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What is the clinical benefit of preoperative chemoradiotherapy with 5FU/leucovorin for T3-4 rectal cancer in a pooled analysis of EORTC 22921 and FFCD 9203 trials: Surrogacy in question?

F. Bonnetain [a,*], J.F. Bosset [b], J.P. Gerard [c], G. Calais [d], T. Conroy [e], L. Mineur [f], O. Bouché [g], P. Maingon [h], O. Chapet [i], L. Radosevic-Jelic [j], N. Methy [a], L. Collette [k]

[a] *Biostatistics and Epidemiology Department, EA 4184 Centre Georges François Leclerc & FFCD, Dijon, France*
[b] *Department of Radiation Therapy, University of Franche-Comté, Besançon, France*
[c] *Department of Radiation Therapy, Centre Antoine Lacassagne, Nice, France*
[d] *Department of Radiation Therapy, University François Rabelais, Tours, France*
[e] *Department of Oncology, Centre Alexis Vautrin, Vandoeuvre-lès-Nancy, France*
[f] *Department of Radiation Therapy, Clinic Sainte-Catherine, Avignon, France*
[g] *Department of Gastroenterology, Centre Hospitalier Universitaire de Reims, Reims, France*
[h] *Department of Radiation Therapy, Centre Georges François Leclerc, Dijon, France*
[i] *Department of Radiation Oncology, Centre Hospitalier Universitaire de Lyon, Lyon, France*
[j] *Department of Radiation Oncology, Institute for Oncology and Radiology, Belgrade, Serbia*
[k] *Statistics Department, European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium*

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Abstract ***Background:*** Two phase III trials of neoadjuvant treatment in T3-4 rectal cancer established that adding chemotherapy (CRT) to radiotherapy (RT) improves pathological complete response (pCR) and local control (LC). We combined trials to assess the clinical benefit of CRT on overall (OS) and progression free survival (PFS) and to explore the surrogacy of pCR and LC.

Patients and methods: Individual patient data from European Organisation for Research and Treatment of Cancer (EORTC) 22921 (1011 patients) and FFCD 9203 (756 patients) were pooled. Meta-analysis methodology was used to compare neoadjuvant CRT to RT for OS, PFS LC and distant progression (DP). Weighted linear regression was used to estimate trial-level association (surrogacy R^2) between treatment effects on candidate surrogate (pCR, LC, DP) and OS.

Results: The median follow-up was 5.6 years. Compared to RT (881 pts), CRT (886 pts) did not prolong OS, DP or PFS. The 5-y OS-rate was 66.3% with CRT versus 65.9% in RT (haz-

* *Corresponding author:* Address: Biostatistic and Epidemiological unit (EA 4184), Centre Georges François Leclerc & FFCD, 1 rue Professeur Marion, BP 77980-21079 Dijon cedex, France. Tel.: +33 3 80 73 77 84; fax: +33 3 80 73 77 34.
E-mail addresses: fbonnetain@cgfl.fr, franck.bonnetain@eortc.be (F. Bonnetain).

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ard ratios (HR) = 1.04 {0.88–1.21}). CRT significantly improved LC (HR = 0.54, 95% confidence interval (CI): 0.41–0.72). PFS was validated as surrogate for OS with $R^2 = 0.88$. Neoadjuvant treatment effects on LC ($R^2 = 0.17$) or DP ($R^2 = 0.31$) did not predict effects on OS. ***Conclusion:*** Preoperative CRT does not prolong OS or PFS. pCR or LC do not qualify as surrogate for PFS or OS while PFS is surrogate. Phase III trials should use OS or PFS as primary endpoint.

1. Introduction

Until the late 80s surgery alone was considered the cornerstone of curative treatment for patients with a rectal cancer, but the risk of local recurrence after surgery was high.[1] In the early 90s, postoperative chemoradiation or moderate dose preoperative radiotherapy was shown to significantly reduce local recurrence and to prolong overall survival (OS).[2] Neoadjuvant radiotherapy (RT) then became the new standard treatment for locally advanced (T3-4) operable rectal cancers.[3–7]

In 1993 the European Organisation for the Research and Treatment of Cancer (EORTC) Radiotherapy Group started a randomised trial (EORTC 22921) that compared neoadjuvant CRT versus RT alone and postoperative chemotherapy (postop CT) versus nil in cT3-resectable T4 M0 disease. A companion trial promoted by the Fédération Francophone de Cancérologie Digestive (FFCD 9203) was conducted in France using the same selection criteria and preoperative treatment schemes as the EORTC trial, but all patients had to receive postop CT. Both trials showed significantly increased pathological complete response (pCR) rates and longer local control (LC) with CRT.[8,9] However they could not demonstrate a significant benefit in OS, their primary endpoint.[8,9] Nevertheless CRT became the standard neoadjuvant treatment. Since results became available 13 years after trial initiation, this prompts the need to identify surrogate endpoints to reduce trial duration.

A recent exploratory study suggested that despite strong correlation pathological parameters assessed on the surgical specimen are not surrogate for OS nor for LC, and that LC is not surrogate for OS nor for DFS.[10] However, recent trials of multimodal treatments for rectal cancer[6,11] use pCR or LC as primary endpoint. The choice of such early endpoints is a matter of debate which should be addressed by more powerful studies to statistically validate their surrogacy.[12–14] While an intermediate endpoint needs to be strongly associated with the final endpoint (i.e. endpoints representing clinical benefit for the patient like OS), its qualification as a surrogate endpoint further requires demonstration of a strong association between treatment effects (hazard ratio) on the surrogate and treatment effects on the final endpoint. The latter can be only demonstrated using meta-analytic approach.[10]

We perform a combined analysis of the EORTC and FFCD trials investigating neoadjuvant treatment in T3-4 rectal cancer,[8,9] to assess the impact of CRT on PFS and OS with increased statistical power and to explore the surrogacy of intermediary endpoints (pathological parameter LC and distant progression) for OS and PFS in that setting.

2. Patients and methods

2.1. Trials and patients

The individual patient data of the FFCD 9203 and EORTC 22921 trials were collated. These trials have been described extensively elsewhere.[8,9] Both trials recruited cT3 or resectable cT4 M0 adenocarcinoma of the rectum, located within 15 cm of the anal verge, a World Health Organisation (WHO) performance status of 0 or 1; aged 80 years or less in EORTC 22921 and 75 years or less in FFCD 9203. Between April 1993 and November 2003, 762 patients entered the FFCD trial (of which 14 were deemed ineligible and six were immediately lost to follow-up). From April 1993 to March 2003, 1011 patients entered the EORTC trial of which 15 were ineligible.

2.2. Endpoints

Overall survival (*OS*) was counted from randomisation to the day of death of any cause.

Progression free survival (PFS) was counted from randomisation to the day of first local or distant progression or day of death of any cause (irrespective of surgical outcome). We used PFS instead of DFS because all randomised patients were not resected and amongst resected patients all of them were not free of detectable cancer disease.

Local Control (LC) was counted from randomisation to the day of first local progression (irrespective of distant progression).

Time to distant progression (DP) was counted from randomisation to the day of first distant progression (irrespective of local progression).

For all endpoints, patients alive and free of the events of interest were censored at their last follow-up. Patients without data were censored at time 0.

Pathological complete response (pCR) was defined as T sterilisation (pT0) and pN0. The pathological stage

(ypT or ypN) was scored by the International Union Against Cancer TNM classification.[7,15]

2.3. Statistical methods

Analyses are by intention to treat in the 1767 patients with information with two-sided significance level of 5%.

All time to event endpoints were estimated by Kaplan–Meier. Hazard ratios (HR) of CRT versus RT and their 95% confidence interval (CI) were estimated by meta-analysis of three trial strata defined according to trial and adjuvant treatment (Adj): EORTC Adj; FFCD Adj and EORTC no Adj. Forest plots and log rank tests for interaction and heterogeneity were used to report results.[16] Median follow-up time was estimated by reverse Kaplan–Meier.

The meta-analytic surrogate validation method necessitates regression of trial results for the two endpoints (candidate surrogate and final endpoint). Since we had only two trials available, we subdivided the studies into 14 smaller randomised patient groups (so-called 'trial-units') separating centres by the three trial strata defined above (EORTC Adj, FFCD Adj and EORTC no Adj) and according to the quintiles of the centre's total accrual (1–17; 18–33; 34–58; 59–75 and $\geqslant$76 pts.[17–19] This way 3 units have been generated for centre that accrued a total of e.g. 1–17 pts: one for EORTC Adj, one for FFCD Adj and one for EORTC no Adj. However, since no FFCD centre included more than 76 pts, the total number of units is only 14.

Because in both trials, randomisation was stratified by centre and adjuvant treatment (EORTC), treatment allocation was properly randomised within trial-units.

To explore surrogacy of LC, DP and PFS for OS, we quantified the association between the effect of treatment on the candidate surrogate endpoints (i.e. LC, DP and PFS) and the effect of treatment on OS using weighted linear regression model. Firstly treatment effects were estimated by log hazard ratios (log HR estimated by Cox model) in each trial unit. The linear regression model was weighted by the trial unit size (number of patients in each defined trial unit) to take into account the uncertainty about the estimated effects. We calculated the coefficient of determination, estimating the trial unit-level association (R^2) between treatment effects on the candidate surrogate and the final endpoint (17–20). Values of $R^2 > 0{\cdot}75$ are indicative of good surrogacy.[19]

Surrogacy of pCR for LC, PFS and OS was explored using similar methods, but the treatment effect on pCR (log OR i.e. log of odd ratio) was estimated by logistic regression.

3. Results

In total, 1767 patients (756 from FFCD 9203 and 1011 from EORTC 22921 trials) were included in the analysis (six FFCD patients with no data were excluded). Of them, 881 had RT and 886 had CRT. The patients were grouped into 14 trial-units for the surrogacy analyses.

Supplementary Table 1 shows the patient and treatment characteristics according to the three trial strata (by trial and adjuvant treatment). The median age was 63 years, 70% are male and 71% had a WHO PS of 0. Over 50% of patients had a tumour located $\leqslant$5 cm from the anal margin and 90% had a cT3 tumour. Surgery was done for 1711 patients (97%) and rectal resection in 1686 of them (98.5%). R0–R1 resection was achieved in 95.6% (1612/1686) and among them 121 (7.5%) had a pCR.

After a median follow-up of 5.6 years, 230 patients had a local progression, 540 distant metastases and 607 patients died. Thus, this analysis has approximately 80% power to detect a treatment effect of the magnitude HR = 0.69 for LC, HR = 0.785 for DP and HR = 0.80 for OS.

3.1. Combined trial results

Clinical characteristics were well balanced according to preoperative treatment (Table 2). Surgery was performed in 860 of 881 pts (98%) and 851 of 886 pts (96%) in the RT and CRT arm, respectively with resection achieved in 847 of 860 (98.5%) and 839 of 851 (98.6%) patients, respectively. Compared to RT, CRT significantly increased the rate of R0–R1 resection: 96.5% (810/839) versus 94.7% (804/847) ($p = 0.0327$); that of ypN0: 69.7% (585/839) versus 63.8% (540/847), ($p = 0.004$) and that of ypT0: 12.9% (108/839) versus 4.7% (40/847) ($p \leqslant 0.0001$) resulting in an increased pCR rate: 11.2% versus 3.7% ($p \leqslant 0.0001$).

CRT did not improve OS over RT (HR = 1.04; 95% CI: 0.88–1.21, $p = 0.66$, Fig. 1a and Supplementary Fig. 1a). The 5-year OS rates were 66.3% (95% CI: 62.6–69.7%) after CRT and 65.9% (CI: 62.2–69.3%) after RT (Supplementary Fig. 2a).

Similarly CRT did not improve PFS (HR = 0.95; 95% CI: 0.83–1.09, $p = 0.49$, Fig. 1b and Supplementary Fig. 1b). The median PFS was 7.4 years (95% CI: 6.3–8.6) after CRT and 7.2 years (95% CI: 5.7–10.0) after RT. The 3-year PFS rate was 64.3% (95% CI: 61.0–67.5%) and 60.6% (95% CI: 57.2–63.9%) after CRT and RT, respectively (Supplementary Fig. 2b).

Compared to RT, CRT improved local control among the resected patients (HR = 0.55; 95% CI: 0.42–0.72, $p < 0.0001$, Fig. 3). LC rates at 1, 2 and 3 years were 97.8% (95% CI: 96.5–98.6%), 93.8% (95% CI: 91.9–95.3%) and 92.3% (95% CI: 90.1–94.0%) in the CRT group and 96.0% (95% CI: 94.4–97.1%), 89.3% (95% CI: 86.9–91.3) and 84.7% (95% CI: 81.9–87.1%) in the RT group, respectively (Supplementary Fig. 2c).

CRT did not prolong time to distant progression (HR = 0.94; 95% CI: 0.80; 1.12, $P = 0.50$, Fig. 3). The

Table 2
Distribution of medical and clinical characteristics according to RT (neoadjuvant radiotherapy) or CRT (neoadjuvant chemoradiotherapy) randomised treatment.

	Randomised treatment group	
	RT $N = 881$ *N* (%)	CRT $N = 886$ *N* (%)
Age (years)		
Median	63.1	63.5
Range	23.3-79.4	22.0-81.5
Sex		
Male	619 (70.3)	624 (70.4)
Female	262(29.7)	262 (29.6)
Performance status		
WHO PS0	637 (72.3)	621 (70.1)
WHO PS1	228 (25.9)	254 (28.7)
Missing	16 (1.8)	11 (1.2)
Distance to anal margin		
0–5cm	437 (49.6)	449 (50.7)
6–10cm	385 (43.7)	400 (45.1)
11–15cm	53 (6.0)	34 (3.8)
Missing	6 (0.7)	3 (0.3)
Clinical T stage		
T3	782 (88.8)	796 (89.8)
T4	92 (10.4)	88 (9.9)
Missing	7 (0.8)	2 (00)
Differentiation		
Well	361 (41.0)	366 (41.3)
Moderately	346 (39.3)	355 (40.1)
Poor	33 (3.7)	39 (4.4)
Not stated	132 (15.0)	115 (13.0)
Missing	9 (1.0)	11 (1.2)
Surgery		
No	15 (1.7)	22 (2.5)
Yes	860 (97.6)	851 (96.0)
Missing	6 (0.7)	13 (1.5)
Patients with surgery	$N = 860$	$N = 851$
Resection		
No	12 (1.4)	11 (1.3)
Yes	847 (98.5)	839 (98.6)
Missing	1 (0.1)	1 (0.1)
Resection	$N = 847$	$N = 839$
R0–R1	802 (94.7)	810 (96.5)
R2	44 (5.2)	26 (3.1)
Missing	1 (0.1)	3 (0.3)
R0–R1patients	802	810
pCR		
Yes	30 (3.7)	91 (11.2)
No	753 (93.9)	696 (86.0)
Missing	19 (2.4)	23 (2.8)

pCR: pathological complete response, WHO: World Health Organisation.

3-year DP-free rates were 71.3% (95% CI: 68.0–74.3) and 70.7% (95% CI: 67.5–713.8%) in the CRT and RT groups, respectively (Supplementary Fig. 2d).

There was no significant heterogeneity of preoperative treatment effects across trial strata (heterogeneity $p > 0.1$, Figs. 1 and 3).

Analyses restricted in both trials to the subset of patients who received four cycles of adjuvant chemotherapy gave similar results: no effect on OS, DP or PFS, and for LC, HR = 0.50 (95% CI: 0.34–0.75, $p < 0.001$).

3.2. Surrogacy of pCR for LC, PFS and OS

These analyses were conducted in all 1686 resected patients from 14 trial-units. However, for pCR one unit (88 patients) had to be excluded because there was no ypT0N0 in the RT group resulting in 1598 patients from 13 trial-units for that analysis.

At the trial-unit level, the associations between the effect of CRT on pCR as candidate surrogate and its effect on OS, on PFS and on LC as true endpoints were all low, with respectively $R^2 = 0.11$ (95% CI, 0.0–0.44); $R^2 = 0.25$ (95% CI, 0–0.66) and $R^2 = 0.23$ (95% CI, 0–0.63). Fig. 4 shows the regression of the trial-unit treatment effects on OS (log(HR)) over those on pCR (log(OR)).

3.3. Surrogacy of LC for OS

The trial-unit level association between the effect of CRT on LC as candidate surrogate and its effect on OS as true endpoint was low, with $R^2 = 0.17$ (95% CI, 0–0.52). Fig. 5a shows the regression of trial-unit treatment effects on OS (log(HR)) against those on LC (log(HR)).

3.4. Surrogacy of DP for OS

The trial-unit level association between the effects of CRT on DP as candidate surrogate and its effect on OS as true endpoint was modest with $R^2 = 0.31$ (95% CI, −0.09 to 0.71) (Fig. 5b).

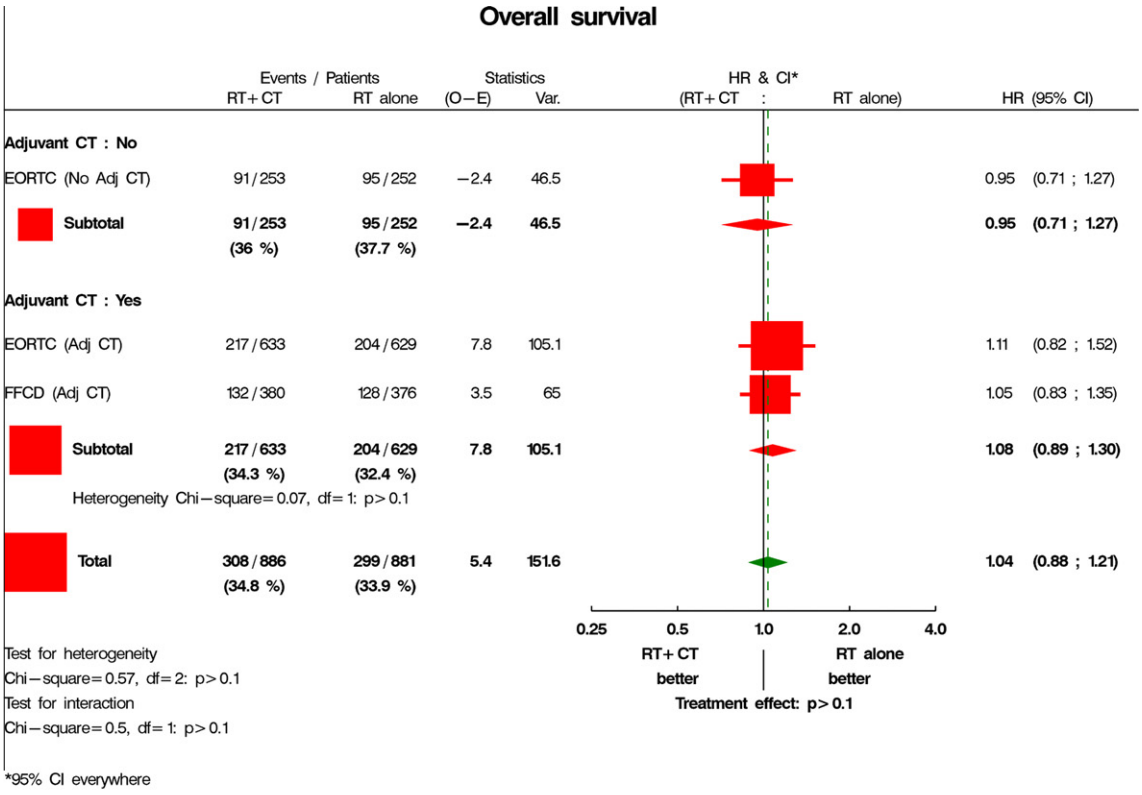
3.5. Surrogacy of PFS for OS

The trial-unit level association between the effects of CRT on PFS as candidate surrogate and its effect on OS as true endpoint was high, with $R^2 = 0.88$ (95% CI 0.77–1) suggesting surrogacy (Fig. 6).

4. Discussion

Using the data from two large randomised trials in T3-T4 rectal cancer we confirmed that in comparison to neoadjuvant RT, neoadjuvant CRT improves local control as well as the pathological complete response rate parameters (+8%) and the feasibility of R0–R1 resections (+2%). However despite increased statistical power, no significant improvement in PFS or OS was seen.

Therefore, the patient's clinical benefit of adding chemotherapy to preoperative radiotherapy remains



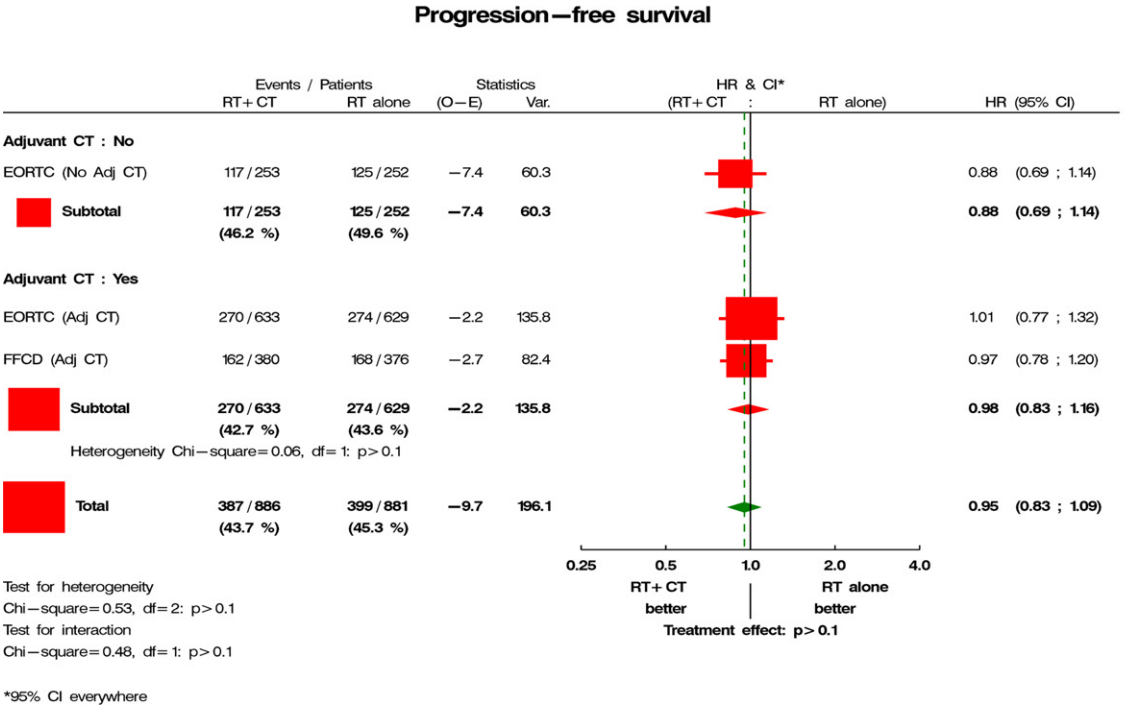


Fig. 1. Forest plots for (a) Overall survival and (b) progression free survival (1749 patients). The centre of the squares is the hazard ratio (HR), bars represent 95% confidence interval, the size of the square is proportionate to the number of events. RT-CT: preoperative chemoradiotherapy; RT: preoperative radiotherapy; CT: chemotherapy; Adj: adjuvant.

debatable. Indeed, according to Fleming[12] and according to the classification of endpoints in oncology[21]; pCR, ypT0 or local control do not represent a clinical benefit on their own, and should not be the final endpoint of phase III clinical trials, but should be regarded as biomarkers.

In this context, we pursued the further objectives of exploring the validity of candidate surrogates for OS.

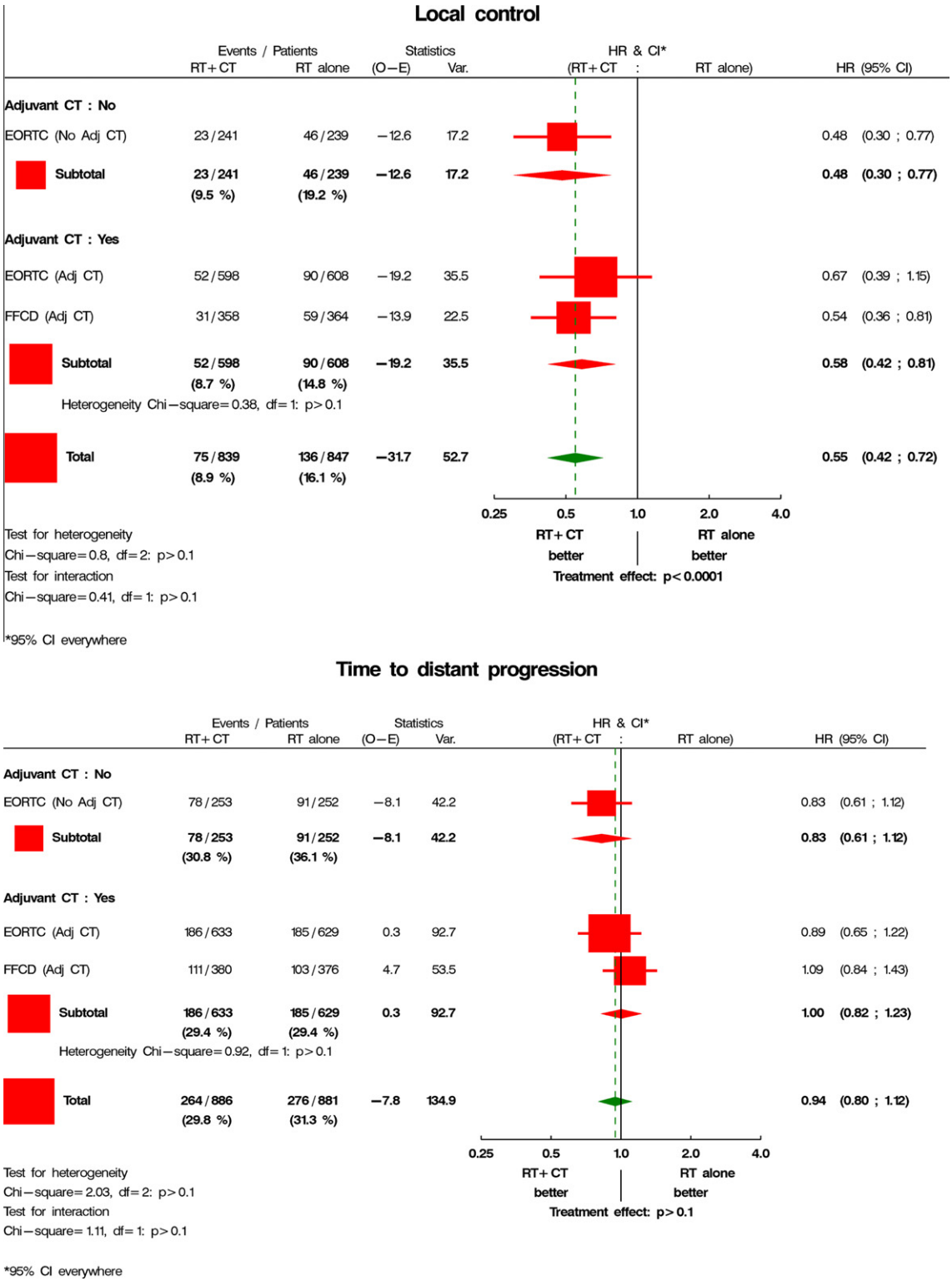


Fig. 3. Forest plot for (a) local control and (b) time to distant progression. The centre of the squares is the hazard ratio (HR), bars represent 95% confidence interval, the size of the square is proportionate to the number of events. RT-CT: preoperative chemoradiotherapy; RT: preoperative radiotherapy; CT: chemotherapy; Adj: adjuvant.

In particular, we wanted to investigate if PFS is a valid surrogate for OS in T3-T4 rectal patients treated by RT or CRT. With a trial-unit level association R^2 of 0.88 (95% CI: 0.77–1.00), our results suggest that with 5 years follow-up, differences in effects of neoadjuvant treatments on PFS were good predictors of eventual treatment differences on OS. These findings concur with those obtained in colon cancer, where DFS or PFS was shown to be a valid surrogate for OS.[22–27] That PFS appears a good surrogate suggests that one needs to capture the

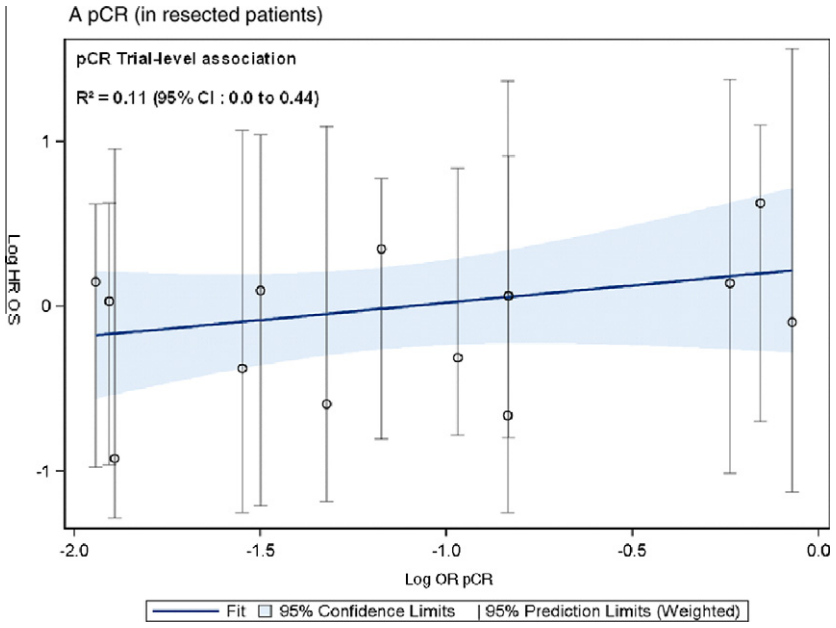


Fig. 4. Weighted linear regression between the treatment effect on overall survival (log hazard ratio (HR) overall survival (OS)) and treatment effect (log OR) on pCR (pathological complete response) to estimate trial-level association (R^2) between the two end points. The circles represent the observations in the 'trial-unit'. The line represents the prediction from the estimated weighted linear regression. Weighted linear regression showing the correlation (trial-level association R^2) between the treatment effect on pathological complete response (pCR) (log OR of pathological complete response) and on overall survival (log HR OS). A $R^2 > 0.75$ indicates surrogacy.

effect of the treatment on all the events that compose PFS (i.e. local progression, distant metastases and death) to predict with accuracy the final treatment effect on OS.

However, our results only demonstrate the surrogacy of PFS for OS for comparisons of neoadjuvant chemo-radiotherapy to neoadjuvant radiotherapy. Its validity as a surrogate of OS needs to be confirmed for trials aiming to assess preoperative treatment regimens that include targeted therapy and/or biotherapy.[12,13]

Our surrogacy study bares some limitations, a larger meta-analysis would include more actual and representative neoadjuvant radiochemotherapy regimens than those included in the EORTC and FFCD studies that involved conventional irradiation and 5-FU single agent. Compared to the two trials in this analysis, the quality of staging (MRI i.e. magnetic resonance imaging), planning and delivery of radiation, surgery (TME i.e. total mesorectal excision) and pathological reporting are clearly improved in current clinical trials and clinical practice. Therefore, our results, particularly regarding pathological complete response may need further validation in more recent series. In our analysis, all treatment differences on PFS and OS were modest; therefore, it would also be relevant to confirm that our results stand in the presence of larger treatment effects but also with longer follow-up for PFS and OS like in colon cancer.[24] However we could not identify studies showing large effects of preoperative treatments on OS or PFS.

Importantly, treatment effects on pCR, LC or DP in our analysis were poor predictors for treatment effects on OS. Our study also showed preoperative treatment effects on pCR were poor predictors of effects on LC, PFS or OS (all $R^2 < 0.5$). Our findings are in line with recent results of a phase III trial showing that effects achieved on pCR or LC do not necessarily translate into improvements of OS.[11,28–30] Whether improvements in pCR and/or LC represent clinical benefit on their own remains a matter of debate among physicians.[12,21] Clinicians consider that local progression has a clear deleterious effect on health-related quality of life (QoL) and therefore prolongation of LC remains one of their major therapeutic goals. Then clinicians are tempted to regard pathological outcome parameters or LC as surrogates[31] for long term clinical benefit in comparative phase III trials instead of intermediate markers of efficacy. They should not be used as definitive endpoints[32] nor should they be regarded as clinical benefit per se.[14,33] Moreover improvement in pCR concerns only a small subset of patients.[33] A recent meta-analysis has shown that pCR is a prognostic factor of OS and DFS[34] suggesting that achievement of pCR by chemo-radiation may indicate a favourable biological tumour profile.[34] However that study did not directly address surrogacy by exploring association between treatment effects at the trial-unit level.[20]

The pooled analysis by Valentini et al.[35] proposes decision support for the delivery of postoperative adjuvant CT based on a nomogram predicting the risk of LR, DM and OS. They also suggested that OS was improved by addition of chemotherapy to preoperative RT and also by adjuvant chemotherapy. However, their analysis

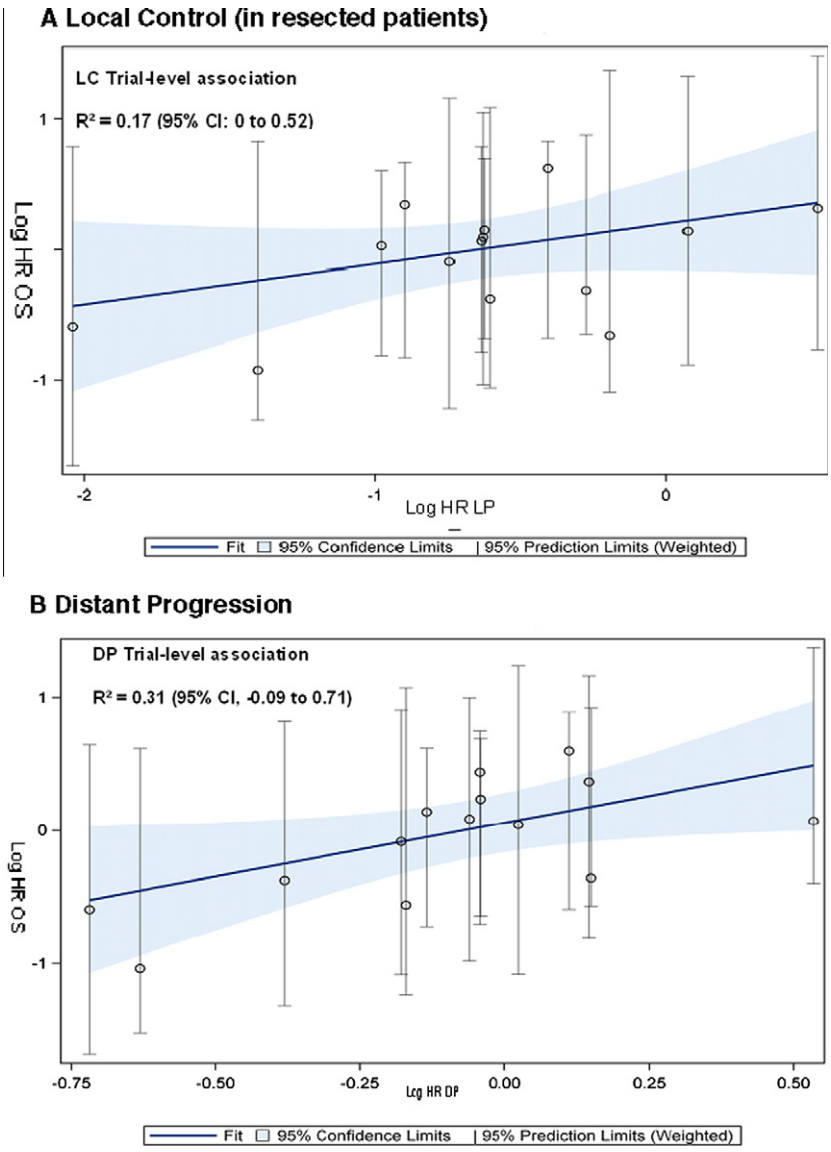


Fig. 5. Weighted linear regression between the treatment effect on overall survival (log hazard ratios (HR) OS) and the treatment effect on local control (log HR local control (LC)) or distant progression (log HR DP) to estimate trial-level association (R^2) between the two end points. The circles represent the observations in the 'trial-unit'. The line represents the prediction from the estimated weighted linear regression. Weighted linear regression showing the correlation (trial-level association R^2) between the treatment effect on LR (log HR of local control) Fig. 6A and on overall survival (log HR OS). A $R^2 > 0.75$ indicates surrogacy. Weighted linear regression showing the correlation (trial-level association R^2) between the treatment effect on DP (log HR of distant progression) Fig. 6B and on overall survival (log HR OS). A $R^2 > 0.75$ indicates surrogacy.

compared non-randomised group of patients across trials as example all patients in German trials seem to account for patients receiving concurrent chemotherapy while they were randomised between pre operative CRT versus post operative CRT, thus limiting the interpretation of their results. In our study all patients were randomised regarding neoadjuvant RT versus CRT allowing a cross comparison using meta-analytic method.

In order to improve the conduct of clinical trial we need endpoints that are reliably measurable, sensitive, easy to interpret and clinically relevant, reflecting a tangible clinical benefit to the patient. Moreover in trials comparing neoadjuvant strategies early endpoints will not be influenced by postoperative and salvage treatments.

In the context of clinical trials in rectal cancer we suggest that LC or pCR could be used as primary endpoint for phase II trials or as an intermediate endpoint in futility stopping rules for phase III trials when OS or PFS is the final endpoint. If new phase III trials need earlier endpoints than OS, we recommend using PFS.

In contrast, we urge for caution with trials that demonstrate significant benefits only in LC and/or pCR, given these benefits are unlikely to translate into benefits in PFS or OS.[36] However, if for pragmatic reasons future trials use LC or pCR as primary endpoint,[36] we strongly suggest to confirm any claimed benefit in pCR and/or LC by comparing the two treatments in terms of QoL to ensure that the observed differences

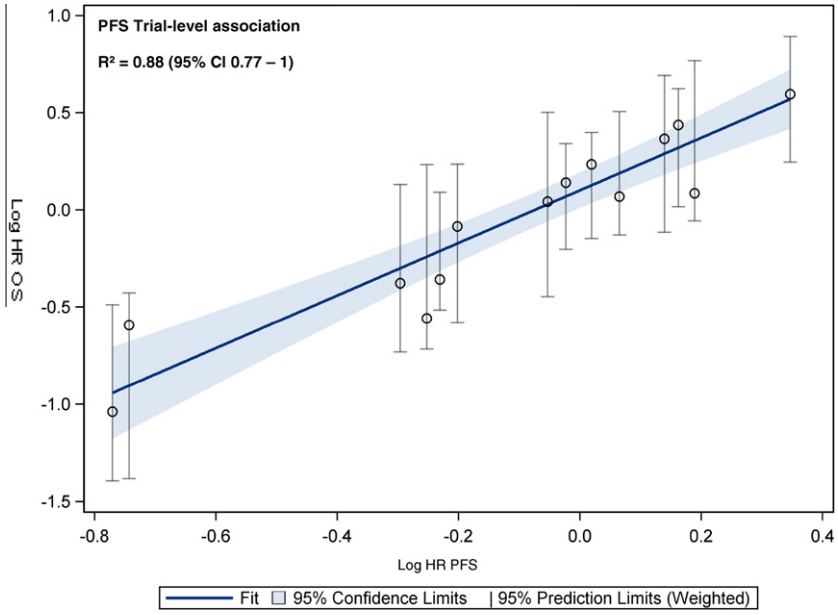


Fig. 6. Weighted Linear regression between the treatment effect on overall survival (log hazard ratio (HR) OS) and the treatment effect on progression free survival (log HR PFS) to estimate trial-level association (R^2) between the two end points. The circles represent the observations in the 'trial-unit'. The line represents the prediction from the estimated weighted linear regression Weighted linear regression showing the correlation (trial-level association R^2) between the treatment effect on progression free survival (PFS) (log HR of PFS) and on overall survival (log HR OS). A $R^2 > 0.75$ indicates surrogacy.

do indeed clinically benefit the patients. We believe that a trial demonstrating early benefits in pCR and/or LC and an improvement in QoL or other patient reported outcomes (PRO) has a greater potential to be regarded as demonstrating a clinical benefit. This is in agreement with FDA stipulating that 'PRO represent a patient perspective of direct clinical benefit' while 'pCR is not a direct measure of benefit in all cases'.[33]

Author contributions

Study concept and design: Franck Bonnetain & Laurence Collette.

Provision of study materials or patients (data acquisition): Jean-François Bosset, Jean-Pierre Gerard, Gilles Calais, Thierry Conroy, Laurent Mineur, Olivier Bouché Philippe Maingon, Olivier Chapet, Ljiljana Radosevic-Jelic.

Quality control of data and algorithms: Franck Bonnetain & Laurence Collette.

Statistical analysis: Franck Bonnetain & Laurence Collette.

Data analysis and interpretation: Franck Bonnetain, Laurence Collette, Jean François Bosset, Jean-Pierre Gérard & Nicolas Methy.

Manuscript preparation: Franck Bonnetain & Laurence Collette.

Manuscript editing: Franck Bonnetain, Laurence Collette, Jean François Bosset, Jean-Pierre Gérard, Thierry Conroy & Philippe Maingon.

Manuscript review: all authors.

Final approval of manuscript: all authors.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2012.03.016.

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