Surrogate end points for overall survival and local control in neoadjuvant rectal cancer trials: statistical evaluation based on the FFCD 9203 trial

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Background: In resectable rectal cancer trials, pathological parameters are early preoperative treatment efficacy measures. Their validation as surrogate end points for long-term clinical outcomes would allow to reduce trial duration. The aim was to evaluate potential surrogates for overall survival (OS) and local control (LC) in preoperative T3/T4 rectal cancer trials. Candidate variables included ypT and ypN stages, T downstaging, tumor regression grade (TRG), and circumferential resection margin (CRM) status.

Patients and methods: In the Fédération Francophone de Cancérologie Digestive (FFCD) 9203 trial, 742 eligible patients were randomly assigned to receive preoperative radiotherapy with or without concurrent chemotherapy. Surrogacy was evaluated using Prentice criteria and the proportion of treatment effect (PTE) explained by each potential surrogate.

Results: None of the candidate surrogates fulfilled all Prentice criteria. Data analyses did not provide interpretable PTE measures for OS. Regarding LC, the highest PTE was reached by TRG, which explained 12% of the effect on local recurrence. This proportion may not exceed 41% [95% confidence interval (CI) 1% to 41%]. PTE explained by the CRM status was associated with a wide uncertainty (95% CI 81% to 105%), which does not exclude a potentially high degree of surrogacy.

Conclusion: In the FFCD 9203 trial, pathological parameters were not surrogate for OS or LC.

Key words: chemoradiation, clinical trial, radiation, rectal neoplasms, surrogate end points

introduction

Overall survival (OS) remains the gold standard end point for the evaluation of a novel therapy in phase III cancer clinical trials [1]. It is an objective and clinically meaningful end point that is expected to measure the survival gain offered by the experimental treatment.

In T3/T4 resectable rectal cancers, where preoperative radiotherapy (RT) with concurrent chemotherapy (CT) has become the standard strategy, OS may require long follow-up times and large numbers of patients. For instance, >10 years were required for the Fédération Francophone de Cancérologie Digestive (FFCD) 9203 trial [2] and the European Organisation for Research and Treatment of Cancer (EORTC) 22921 trial [3] to include and follow their patients. Extensive follow-up and inclusion periods delay the conclusions of the trial and the dissemination of the potentially effective new treatment in current practice [4].

Another drawback to using long-term outcomes is the risk of confounding effect from subsequent therapies [5]. This has been investigated for the evaluation of first-line CTs in advanced colorectal cancer because of the availability of further lines and the potential effect of crossover on the primary end point [6, 7]. In rectal cancer, OS may reflect the effect of pre- and postoperative treatments, and possible subsequent lines.

Locoregional relapse is the predominant form of treatment failure considered by radiotherapists. Then, local control (LC) is another standard end point used in rectal clinical trials [8]. Although relapses can be observed sooner than deaths, this end point remains time consuming [8].

To use an earlier end point to conclude on the efficacy of a new treatment would allow to reduce the duration of the studies and would be supposed to evaluate with better specificity the proper effect of the experimental treatment. Glynne-Jones et al. [8] have thoroughly reviewed the end points usually recorded in rectal cancer trials comparing
preoperative strategies, to identify possible alternative end points, based on evidence from phase II and phase III trials. In addition to survival and LC, they discussed pathological parameters such as the circumferential resection margin (CRM) and measures of the degree of response to chemoradiation. Pathological parameters seem interesting end points for the reason that they are rapidly assessable and able to reflect the specific effect of the preoperative treatment.

Nevertheless, before being used as primary end point in a trial, these alternative end points should be validated as surrogates for the clinical end point it is supposed to substitute for. Prior specific statistical validation is required [9, 10] to ensure that conclusion drawn from the surrogate reflects clinical benefit for the patients. Indeed, several examples showed in the past that decision regarding a new treatment based on an intermediate event can lead to wrong conclusions concerning the final end point [11].

Based on the FFCD 9203 trial, the aim of this study was to evaluate the surrogacy value of some pathological parameters to substitute for OS or LC in T3/T4 neoadjuvant rectal cancer clinical trials. Candidate surrogates were ypT and ypN stages, T downstaging, tumor regression grade (TRG), and CRM status. We also evaluated time to local recurrence and time to progression as surrogates for OS.

patients and methods
the FFCD 9203 trial
Our analyses were based on the FFCD 9203 trial whose design and results were detailed previously [2]. Patients were eligible if they presented a T3/T4, Nx, M0 histologically confirmed, previously untreated rectal adenocarcinoma accessible to digital rectal examination. They were younger than 75 years with a World Health Organization performance status of 0 or 1. They were randomly allocated to either preoperative radiation alone or concurrent RT–CT from April 1993 to November 2003.

Evaluation of the extent of the disease, including preoperative imaging, was described previously [2]. Tumor staging was clinical. The total dose of the preoperative RT was 45 Gy delivered in 25 fractions during 5 weeks. Concurrent CT with fluorouracil 350 mg/m²/day during 5 days, together with leucovorin, was administered during the first and fifth week in the experimental arm. Surgery was planned 3–10 weeks after the end of RT (with or without CT). All patients were scheduled to receive adjuvant CT with leucovorin, was administered during the first and fifth week in the experimental arm.

A total of 742 patients were eligible. The median follow-up time was 81 months (range 17–145 months). The results showed significant treatment effect neither on OS (5-year OS rate: 67.9% in the RT arm versus 67.4% in the CT arms, \( P_{\text{Log-Rank}} = 0.68 \)) nor on progression-free survival (PFS; 5-year PFS rate: 55.5% in the RT arm versus 59.4% in the RT–CT arm, \( P_{\text{Log-Rank}} = 0.73 \)). Among the 674 patients who underwent a macroscopically complete resection (R0–1), the 5-year cumulative local recurrence rate was 16.5% in the RT arm and 8.1% in the RT–CT arm (\( P = 0.004 \)), which was presented as the major clinically relevant result of the trial. The pathological sterilization rate was significantly higher in the RT–CT arm (11.4% versus 3.6%, \( P < 0.0001 \)) [2].

definitions of the end points
OS and time to local recurrence (LC) were the final end points for which we tested potential surrogates. We also looked for time to local recurrence and time to progression as surrogates for OS.

OS was defined as time from randomization to death from any cause. Alive patients were censored at the last follow-up. Time to local recurrence was defined as time from randomization to the first local recurrence with or without associated distant metastasis. Patients without local recurrence were censored at the last follow-up. Local recurrence was defined as any clinically proven tumor relapse within the pelvis or perineum and was calculated among patients who underwent a gross complete resection (R0–1). Time to progression was defined as time from randomization to any first local or distant relapse of cancer.

The pathological stage (ypT or ypN) was recorded according to the American Joint Committee on Cancer TNM (tumor–node–metastasis) system. Tumor regression was staged into three categories: sterilized specimen (no visible cancer cells, corresponding to a ypT0 stage), few residual isolated tumor cells, or residual evolutive tumor. The CRM, measured according to each pathological laboratory technique, was considered as positive if the microscopic tumor extension reached the margin. Central quality control for pathological examinations was not carried out.

statistical methods
To evaluate the statistical validity of the candidate variables as surrogates for OS and time to local recurrence, we used single-trial validation methods: Prentice criteria [12] and Freedman’s proportion of treatment effect (PTE) explained by the surrogate [13]. They are supposed to translate into statistical terms the fact that the candidate surrogate is an intermediate variable in the course of the disease from diagnosis to death, and that the effect of the treatment on this variable is responsible for the effect observed on the final end point. That is why after adjustment for such an intermediate variable, the effect of the treatment on the final end point is expected to statistically disappear (effect fully captured by the surrogate, Prentice approach) or diminish (PTE measure).

According to Prentice method, a surrogate is validated if it fulfills a set of four conditions [14]: (i) treatment has a significant effect on the surrogate; (ii) treatment has a significant effect on the final end point. In the corresponding Cox model, the parameter \( \beta_s \) associated with the treatment variable is different from zero; (iii) the surrogate has a significant effect on the final end point. When the final end point is OS, this means that the surrogate has a significant prognostic value; (iv) adjusting for the surrogate, treatment effect on the final end point is no longer significant. In the corresponding Cox model with both the treatment and the surrogate as covariables, the parameter associated with the treatment variable (\( \beta_t \)) is equal to zero. In Cox regressions modeling OS, local recurrence and progression were considered as time-dependent covariables.

To quantify the PTE on the final end point that can be attributed to its effect on the candidate surrogate, PTE was calculated for each potential surrogate after checking for no interaction between the treatment and the candidate surrogate. PTE is equal to \( 1 - \frac{\beta_t}{\beta_s} \). The 95% confidence interval (CI) of the PTE was estimated with a bootstrap method (1000 samples). A variable would be considered as an acceptable surrogate if the lower bound of the 95% CI is higher than 0.5 [13].

Categorical variables were described using frequency and percent, and compared using Fisher’s exact tests. The survival curves were estimated with the Kaplan–Meier method and compared with the log-rank test. The Cox proportional hazards model was used to estimate hazard ratios (HRs). All tests were two sided.

results
patient characteristics
Baseline patient characteristics were well balanced between the two treatment groups (Table 1).
effect of treatment on the candidate surrogates

Regression grade significantly differed between the two treatment arms. The rates of ‘complete sterilized specimen’ and ‘few residual cancer cells’ were both increased in the RT–CT arm (11.4% versus 3.6% and 18.7% versus 10.3%, respectively), whereas the modality ‘evolutive residual cells’ was lower (67.1% versus 84.4%; \( P < 0.0001 \) overall). The distribution of the ypT stage differed significantly between the two groups, with a higher proportion of ypT0 and a lower proportion of ypT3 in the RT–CT group as compared with the RT arm (\( P < 0.0001 \) overall). There were no differences in the rate of ypN0 stage, neither in the rate of negative CRM (Table 2).

effect of treatment on the final end points

A total of 124 deaths occurred in the RT group and 128 in the RT–CT group. The 5-year OS rate was 67.9% in the RT arm and 67.4% in the RT–CT arm (\( P \) Log-Rank = 0.68). The univariate HR for death in the RT–CT group was 1.05 (95% CI 0.82–1.35) so that the condition 2 in Prentice method was not satisfied.

Among the 674 patients who underwent a macroscopically complete resection, 49 local recurrences were observed in the RT arm and 25 in the RT–CT arm. The 5-year local recurrence-free time rates were, respectively, 84% and 92% (\( P_{\text{Log-Rank}} = 0.0035 \)). The HR for local recurrence in the RT–CT group was 0.50 (95% CI 0.31–0.80).

effect of the potential surrogates on OS and LC

In univariate analysis, several of the candidate variables we tested for surrogacy revealed prognostic value for death and for local recurrence (Table 3; Figures 1 and 2). Macroscopically incomplete resection, local recurrence, and progression were highly predictive of death (\( \text{HR}_{\text{OS}} = 5.7, 8.8, 16.3, \) respectively, \( P < 0.0001 \)). TRG, ypT and ypN stages, and T downstaging were also significantly associated with OS and time to local recurrence, whereas CRM status did not reach statistical significance (\( \text{HR}_{\text{OS}} = 1.47, P = 0.18 \) and \( \text{HR}_{\text{Time-to-local recurrence}} \) = 1.81, \( P = 0.15 \)). Adjustment for treatment had no influence on these associations (data not shown).

Prentice’s fourth criterion and PTE

The fourth condition in Prentice method requires treatment effect to become nonsignificant after adjustment for the surrogate. Without adjustment for the surrogate, treatment effect on OS is already nonsignificant, so that this condition could not be validated. Furthermore, the very-close-to-zero value of the corresponding Cox parameter did not allow any
Table 3. Prognostic value of the potential surrogate end points (univariate analysis)

<table>
<thead>
<tr>
<th>Candidate surrogate end point</th>
<th>Dependent variable</th>
<th>OS[^a]</th>
<th>HR (95% CI)</th>
<th>P</th>
<th></th>
<th>Time to local recurrence[^b]</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression[^c], yes versus No</td>
<td>OS[^a]</td>
<td>16.3 (12.2–21.7)</td>
<td>&lt;0.0001</td>
<td>–</td>
<td>–</td>
<td></td>
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<tr>
<td>Local recurrence[^d], yes versus no</td>
<td>OS[^a]</td>
<td>8.76 (6.38–12.0)</td>
<td>&lt;0.0001</td>
<td>–</td>
<td>–</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Resection[^e], R2 versus R0—1</td>
<td>OS[^a]</td>
<td>5.71 (4.67–9.54)</td>
<td>&lt;0.0001</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor regression[^f]</td>
<td>Reference</td>
<td>0.67 (0.38–1.18)</td>
<td>0.16</td>
<td>0.43 (0.13–1.36)</td>
<td>0.15</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Evolutive residual cells (iii)</td>
<td>Reference</td>
<td>0.68 (0.48–0.95)</td>
<td>0.25</td>
<td>0.48 (0.25–0.94)</td>
<td>0.033</td>
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<tr>
<td>YpT stage[^g], ypT3 versus ypT0—2</td>
<td>OS[^a]</td>
<td>2.44 (1.80–3.29)</td>
<td>&lt;0.0001</td>
<td>2.93 (1.68–5.09)</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>T downstaging[^h], yes versus No</td>
<td>OS[^a]</td>
<td>0.58 (0.44–0.75)</td>
<td>&lt;0.0001</td>
<td>0.45 (0.27–0.73)</td>
<td>0.0013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YpN stage[^g], ypN+ versus ypN0</td>
<td>OS[^a]</td>
<td>2.16 (1.67–2.81)</td>
<td>&lt;0.0001</td>
<td>2.18 (1.37–3.45)</td>
<td>0.0010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRM[^i], positive versus Negative</td>
<td>OS[^a]</td>
<td>1.47 (0.83–2.58)</td>
<td>0.18</td>
<td>1.81 (0.81–4.08)</td>
<td>0.15</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; CRM, circumferential resection margin; HR, hazard ratio; OS, overall survival.

[^a]: Calculated among all eligible patients (n = 742).
[^b]: Calculated among patients with gross complete resection (n = 674).
[^c]: Introduced in the Cox model as time-dependent variable.
[^d]: Histological response mediated through the achievement of a complete pathological response (ypT0, ypT0 plus ypTmic, or ypT0N0) [16] and no established system of classification of the tumor regression grade [8]. The low proportions of treatment effect explained by these end points confirm that there are other events not necessarily predicted by the CRM status. There was also a large proportion of patients for whom the CRM status was not assessable or missing (257 of 674), which contributed to the width of the CI.
[^e]: Categorized as positive if the microscopic tumor extension reached the margin.
[^f]: Considered as positive if the microscopic tumor extension reached the margin.
[^g]: T was considered downstaged when ypT stage (from 0–3) was lower than clinical stage (3 or 4).
[^h]: Limited to patients undergoing surgery (n = 719).
[^i]: Temporally ordered and determined before the beginning of the study.

To our knowledge, this is the first statistical study that evaluates potential surrogates for preoperative treatment for rectal cancers. Nevertheless, our study should be viewed as an exploratory and preliminary work, and results must be interpreted with caution.

Concerning LC, treatment effect remained significant after adjustment for each of the candidate surrogates, so that the fourth Prentice condition was not fulfilled (Table 4). The lower bound of the 95% CI of the PTE was far from 0.5 for each variable. The highest proportion was reached by tumor regression, with a PTE equal to 12.1%. In regards to the 95% CI, tumor regression may not explain more than 41% of the treatment effect on LC (95% CI 0.9% to 40.7%). Although the CRM status captured only 4.9% of the treatment effect on LC in this trial, this estimation was associated with a large 95% CI that includes 100% (0.9% to 40.7%). On the contrary, the PTE explained by the CRM status may reach 100% (PTE 95% CI 0.9% to 105.3%), which does not exclude the hypothesis of a potentially high degree of surrogacy (Table 4).

**discussion**

Based on our dataset, ypT and ypN stages, T downstaging, CRM status, and TRG were not validated as surrogates for OS or LC. None of them fulfilled the four Prentice criteria, and each PTE was far from the critical value of 0.5 required for the lower bound of the 95% CI [13]. With a PTE equal to 12.1%, tumor regression was found to explain the highest proportion of the treatment effect observed on LC. This means that the positive effect of the experimental treatment on LC in this trial was not completely due to its effect through the regression of the tumor or to any other single pathological parameter. In regards to the 95% CI, tumor regression may not contribute to >41% of the effect on LC (PTE 95% CI 0.9% to 40.7%). On the contrary, the PTE explained by the CRM status may reach 100% (PTE 95% CI 0.9% to 105.3%), so that a good surrogacy value of the CRM cannot be rejected.

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Preoperative treatments may be affected by intra- and interobserver variability. Lack of standard procedures and analysis techniques has been reported for the evaluation of a complete pathological response and the scoring of residual cancer [8, 16, 17], such as for the determination of the CRM status [8, 15]. The time interval between completion of the preoperative treatment and surgery was also said to influence pathological response rate [16, 18], downstaging or CRM [19]. These sources of variability represent current limitations for the demonstration of a surrogacy value because precision and reproducibility of a surrogate are important points that contribute to its relevance [20].

Such difficulties also appear with the so-called LC end point because local recurrence may be difficult to establish and lacks standardized definition and method of reporting [8]. For example, the FFCD 9203 trial reported local recurrence among eligible patients with R0–1 resection, whereas the EORTC 22921 reported local recurrence among all randomized patients. Another important general issue is the surveillance interval to check for relapse, which is known to influence the corresponding results [21].

Most of the variables we tested were prognostic for OS and local recurrence in univariate analyses. A correlation between the candidate surrogate and the final end point is not sufficient to make a surrogate [11], even if the correlation is perfect [22]. It gives information on the individual-level surrogacy [14] but does not provide evidence that an effect of the treatment on the intermediate variable will translate into an effect on the final end point.

The methodology we used aims at verifying that the candidate surrogate is an intermediate variable that captures all—or a sufficiently high proportion of—treatment effects. It is

![Figure 1. Prognostic value of ypT stage (A) and tumor regression grade (B) for overall survival.](image-url)
thus expected that, in a future trial using an agent of the same class, an effect on the surrogate would translate into an effect on the final end point. This approach has the advantage of being implementable on the basis of one single trial but showed conceptual limits and was criticized [14, 23–25].

By contrast, combining results from several completed trials, the meta-analytical methodology for the evaluation of a surrogate end point allows to establish the trial-level surrogacy [23] and to estimate the predicted effect on the final end point based on the observed effect on the surrogate. This approach allows to verify if the surrogate can be "expected to predict clinical benefit" [26] but requires the integration of several completed trials. Disease-free survival (DFS) in adjuvant colon cancer trials [27, 28] and PFS in advanced colorectal cancer trials [7] were validated that way as surrogates for OS. Results concerning DFS in the adjuvant setting seemed to extrapolate to rectal cancer [29]. The meta-analytic technique allows robust validations; in this way, we have planned to reevaluate the surrogacy value of the early pathological parameters using this approach. This work is currently done using a trial from the EORTC [3].

To validate surrogate end points aims at ensuring that treatment effect on the surrogate is predictive of an improvement in a clinically relevant outcome for the patient, mainly in terms of OS. Nevertheless, a surrogate can also be considered as a clinically relevant end point in itself. This was argued for PFS in metastatic colorectal cancers [30] and for DFS in colon and rectal cancers [8]. Based on clinical and statistical considerations, DFS is advised as a primary end point in the neoadjuvant setting and CRM as a secondary end point [8], although formal statistical validation study remains to be done in this particular setting.

This preliminary work did not allow to validate any surrogate end point for either OS or LC for the preoperative treatment for rectal cancers. Results require confirmation with other datasets, in particular for the CRM status. The nonsignificant effect on OS generally observed in the different rectal neoadjuvant trials adds to the need for a meta-analytical validation approach.

Table 4. Prentice criteria and PTE for local control, among patients with gross complete resection (n = 674)

<table>
<thead>
<tr>
<th>Candidate surrogate end point ($) for time to local recurrence</th>
<th>yrT0</th>
<th>yrT1</th>
<th>T downstaging</th>
<th>yrN</th>
<th>CRM</th>
<th>Tumor regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment effect on local recurrence (RT–CT versus RT)</td>
<td></td>
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<tr>
<td>HR (95% CI)</td>
<td>0.50 (0.31 to 0.80)</td>
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<tr>
<td>$\beta$</td>
<td>−0.70</td>
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<tr>
<td>$P$</td>
<td>0.004</td>
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<tr>
<td>Treatment effect on local recurrence, adjusted for S (RT–CT versus RT)</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.52 (0.32 to 0.84)</td>
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<tr>
<td>$\beta_S$</td>
<td>−0.66</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>$P$</td>
<td>0.008</td>
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<tr>
<td>PTE (%) = 1 − $\beta_S$/$\beta$</td>
<td>6.8 (−8.8 to 28.7)</td>
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<tr>
<td>(95% CI)</td>
<td>4.9 (−6.6 to 16.8)</td>
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</tbody>
</table>

$\beta$ and $\beta_S$, Cox coefficients; CI, confidence interval; CRM, circumferential resection margin; HR, hazard ratio; PTE, proportion of treatment effect; RT, radiotherapy; RT–CT, radiotherapy and chemotherapy.

$^a$Introduced in Cox models as dichotomous covariables.

$^b$T was considered downstaged when ypT stage (from 0–3) was lower than clinical stage (3 or 4).

$^c$Considered as positive if the microscopic tumor extension reached the margin.
references