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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.**

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

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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)[1,14]. 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.

Table 1

BED $\alpha/\beta=10$ Gy hypothesis	SRCT/DCRCG BED_1 (Gy)	HART 93-01 BED_2 (Gy)	Index BED_2/BED_1
Lag period 0 days	35	39.8	1.14
(*)	32.5	37.3	1.15
Lag period 5 days	37.5	42.3	1.13
(*)	35	39.8	1.13
Lag period 10 days	37.5	44.8	1.19
(*)	37.5	42.3	1.13
No repopulation	37.5	48.3	1.29

BED = biological effective dose = [physical dose × (relative effect)] − [0.5 Gy/day × (OTT_R − lag)]. OTT_R 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 (*).

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

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 abdominoperinal 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 confounded 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 Willcoxon 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 $P \leq 0.05$ 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 pararectal 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 $91.7 \pm 0.02\%$ (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 $59.6 \pm 3.7\%$ (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 $71.5 \pm 3.5\%$ (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].

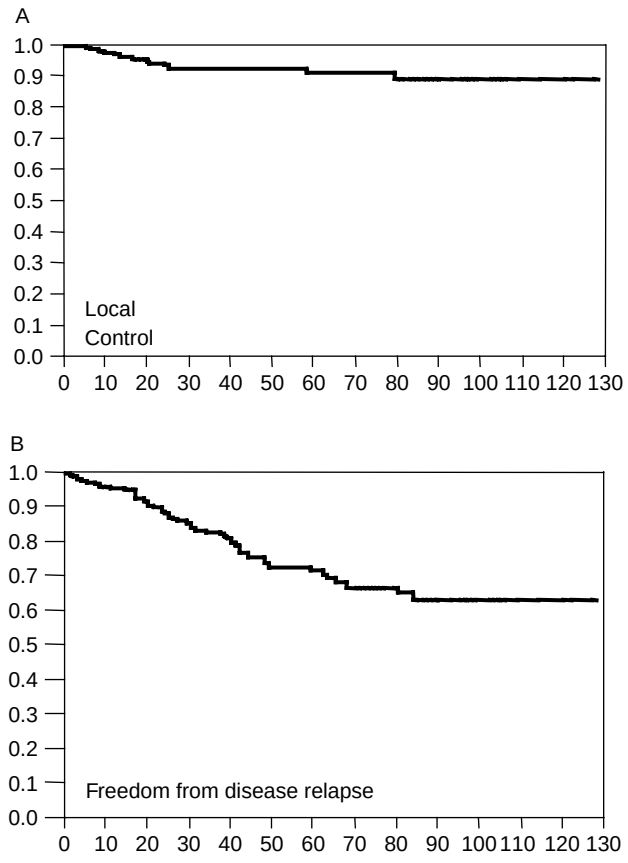

Fig. 1. (A) Actuarial local control as a function of time expressed in months; (B) actuarial freedom from disease relapse expressed in months after initiation of HART.

Multivariate analysis

For the multivariate analysis (proportional hazards model), only those factors reaching a $P \leq 0.05$ 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 ypN_0 and VI_0. The factors predictive for a better FDR were clinical T-stage less than cT4, ypN_0 and VI_0. 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

Table 2
Univariate analysis with LC as an endpoint

Grouped by	Cut-off value	5 Years results		*P*-value	
		< c-o-v (%)	> c-o-v (%)	Log-Rank	Wilcoxon
Clinical T-stage	T2-T3 vs T4	93.5	83.8	0.03	0.01
Tumor thickness	≤8 mm	94.4	88.3	0.02	0.02
Lateral clearance	2 mm	81.1	94.3	0.0006	0.0006
Vascular invasion (VI)	VI_0 vs VI_+	93.2	86.6	0.10	0.07
Microscopic complete resection	R_0 vs R_1	94.1	80.7	0.07	0.03

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.

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 on OS and FDR. The calculation of the biological effectiveness of HART, both for tumor tissue ($\alpha/\beta=10$ Gy) and healthy tissue ($\alpha/\beta=3$ Gy), yields a theoretical advantage compared to the SRCT/DCRCG schedule. Local control could potentially be increased by 13-29%. The advantage in late toxicity is less obvious (4% reduction of late effects). Such a small difference in late complications will be difficult to highlight within a randomized controlled trial of a reasonable size.

As we report our results with a median overall follow-up of 39 months, we can compare with the SRCT/DCRCG figures. However, in our non-randomized 93-01 Trial we have included only patients with resectable stages II and III disease (no stage I disease). For advanced inoperable rectal cancer we considered that other radiation techniques are more adequate [23]. There were only four patient with cT2, but for these patients there was a clear clinical and/or radiological suspicion of nodal involvement (cT2N+=stage II). All the other patients presented with cT3 ($N=201$) and cT4 tumors ($N=45$). Therefore we cannot directly compare our data with the DCRCG since up to 30% of patients had stage I tumors in the latter.

There is another more fundamental reason why direct comparison with DCRCG data is difficult. In Trial 93-01 we are not able to define a posteriori whether lege artis TME with sharp dissection has been performed. There has been no quality control implemented nor training performed amongst the surgeons involved in this trial. We are agreeing that this is a major limitation in the interpretation of our data. On the other hand, the 'negative' selection of patients (low lying tumors, mostly tethered or fixed and no stage I) and the absence of quality control for surgery, illustrates

Table 3
Multivariate analysis considering only factors issued from univariate analysis with a *P*-value of ≤0.05 (Log-Rank)

Endpoint	Discriminator	*P*-value	RR	CI
OS	Age<64	0.03	0.78	0.62-0.97
	ypN_0	0.0006	0.67	0.52-0.84
	VI_0	0.006	0.72	0.57-0.91
FDR	Stage<cT4	0.04	0.73	0.55-0.98
	ypN_0	0.0004	0.59	0.43-0.79
	VI_0	0.01	0.69	0.52-0.92
LC	Clearance> 2 mm	0.002	0.45	0.27-0.74

RR, risk ratio; CI, confidence interval.

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 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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References

[1] Bosset JF, Calais G, Mineur L, et al. Preoperative radiation (Preop RT) in rectal cancer: effect of timing of additional chemotherapy (CT) 5-year results of the EORTC 22921 trial. J Clin Oncol 2005;23:3505.

[2] Bouzourene H, Bosman FT, Seelentag W, et al. Importance of tumour regression assessment in predicting the outcome of patients with locally advanced rectal carcinoma who are treated with preoperative radiotherapy. Cancer 2001;94: 1121–30.

[3] Bouzourene H, Bosman FT, Matter M, et al. Predictive factors in locally advanced rectal cancer treated with preoperative hyperfractionated and accelerated radiotherapy. Hum Pathol 2003;34:541–8.

[4] Bouzourene H, Chaubert P, Gebhard S, et al. Role of methallothionein in irradiated human rectal carcinoma. Cancer 2002;95:1003–8.

[5] Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomized trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol 2003;72:15–24.

[6] Camma C, Giunta M, Fiorica F, et al. Preoperative radiotherapy for resectable rectal cancer. J Am Med Assoc 2000;284: 1008–15.

[7] Coucke PA, Cuttat J-F, Mirimanoff R-O. Adjuvant postoperative accelerated hyperfractionated radiotherapy in rectal cancer: a feasibility study. Int J Radiat Oncol Biol Phys 1993;27:885–9.

[8] Coucke PA, Sartorelli B, Cuttat J-F, et al. The rationale to switch from postoperative hyperfractionated accelerated radiotherapy to preoperative hyperfractionated accelerated radiotherapy in rectal cancer. Int J Radiat Oncol Biol Phys 1995; 32:181–8.

[9] Dahlberg M, Glimelius B, Pahlman L. Improved survival and reduction in local failure rates after preoperative radiotherapy: evidence for the generalizability of the results of Swedish Rectal Cancer Trial. Ann Surg 1999;229:493–7.

[10] Dahlberg M, Glimelius B, Graf W, et al. Preoperative irradiation affects functional results after surgery for rectal cancer. Dis Colon Rectum 1998;41:543–51.

[11] Dahlberg M, Sternberg A, Pahlman L, et al. Cost effectiveness of preoperative radiotherapy in rectal cancer: results from the Swedish Rectal Cancer Trial. Int J Radiat Oncol Biol Phys 2002; 54:654–60.

[12] François Y, Nemoz C, Baulieux J, et al. Influence of the interval between preoperative radiation therapy and surgery in down-staging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. J Clin Oncol 1999; 17:2396–402.

[13] Gerard JP. Radiotherapy in the conservative treatment of rectal cancer. Evidence-based medicine and opinion. Radiother Oncol 2004;74:227–33.

[14] Gerard JP, Bonnetain F, Conroy T, et al. Preoperative (preop) radiotherapy (RT) in T3-4 rectal cancers: results of the FFCD 9203 randomized trial. J Clin Oncol 2005;23:3504.

[15] Giralt J, de las Heras M, Cerezo L, et al. The expression of epidermal growth factor receptor results in a worse prognosis for patients with rectal cancer treated with preoperative radiotherapy: a multicenter, retrospective analysis. Radiother Oncol 2005;74:101–8.

[16] Glimelius B, Isacsson U, Jung B, et al. Radiotherapy in addition to radical surgery in rectal cancer: evidence for a dose response effect favouring preoperative treatment. Int J Radiat Oncol Biol Phys 1997;37:281–7.

[17] Glimelius B. Role of adjuvant chemoradiotherapy for abdominal malignancies. Dig Surg 2003;20:169–79.

[18] Graf W, Dahlberg M, Osman MM, et al. Short-term preoperative radiotherapy results in down-staging of rectal cancer: a study of 1316 patients. Radiother Oncol 1997;43:133–7.

[19] Gunderson LL, Russell HA, Llewellynn HJ, et al. Treatment planning for colorectal cancer. Radiation and surgical

techniques and value of small bowel films. Int J Radiat Oncol Biol Phys 1985;11:1379–93.
[20] Heald RJ, Ryall RDH. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1986;1:1479–82.
[21] Heald RJ, Moran BJ, Ryall RDH, et al. The Basingstoke experience of total mesorectal excision, 1978–1997. Arch Surg 1998;133:894–9.
[22] Hermanek P, Hermanek PJ. Role of the surgeon as a variable in the treatment of rectal cancer. Semin Surg Oncol 2000;19: 325–9.
[23] Hoskin PJ, de Canha SM, Bownes P, et al. High dose rate afterloading intraluminal brachytherapy for advanced inoperable rectal carcinoma. Radiother Oncol 2004;73:195–8.
[24] Kapiteijn E, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638–46.
[25] Kapiteijn E, Putter H, van de Velde CJH, Cooperative investigators of the Dutch ColoRectal Cancer Group. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. Br J Surg 2002;89:1142–9.
[26] King M, Tolan S, Giridharan S, et al. Late toxicity after short course preoperative radiotherapy and total mesorectal excision for resectable rectal cancer. Clin Oncol 2003;15:233–6.
[27] Lusinchi A, Wibault P, Lasser P, et al. Abdominoperineal resection combined with pre- and postooperative radiation therapy in the treatment of low-lying rectal carcinoma. Int J Radiat Oncol Biol Phys 1997;37:59–65.
[28] MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excsion for rectal cancer. Lancet 1993;341:457–60.
[29] Marijnen CAM, Nagtegaal ID, Klein Kranenbarg E. No downstaging after short term-preoperative radiotherapy in rectal cancer. J Clin Oncol 2001;19:1976–84.
[30] Marijnen CAM, Kapiteijn E, van de Velde CJH, et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 2002;20:817–25.
[31] Marijnen CAM, Nagtegaal ID, Kapiteijn E, et al. Radiotherapy does not compensate for positive resection margins in rectal cancer patients: report of a multicenter randomized trial. Int J Radiat Oncol Biol Phys 2003;55:1311–20.
[32] Martling AL, Holm T, Rutqvist L-E, et al. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Lancet 2000;356:93–6.
[33] Nagtegaal ID, Marijnen CAM, Klein Kranenbarg E, et al. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma. Not one millimeter but two millimeters is the limit. Am J Surg Pathol 2002;26:350–7.
[34] NIH Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. J Am Med Assoc 1990;264:1444–50.
[35] Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55.
[36] Onaitis MW, Noone RB, Fields R, et al. Complete response to neoadjuvant chemoradiation for rectal cancer does not influence survival. Ann Surg Oncol 2001;8:801–6.
[37] Pahlman L, Glimelius B. Pre- or postoperative radiotherapy in rectal and rectosigmoid carcinoma. Report from a randomized multicenter trial. Ann Surg 1990;211:187–95.
[38] Quirke P. The pathologist, the surgeon and colorectal cancer—get it right because it matters. Prog Pathol 1998;4:201–13.
[39] Quirke P, Dixon MF. How I do it. Prediction of local recurrence in rectal adenocarcinoma by hostopathological examination. Int J Colorectal Dis 1988;3:127–31.
[40] Quirke P, Durdey P, Dixon MF, et al. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection: histopathological study of lateral tumor spread and surgical excision. Lancet 1986;2:996–9.
[41] Read TE, Myerson RJ, Fleshman JW, et al. Surgeon specialty is associated with outcome in rectal cancer treatment. Dis Colon Rectum 2002;45:904–14.
[42] Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;17:1731–40.
[43] Sigmon WR, Randall ME, Olds WO, et al. Increased chronic bowel complications with split-course pelvic irradiation. Int J Radiat Oncol Biol Phys 1994;28:349–53.
[44] Sobin LH, Wittekind C, editors. TNM classification of malignant tumors. 5th ed. New York: Wiley; 1997.
[45] Stein DE, Mahmoud NN, Rani Anné P, et al. Longer time interval between completion of neoadjuvant chemoradiation and surgical resection does not improve downstaging of rectal carcinoma. Dis Colon Rectum 2003;46:448–53.
[46] Suwinsky R, Taylor JMG, Withers HR. Rapid growth of microscopic rectal cancer as a determinant of response to preoperative radiation therapy. Int J Radiat Oncol Biol Phys 1998;42:943–51.
[47] Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997;336:980–7.
[48] Valentini V, Glimelius B, Minsky B, et al. The multidisciplinary rectal cancer treatment: main convergences, controversial aspects and investigational areas with support the need for an European concencus. Radiother Oncol 2005;76:241–50.
[49] Voelter V, Stupp R, Matter M, et al. Preoperative hyperfractionated accelerated radiotherapy (HART) and concommittant CPT-11 in locally advanced rectal carcinoma. A phase I study. Int J Radiat Oncol Biol Phys 2003;56:1288–94.