Organ preservation for rectal cancer

GRECCAR trials

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Association between nodal and tumour response

- 644 patients:
  - RT (n=450) or CRT (n=194) and TME
  - Rate of pN+ on specimen:
    - ypT0 2%
    - ypT1 4%
    - ypT2 23%
    - ypT3 47%
    - ypT4 48%

Read TE et al. Dis Colon rectum 2004

French GRECCAR 2 trial

- Inclusion criteria
  - Small T2 and T3
  - N0 and N1 (≤ 8 mm)
- 3-step selection
  - Before treatment ≤ 4 cm
  - After treatment ≤ 2 cm
  - After pathology ypT0-1
- Randomisation phase III

Neoadjuvant treatment

Radiotherapy 50 Gy (5 weeks)

Concomitant Chemotherapy

Capecitabine 1600 mg/m²/d

Oxaliplatine 50 mg/m²/week (end 2009)

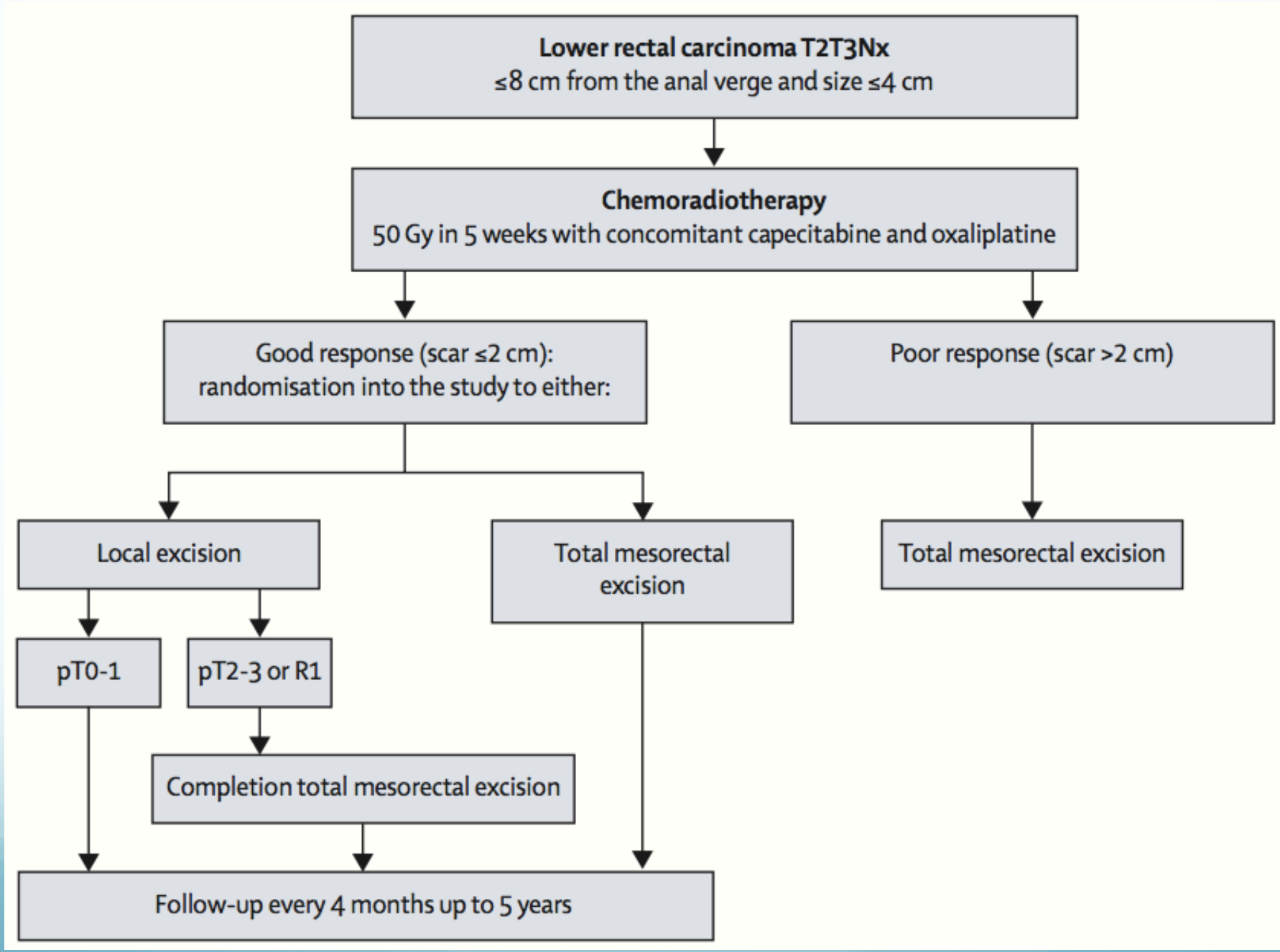
Surgery 6 - 8 semaines later

Tumor response assessment

Rectoscopy
endorectal US
MRI

- Clinical good responder
  - Residual tumor ≤ 2 cm
  - Ulcerative scar
  - No vegetative component
  - No induration

MRI good response = downsizing ≤ 2 cm


Lower rectal carcinoma T2T3Nx
≤8 cm from the anal verge and size ≤4 cm
Chemoradiotherapy
50 Gy in 5 weeks with concomitant capecitabine and oxaliplatine
Good response (scar ≤2 cm):
randomisation into the study to either:
Poor response (scar >2 cm)
Local excision
Total mesorectal excision
Total mesorectal excision
pT0-1
pT2-3 or R1
Completion total mesorectal excision
Follow-up every 4 months up to 5 years

Primary end point

- Composite outcome
  - Death
  - Recurrence
  - Major morbidity : Dindo stage III-IV-V
  - Severe after effects
    - Impotence, incontinence, colostomy
- At 2 years

Hypothesis: Superiority trial

	TME	Local excision
Operative death	2%	0
Local recurrence	5%	5%
Metastatic recurrence	10%	10%
Major morbidity	20%	5%
Severe after effects	25-50%	5%
Patients with at least one component	60%	25%

Sample size: 60 + 60 patients (α 0.05, β 0.10)

Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial

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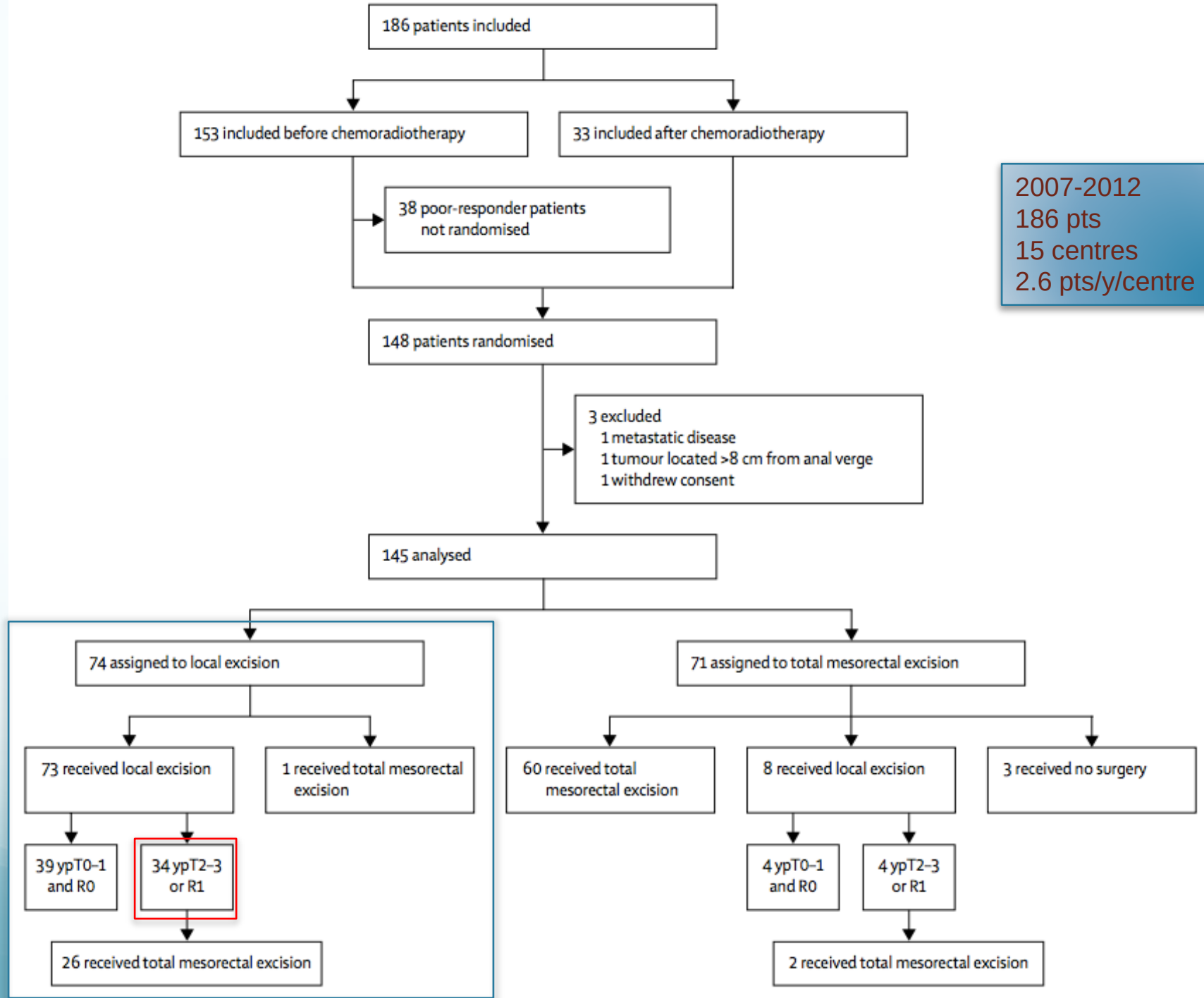


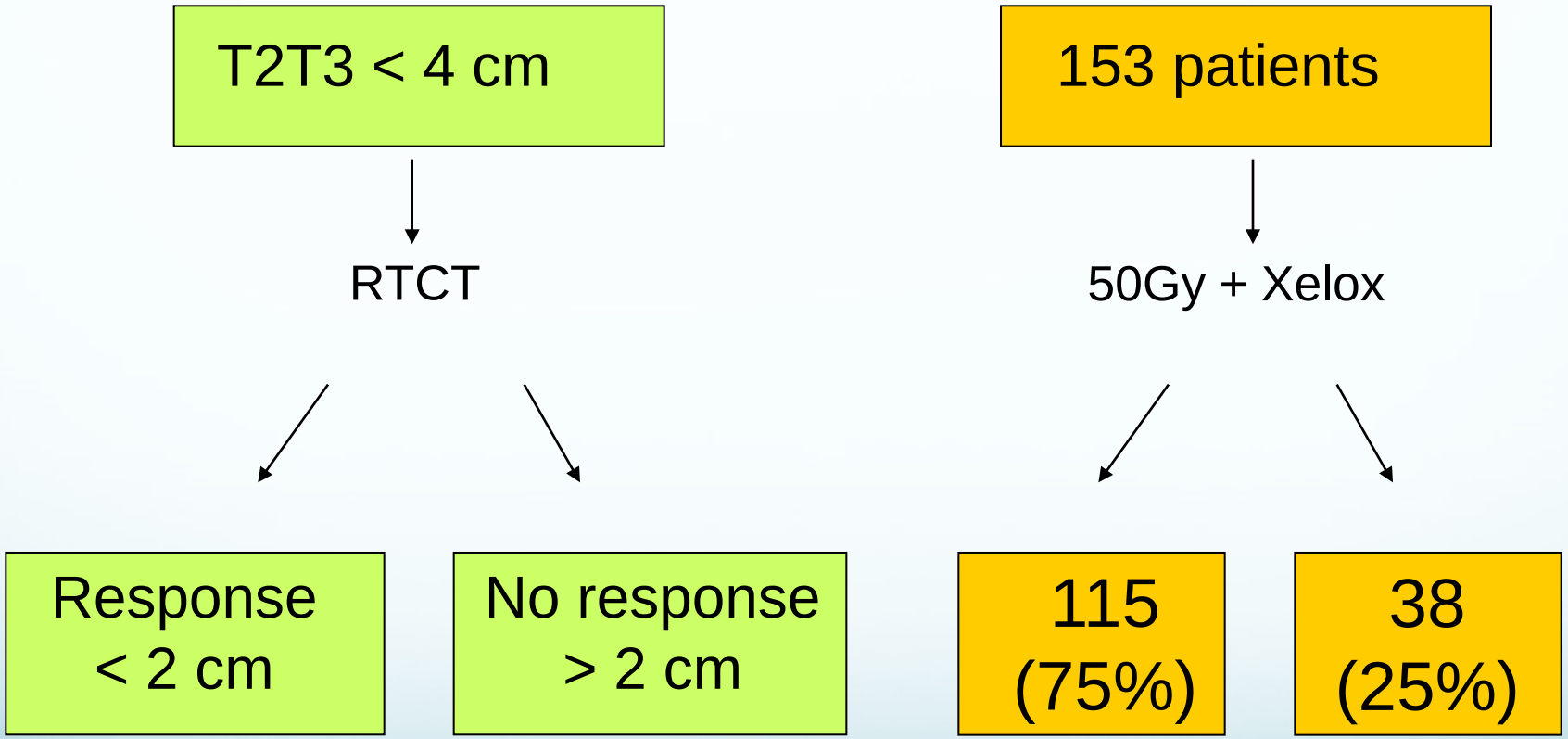
2007-2012
186 pts
15 centres
2.6 pts/y/centre

	Local excision (n=74)	Total mesorectal excision (n=71)
Age (years)*	61 (35–84;55–71)	64 (40–88; 53–72)
Sex		
Male	50 (68%)	43 (61%)
Female	24 (32%)	28 (39%)
ECOG performance status		
0	68 (92%)	68 (96%)
1 or 2	6 (8%)	3 (4%)
Distance from anal verge (cm)*	4·0 (2·5–8·0; 3·0–6·0)	4·0 (2·5–7·0; 3·0–5·0)
Distance from anal ring (cm)*	1·5 (0·0–5·0; 1·0–3·0)	1·0 (0·0–4·5; 1·0–2·0)
Tumour size (cm)*	3·0 (1·3–4·0; 3·0–4·0)	3·0 (2·0–4·0; 3·0–4·0)
Tumour location		
Anterior	23 (31%)	22 (31%)
Posterior	34 (46%)	31 (44%)
Lateral	17 (23%)	18 (25%)
Tumour stage		
T2	41 (55%)	36 (51%)
T3	33 (45%)	35 (49%)
Nodal stage		
N0	42 (57%)	48 (68%)
N1	32 (43%)	23 (32%)

Surgery performed

	Local excision (n=74)	Total mesorectal excision (n=71)
Surgery undertaken		
Local excision	47 (64%)	6 (8%)
Local excision plus completion total mesorectal excision*	26 (35%)	2 (3%)
Total mesorectal excision†	1 (1%)	60 (85%)
No surgery	0	3 (4%)

Clinical response after RTCT



Data from patients included before RTCT n= 153; 33 were included after RTCT

Pathologic response

	LE	TME	All	
Tumor response	(n=74)	(n=68)	(n=142)*	
ypT0	26	31	57	40.1%
ypT1	15	14	29	20.4%
ypT2	27	17	44	31.0%
ypT3	6	6	12	8.5%
Nodal response	(n=27)	(n=62)	(n=89)	
ypN0	23	59	82	92.1%
ypN1	4	3	7	7.9%

61% ypT0-1

*3 had no surgery

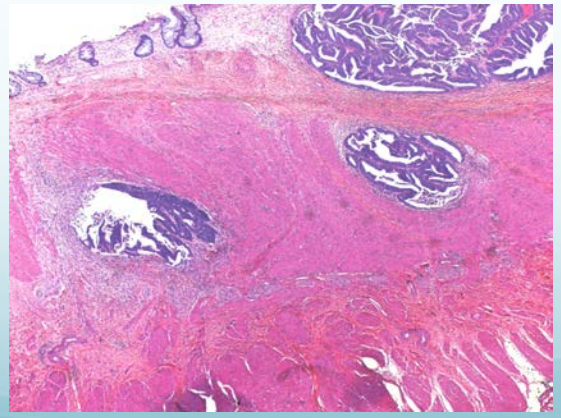
	ypN1	% ypN1
ypT0	0/30	0
ypT1	0/13	0
ypT2	3/36	8
ypT3	4/10	40

Factors of positive lymph nodes

	% ypN1	p
Tumour size		***0.087***
0-2.9	***0***	
3-3.5	***8***	
3.6-4	***16***	
Tumour stage		***0.908***
cT2	***7***	
cT3	***8***	
Nodal stage		***0.007***
cN0	*2*	
cN1	*18*	
Pathol Tumour stage		***0.012***
ypT0	*0*	
ypT1	*0*	
ypT2	*8*	
ypT3	*40*	
TRG		***0.108***
TRG 3-4	***5***	
TRG 0-2	***20***	
Type of chemotherapy		***0.242***
Capox	***4***	
	11	

First message from the GRECCAR 2 trial

- ✓ The rate of positive lymph nodes in small irradiated tumors is lower than in big irradiated tumors.
- ✓ This confirms our hypothesis, that is salvage TME is not necessary in pT0-1, and suggests it is also not useful in some ypT2 (subgroup ypT2/cN0).



Chance of organ preservation

T2T3 low rectal cancer ≤ 4 cm

↓

Radiochemotherapy and surgery at 8 weeks

↓

75% good clinical response ≤ 2 cm

↓

61% chance of pT0-1

↓

100% chance of pN0

46% rectal preservation (0.75 x 0.61)

Primary outcome at 2 years

	Local excision (n=74)*	Total mesorectal excision (n=71)*	Odds ratio (95% CI)	p value†
Primary outcome: composite of death, tumour recurrence, morbidity, and side-effects at 2 years				
One or more events present	41/73 (56%)	33/69 (48%)	1·33 (0·62–2·86)	0·43
Details of composite outcome				
Death	4/74‡ (5%)	4/71‡ (6%)	0·98 (0·18–5·24)	0·98
Tumour recurrence	11/71 (16%)	14/70 (20%)	0·81 (0·32–2·03)	0·63
Major morbidity	17/70 (24%)	15/69 (22%)	1·18 (0·51–2·72)	0·68
Side-effects total	24/69 (35%)	19/65 (29%)	1·29 (0·53–3·14)	0·54
Colostomy	9/70 (13%)	5/68 (7%)	1·76 (0·61–5·02)	0·27
Faecal incontinence§	3/62 (5%)	9/65 (14%)	0·60 (0·20–1·82)	0·34
Sexual dysfunction	17/73 (23%)	12/67 (18%)	1·10 (0·46–2·64)	0·81

*Frequency varies because proportions in the two groups are based on available data. †p values were based on a modified intention-to-treat comparison, in which missing data were replaced by occurrence of the event (missing=failure) and adjusted on centres, tumour, and nodal stages. ‡No postoperative deaths. §Assessed in patients without previous colostomy.

***Table 2*: Primary composite outcome at 2 years (modified intention-to-treat analysis)**

Complications and side-effects according to type of surgery

1

	Local excision (n=53)*	Total mesorectal excision (n=61)*	Local excision plus completion total mesorectal excision (n=28)*	p value†
Major morbidity or side-effects total	14/48 (29%)	22/58 (38%)	21/27 (78%)	0·0001
Major morbidity (Dindo III-V)	6/48 (12%)	13/60 (22%)	13/28 (46%)	0·0031
Early morbidity (1 month)	3/53 (6%)	6/61 (10%)	7/28 (25%)	0·0291
Late morbidity (up to 2 years)	3/48 (6%)	10/60 (17%)	8/28 (29%)	0·0322
Side-effects	9/48 (19%)	17/57 (30%)	16/27 (59%)	0·0013
Definitive colostomy	2/48 (4%)	5/59 (9%)	7/28 (25%)	0·0178
Faecal incontinence‡	0	9/56 (16%)	3/22 (14%)	0·0056
Sexual dysfunction	7/53 (13%)	10/58 (17%)	11/27 (41%)	0·0113

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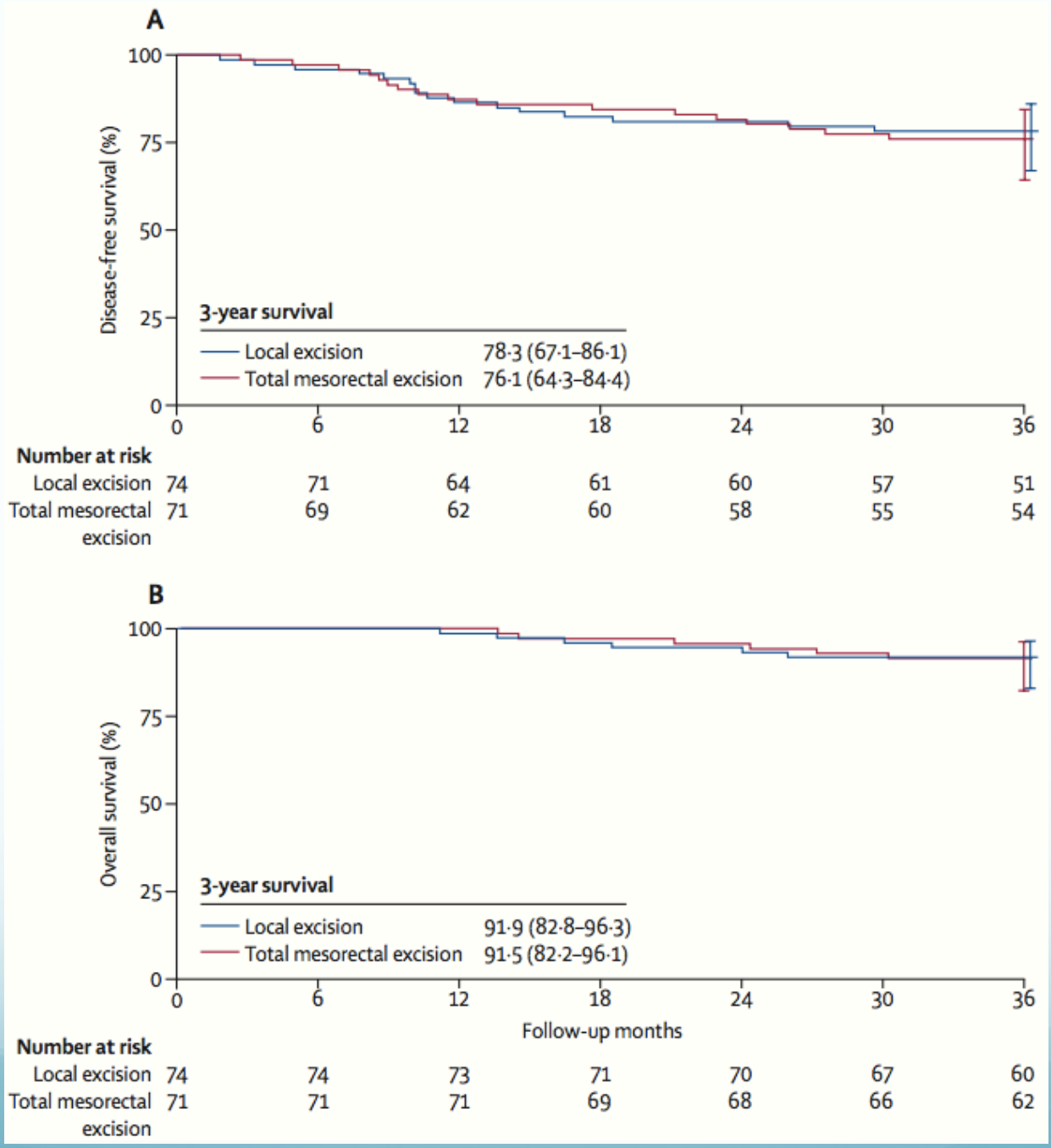
Soft surgery = light complication

	Local excision (n=53)*	Total mesorectal excision (n=61)*	Local excision plus completion total mesorectal excision (n=28)*	p value†
Details of major morbidity				
Pelvic abscess or leakage	2 (4%)§	6 (10%)	8 (29%)	NA
Pelvic haematoma	0	0	1 (4%)	NA
Small bowel obstruction	0	1 (2%)	3 (11%)	
Colonic ischaemia	0	3 (5%)	0	NA
Vaginal stenosis	0	1 (2%)	0	NA
Rectal bleeding after local excision	2 (4%)	0	0	NA
Anastomotic coloanal stenosis	0	1 (2%)	1 (4%)	NA
Prolapse of ileostomy	0	1 (2%)	0	NA
Late rectal stenosis after local excision	1 (2%)	0	0	NA
Cardiac arrhythmia	1 (2%)	0	0	NA
Cerebrovascular accident		1 (2%)		
Pulmonary embolism	0	0	1 (4%)	NA
Overall major morbidity (number)	6 (11%)	13 (21%)	13 (46%)	NA

3-year oncologic outcome

	Local excision	Total mesorectal excision	Hazard ratio (95% CI)	p value*
Modified intention-to-treat population	n=74	n=71	NA	NA
Local recurrence†	4 (5%)	4 (6%)	0·74 (0·18–3·07)	0·68
Metastatic recurrence†	9 (12%)	12 (17%)	0·68 (0·25–1·82)	0·44
Uncontrolled local recurrence†	1 (1%)	3 (4%)	0·24 (0·02–2·30)	0·21
Disease–free survival‡	58 (78%)	54 (76%)	0·75 (0·35–1·60)	0·45
Overall survival‡	68 (92%)	65 (92%)	1·06 (0·30–3·71)	0·92
Per-protocol population	n=81	n=61	NA	NA
Local recurrence†	5 (6%)	2 (3%)	1·58 (0·25–9·77)	0·63
Metastatic recurrence†	12 (15%)	8 (13%)	0·68 (0·24–1·93)	0·47
Uncontrolled local recurrence†	1 (1%)	2 (3%)	0·34 (0·03–4·44)	0·41
Disease–free survival‡	61 (75%)	50 (82%)	0·92 (0·40–2·12)	0·84
Overall survival‡	72 (89%)	58 (95%)	1·82 (0·46–7·26)	0·40

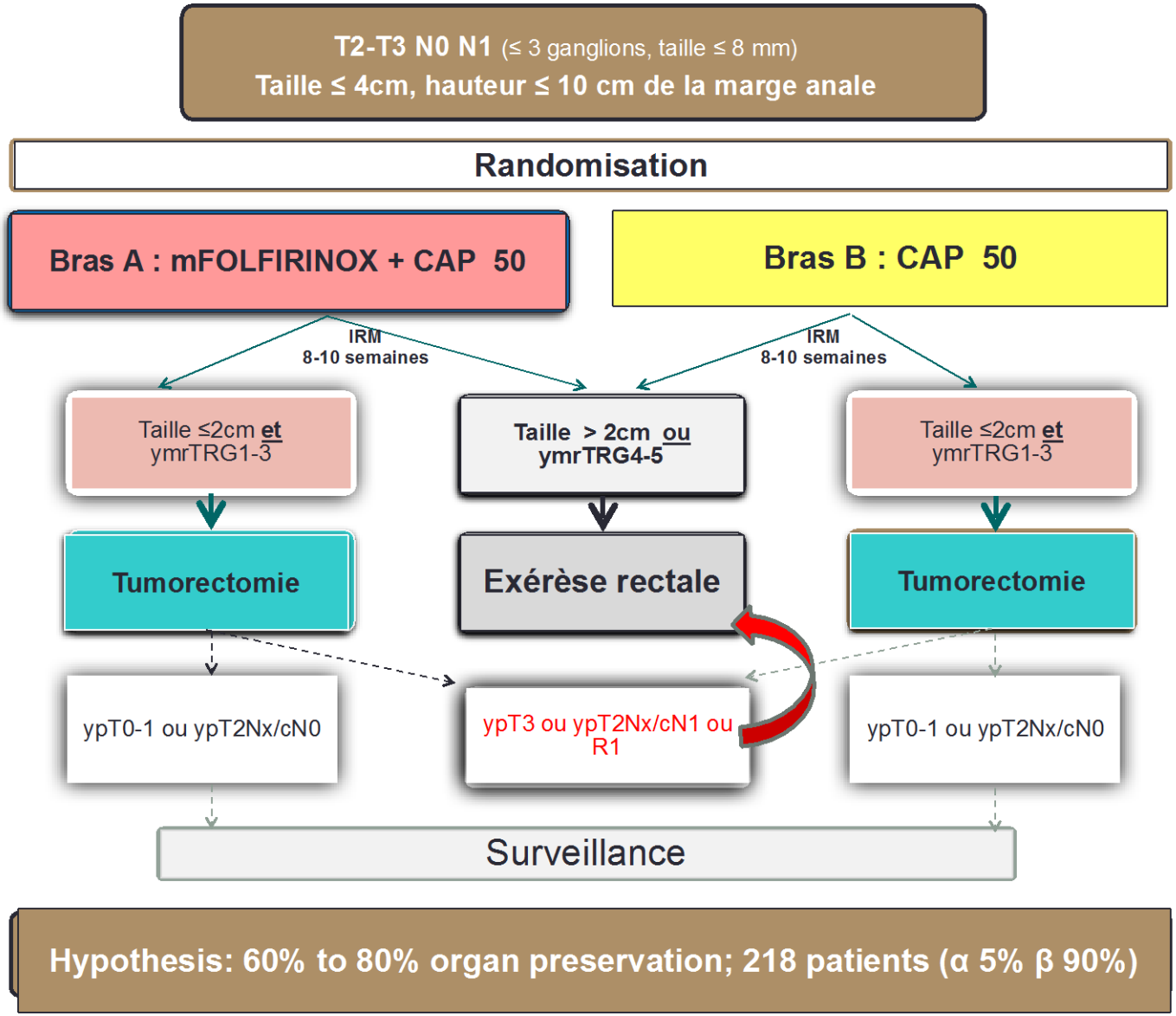
Kaplan Meier


A
100
75
50
25
0
Disease-free survival (%)
3-year survival
Local excision 78·3 (67·1–86·1)
Total mesorectal excision 76·1 (64·3–84·4)
0 6 12 18 24 30 36
Number at risk
Local excision 74 71 64 61 60 57 51
Total mesorectal excision 71 69 62 60 58 55 54
B
100
75
50
25
0
Overall survival (%)
3-year survival
Local excision 91·9 (82·8–96·3)
Total mesorectal excision 91·5 (82·2–96·1)
0 6 12 18 24 30 36
Follow-up months
Number at risk
Local excision 74 74 73 71 70 67 60
Total mesorectal excision 71 71 71 69 68 66 62

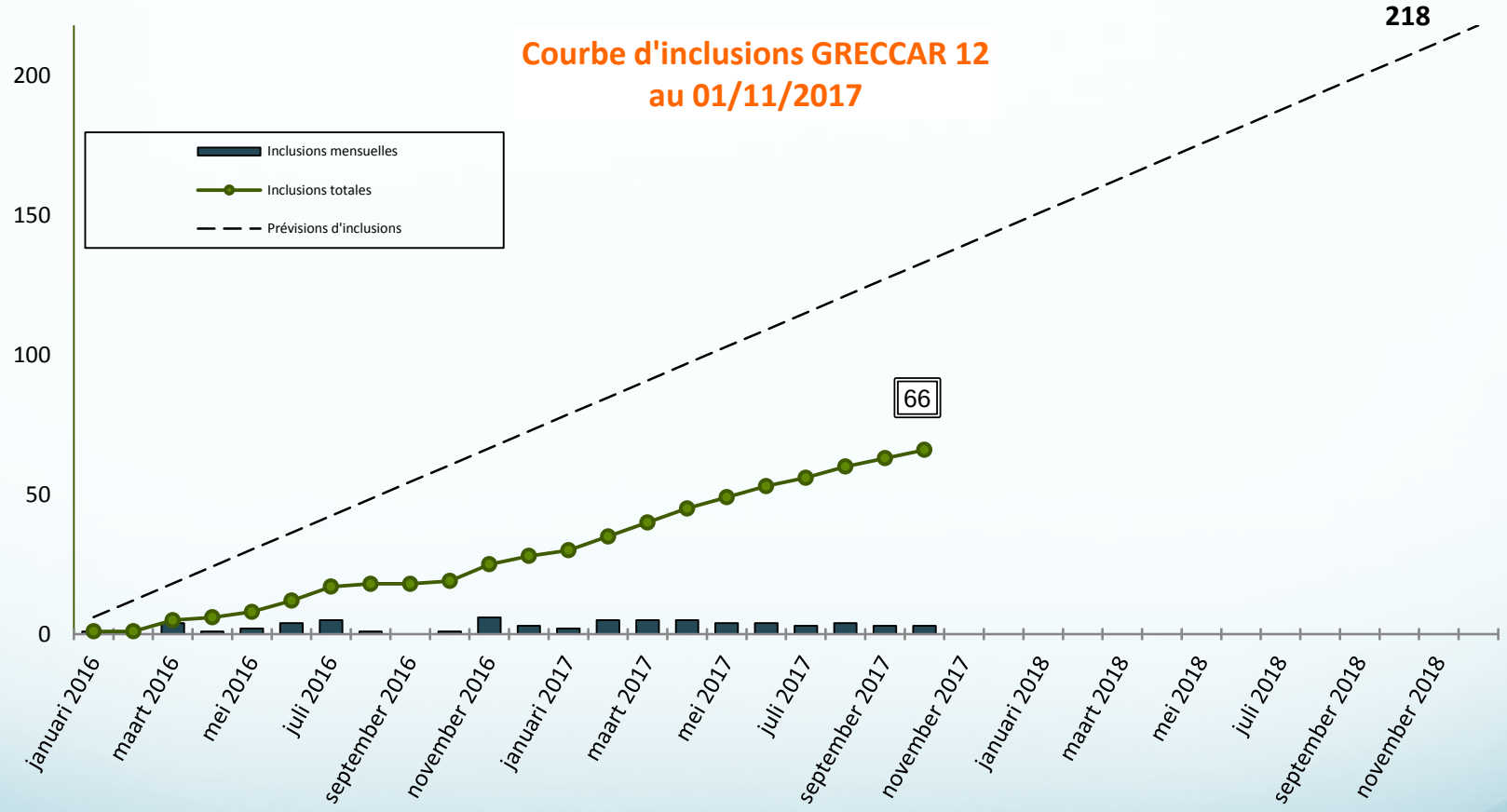
Conclusion

- Local excision is oncologically safe
- The strategy is not superior to TME due to a high rate of completion TME that increases complication and side effects
- Positive lymph nodes are present only in 8% of irradiated small T2T3 rectal cancers
- The stragegy can therefore be improved by avoiding un necessary completion TME in ypT2/N0

GRECCAR 12


T2-T3 N0 N1 (≤ 3 ganglions, taille ≤ 8 mm)
Taille ≤ 4cm, hauteur ≤ 10 cm de la marge anale
Randomisation
Bras A : mFOLFIRINOX + CAP 50
Bras B : CAP 50
IRM
8-10 semaines
IRM
8-10 semaines
Taille ≤2cm et ymrTRG1-3
Taille > 2cm ou ymrTRG4-5
Taille ≤2cm et ymrTRG1-3
Tumorectomie
Exérèse rectale
Tumorectomie
ypT0-1 ou ypT2Nx/cN0
ypT3 ou ypT2Nx/cN1 ou R1
ypT0-1 ou ypT2Nx/cN0
Surveillance
Hypothesis: 60% to 80% organ preservation; 218 patients (α 5% β 90%)

GRECCAR 12


Courbe d'inclusions GRECCAR 12
au 01/11/2017
218
66
Inclusions mensuelles
Inclusions totales
Prévisions d'inclusions
200
150
100
50
0
januari 2016
maart 2016
mei 2016
juli 2016
september 2016
november 2016
januari 2017
maart 2017
mei 2017
juli 2017
september 2017
november 2017
januari 2018
maart 2018
mei 2018
juli 2018
september 2018
november 2018

Greccar 2

Messages

Complete and subcomplete responses depend on the tumor

	T3T4[1]	T2T3 < 4 cm[2,3]
pT0	16%	40%
pT0-1	25%	60%

[1] Maas M et al. Lancet Oncol 2010
[2] Garcia-Aguillar Ann Surg Oncol 2011
[3] Rullier E Lancet 2017

Tumor response and risk of ypN+

Tumour response	**Positive LN In T2T3 < 4 cm Greccar 2**	**Positive LN In T3T4 any size Polish trial [1]**
ypT0	0	5
ypT1	0	8
ypT2	8	26
ypT3	40	55

[1] Bujko C et al Radiother Oncol 2005