Phase II trial

Preoperative hyperfractionated accelerated radiotherapy (HART) in locally advanced rectal cancer (LARC) immediately followed by surgery. A prospective phase II trial

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Abstract

Background and purpose: We aim to report on local control in a phase II trial on preoperative hyperfractionated and accelerated radiotherapy schedule (HART) in locally advanced resectable rectal cancer (LARC). This fractionation schedule was designed to keep the overall treatment time (OTT) as short as possible.

Patients and methods: This is a prospective trial on patients with UICC stages II and III rectal cancer. The patients were submitted to a total dose of 41.6 Gy, delivered in 2.5 weeks at 1.6 Gy per fraction twice a day with a 6-h interfraction interval. Surgery was performed within 1 week after the end of irradiation. Adjuvant chemotherapy was delivered in a subset of patients.

Results: Two hundred and seventy nine patients were entered and 250 are fully assessable, with a median follow-up of 39 months. The 5-years actuarial local control (LC) rate is 91.7%. The overall survival (OS) is 59.6%. The freedom from disease relapse (FDR) is 71.5%. Downstaging was observed in 38% of the tumors.

Conclusion: The actuarial LC at 5 years is 91.7%, although we are dealing with stages II–III LARC, mainly located in the lower rectum (median distance = 5 cm). The pattern of failure is dominated by distant metastases and treatment intensification will obviously require a systemic approach.

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Keywords: Rectal cancer; Preoperative radiotherapy; Hyperfractionation

In Europe, in contrast to the United States and Canada, a preoperative approach has been considered as the preferred treatment option for locally advanced rectal cancer (LARC) to reduce the incidence of local recurrence. This European option is based on the knowledge that irradiation before surgery is more dose-effective and cost-effective than postoperative irradiation and in general less toxic [11,16,19,37,48].

Even if there is a major decrease in the rate of local recurrences, especially if surgeons are instructed to replace the blunt dissection with a sharp dissection of the mesorectum, there is little doubt about the requirement for radiotherapy at least in the preoperative setting [6,9]. This has been confirmed by the results of the Swedish rectal cancer trial (SRCT) and the Dutch colorectal cancer group trial (DCRCG) [24,47].

However, there is no consensus amongst the published literature about what should be the ‘standard’ treatment and the primary endpoint in rectal cancer (survival, disease free survival, local control, sphincter sparing surgery or quality of life).

To date, the only trial showing a significant impact of radiotherapy alone on LC and OS is the SRCT [47]. The positive impact on LC by the five consecutive 5 Gy of pelvic radiation therapy, as used in the SRCT, has been recently confirmed by the Dutch colorectal cancer group trial (DCRCG) [24]. In the latter study, the follow-up is too short to determine the impact of this approach on OS.

In the EORTC 22921 (European Organization Research Treatment Cancer) and FFCD 9203 (Fondation Française de Cancérologie Digestive) trials, in contrast to the SRCT and the DCRCG, a ‘conventional’ preoperative fractionation and total...
dose of radiotherapy (45 Gy in 25 fractions) and timing of surgery (i.e. a gap of at least 4 weeks after neo-adjuvant treatment) have been used [1,14]. In the EORTC 22921, the local failure rate has been reduced in the three groups with chemotherapy (8.8% preoperative radio-chemotherapy, 9.6% preoperative radiotherapy and postoperative chemotherapy, 8.0% preoperative radio-chemotherapy and postoperative chemotherapy) [1]. The results do not indicate the best timing and do not suggest a benefit for the combined use of preoperative and postoperative chemotherapy.

It is obvious that if OS and DFS are the primary endpoints, emphasis should be put on the development of systemic treatment and optimization of its use [17]. Both the EORTC-22921 trial and the FFCD 9203 trial do not show an impact of chemotherapy on overall survival (OS) or progression free survival (PFS). Moreover, in the FFCD 9203 the sphincter preservation rate is not increased [14].

The German intergroup study, a randomized study comparing postoperative radio-chemotherapy to preoperative radio-chemotherapy, demonstrates an advantage in local control in favor of the latter and hence reinforces a neo-adjuvant approach and the choices made in both the ECOG 3201 and the NSABP R-04 trials [42]. In these trials, there is no postoperative radiotherapy arm anymore, illustrating a change in paradigm in the United States and Canada where postoperative radiotherapy combined with chemotherapy is the most frequently used approach [34].

As no radiotherapy schedule can be considered 'standard', we intend to report our own results on HART. HART was designed to keep the overall treatment time (OTT) as short as possible without using hypo-fractionation as in the SRCT and DCRCG trials. We decided to use a twice a day accelerated hyper-fractionated schedule. Theoretical calculations using the linear quadratic model, yielded a potential benefit of 13-29% in anti-tumor effect (\(\alpha/\beta=10\) Gy) and a theoretical reduction of 4% in late toxicity (\(\alpha/\beta=3\) Gy) (see Table 1).

As a possible decrease of 4% in late complications is not easy to highlight, our primary aim was to evaluate the impact of HART on LC.

### Materials and methods

#### Patient population

This trial was conducted from 1993 to 2002 at two radiation oncology centers, Lausanne (LS) and Aarau (AA), and was approved by the Human Investigations Committee at both centers. All patients with LARC were treated on protocol after obtaining informed consent for treatment. We considered a target of 250 eligible patients in order to have an appropriate estimation of the effect of HART on local control.

All those patients underwent a complete clinical examination, a chest X-ray, together with an abdomino-pelvic computed tomography (CT), a transrectal ultrasound (TRUS), a complete colonoscopy and a thorough digital rectal examination (DRE) by the attending radiation oncologist. All tumors were confirmed to be malignant on biopsy. Patients were deemed eligible for Trial 93-01 if they presented with clinical stage T3-T4 or in T1-T2 rectal cancer provided that in the latter cases, there was compelling evidence for clinical and/or radiological nodal invasion (TNM classification of malignant tumors) [44]. The criteria for T4 disease were evidence of adjacent organ invasion on CT or TRUS. The level of the tumor within the rectum was measured from the anal verge with a rigid sigmoidoscope and checked at DRE by the radiation oncologist. The maximal allowed distance to the anal margin was 15 cm. Laboratory studies included estimation of pretreatment complete blood count, liver and kidney function and CEA-level.

Exclusion criteria included any of the following: no informed consent, age younger than 18 years, ECOG performance status of 4 [35], pregnant or lactating women, prior pelvic irradiation therapy, treatment with chemotherapy prior to the initiation of radiotherapy, other malignant tumor history, or any other serious illness and/or major organ dysfunction that could potentially preclude the feasibility of the preoperative radiotherapy followed by surgery with curative intent. There was no upper age limit in this trial.

#### Treatment characteristics

A detailed description of the treatment technique has been previously published [7,8]. All patients received preoperative pelvic irradiation in prone position. The treatment was given with a linear accelerator with a minimum energy of 6 MV through a four field technique with every field irradiated twice daily. The schedule consisted of a total dose of 41.6 Gy applied in 1.6 Gy twice a day with a 6 h free interval between the fractions. The overall treatment time including the weekends counted 17 days (no treatment on Saturday and Sunday).

The dose prescription was done at the intersection of the four fields. The requirement for dose homogeneity were

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### Table 1

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>SRCT/DCRCG</th>
<th>HART 93-01</th>
<th>Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a/b = 10) Gy</td>
<td>(BED_a) (Gy)</td>
<td>(BED_b) (Gy)</td>
<td>(BED_2/BED_1)</td>
</tr>
<tr>
<td>Lag period 0 days</td>
<td>35</td>
<td>39.8</td>
<td>1.14</td>
</tr>
<tr>
<td>Lag period 5 days</td>
<td>37.5</td>
<td>42.3</td>
<td>1.13</td>
</tr>
<tr>
<td>Lag period 10 days</td>
<td>35</td>
<td>39.8</td>
<td>1.13</td>
</tr>
<tr>
<td>No repopulation</td>
<td>37.5</td>
<td>44.8</td>
<td>1.19</td>
</tr>
</tbody>
</table>

\(BED = \text{biological effective dose} = [\text{physical dose} \times (\text{relative effect})] - [0.5 \text{ Gy/day} \times (\text{OTT}_{T} - \text{lag})].\) OTTR is the overall treatment duration in days of the preoperative irradiation. Relative effect = \(1 + d/\alpha/\beta.\) The lag period is defined as the period before which there is no any dose compensation necessary to counteract proliferation. Lag period = 0 days means immediate repopulation. Following assumptions were made for calculation: (1) a dose increment of about 0.5 Gy per day of radiation treatment extension is required to compensate for rapid growth [46]; (2) the gap (= time delay) between the end of the five times 5 Gy and the surgery (SRCT and DCRCG) is of the same magnitude as the one observed in the HART 93-01 trial. The decrease of biological effect would be similar and therefore not accounted for in the calculation; (3) the gap between end of radiotherapy and surgery is accounted for in the calculation of BED values. **See (*)**.

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a planning target volume (PTV) covered at least by the 95% isodose (lower limit), with an upper limit set at 110%.

No radiation therapy was performed after surgery, even if the radial resection margin (RRM) was positive (i.e. an R1=microscopic invasion or R2=macroscopic invasion) on pathological specimen. Radiation therapy was never given after surgery to avoid the increased risk of late complications [27,43].

Surgical procedure, postoperative chemotherapy

The protocol required surgery within 1 week of completion of radiotherapy. The surgeons were asked to perform a total mesorectal excision (TME) with a sharp dissection for distally located tumors and a partial mesorectal excision for tumors in the upper third of the rectum [20,21,28]. However, no quality control could be performed on the surgical procedure. The decision to perform a low anterior resection (LAR) vs an abdominoperineal resection (APR) was left to the discretion of the individual surgeon. In case an attempt was made to perform a SSP, we suggested a temporary diverting colostomy. If an SSP was performed, the protocol suggested a colorectal or coloanal anastomosis with reconstruction of a reservoir function (colonic pouch). Postoperative chemotherapy was performed in selected patients (essentially in case of ypN+).

Pathology review

All records from one single reference center (LS) (N=136), were systematically submitted to an extensive quality control by the attending study pathologist (HB) according to the methodology described by Quirke [38-40]. These data were already published in part elsewhere [2-4]. For the remaining a central pathology review was not performed because of economic and logistical difficulties. In the present analysis we decided to include following factors: tumor differentiation, tumor stage (both T-stage and N-stage), downstaging (ypT<ct and not to be con
ound with downsizing), resection margins and especially RRM and clearance (defined as the distance between the peripheral tumor rim and the radial resection margin).

Follow-up of patients

All patients were followed prospectively every 3 months the first year and every 6 months thereafter. At follow-up patient history has been recorded and a physical examination was systematically performed. This was completed by a test for CEA and a TRUS if patient were submitted to a SSP. If not, this TRUS was replaced by an abdominal and pelvic CT-scan every 6 months for 2 years and yearly thereafter. If they did not present at their bi-annual exam, a phone call was given to the general practitioner in charge of this patient or directly to the patient to recover the necessary information. Every failure, whether it was the primary failure or not, was recorded and verified by reviewing the multidisciplinary medical records.

Statistical analysis

Statistical analysis was performed with JMP 5.0 (from SAS Institute, Inc., Cary, NC, USA) on a Powerbook G4. Outcome estimates were calculated with the product limit survival method.

For local control, only recurrence within the irradiated pelvis was scored as an event. Local recurrence was defined as any evidence of tumor within the surgical bed and the volume encompassed by the radiation fields (PTV). Every failure outside the PTV, whether abdominal or extra-abdominal, was defined as a distant failure (metastatic disease).

OS was calculated from the initiation of the radiation treatment until death, whatever the reason of death. Freedom from disease relapse (FDR) has been calculated considering local recurrence, distant failure and death due to cancer as an event. Therefore, patients dying from unrelated causes were not added to treatment failures.

Grouping was generally performed on the basis of the median value for quantitative data (if not this is specified). A two-sided Log-Rank test was used to assess statistical significance of the difference between strata. A difference between curves was considered significant if a P-value of ≤0.05 was reached. We used a Wilcoxon test for evaluating a difference between two survival curves, provided these curves are initially dissociating but rejoining at a given time point later. Factors reaching a P-value of P≤0.05 in the univariate analysis (Log-Rank test), were introduced in the Cox proportional hazard model. Before doing so we used a non-parametric Spearman’s rank correlation test (assuming that for some parameters the distribution is not necessarily Gaussian) to test for correlations between parameters. This allowed us to check for multicolinearity between parameters. We tested in the multivariate model whether substitution for example of ct and ypT or vice versa did modify the final model, as both were likely to act as surrogates for disease control.

Results

Characteristics of patient population and treatment

Two hundred and seventy nine patients with LARC were enrolled on Trial 93-01 from 1993 to 2002. Twenty-four patients were excluded as they presented with liver metastasis at surgery (treatment considered palliative) and five because of missing surgical and/or pathological data and/or because of missing follow-up. Of the remaining 250 patients, there were 164 males and 86 females.

The median follow-up for all patients is 39 months and for surviving patients 52 months.

The median pretreatment CEA level was 3.1 ng/ml (normal value ≤5 ng/ml). There were only four patients presenting with ct2, but with a clear clinical (at DRE a para-sternal node was discovered in two cases) and/or radiological suspicion (TRUS and/or CT) of nodal disease. There were 201 ct3 patients and 45 ct4. The median distance to the anal verge was 5 cm (mean 5.6±0.2 cm, range 0-15 cm). At DRE the tumor is considered ‘tethered’ or ‘fixed’ in 196 patients (78%). Fixed tumors are not considered ct4 except if there is a radiological suspicion (TRUS or CT). The rectal tumor has been labelled ‘mobile’ in 25 patients (10%). This clinically retrievable information was not available in 29 patients.
All patients received radiation therapy as per the protocol. There were no treatment interruptions for acute toxicity. The only interruptions recorded were due to holidays or engine downtime. The maximal treatment duration registered for one single patient was 22 days due to misunderstanding of the protocol. The gap between the end of the radiation therapy and the surgery was per protocol (median = 5 days; range: 1-120 days; 75th percentile = 7 days, 90th percentile = 12 days, 10th percentile = 2 days).

In total, there were 23 surgical departments participating to this trial. Due to the large number of surgical departments and the number of surgeons per department in the present trial, the mean number of patients per surgeon is low. This has to be considered as a major risk factor for local recurrence [22, 25, 32, 38, 41].

A majority of patients (N=141) underwent an SSP (56.4%). On the 250 patients there were 109 APR, 137, LAR, three Hartman procedures and one transanal resection. Most of the tumors were located in the middle and lower third of the rectum. In 133 patients the distance to the anal margin was ≤ 5 cm and in 37 of these patients an SSP was performed (28%). In only 7 out of 76 patients an SSP was attempted when the lower end of the tumor was located at ≤ 3 cm from the anal margin.

At pathological examination there were 21 ypT4 (8.4%), 161 ypT3 (64.4%), 57 ypT2 (22.8%), 8 ypT1 (3.2%) and finally three complete responses ypT0 (1.2%). Comparing ypT to cT yielded a downstaging rate of 38%. One hundred and eighteen patients (47%) had positive nodes at pathological examination. The median number of nodes retrieved by the pathologist on the specimens was 13. Vascular invasion was observed in 57 cases and was absent in 189 patients (information was not available in four). In 44 cases a resection margin was positive (18%). In three patients out of these 44, the margin involved was not the circumferential but the distal margin. Eighty patients (32%) received 5-FU based adjuvant chemotherapy because positive lymph nodes were detected on surgical specimens.

Local control, survival and freedom from disease relapse

The actuarial local control (LC) at 5 years is 91.7 ± 0.02% (patients at risk at 5 years = 70). Only 16 patients failed locally. The median for LC is not reached (Fig. 1A). The actuarial 5-years overall survival (OS) is 59.6 ± 3.7% (number of patients remaining at risk at 5 years = 70). The median OS is not yet reached. The 5 years actuarial freedom from disease relapse (FDR) is 71.5 ± 3.5% (patients at risk at 5 years = 70)(Fig. 1B). The median is not yet reached.

Univariate analysis

A variety of patient’s and tumor related factors were tested in the univariate analysis for LC, OS and FDR. We report only on the results for local control in Table 2. The cut-off values for quantitative data (cov), are the median values, except for the lateral clearance where the value of 2 mm has been used [31, 33].

Multivariate analysis

For the multivariate analysis (proportional hazards model), only those factors reaching a P ≤ 0.05 in the univariate analysis (Log-Rank) were selected (see Table 3). This yielded in the final model a better OS for patients aged less than 64, with ypN0 and VI0. The factors predictive for a better FDR were clinical T-stage less than cT4, ypN0 and VI0. Finally for LC, the only factor which was predictive for a better outcome is a clearance of more than 2 mm.

Discussion

Preoperative radiotherapy does reduce the risk of local recurrence in rectal cancer [6, 9, 13, 24, 48]. If the concept of preoperative radiotherapy seems to be widely accepted nowadays, there is still a debate ongoing what should be considered as ‘standard’ total dose and fractionation [5, 48]. Hypo-fractionation, i.e. five times 5 Gy applied in five consecutive days, has been extensively tested in Europe. The effect of this fractionation on local control observed for the first time in the Swedish rectal cancer trial (SRCT) have recently been confirmed by the investigators of the Dutch colorectal cancer group (DCRCG). It has been estimated that only 50% of the patients in the SRCT trial were submitted to a ‘lege artis’ TME [9]. Therefore, if one could initially doubt about the adequacy of the surgery in the SRCT, this
argument is of no value for patients in the DCRCG-trial [24]. In this large recently published multicenter trial, special effort has been dedicated to optimizing and standardizing the TME procedure and training the surgeons [25].

There is no consensus on the duration of the interval (‘gap’) between the end of the radiotherapy and the surgery [12,26,29,36,45,48]. In the SRCT the surgery was generally performed immediately after the weekend following the end of the irradiation, whereas in the DCRCG trial the total duration of the radiotherapy and the gap to the surgery had to be contained within 10 days [24,47].

What are the arguments against hypofractionation? One might argue that the hypo-fractionation is responsible for the high rate of postoperative complications reported by those groups (perineal complication rate after 5×5 Gy and APR=29% in the DCRCG) [10,26,30]. On the other hand, the short interval between the radiotherapy and the surgery does not allow for a significant tumor downsizing considered as the primary endpoint by surgeons aiming at increasing the rate of SSP. Downstaging is also not obvious, but apparently this seems not a prerequisite for a better survival [18,29,45].

If one considers a rapid schedule as a ‘standard’ (based on the absolute numbers of patients introduced in SRCT and DCRCG, compared to the limited data available for more ‘conventional’ fractionation), there is still a debate ongoing on the necessity of hypo-fractionation to obtain both an effect on local control and survival.

In Lausanne we initiated in 1989 a modified fractionation schedule, initially in the postoperative setting after curative resection for LARC [7]. Aware of the advantage of using pre instead of postoperative radiotherapy, we decided to use this hyperfractionated accelerated radiotherapy in a neo-adjuvant setting, but lowering the total dose from 48 Gy in the postoperative setting to 41.6 Gy in the preoperative setting [8]. As in the SRCT, we decided to keep the interval between the radiotherapy and the surgery as short as possible (1 week suggested in the protocol outline). The feasibility of this HART approach in a preoperative setting has been published earlier [7,8]. As toxicity has been minimal in the phase I trial, we decided to prospectively accrue patients in two centers in order to evaluate the impact of HART especially on local control and eventually OS and FDR. The calculation of the biological effectiveness of HART, both for tumor tissue ($\alpha/\beta = 3$ Gy) and healthy tissue ($\alpha/\beta = 10$ Gy) and healthy

### Table 2

<table>
<thead>
<tr>
<th>Grouped by</th>
<th>Cut-off value</th>
<th>5 Years results</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$&lt; c-o-v$ (%)</td>
<td>$&gt; c-o-v$ (%)</td>
</tr>
<tr>
<td>Clinical T-stage</td>
<td>T2-T3 vs T4</td>
<td>93.5</td>
<td>83.8</td>
</tr>
<tr>
<td>Tumor thickness</td>
<td>$\leq 8$ mm</td>
<td>94.4</td>
<td>88.3</td>
</tr>
<tr>
<td>Lateral clearance</td>
<td>2 mm</td>
<td>81.1</td>
<td>94.3</td>
</tr>
<tr>
<td>Vascular invasion (VI)</td>
<td>$V_0$ vs $V_+$</td>
<td>93.2</td>
<td>86.6</td>
</tr>
<tr>
<td>Microscopic complete resection</td>
<td>$R_0$ vs $R_1$</td>
<td>94.1</td>
<td>80.7</td>
</tr>
</tbody>
</table>

Table 2: Univariate analysis with LC as an endpoint

Not listed in the table of contents though tested are the following: gender, age, WHO status, CEA-level prior to treatment, assessment of clinical fixation, surgical procedure, axial and transverse tumor diameter, histological differentiation, pathological T-stage and N-stage, downstaging, and adjuvant chemotherapy. For all the other factors a difference is considered significant if a $P \leq 0.05$ is reached. Only those factors reaching a $P \leq 0.05$ with the Log-Rank test are considered for the proportional hazards model.

### Table 3

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Discriminator</th>
<th>$P$-value</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>Age $&lt; 64$</td>
<td>0.03</td>
<td>0.78</td>
<td>0.62–0.97</td>
</tr>
<tr>
<td></td>
<td>$y_{pN_0}$</td>
<td>0.0006</td>
<td>0.67</td>
<td>0.52–0.84</td>
</tr>
<tr>
<td></td>
<td>$V_0$</td>
<td>0.006</td>
<td>0.72</td>
<td>0.57–0.91</td>
</tr>
<tr>
<td>FDR</td>
<td>Stage $&lt; cT4$</td>
<td>0.04</td>
<td>0.73</td>
<td>0.55–0.98</td>
</tr>
<tr>
<td></td>
<td>$y_{pN_0}$</td>
<td>0.0004</td>
<td>0.59</td>
<td>0.43–0.79</td>
</tr>
<tr>
<td></td>
<td>$V_0$</td>
<td>0.01</td>
<td>0.69</td>
<td>0.52–0.92</td>
</tr>
<tr>
<td>LC</td>
<td>Clearance $&gt; 2$ mm</td>
<td>0.002</td>
<td>0.45</td>
<td>0.27–0.74</td>
</tr>
</tbody>
</table>

Table 3: Multivariate analysis considering only factors issued from univariate analysis with a $P$-value of $\leq 0.05$ (Log-Rank)
the efficacy of the present fractionation schedule for obtaining good local control in LARC. The actuarial local recurrence rate at 2 years in Trial 93-01 is 6.4%, compared to 2.4% in the DCRCG trial and 8.3% in the SRCT [24,47].

As the major event in our cohort is the appearance of distant metastases, it is obvious that one has to consider a treatment approach aiming at preventing and/or eradicating metastases. Therefore, our group has been running in parallel to Trial 93-01, Trial 98-02 in which we have been treating patients with LARC with HART and CPT-11. This Trial 98-02 is a pure phase I trial, and we are only able to report on feasibility [49]. However, adding chemotherapy to our HART schedule should remain experimental and performed within the strict limits of well designed clinical trials.

How do our data compare with those from trials in which chemotherapy has been added? The German trial (CAO/ARO/AIO-94), shows that the 5-years pelvic recurrence rate is 6% for the preoperative combined chemo-radiotherapy compared to 13% for the postoperative combined treatment ($P=0.006$). Disease free survival and overall survival are similar (respectively 68 vs 65% and 76 vs 74%; $P$-values not significant) [42]. The recently presented EORTC 22921 trial concludes that adding chemotherapy to radiotherapy does not modify OS (ranging from 64.8 to 67.1% compared to 63.2% if no chemotherapy at all) or progression free survival (ranging from 54.5 to 58.15 compared to 52.2%, respectively) [1]. There is a significant impact on local control (recurrence rate 8–9.6% vs 17.2%), but there is no indication on the best timing of the chemotherapy. The local control rate is the same if patients receive preoperative radiotherapy and postoperative chemotherapy. Moreover, there is no supplementary benefit if chemotherapy is applied both in the preoperative and postoperative setting. The FFCD 9203 randomized trial does not show an improvement in 5 year overall survival (66.6 vs 67.8%) if bolus 5-fluoro-uracil and folinic acid is added to preoperative irradiation. The sphincter preservation is identical in both arms (51.7 and 52.6%) [14].

In conclusion, taking into account the high risk patient group (stages II and III and low located tumors) and the lack of quality control for surgery, our rate of local control at 5 years (91.7%) as well as survival figures (OS 59.6% and FDR 71.5%) compare favorably with those issued from large randomized trials. Distant metastases are the most common site of failure. Hence, effective systemic chemotherapy combined or not to targeted agents given pre or postoperatively will be required to modify significantly OS or FDR [15,48].

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