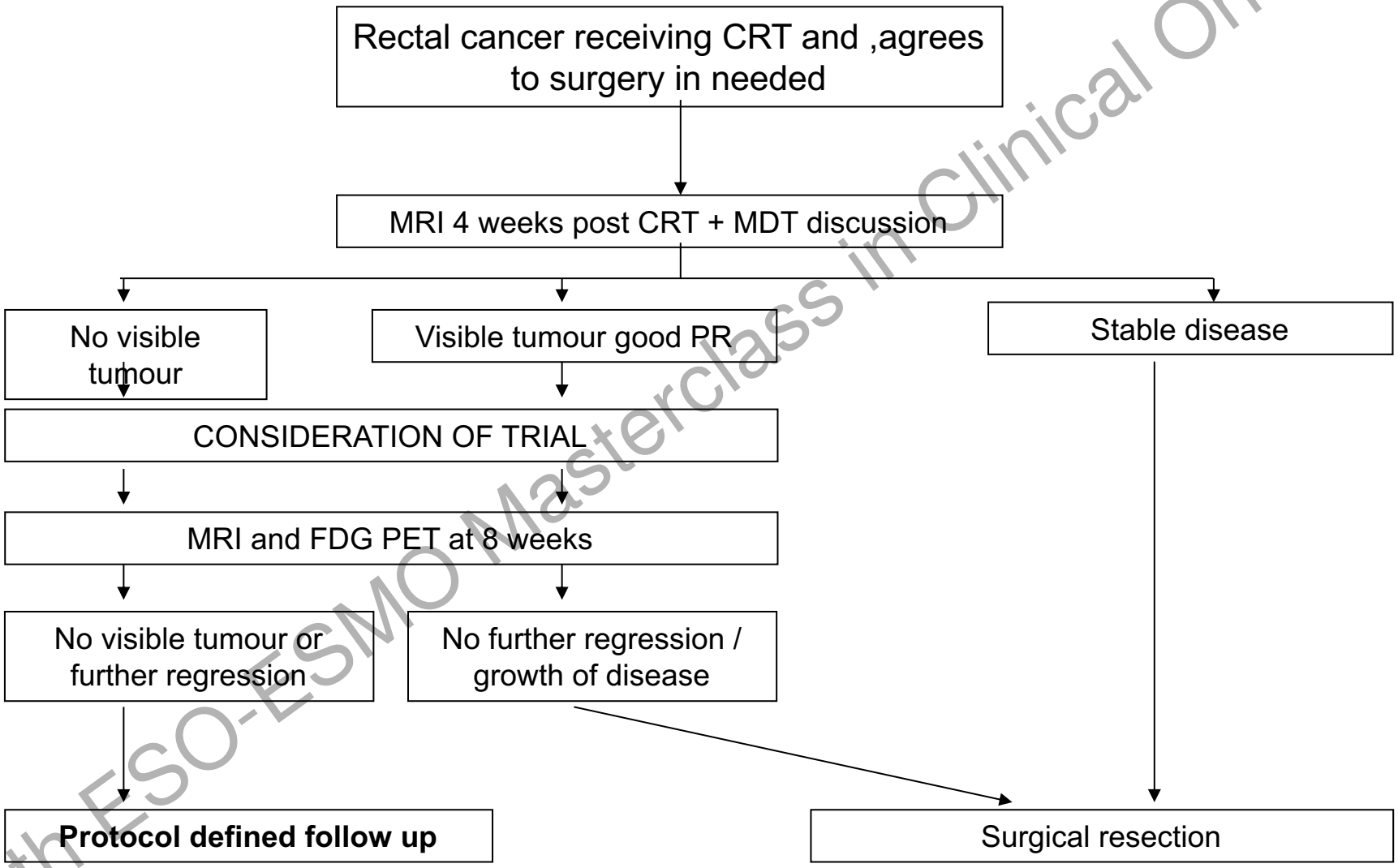


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# STARTREC – Study design
# Phase II/III clinical trial

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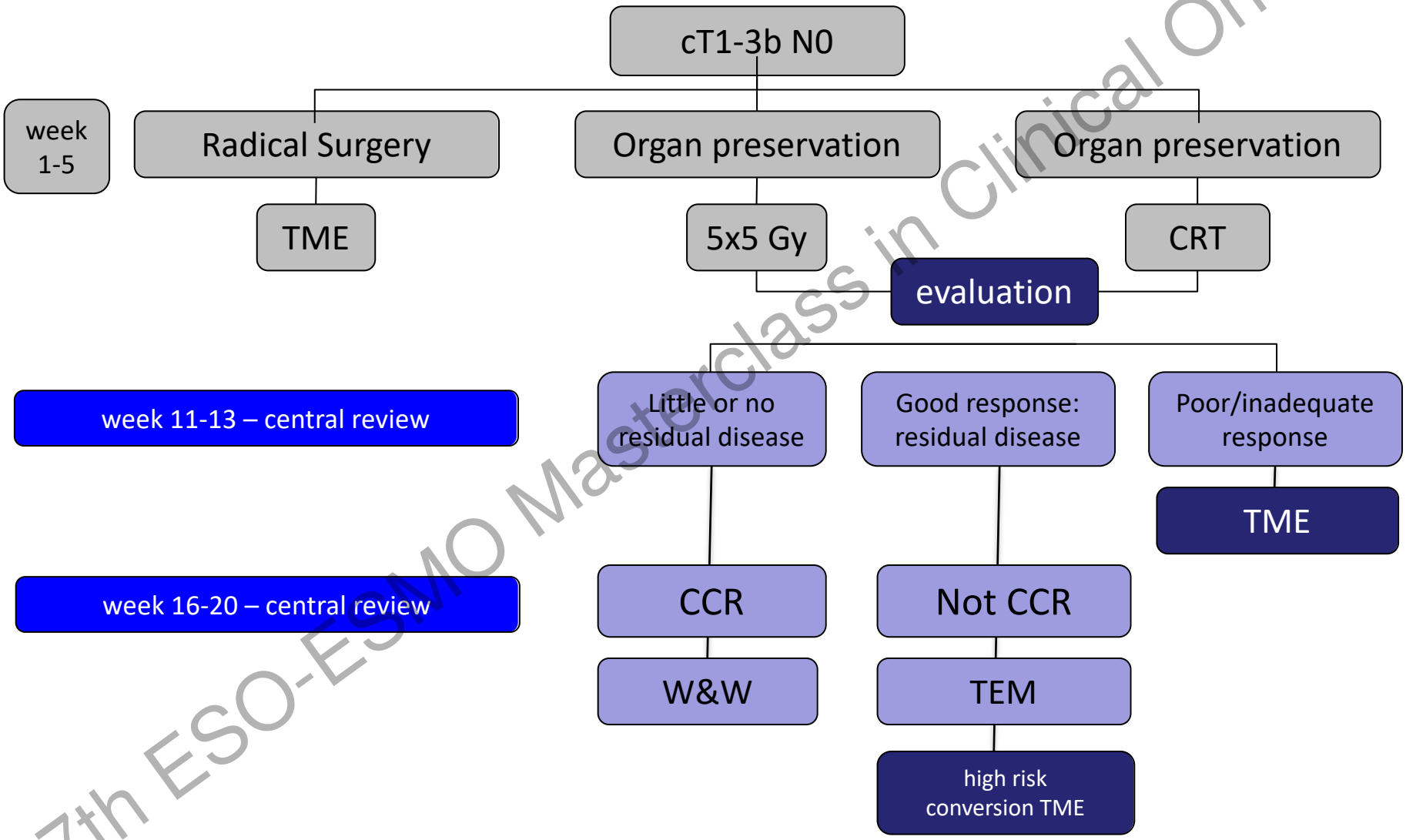


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