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Quality assurance in the EORTC 22921 trial on preoperative radiotherapy with or without chemotherapy for resectable rectal cancer: evaluation of the individual case review procedure

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Abstract

The aim of this study was to assess any inconsistency with the protocol guidelines for preoperative radiotherapy for rectal cancer among radiotherapy institutions participating in the framework of a multicentre phase-III European Organization for Research and Treatment of Cancer (EORTC) clinical trial. Twelve radiotherapy departments with more than 10% of the evaluable patients recruited in the trial, were invited to participate in this individual case review. Participating institutions were asked to send five full patient records with the chemotherapy charts, surgical and pathology reports, radiation treatment charts, treatment planning calculations, computed tomography (CT) scans, portal images and follow-up charts. The sample of the 5 patients per institution was randomly selected at the EORTC Data Center. All 12 departments participated. In 21 (35%) of the cases, a three-field technique with two lateral opposed wedge fields and a posterior field was used, while in 39 (65%) of the cases a four-field pelvic box technique was used. All participants used linear accelerators with a minimum of 6 MeV photon-beam energy. In general, the patients were eligible, documentation of clinical data was fair to good and there were no systematic major protocol deviations. The actual total dose was 44.7±a standard deviation (S.D.) of 4.6 Gy. Some variation was found in the fraction size. All institutions complied with the protocol in specifying the reference dose at the ICRU point. The clinical target volume (CTV) drawn on the CT scan was narrow in 7 (12%) cases, but eventually the actually treated volumes in terms of planned treatment volume (PTV) were correct. In two institutions, although the CTV was drawn correctly, the fields appeared to be narrow especially in cranio-caudal direction. Variations in treated volumes and total radiation dose were encountered in the individual case review. By providing recommendations early during the course of the trial, we expect to improve the inter-institutional consistency and to promote a high quality treatment in all of the participating institutions.

Keywords: EORTC phase III trial; Individual case review; Quality assurance; Radio-chemotherapy; Rectal cancer

1. Introduction

Moderate dose preoperative radiotherapy has demonstrated its value in dramatically decreasing local failure in patients with locally advanced rectal cancer, whether they were subsequently submitted to a conventional surgical resection or to a mesorectal excision [1,2]. To further improve this result, clinical research examining the addition of chemotherapy to preoperative radiotherapy looks attractive [3]. The European Organization for Research and Treatment of Cancer (EORTC) Radiotherapy Group have already published results defining the optimal dose of 5-fluorouracil (5-FU) combined with low dose leucovorin (LV) and pelvic irradiation in rectal cancer [4,5]. These results served to define the optimal doses of 5-FU-based chemotherapy to be used

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concomitantly with preoperative radiation. In 1993, a four-arm phase III clinical trial comparing preoperative radiotherapy with preoperative radio-chemotherapy with or without additional postoperative chemotherapy was initiated [6].

Quality assurance is increasingly recognised as an important integral part of clinical research and is now incorporated in all trials of the EORTC Radiotherapy Group [7]. In general terms, it may include various aspects such as verification of data consistency; a dummy run; an early eligibility and treatment compliance check; site visits and verification of physical parameters by thermoluminescent dosimeters (TLD) measurement in various conditions [8]. Ideally, it should be initiated and conducted soon after trial activation.

None the less, detailed published data on quality assurance issues in radiotherapy for rectal cancer are scarce [9–11], although it has been generally incorporated in major clinical trials [12,13]. Treatment technique and protocol inconsistencies seem to be important with respect to the rate of adverse effects, as well as for the response to treatment [14–16]. We therefore launched an individual case review procedure [8,17] concurrently with the commencement of the prospective multicentre phase III EORTC 22921 clinical trial investigating a new combination of neoadjuvant and adjuvant treatment of rectal cancer, with preoperative radiotherapy as an integral part of this protocol. The randomisation includes four arms: preoperative radiotherapy; preoperative radiotherapy with concurrent 5-FU-LV; preoperative radiotherapy and postoperative chemotherapy 5-FU-LV; preoperative radiotherapy with concurrent 5-FU-LV and postoperative chemotherapy 5-FU-LV. In short, preoperative radiotherapy (45 Gy, 1.8 Gy/fraction, in 5 weeks) is followed by tumour dissection. Two courses of preoperative chemotherapy are given: (days 1–5 and days 29–33), both including 5-FU (350 mg/m^2/day) and LV (LV: 20 mg/m^2/day). Postoperative chemotherapy is given in four courses of the same regimen as the preoperative (5-FU + LV) schedule. According to the protocol, the mandatory pretreatment evaluation includes clinical examination, World Health Organization (WHO) status, digital rectal examination (DRE), rigid rectoscopy, body weight and height, liver ultrasound or computed tomography (CT) scan, chest X-ray, pelvic CT scan, complete blood count, urea, creatinine, carcinoembryonic antigen (CEA), aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT), alkaline phosphatase and bilirubin [6].

In this study, an individual case review was performed in order to evaluate data consistency and to detect deviations from the protocol guidelines, the variability of the treated volume and dose homogeneities in a random selection of patients accrued by the most active centres. In terms of the current status (December 2001) of the study, 906 eligible patients have already entered the trial, while the target sample size is 1000 patients.

2. Patients and methods

2.1. Design

Twelve radiotherapy departments having accrued more than 10% of evaluable patients in the trial, were invited to participate in this individual case review. 5 patients per institution were randomly selected at the EORTC Data Center and a copy of the full patient file including chemotherapy charts, surgical and pathology reports, radiation treatment charts, treatment-planning calculations, CT scans, portal images and follow-up charts were requested from each invited centre. The clinical and treatment data were reviewed by a team consisting of a radiation oncologist, a radiation physicist and a data manager and compared with the recorded data on the case report forms available at the EORTC Data Center.

2.2. Items checked for eligibility and follow-up

According to the protocol, the inclusion criteria were: patients fit to undergo treatment; rectal adenocarcinoma T3-T4 Nx MO (International Union against Cancer (UICC) 1987), defined clinically or by endorectal ultrasound (US) as resectable. A tumour location within 15 cm from the anal margin (defined with rigid rectoscopy) was required. WHO performance status 0–1, age $\leqslant 75$ years, creatinine <120 μmol/l, granulocytes $>2\ 10^9$ cells/l and platelets $>130\ 10^9$ cells/l.

The surgery was planned 3–10 weeks after completion of the preoperative treatment by an anterior resection with anal sparing (ARAS) or abdominoperineal resection (APR) both with total mesorectal fat dissection. When an ARAS procedure was performed, ideally, a 2-cm distal margin from the initial gross tumour was respected. Handsewn or stapled anastomosis was allowed. If difficulties had been encountered in performing the anastomosis, or in cases of a colo-anal anastomosis, it was recommended to perform a protective colostomy. Primary closure of the perineal and subcutaneous tissues was recommended after APR. Before surgery, clinical and endorectal US assessment of local tumour response to the preoperative treatment was mandatory. Conditions to withdraw or postpone surgery were: patient refusal; WHO $\geqslant 2$; persistent grade $\geqslant 3$ gastro-intestinal or grade $\geqslant 2$ haematological toxicity; evidence of progressive disease outside of the pelvis. Conditions to withdraw or postpone postoperative chemotherapy were: patient refusal; unresected tumours or macroscopically incomplete surgery or evidence of metastatic abdominal disease even if

resected; WHO $\geqslant 2$; persistent grade $\geqslant 3$ gastrointestinal or grade $\geqslant 2$ haematological toxicity; evidence of progressive disease outside the pelvis. Surgery later than the 10th week after the completion of preoperative treatment and postoperative chemotherapy later than the 10th week after surgery were considered as protocol violations.

Several items of tumour pathology were checked: size of the primary gross tumour; distance between the lower section and tumour (if ARAS performed) or between the tumour and anal margin if APR performed); macroscopic extension to adjacent organs; histological type and differentiation; microscopically complete resection, complete or not; distal section, involved or not; contiguous peritoneal involvement; extension into rectal wall; status of radial margin in cases of tumour beyond the muscularis propria; specific invasion to venous, perineural or lymphatic systems and regional lymph node status.

Follow-up was scheduled every 6 months and included clinical examination, WHO status, body weight, DRE, CEA, liver US or CT scan, chest X-ray and evaluation of late toxicity. Additionally, coloscopy was ideally performed every 12 months.

2.3. Items checked for radiotherapy

The target volume for radiotherapy was limited to the potential extension of the tumour and to the perirectal nodes below the level of S3, including 5 cm above and 5 cm below the primary tumour in the direction of the bowel. If the tumour was located in the upper third of the rectum (10–15 cm from the anal margin), the target volume extended to only 3 cm above the tumour. If the tumour was located in the lower third of the rectum (0–5 cm from the anal margin), the target volume extended to the S2–S3 junction in order to include the perirectal nodes and the entire perineum. Posteriorly, the target volume included the posterior pelvis and the anterior part of the corresponding portion of the sacrum. When the tumour was confined to the posterior part of the rectum, the target volume included 3 cm of the tissue in front of the anterior rectal wall. In other cases, and particularly when the tumour was situated on the anterior wall of the rectum, the target volume included 3 cm of tissue in front of the macroscopical extension of the tumour. Laterally, the target volume provided a safety margin of minimum of 3 cm beyond the macroscopical extension of the tumour. Participants were asked to calculate the dose in accordance with the International Commission on Radiation Units (ICRU) Report No. 50 and to report mean, maximal and minimal doses relative to the ICRU point for the planned treatment volume (PTV) [18]. Comparative measurements of the clinical target volumes (CTVs) and PTVs drawn by the participants were made in the central plane defined by the responsible physician using the paper printouts of their computerised planning systems. The beam widths of the irradiation fields for the CT-based treatment plan were read from the treatment planning charts and were also assessed on the simulation films. The check of the simulation films also included an estimation of the amount of small bowel included in the irradiated fields. The target volume was checked and evaluated by means of an available CT scan. Several checks were also made for fractionation, first/last day of irradiation, total dose given at ICRU point, photon-beam energy, radiotherapy interruptions and minimum/maximum dose in the PTV. As a mean of assessing the dose effects, all doses were converted into biological effective dose (BED) values taking into account the fractionation schedule [19]. The alpha/beta ratio for the linear quadratic model was taken as equal to 10, which is the common value for cancerous tissue [20]. Consequently, the equation used for the BED was the following:

$$BED = \sum_{1}^{k} n_k d_k \left(1 + \frac{d_k}{\alpha/\beta}\right)$$

where k stands for the number of different schedules administered per patient, n_k stands for the number of fractions with a dose per fraction of d_k gray and α/β represents the alpha/beta ratio. All numerical values were expressed as mean ± 1 standard deviation (S.D.) and range.

2.4. Items checked for chemotherapy

According to the protocol, the first course of preoperative chemotherapy should be given on days 1–5 of radiotherapy, with 350 mg/m^2/day 5-FU and 20 mg/m^2/day LV. The second course of preoperative chemotherapy should be given on days 29–33. The postoperative chemotherapy dose was identical to the preoperative. However, the first course should be given no sooner than 3 weeks and no later than 10 weeks after surgery, and a total of four courses should be administered at 3-weekly intervals. Modifications for dose were allowed under certain conditions in terms of acute toxicity according to the Common Toxicity Criteria (CTC) scale [21]: in cases of grade 1 haematological toxicity, the dose was reduced to 75%, while if grade 2 or more was seen the treatment was stopped; in cases of grade 2 gastrointestinal toxicity the dose was reduced to 75%, while for cases of grade 3 or more treatment was stopped. By using the chemotherapy treatment charts, several checks were made concerning the dose, the schedule and the timing of treatment. In cases of a shorter time interval between sessions, shorter time or higher doses, the patient was characterised as being overtreated. Similarly, those cases with a longer time interval or given lower doses were classified as undertreated.

3. Results

All 12 invited radiotherapy departments participated in this review. In 21 (35%) of the cases, a three-field technique with two lateral opposed wedge fields and one posterior field was used, while in 39 (65%) of the cases a four-field pelvic box technique was used. All participants used linear accelerators with the patient treated in a prone position. The nominal energy used was 6 MeV in 46 cases (77%), 10 MeV in 5 cases (8%) and 18 MeV in 11 cases (18%).

3.1. Evaluation of eligibility and follow-up

In general, the patients were eligible, documentation of the clinical data was fair to good and there were no systematic major protocol deviations. In terms of eligibility, 1 patient was found to be ineligible for the trial, due to a later discovery of extensive disease. Initially, this patient was judged as clinically resectable. However, in a new CT scan before surgery, a 2-cm lesion was found in the liver. During surgery, a large unresectable T4 tumour that had infiltrated the prostate and bladder was found. This patient underwent an anterior resection including radical cysto-prostatectomy and a partial hepatectomy for the single liver metastasis. While another patient was characterised as undertreated due to the prescribed time interval of 10 weeks between radiotherapy and surgery having been exceeded.

In 7 patients (12%), the CEA values and in 6 patients (10%), the results of liver US or abdominal CT scan were not reported. However, all this information was available in the patients' records. In six records (10%), there were some inconsistencies between the clinical and pathological staging results. 3 patients (5%) in the review had evidence of perirectal and iliac nodal metastases on their CT scans.

The review of the pathology forms revealed some misinterpretations regarding the size of the primary tumour. In 10 records (17%), the size of the pathology specimen written on the 'on study' form differed from the pathology report, due to wrong data entry.

3.2. Variations in dose distribution and in field sizes

Field dimensions as defined by the participants in the treatment charts are reported in Table 1. Two specific sub-groups were evaluated separately: group A for tumours located 10–15 cm from the anal margin and group B for tumours located 0–5 cm from the anal margin. Dose reports for PTV are listed in Table 2. All institutions complied with the protocol in specifying the reference dose at the ICRU point, being the isocentre in all cases. The CTV drawn on the CT scan was very narrow in 7 (12%) cases of group A. In these cases, the perineum and the perirectal nodes were not included as clinical targets. However, the actually treated volumes in terms of the PTV were correct. In two institutions, although the CTV was drawn correctly, the fields appeared to be narrow especially in cranio-caudal direction. These institutions were advised to adhere strictly to the protocol. By reviewing the portal films, in 42% of cases, part of the small bowel was inside the irradiated field.

Table 1
Dimensions of the portals as defined by the participants in the radiotherapy treatment charts

Dimensions of portals	Group A (tumour located at 10–15 cm from the anal margin; $n=10$)			Group B (tumour located at 0–5 cm from the anal margin; $n=32$)			All cases ($n=60$)		
	Mean (cm)	±S.D.	Range (cm)	Mean (cm)	±S.D.	Range (cm)	Mean (cm)	±S.D.	Range (cm)
Height of anterior-posterior fields	15.2	2.9	12.0–20.0	17.7	3.1	15.0–24.2	16.0	2.9	12.0–25.0
Width of anterior-posterior fields	14.1	1.7	11.0–16.5	14.3	2.5	11.0–20.5	14.1	2.4	11.0–20.5
Height of lateral fields	13.0	1.9	11.0–16.0	13.1	2.8	11.0–20.0	13.3	2.5	11.0–20.0
Width of lateral fields	14.5	3.1	12.0–20.0	17.1	3.3	15.0–22.8	16.2	3.3	12.0–25.0

S.D., standard deviation.

Table 2
Dose-specifications for PTV, expressed as a percentage of the reference dose at the ICRU point

	Absolute values (Gy)			Normalised to the actual prescribed dose			Normalised to the protocol prescribed dose (45 Gy)		
	Mean	S.D.	Range	Mean	S.D.	Range	Mean	S.D.	Range
PTV: maximal dose	46.9	2.2	42.2–55.1	103.5	3.8	100.0–117.7	104.1	4.8	94.8–122.4
PTV: minimal dose	43.3	2.1	36.0–49.9	95.5	3.6	90.4–100.0	96.1	4.6	90.4–110.9
PTV: prescribed dose	44.7	4.6	10.8–50.4	–	–	–	100.6	2.7	92.0–112.0

PTV, planning target volume; S.D., standard deviation.

3.3. Variations in the irradiation schedule

Several variations were found during the individual case review. In particular, in 47 cases (78%) the fractionation schedule during the whole treatment period was according to the protocol: 25 sessions of 1.8 Gy/fraction. However, in 11 cases (18%) radiotherapy was changed to either 2 Gy/fraction or an additional fraction was given to compensate (in radiobiological terms) for the interruption of treatment due machine breakdown or extended legal holidays. In two cases (3%) the last two fractions of radiotherapy were not given due to radiation-induced toxicity, which was according to the protocol guidelines. The BED values for the 60 patients ranged from 12.7 to 59.5 Gy with a median value of 53.1 (mean = 52.8 ± 5.5). The diagram of the BED values stratified by institution is shown in Fig. 1. A tolerance level of ±5% and a critical level of ±10% was defined around the prescribed BED of 53.1 Gy (25 fractions of 1.8 Gy, 5 days per week, $\alpha/\beta = 10$ Gy). These limits of BED deviations were taken as an expansion to the European Society Therapeutic Radiology Oncology—Quality Assurance Laboratory (ESTRO-EQUAL) recommendations by measuring the physical dose [22]. One patient stopped irradiation after six fractions due to tumour progression, resulting in a BED value of 12.7 Gy (Fig. 1).

3.4. Chemotherapy evaluation

Among the 60 cases analysed in this study, 8 cases presented variations from the prescribed chemotherapy schedule. In particular, 1 case was characterised as overtreated due to 600 mg/m^2/day of 5-FU being administered instead of 350 mg/m^2/day. The other 7 cases were evaluated as undertreated: 3 patients refused the assigned postoperative chemotherapy, 3 did not receive the prescribed postchemotherapy schedule and went 'off study' due to the discovery of liver metastases or a second primary during surgery, and in 1 patient postoperative chemotherapy was reduced due to renal insufficiency. However, in all 60 cases, even taking into account the above variations, the data recorded on the case report forms agreed with the patient records and there were no major protocol violations. The overtreated case was considered as a minor deviation and the reasons for the undertreated cases were consistent with the relevant advice given in the protocol guidelines.

4. Discussion

Adjuvant 5-FU plus LV has not yet been confirmed as standard treatment for rectal cancer, whereas pre-

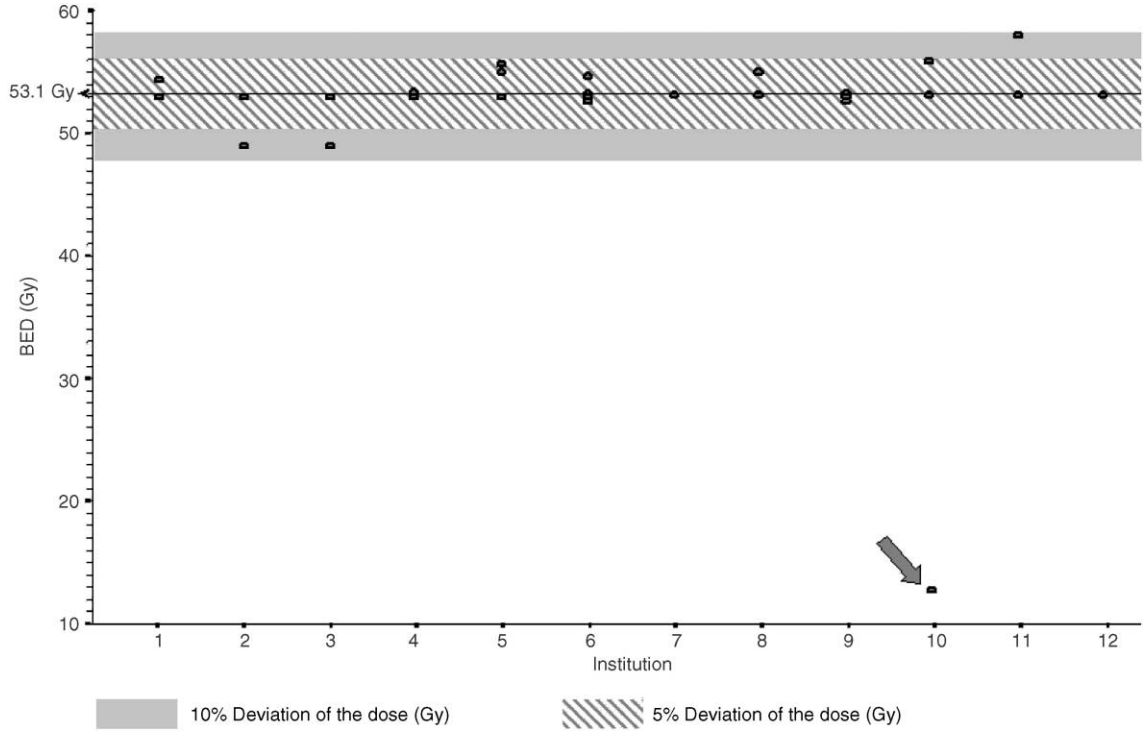

Fig. 1. Diagram of the biological effective doses stratified per institution. The grey area and the hatched area represent the ±10% and the ±5% of the critical and the tolerance level, respectively, concerning the deviation from the stated BED dose which was 53.1 Gy. One protocol deviation was found (gray arrow) concerning a permanent interruption of radiotherapy after six fractions due to recto-vaginal fistula.

operative irradiation alone or postoperative chemo-radiotherapy are accepted as standard treatments [23]. The optimum management of rectal cancer in terms of pre- or postradio-chemotherapy still remains undecided [24,25]. Several reports have shown a role for preoperative radio-therapy or radio-chemotherapy in the management of rectal cancer. In 2000, a rigorous meta-analysis of 14 trials performed by Camma and colleagues showed a significant benefit for preoperative irradiation compared with surgery alone, but the magnitude of the benefit was relatively small indicating that the results are subject to several limitations. However, variations in the irradiation techniques and radiotherapy regimens may limit the accuracy of this meta-analysis [26]. Dube and colleagues in a meta-analysis of 39 trials published between 1959 and 1993 concerning adjuvant treatment in colorectal cancer concluded that high quality trials resulted in more positive outcomes with a higher significance, emphasising the role and need for quality assurance in large randomised trials [27].

The variations in the radiotherapy schedule found in this study, expressed in terms of BED values were considered as acceptable, ranging within a critical limit of $\pm 10\%$. Furthermore, the diagram of the BED values stratified by institution (Fig. 1) revealed that 54 out of 60 values (90%) were inside the tolerance level of $\pm 5\%$. The exceptional case of 12.7 Gy concerned a permanent interruption of irradiation (progressive disease/recto-vaginal fistula) and was considered as a minor deviation. The dose higher than 45 Gy prescribed in some cases for compensating the treatment interruption was also reflected in the range of minimal doses (Table 2).

In preoperative radiation of rectal cancer, the definition of the target volume has either to depend on anatomical landmarks visible on simulation films, or on the delineation of the target on CT scans, or on a combination of both [28,29]. A further problem in preoperative, as opposed to postoperative, treatment may arise as there is no additional information available from surgical reports or inserted clips as markers at critical regions. Therefore, geographical misses might occur in this setting. Frequently, the gross tumour volume (GTV) is outlined on CT scans, while the CTV is defined with reference to bony landmarks on simulation films. Within a trial, credible assessment of the role of radiotherapy with respect to local failure is only possible if the treated volumes are well documented and show a sufficient degree of homogeneity for the study population. In the present study, the use of conventionally designed portals resulted in a higher treatment homogeneity among the different institutions than the CT-based definition of CTUs. In light of this individual case review, the ongoing radiotherapy protocol of this trial favours the definition of treatment volumes by field margins rather than by CT-based target volumes. This was also reflected in the narrow margins of the CTV drawn on the CT slices, whereas the actual treated volume in terms of PTV and 95% isodose distribution were sufficiently wide.

The issue of comparability within a multicentre trial would be missed if only dose reports with respect to dose homogeneities would be taken into account. In our study, a homogeneity of 4.6 and 4.8% was measured for the minimal and maximal doses within the PTV (Table 2), with a slight tendency to underdosage in terms of the ICRU recommendations: the reported minimum doses in the PTV relative to the dose at the ICRU point was 90.4%, considered as a minor deviation. Variability decreased for the mean doses reported (2.7%). Within a given PTV, the minimum requirement for dose homogeneity is defined in the ICRU Report No. 50, allowing for a $\pm 5\%$ of dose variation [18]. This definition does not resolve the main problem, how a PTV is defined and employed in a constant manner by all radiation oncologists for a given diagnosis. Even rather small variations in PTV delineation result in much greater variations in the dose actually delivered to a region of interest. Although the recommended treatment portals for rectal cancer have been described in detail and have been outlined quite rigorously in the trial guidelines, some variations in the dimension of fields were found, as shown in Table 1. In a dummy run performed by Widder and colleagues concerning a multicentre phase II trial for rectal cancer in Austria, the dose dropped from 90% at the field margin to 50–70% 1 cm outside the field margins in a pelvic box technique, resulting in a considerable variation in the actual field dimensions [12]. In comparison with this study, the variations we found are considered reasonable.

Toxicity from the protocol treatment usually involves the small intestine. In 25 out of the 60 records, part of the small bowel was within the irradiated field. Two reasons for this can be identified: either the bladder was not full allowing an increased volume of small bowel in the irradiation field, and/or no specific blocks were used to spare the small bowel. These cases were considered as minor deviations from the protocol. However, no significant statistical correlation was found between the irradiated small bowel and the reported acute radiation gastrointestinal mucositis. This might be attributed to the advice given to all participating departments to be careful not to include a significant amount of small bowel in the irradiated fields. Another possible explanation could be that the small bowel is mobile and thus not irradiated permanently throughout the entire treatment schedule of 5 weeks. Several small-bowel complications related to the dose-volume effect in patients treated for rectal cancer have already been reported [30]. Minsky and colleagues from a national survey of 507 eligible patients in the United States of America (USA), who received radiation therapy as a component of their treatment for rectal cancer, reported that techniques to identify and help exclude the small bowel from the radiation field were not routinely used [16]. Therefore, we strongly suggest shielding the small bowel as much as possible within the treatment portals and advise the

use of treatment portal verification to measure the treatment set-up variability to limit the target volume margins as much as possible in routine clinical practice.

The clinical distinction between tumour stages T2 and T3 is difficult. Indeed, some inconsistencies were found between the clinical and pathological staging. This can be attributed not only to the up- or downstaging in clinical staging using endosonography [31], but also to tumour reduction induced by the preoperative treatment.

An individual case review is an adequate instrument to assess the degree of homogeneity of treatment delivery in a multicentre setting [8]. This procedure has to be interactive in terms of continuous evaluation of deviations leading to amendments to the protocol guidelines to correct for systematic errors related to incoherence, tracked early during the on-going study. It has, however, to be complemented by continuing re-evaluations throughout the trial to make sure that there is a convergence rather than a divergence of treatment delivery with increasing study routine. Presently, local audits and individual case review are used. The individual case review as part of the quality assurance programme of this trial has revealed a number of protocol deviations, which might influence the results. Quick identification of possible deviations and immediate feedback to the participating centres can reduce treatment variation and improve the adherence to the protocol, limiting the variations seen in a multi-institutional setting. In conclusion, we emphasise that, based on the findings of this individual case review study, the delivery of specific guidelines to all participants to improve adherence to the trial protocol resulted in an enhancement of the reliability of the final clinical results.

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