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ORIGINAL CONTRIBUTION

Tailored Strategy for Locally-Advanced Rectal Carcinoma (GRECCAR 4): Long-term Results from a Multicenter, Randomized, Open-Label, Phase 2 Trial

Running Head: Locally advanced rectal carcinoma

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ABSTRACT

Background: Systematic preoperative radiochemotherapy and total mesorectal excision are standard-of-care for locally-advanced rectal carcinoma. Some patients can be over- or undertreated.

Objective: Long-term oncological, functional and late morbidity outcomes after tailored radiochemotherapy and induction high-dose chemotherapy

Design: Prospective, phase II, multicenter, open-label study at 16 tertiary centers in France.

Settings: Patients operated by surgeons from the French GRECCAR group

Patients: 206 patients were randomly assigned to treatment: good responders after chemotherapy (≥75% tumor volume reduction) to immediate surgery (arm A) or standard radiochemotherapy (Cap 50) plus surgery (arm B); poor responders to Cap 50 (arm C) or intensive radiochemotherapy (Cap 60 (60 Gy irradiation) (arm D) before surgery.

Interventions: Tailored treatment according to MR response to induction CT.

Results: After induction treatment, 194 patients were classified as good (n=30, 15%) or poor (n=164, 85%) responders, and included in arms A and B (16 and 14 patients) or C and D (113 and 51 patients). The primary objective was obtained: R0 resection rates [90% confidence interval] in the four arms respectively were 100% [74–100], 100% [85–100], 83% [72–91], and 88% [77–95]. At 5 years, rates were: overall survival 90% [47.3–98.5], 93.3% [61.3–99.0], 84.3% [71.0–91.8], 86.1% [71.6–93.5]; disease-free survival 80% [40.9–94.6], 89.5% [64.1–97.3], 72.9% [58.5–82.9], 72.8% [57.7–83.2]; local recurrence 0, 0, 2.1% [0.3–13.9], 9.3% [3.6–23.0]; metastasis 20% [5.4–59.1], 10.5% [2.7–35.9], 18% [31.8–94.6], 18.8% [10.2–33.0]. Late morbidity and quality of life evaluations showed no significant difference between arms.

Limitations: limitations due to the small number of patients randomized in the good responder arms, especially arm A without radiotherapy.

Conclusion: Tailoring preoperative radiochemotherapy-based on induction treatment response appears to be promising. Future prospective trials should confirm this strategy. See **Video Abstract** at http://links.lww.com/DCR/B761 .

ClinicalTrials.gov Identifier: NCT01333709.

ESTRATEGIA HECHA A MEDIDA PARA EL TRATAMIENTO DEL CARCINOMA DE RECTO LOCALMENTE AVANZADO (GRECCAR 4): RESULTADOS A LARGO PLAZO DE UN ESTUDIO ALEATÓRIO MULTICÉNTRICO Y ABIERTO DE FASE II°

Antecedentes: La radio-quimioterapia pré-operatoria sistemáticas y la excisión total del mesorrecto son el estándar en el tratamiento del carcinoma de recto localmente avanzado. En éste sentido, algunos pacientes podrían recibir un sobre o un infra-tratamiento.

Objetivo: Evaluar los resultados oncológicos, funcionales y de morbilidad a largo plazo después de radio-quimioterapia personalizada y quimioterapia de inducción a dosis elevadas.

Diseño: Estudio aleatório multicéntrico y abierto de Fase II° realizado en 16 centros terciarios en Francia.

Ajuste: Aquellos pacientes operados por cirujanos del grupo GRECCAR francés.

Pacientes: 206 pacientes fueron asignados aleatoriamente al tratamiento: los buenos respondedores después de quimioterapia (reducción del volumen tumoral ≥75%) a la cirugía inmediata (brazo A) o a la radio-quimioterapia estándar (Cap 50) asociada a la cirugía (brazo B); los malos respondedores a Cap 50 (brazo C) o a la radio-quimioterapia intensiva (Cap 60 (irradiación de 60 Gy) (brazo D) previas a la cirugía.

Intervenciones: Tratamiento adaptado según la respuesta de la RM a la TC de inducción.

Resultados: Después del tratamiento de inducción, 194 pacientes fueron clasificados como buenos (n = 30, 15%) o malos (n = 164, 85%) respondedores, y se incluyeron en los brazos A y B (16 y 14 pacientes) o C y D (113 y 51 pacientes). Se alcanzó el objetivo principal: las

tasas de resección R0 [intervalo de confianza del 90%] en los cuatro brazos respectivamente, fueron del 100% [74-100], 100% [85-100], 83% [72-91] y 88% [77 –95]. A los 5 años, las tasas fueron: de sobrevida global 90% [47,3-98,5], 93,3% [61,3-99,0], 84,3% [71,0-91,8], 86,1% [71,6-93,5]; de sobrevida libre a la enfermedad 80% [40,9-94,6], 89,5% [64,1-97,3], 72,9% [58,5-82,9], 72,8% [57,7-83,2]; de recidiva local 0, 0, 2,1% [0,3-13,9], 9,3% [3,6-23,0]; de metástasis 20% [5,4-59,1], 10,5% [2,7-35,9], 18% [31,8-94,6], 18,8% [10,2-33,0]. La evaluación tardía de la morbilidad y la calidad de vida no mostraron diferencias significativas entre los brazos.

Limitaciones: Debido al pequeño número de pacientes asignados al azar en los brazos de buenos respondedores, especialmente en el brazo A de aquellos sin radioterapia.

Conclusión: Parecería muy prometedor el adaptar la radio-quimioterapia pré-operatoria basada en la respuesta al tratamiento de inducción. Estudios prospectivos en el futuro podrán confirmar la presente estrategia. Consulte **Video Resumen** en http://links.lww.com/DCR/B761 . *(Traducción—Dr. Xavier Delgadillo)*

Identificador de ClinicalTrials.gov: NCT01333709. Groupe de REcherche Chirurgicale sur le CAncer du Rectum

KEY WORDS: High-dose neoadjuvant chemotherapy; Locally advanced rectal carcinoma; Tailored management; Tumoral response.

INTRODUCTION

Standard treatment for locally-advanced rectal carcinoma (LARC) comprises induction radiochemotherapy (RCT) with fluoropyrimidine and proctectomy with total mesorectal excision (TME). With some variations linked to the definition of LARC, oncological results show a pathological complete response (pCR) rate of 13-17%, a 5-year survival rate of 55-65%, a local recurrence rate <10%, and a metastasis rate of 30-40%.[1–3] Results are worse for specific aggressive tumors with a positive radial margin after RCT, with a metastasis rate of 60% and an overall 5-year survival rate <55%.[1] With this standard induction treatment, about 15-17% of patients with complete pathological response could be considered overtreated, while 30% with a metastatic evolution are undertreated. Furthermore, aggressive preoperative treatment induces specific morbidity, especially radiotherapy which may cause sexual or defecation dysfunction with[4] or without surgery.[5]

Various intensification methods have been used to avoid undertreatment, including adding drugs to the 5-fluorouracil stage of RCT. Four phase III trials of FOLFOX showed no oncological outcomes differences, with more grade 3 diarrhea.[6–9] Targeted therapy with bevacizumab,[10–12] panitumumab,[13] or cetuximab[14] increased toxicity without significant oncological impact for non-metastatic patients. Thus, the unselected use of other drugs added to fluoropyrimidines cannot be recommended outside trials.

Another intensification method is total neoadjuvant therapy (TNT), defined as chemotherapy using cycles of induction and/or consolidation in conjunction with standard RCT prior to surgery.[15] Induction CT aims to deliver full-dose chemotherapy with good compliance to target subclinical metastases.[16] First results of Prodige 23 trial show an improvement with induction chemotherapy for 3- year disease free survival and metastasis free survival.[17] Consolidation CT increases disease-free survival in LARC,[18] compliance was better and pCR rate was increased (17% vs. 25%; p<0.001). The Rapido trial confirm a decreased probability

of disease-related treatment failure in the consolidation group.[19] The interval time between the end of radiotherapy and surgery can also have a significant impact on pCR.[20] Compared to total intensification without patient selection, the tailored strategy attempts to deliver a suitable strategy according to early tumoral response, to avoid under- and overtreatment. An ongoing phase III prospective trial, PROSPECT,[21] is assessing LARC patients randomized to radiotherapy after induction FOLFOX chemotherapy according to their early response (cutoff: 20% tumoral volume reduction), with results expected June 2021. In 2017, we published the preliminary results of the GRECCAR4 study,[22] which identified good and bad responders after four FOLFORINOX cycles. Initial conclusions demonstrated that performing curative surgery according to the early tumoral response was safe according to the pathological data. The current article reports the long-term results of GRECCAR4 in particular the oncological, functional and late morbidity outcomes.

METHODS

Patients and study design

GRECCAR4 is a national, phase II, multicenter, open-label, randomized study of patients with non-metastatic LARC treated at 16 French centers. Initial staging was complete with clinical examination, thoraco-abdominal tomodensitometry, rectal magnetic resonance imaging (MRI), coloscopy and CEA marker. The main inclusion criterion was a primary tumor (initial stage: mriT3 ≥ c or mriT4) with an MRI predictive circumferential resection margin (CRM) ≤1 mm.

The early tumor response was determined by measuring the tumor volume by using specific software that automatically delineated the tumor (centralized reviewing) on MRI two weeks after completing induction chemotherapy. Patients were divided according to their tumor response (Fig. 1). A favorable response (good responder, GR) was defined as ≥75% shrinkage from the initial tumor volume, with a predictive CRM >1 mm. These patients were

randomly assigned (1:1 ratio) to receive immediate surgery (experimental arm, arm A) or classical RCT (capecitabine (Cap) 50; see Treatments section) followed by surgery (standard arm, arm B). An unfavorable response (bad responder, BR) was defined as <75% shrinkage from the initial tumor volume or a predictive CRM ≤1 mm. These patients were randomly assigned to receive Cap 50 (standard arm, arm C) or intensified RCT (Cap 60; experimental arm, arm D). Randomization was centralized and stratified by center and initial tumor stage. All patients provided written and signed informed consent before enrollment. The protocol was approved by the local ethics committee and was conducted in accordance with ethical standards (trial registration NCT01333709).

Treatments

Neoadjuvant treatment. Induction chemotherapy was a FOLFIRINOX regimen. The standard Cap 50 RCT regimen combined 50 Gy irradiation with concomitant oral capecitabine. The experimental Cap 60 regimen consisted of 60 Gy irradiation (16-Gy boost to a reduced target peritumoral volume), with the same Cap intake. Details of treatment were developed in the first publication.[22]

Surgery. Radical proctectomy with TME was performed as laparoscopic or robotic surgery, or conventional laparotomy.

Adjuvant treatment. This was left to the investigators' discretion; the expert committee suggested six FOLFOX cycles for ypT ≥2 or ypN ≥1 tumors.

Outcomes

The primary endpoint, published in 2017,[22] was the R0 resection rate (CRM >1 mm). The early secondary endpoints were MRI-assessed tumor volume, CRM, and response rate after induction chemotherapy, preoperative treatment toxicity (NCI CTC-CAE v4.0), pCR, peri/postoperative morbidity, and sphincter-saving surgery rates. The late secondary outcomes were oncological results (overall survival; disease free survival; local relapse free

survival; metastasis rate), functional results (digestive; urinary, sexual) and quality of life (QOL).

The present publication reports these late secondary results with a 5-year follow-up. Oncological data were calculated from the date of inclusion until the date of first events Patients without events at the time of analysis had their data censored on the date of last informative follow-up. Quality of life was assessed using the QLQ-C30 questionnaire. Health-related quality of life (HRQoL) over time was described per treatment arm using the fill rate at each visit. Longitudinal analyses were performed using the time until definitive deterioration (TUDD).[23] Digestive function (LARS) and sexual function (IIEF5) were studied according to a specific questionnaire. Follow-up was performed at inclusion, and at 1, 4, 8, 12, 24, 36, 48, and 60 months.

Statistical considerations

The statistical analysis was performed by FC and SG. The sample size was calculated based on the assumption that 40% of patients would likely show a good response to induction chemotherapy but this rate was 15% in reality.[22] After a planned interim analysis, an independent committee (IC) decided to continue including patients until the required number of evaluable patients was accrued for GR. For BR, randomization was stopped following an amendment after inclusion of 103 evaluable patients. Later, a second IC decided to stop inclusions because of the low accrual rate for GR. Survival analyses were performed on a modified intention-to-treat (ITT) population. Because of the study design, no statistical comparison between arms was performed, with the exception of baseline characteristics and toxicity data during induction chemotherapy. These data were compared among all four arms using Kruskal-Wallis or Wilcoxon tests for quantitative variables and $\chi 2$ or Fisher tests for qualitative variables. Data were analyzed using Stata software, version 13 (College Station, TX). The database was frozen December 12, 2019.

RESULTS

Between May 2011 and October 2014, 206 LARC patients were enrolled (Fig. 2). After induction chemotherapy (n=204), 194 patients were evaluated by MRI: 30 (15%) were classed as GR and 164 (85%) were BR. Randomized patients (n=133) were analyzed based on treatment received: arm A (11 patients), arm B (19; five from arm A were switched to arm B due to an ultra-low tumor), arm C (52), or arm D (51). At diagnosis, 89% of patients (119/133) had a predictive positive radial margin status. MRI-centralized readings from the initial population identified lower tumors for arms A and B and more bulky tumors for arms C and D (Table 1). The median CRM was 0 for each group; nodes were most often considered N1.

127 patients had been operated (Fig. 2). For arms A–D, respectively, the R0 resection rates [90% confidence interval, CI] were 100% [74–100], 100% [85–100], 83% [72–91], and 88% [77–95], and the pCR rates were 10%, 58%, 13.5%, and 20%. CRMs <1 mm were reported for 0%, 0%, 12%, and 5% of patients, respectively, whereas positive distal margins were reported for 0%, 0%, 11%, and 2% of patients. All GR had sphincter saving surgery despite the lowest initial topography; 8.3% of BR underwent abdominal perineal resection. The postoperative reoperation rate was 10%, 16%, 12% and 20%, mainly for anastomotic leakage. At present, the median follow-up is 65.7 (65.3-66.3) months. The global late morbidity between arms A-D increased after radiotherapy (30%, 58%, 50%, 52% of patients, respectively). Morbidity included late fistula including chronic presacral sinus (10%, 21%, 18%, 16%), urinary dysfunction (0, 21%, 18%, 22%), digestive dysfunction (LARS > 20) (70%, 95%, 73%, 71%), sexual dysfunction (IIEF5 <20) (10%, 26%, 33%, 36%), and no stoma closure (0, 5%, 13%, 14%). The median delay for stoma closure between arms was16 weeks.

Five-year oncological results showed that the local recurrence rate was 0% for GR and 4.8% for BR (1/52 and 4/51). For arms A-D, the metastasis rate [90% CI] was 20% [5.4–59.1], 10.5% [2.7–35.9], 18% [9.8–94.6], 18.8% (10.2–33.0). A second cancer occurred three times in arm A, once in arm B, twice in arm C, and three times in arm D. The global 5-year overall survival (5y-OS) was 86.7% [90% CI: 79.2–91.7] with a global 5-year disease-free survival (5y-DFS) of 75.0% [90% CI: 66.5–81.6]. Respectively for each group, rates [90% CI] were: 5y-OS 90.0% [47.3–98.5], 93.3% [61.3– 99.0], 84.3% [71.0–91.8], and 86.1% [71.6–93.5]; 5y-DFS, 80% [40.9–94.6], 89.5% [64.1–97.3], 72.9% [58.5–82.9], and 72.8% [57.7–83.2] (Fig. 3). With regard to quality of life (Fig. 4), treatment arms A, B, C and D showed high baseline compliance: 91% of patients (10/11), 84% (16/19), 90% (47/52), and 90% (46/51) of QLQ-C30 questionnaires. Subsequently, compliance decreased similarly over follow-up for both arms. Baseline QLQ-C30 domain scores showed no statistical differences between treatment arms. At baseline, high physical (88-93) and cognitive scores (87-94), and intermediate role (79-88) and social (79-83) scores, were observed. The highest symptomatic scores included fatigue (21-27), insomnia (25-40), and diarrhea (20-32). Over time, HRQOL was similar between the treatment arms of each stratum, with results confirmed by the TUDD analysis for bad responders.

Regarding the evolution of digestive function, major LARS was found for 40% of patients in all arms at diagnosis, which decreased to 20% before surgery, increased to 30% at 4 months, stabilized at 12 months, then decreased to <20% at 48 months.

At the 36-month follow-up, 95% of patients in the four arms had stoma closure: 50% of patients kept losing gas, 30% wore pads and had fecal urgency with 70% fragmentation without difference between the four arms. Liquid incontinence was higher for patients having radiotherapy (50% vs. 25%), and incontinence affected quality of life in 24%, 60%, 53%, and 56%, in the four arms respectively. Recovery of urinary function was most often complete

(i.e. >90%). Normal erectile function was most often affected after radiotherapy than baseline (90% vs. 45%). Global satisfaction with this tailored management was high at about 95%.

DISCUSSION

GRECCAR4 is the first published study that aimed to select patients based on their early tumoral response. Our results revealed the predictive value of the tumoral response after high-dose FOLFIRINOX chemotherapy and the ability to tailor management according to this response.[22,24] With a 5-year follow-up, we confirmed the safety of this strategy and the high prediction value of the early tumoral response.

The optimal therapeutic sequence for patients with non-metastatic locally-advanced rectal cancer is controversial. A positive predictive radial margin at diagnosis clearly defines this group[25–29] and poor metastasis rates remain a reason for failure. Post-treatment restaging highlights the bad prognosis of a persistent unsafe plane[1,29] not compensated by aggressive surgery. These characteristics clearly explain the current tendency towards intensified neoadjuvant treatment by induction chemotherapy, which may theoretically be associated with better efficacy and compliance. Many studies have analyzed the TNT management for all patients, but its impact on DFS was uncertain.[15,16] A recent publication from the Prodige 23 trial, shows a better 3y DFS for TNT management compared to classical CRT (75.7% TNT group vs 68.5% CRT group; p:0.034).[17] According to the National Cancer Database, the use of induction chemotherapy before RCT has increased significantly over time in the US (5.5% in 2006 vs. 16% in 2015; p<0.001), without improvements in pathologic (pCR 32% vs. 30%) or oncologic outcomes (5-year survival 82% vs. 81%).[28] RCT followed by chemotherapy resulted in better compliance to chemotherapy than first and higher pCR (25% vs. 17%) but the impact on oncologic outcome is unknown.[15–21] Patients who received TNT and surgery had better overall survival than whose who received RCT only (hazard ratio 0.73; p=0.004).[15–21]

In our overall population, our trial demonstrated a global 5y-OS of 86.7% with a global 5y-DFS of 75.0%. These results are relatively good because of the patient selection criteria, i.e., LARC with positive predictive radial margin. For a specific group of LARC patients with residual positive circumferential margin after RCT, the 5y-OS was 68.4%; in those with a bad histological response, 5y-OS fell to 32.4%.[29] Furthermore, Kim et al[1] studied two groups of matched patients with positive and negative CRM after RCT. The overall survival was smaller for residual positive vs. negative CRM (55.8% vs. 67.5%; p=0.186), with a higher rate of metastasis (54.9% vs. 38.5%). Initial positive predictive CRM is a strong marker of bad prognosis for LARC, clearly magnified in cases of residual positive CRM after neoadjuvant therapy.

Our 5-year follow-up confirmed the good prognosis for good responders (5y-OS 100% and 90%; 5y-DFS 80% and 89% for arm A and B, respectively). Unfortunately, the small number of patients and the early discovery of two lung metastatic patients in arm A did not allow us to reach a significant conclusion. These metastatic lungs were certainly present at diagnosis but not diagnosed. Avoiding radiotherapy for good responders had no impact on the local control (100%), while adding RCT led to 60% of sterilized specimens. This late results could be a promising way of research for organ preservation because this pCR rate was never published for LARC. This data must be confirmed; it underlines the high prognostic value of an early good tumoral response.

Conversely, the predictive poor prognosis of early bad responders remained pejorative even with intensive radiotherapy or classical adjuvant chemotherapy.

For ultra-low rectal tumors (tumor inferior pole less than 1 cm from levator ani), we have done an amendment to allow Radiotherapy even in case of good response. Our fear was a positive margin on specimen. We believe that these ultra-low tumors could be a limit to this tailored management without radiotherapy.

The cutoff of the early tumoral response after high-dose chemotherapy is crucial to define the prognostic groups. In our trial, MRI data were reviewed by two experimented radiologists (SN, BG), and the tumor volume was calculated by using dedicated software. The cutoff of 75% reduction in volume was based on the study by Kang et al,[27] showing that more than 75% tumor volume reduction after CRT was significantly associated with high pCR rates. This cutoff appeared high,[30] particularly for arms C and D (65% of patients had 50–75% volume reduction and 23% had <50% volume reduction). We recently reviewed 133 randomized patients of GRECCAR4.[24] A more thorough analysis of the tumoral volume response showed that a large number of patients had a reduction of 60–75%: 40.8% in arm C (20/49) and 36% in arm D (18/50). These patients had a 92% R0 resection rate: 95% for arm C and 88.2% for arm D. So we could conclude that only a tumor volume regression ≤60% after induction chemotherapy was associated with a poor outcome.

In the PROSPECT trial (NCT01515787), the tumoral cutoff after six FOLFOX cycles was a 20% decrease in size to avoid radiotherapy.[21] It will be essential to define the best number because a lower cutoff will reduce the discriminating power of the tumoral response. Similar to Han et al,[28] we suggest that a 60% tumoral response could be sufficient.[22]

Today, very few tumoral markers can predict the aggressiveness of LARC at diagnosis. A recent publication[31] suggested an association between TP53 mutations and MRI-detected extramural vascular invasion at baseline and poor tumor regression after neoadjuvant treatment. In patients who were treated with chemotherapy and RCT univariate analysis indicated that BRAF mutations were associated with a worse overall survival. Such studies are desirable, but unfortunately no valid markers are available. Early discovery of the prognosis through the tumoral response should be important to manage the neoadjuvant sequence. Our results highlighted the significance of an early good response to high-dose

chemotherapy through the pathological results; the 60% pCR rate for good responders with classical RCT is an interesting indicator in this highly selected group of LARC.[22]

Our trial has strong limitations due to the small number of patients randomized in the good responder arms, especially arm A without radiotherapy. In our defense, GRECCAR4 was the first tailored trial for LARC, and we defined a high cutoff of tumoral response to secure the non-radiotherapy group of good responders. We have submitted a prospective Phase II-III non inferiority trial to the French PHRC 2021, which take into account these 5-y results (GRECCAR 14).

CONCLUSIONS

Long-term follow-up of GRECCAR4 confirms the interesting prognostic value of the tumoral response after high-dose chemotherapy. For good responders, it is important not to jeopardize the local control to avoid radiotherapy, while association with a classical CAP50 regimen allows a pCR rate of 60%. For bad responders, intensive RCT cannot enable improvements in their worse prognosis, and new agents are needed. Tailored management of LARC seems promising. Further prospective trials will confirm this strategy and clarify the cutoff level for the early tumoral response.

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FIGURES LEGEND

Figure 1: Trial design.

Figure 2: Flow chart.

Figure 3: Five-year results: a) overall survival; b) disease-free survival; c) metastasis rate.

Figure 4: Quality of life: health status.

Table 1. Patient characteristics at baseline (n=133).

	Good responders		Bad responders	
	Arm A (n=11)	Arm B (n=19)	Arm C (n=52)	Arm D (n=51)
Sex, n (%)				
Male	5 (45.5)	11 (57.9)	34 (65.4)	40 (78.4)
Female	6 (54.5)	8 (42.1)	18 (34.6)	11 (21.6)
Age (years), median (range)	66.0 (44-78)	63.0 (39-75)	61 (22-82)	62 (22-80)
WHO Performance Status, n (%)				
0	10 (90.9)	15 (79.0)	40 (76.9)	35 (68.6)
1	1 (9.1)	4 (21.0)	11 (21.2)	14 (27.4)
2	0	0	1 (1.9)	2 (3.9)
BMI, median (range)	25.3 (18.5-33.6)	24.6 (16.9-32.5)	25.4 (16.9-34.0)	25.5 (18.3-41.3)
Tumor topography, LP-LA (cm), median (range)	1.5 (0-5.8) *	0 (0-10) *	3.3 (0-11) *	2.2 (0-44) *
Circumference ≥50%, n (%)	6 (66.7)	6 (50.0)	35 (94.6)	26 (74.3)
Tumor volume (cm^3), median (range)	23.0 (3.0-148) *	22.0 (10.0-57.4) *	43.0 (8.3-387) *	47.4 (3.3-312) *
CRM (mm), median (range)	0 (0-3)	0 (0-5)	0 (0-20)	0 (0-5)
EMS (mm), median (range)	6.0 (3.0-11.0) *	4.0 (1.0-16.0) *	10.0 (1.5-40.0) *	12.0 (0.5-50.0)

T stage, n (%)				
T3	11 (100)	19 (100)	40 (76.9)	38 (74.5)
T4	0	0	12 (23.1)	13 (25.5)
N stage, n (%)				
N0	2 (18.2)	4 (21.0)	2 (3.8)	1 (2.0)
N1	9 (81.8)	14 (73.7)	50 (96.2)	4 (98.0)
Nx	0	1 (5.3)	0	0

*(Statistically significant results: $p<0.05$). Arm A: immediate surgery; arm B: standard radiochemotherapy (Cap 50: 50 Gy irradiation and 1600 mg/m^2 oral capecitabine daily) plus surgery; arm C: Cap 50 before surgery; arm D: intensive radiochemotherapy (Cap 60: 60 Gy irradiation) before surgery. BMI: body mass index; CRM: circumferential resection margin; EMS: extramural spread; LP-LA: lower pole-levator ani; WHO: World Health Organization.

Figure 1. Trial design.

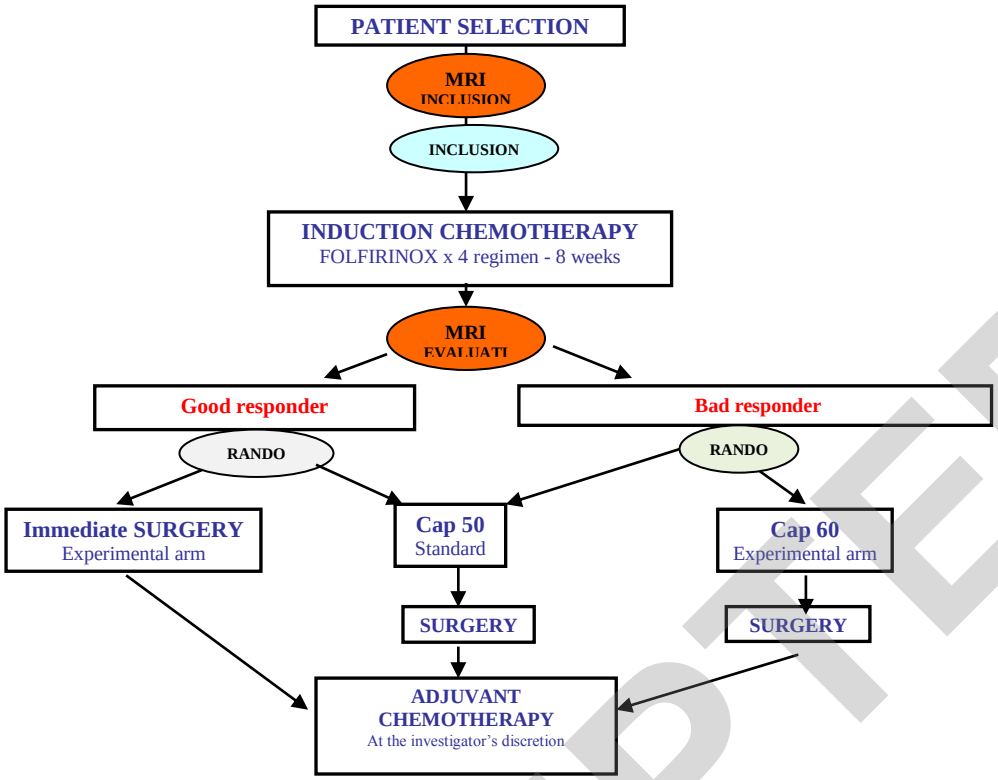


Figure 2. Flow chart.

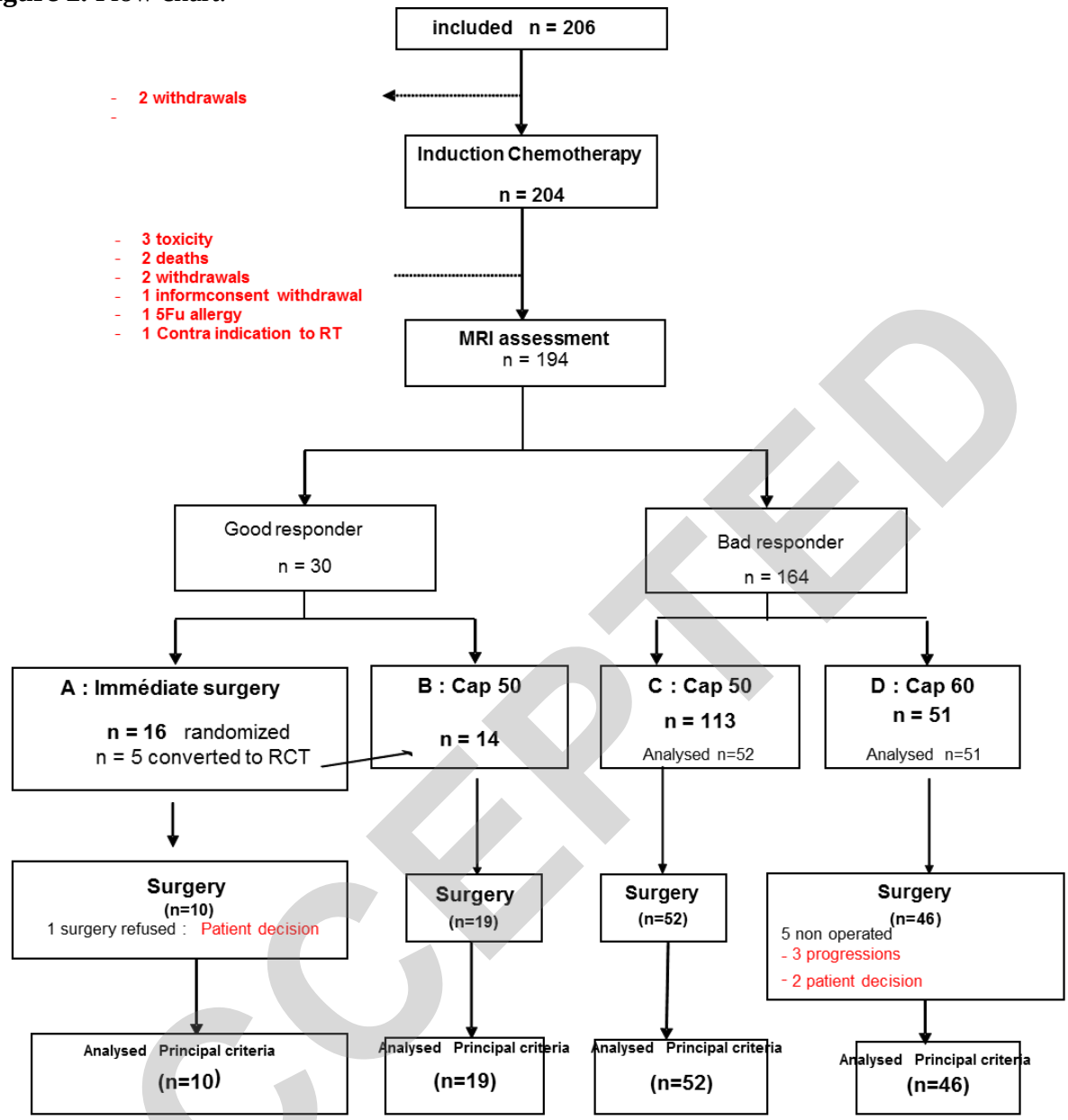
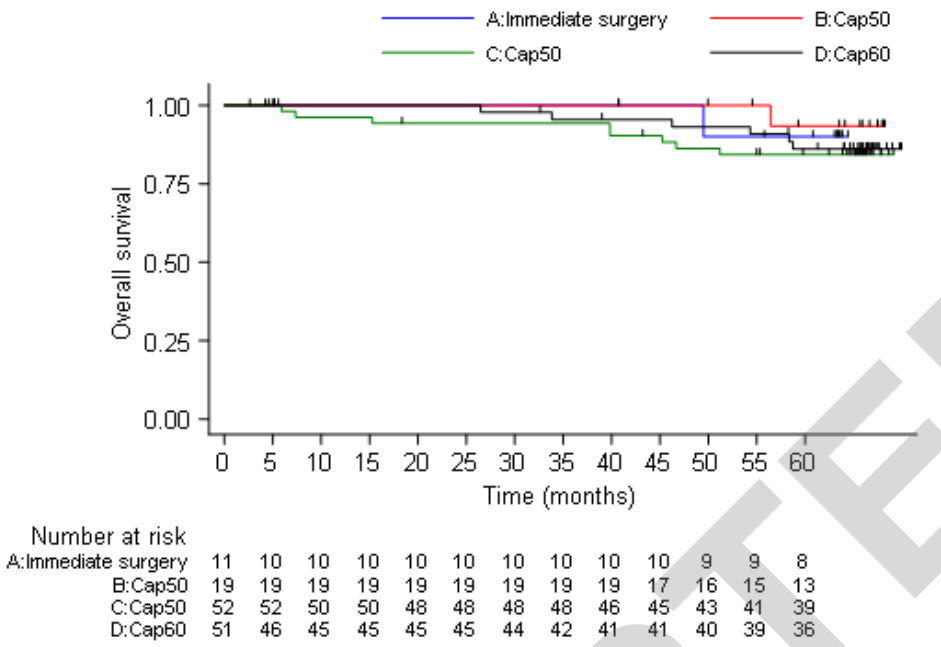
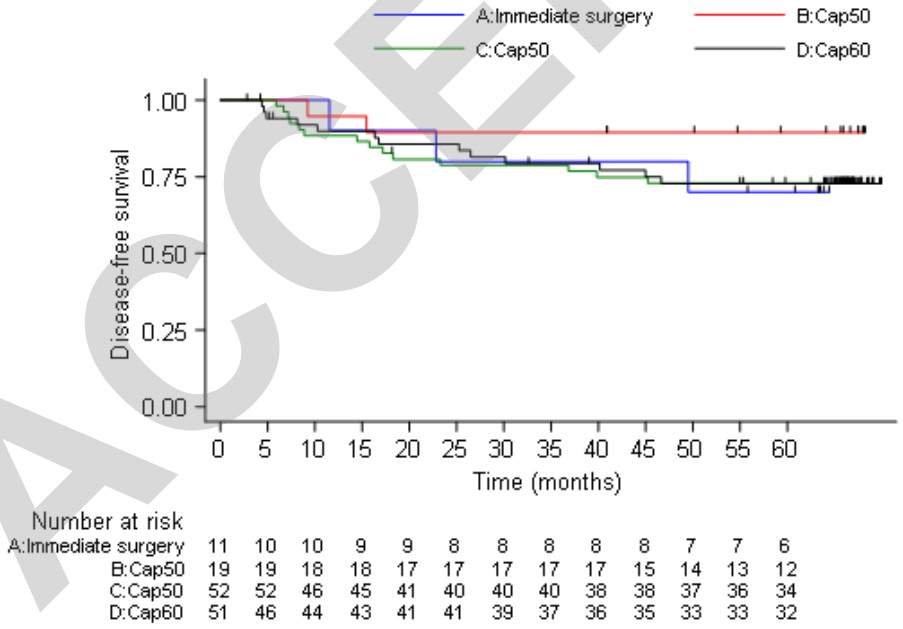


Figure 3. 5-year results: a) overall survival; b) disease-free survival; c) metastasis rate.

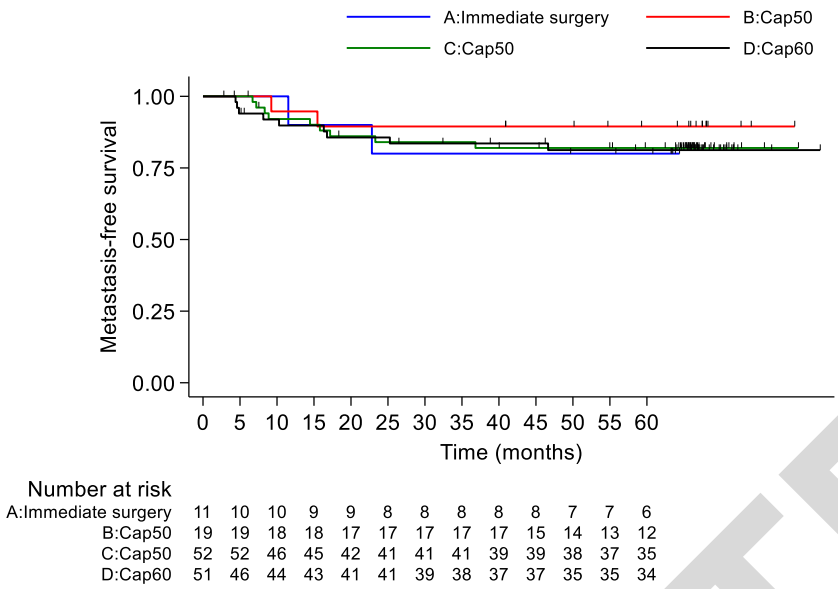
a)



b)



c)

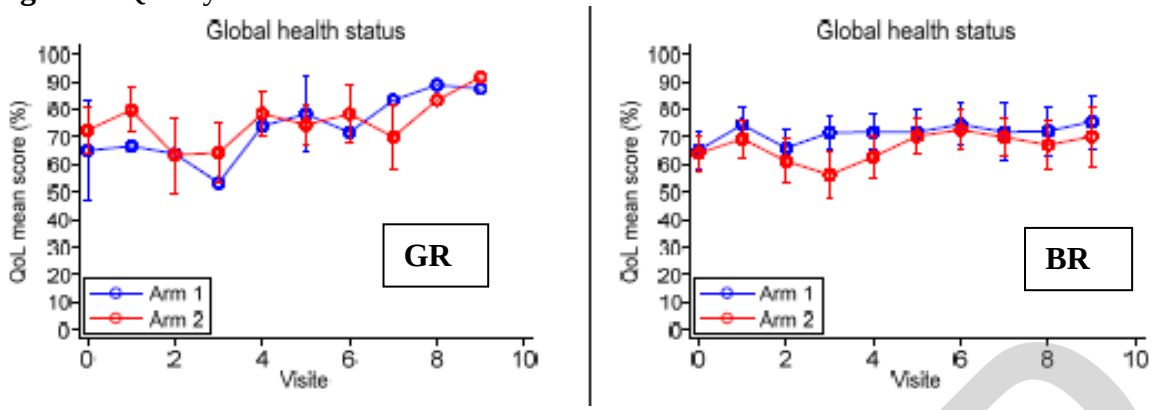


Number at risk

A:Immediate surgery	11	10	10	9	9	8	8	8	8	8	7	7	6
B:Cap50	19	19	18	18	17	17	17	17	17	15	14	13	12
C:Cap50	52	52	46	45	42	41	41	41	39	39	38	37	35
D:Cap60	51	46	44	43	41	41	39	38	37	37	35	35	34

Good responders: Arm A, immediate surgery; arm B, radiochemotherapy (Cap50) before surgery; Bad responders: arm C, radiochemotherapy (Cap50) before surgery; arm D, radiochemotherapy (Cap 60) before surgery.

Figure 4. Quality of life: health status.



Left: GR=good responder. Arm A (1), surgery; arm B (2), radiochemotherapy (Cap50: 50 Gy irradiation and 1600 mg/m^2 oral capecitabine daily) + surgery. Right: BR=bad responder. Arm C (2), radiochemotherapy (Cap50) before surgery; arm D (2), radiochemotherapy (Cap 60: 60 Gy irradiation) before surgery.