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RESEARCH ARTICLE

Regional hyperthermia added to intensified preoperative chemo-radiation in locally advanced adenocarcinoma of middle and lower rectum

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Abstract

Purpose: To evaluate the safety of delivering pre-operative regional hyperthermia (HT) plus an intensified chemo-radiotherapy (CRT) regimen in patients suffering from locally advanced rectal cancer.

Methods: Between June 2000 and April 2006, 76 patients with locally advanced (cT3-4 N0/+) rectal adenocarcinoma were treated with HT plus CRT. HT was given once a week, to a total of five treatments, 1 to4 h after radiotherapy (50 Gy with 2-Gy fractions for 5 weeks, plus a 10-Gy boost on the tumour bed, with the same fractionation schedule). Chemotherapy consisted in 5FU 200 mg/m^2 continuous infusion throughout the 6 weeks of irradiation and OXA 45 mg/m^2 in a weekly bolus. Surgery followed 4 to 6 weeks after the completion of HT plus CRT.

Results: HT plus CRT was generally well tolerated. At pathologic examination, there was a pathologic complete response (pCR) (ypT0 ypN0) in 18 out of 76 patients (23.6%), a partial response (PR) in 34/76 ones (44.7%) and a stable disease (SD) in 20/76 (26.3%) ones; 4/76 patients (5.2%) had a progression disease (PD) (distant metastases) at the time of surgery. Good predictors of a longer disease-free survival (DFS) were in order ypN status (log-rank test: $p = 0.0008$), ypT status ($p = 0.002$) and pCR ($p = 0.03$).

Conclusion: Preoperative CRT combined with regional HT yielded acceptable toxicity. The rate of pCR was encouraging, although further studies are needed to prove the long-term efficacy of adding HT to CRT.

Keywords: *rectal cancer, preoperative chemo-radiation, hyperthermia*

Introduction

In locally advanced mid-low rectal cancer, the major goal is to achieve a high rate of resectability, thus allowing sphincter-saving surgical procedures. Neoadjuvant CRT achieves a high rate of pCR [1, 2], nevertheless the impact of pCR on outcome is still a controversial issue [3, 4]; it seems, however, that patients with a complete or nearly complete response after CRT have a better local control and survival [5–7]. In recent years, several investigators have tried new CRT regimens, either by associating 5FU with new available drugs (such as OXA [8–10], raltitrexed [11], or irinotecan [12, 13]), or administering capecitabine [14], or capecitabine plus OXA [15–17]. Many institutions have also tested the new biologic agents in various associations with chemotherapy and radiotherapy, using cetuximab [18–20], or gefitinib [21], or bevacizumab [22, 23]. These new intensive regimens have put into evidence the issue of how much they impact on patient quality of life [24, 25].

Another major question rises about the efficacy of adjuvant chemotherapy after preoperative CRT and surgery; a retrospective study by Fitkau et al. [26] suggested that, for ypN0 patients, postoperative chemotherapy could be spared; for patients with ypN2 status, an intensification of the postoperative

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chemotherapy should be considered. In an EORTC trial, Collette et al. found no difference in DFS and OS comparing the patients who received postoperative chemotherapy or not [27]. A letter by Fitkau outlines that it is not defined what parameter may be the best for the selection of the patients to postoperative chemotherapy following neoadjuvant CRT [28].

Regional HT has already been tested in locally advanced rectal cancer in a preoperative setting in association with CRT [29–32]. In vitro temperatures of 40°–43°C enhance the effect of radiotherapy (as they interfere with the repair of radiation-induced DNA damage) and of some cytotoxic drugs, such as alkylating agents, nitrosoureas, platinum compounds, and antibiotics. HT is able to increase the anti-proliferative effect of OXA in in vitro colon cancer cells with a G1/S arrest and a G1/G0 reduction [33]. Besides, HT enhances the effect of radiotherapy in human colon cancer cells transplanted into nude mice by changing the expression of the apoptosis genes, such as p53, Bcl-2 and Bax [34].

In this phase II trial we investigated the safety and efficacy of adding regional HT to CRT (5FU 200 mg/m^2 continuous infusion for 6 weeks plus weekly OXA 45 mg/m^2) as neoadjuvant treatment. Primary endpoints were acute and late toxicities; secondary end-points were percentage of pCR and rate of sphincter-sparing surgery.

Patients and methods

Patients

Between June 2000 and April 2006, 76 patients with biopsy-proven locally advanced (cT3-4 N0/+) rectal adenocarcinoma of the middle and lower rectum, located within 12 cm from the anal verge, were included in the study. Staging was performed by pelvic CT or MRI or by transrectal ultrasonography (TRUS). Inclusion criteria were a biopsy-proven rectal carcinoma, stage cT3-4 N0-1, adequate renal and liver function, normal white blood count and platelet count. Exclusion criteria were medical conditions that could make the patients unfit for surgery, chronic inflammatory bowel disease, tumour located above 12 cm from anal verge. Patient characteristics are shown in Table I.

The local ethical committee approved the protocol and all patients gave written informed consent.

Treatment

Radiotherapy consisted of prone-position irradiation, using a four-field box technique with 6 MV photons. The target volume was meant to include the macroscopic tumour, the mesorectum and the internal iliac and presacral nodes up to the L5-S1 junction. The upper border of the radiation fields was at the L5-S1 interspace. The distal border was 5 cm below the distal margin of the macroscopic tumour or at the bottom of the obturator foramina. Lateral limits of the anteroposterior and posteroanterior fields were 1.5 cm lateral to the margins of the bony pelvis. Lateral fields encompassed the entire sacrum posteriorly and extended anteriorly to the anterior margin of the symphysis pubis. The dose delivered to the pelvis in this way was of 50 Gy in 25 daily fractions of 2 Gy, Monday to Friday over a period of 5 weeks; then a boost of 10 Gy with the same fractionation schedule was delivered to the tumour, identified by endoscopy.

Chemotherapy started simultaneously with radiotherapy. 5FU was infused continuously for all the duration of irradiation through an implantable subcutaneous i.v. access device using a portable elastomeric pump, at a dose of 200 mg/m^2/day. OXA was given as a 2-hour i.v. infusion at 45 mg/m^2 on the first day of each week of radiotherapy for a total of six courses (Figure 1).

All patients received premedication with corticosteroids.

Table I. Patient characteristics ($n = 76$).

	n (%)
Age, years	
Median	60
Range	38–82
Sex	
Male	50 (65.7)
Female	26 (34.2)
ECOG performance status	
0	48 (63.2)
1	28 (36.8)
Tumor distance from anal verge, cm	
Median	6
Range	1–12
TNM clinical stage	
T3 N0 M0	29 (38.1)
T3 N+ M0	39 (51.3)
T4 N0 M0	6 (7.9)
T4 N+ M0	2 (2.7)
Baseline tumor assessment	
Pelvic CT scan	34 (44.7)
Trans – Rectal Ultrasonography (TRUS)	4 (5.3)
CT plus TRUS	8 (10.5)
CT plus MRI	19 (25)
CT plus TRUS plus MRI	11 (14.5)

Hyperthermia

HT was delivered once weekly during CRT, 1-4 hours after radiotherapy, to a total of five treatments, using the BSD-2000 system with a Sigma-60 applicator. Endoluminal thermometry catheters were placed in the rectum, bladder, and vagina. Temperature position curves were recorded along

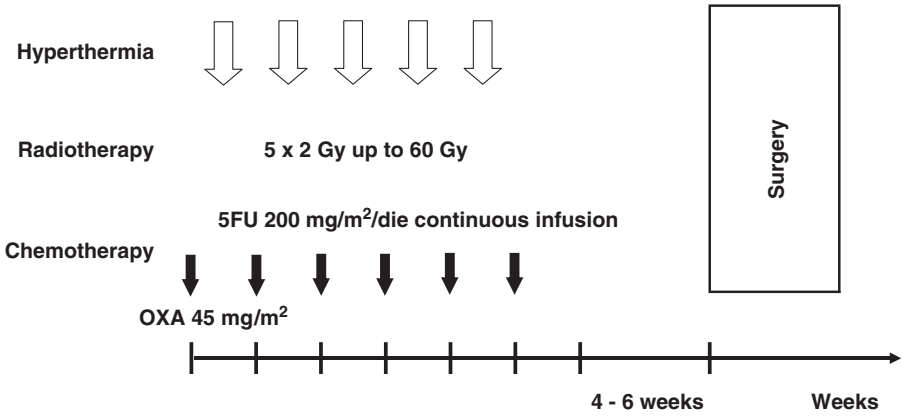

Figure 1. Scheme of the trial.

the catheters at intervals of 5 to 10 minutes. No invasive thermometry was made, so the temperature was not registered directly in tumours but only along the catheters. The part of the catheter related to the tumour was specified through CT, TRUS, or endoscopy.

The aim was to continue the treatment for 60 minutes after tumour temperature had reached 40.5°C, or generally for a maximum total duration of 90 minutes. Temperature position curves were recorded along the catheter at intervals of 5 to 10 minutes. We determined index temperatures, T_{max} T_{90} and T_{min}, by taking into consideration all tumour-related measurement points during the therapeutic range of time. T_{90} is the temperature reached or exceeded by 90% of the tumour-related measurement points; T_{max} and T_{min} are the maximal and minimal temperatures achieved at each HT session, respectively.

Patients were instructed to refer any bad sensation suggestive of hot spots, such as a burning sensation, a feeling of pressure, or any pain. Any symptom mentioned by the patient that disappeared within one minute of power decrease was taken to show that the temperature was too high: in these cases, we took adjustments of treatment settings, such as changes in power output per channel, frequency or phase settings, or placement of an additional water bolus.

Toxicity scoring

Acute CRT toxicity was defined as the adverse effects occurring during the treatment or within 6 months from the end of it; late toxicity was defined as the one occurring after 6 months from the completion of treatment. Toxic effects were registered according to RTOG-EORTC scoring criteria [35].

HT toxicity was registered according to the score system proposed by the Berlin group [29] (Table II).

Table II. HT toxicity score, from B. Rau et al. [29].

Toxicity score for regional hyperthermia	
Grade	Criteria
0	General discomfort (bolus pressure, systemic stress); no limitation of heat treatment
1	Local discomfort (hot-spot phenomenon, positioning), which requires rearrangement of treatment set-up; heat treatment can be accomplished with some restrictions in total power and power distrbution
2	More severe local discomfort or systemic stress, which persists after the end of treatment and evidently limits the efficiency
3	Every kind of toxicity, which causes the patient to refuse further heat treatments (hot-spots, musculoskeletal syndrome, claustrophobia, etc.)
4	Bums or tissue damage or any other complication related to the heat treatment

Post-CRT restaging

After the completion of CRT, within the 4–6 weeks of interval before surgery, patients underwent a restaging procedure (endoscopy or TRUS) to assess the new clinical stage.

Surgery and postoperative treatment

Surgery was planned 4 to 6 weeks after the end of CRT. Any attempt was made to do a conservative surgery (TME) if at least a 2-cm distal margin of safety could be obtained. The anastomosis usually was created with the 'double-stapling' technique [36]. If this could not be achieved, an abdomino-perineal excision was performed. In low-lying tumours, the choice was left to the discretion of the surgeon provided that a free distal margin more than 1 cm was maintained. Lymph node dissection up to the stem of the inferior mesenteric artery and including the total mesorectum was generally performed.

Adjuvant chemotherapy was performed in single cases, at the discretion of the medical oncologist, mostly in cases of SD or PD.

Assessment of pathologic response

Visible residual tumour or the corresponding fibrotic area as well as perirectal lymph nodes, distal and lateral resection margins and mesorectal tissue distal to the tumour were examined to assess the radicality of the surgical resection and to determine the pathological stage according to the AJCC-TNM classification. All surgical specimens underwent routine pathological processing, which included fixation in 10% formalin, painting of the circumferential margin (CRM), and serial slicing from the distal margin at 3 to 5 mm intervals. To determine the CRM, the lateral resection margin of the fresh specimen was inked and subsequently the specimen was fixed in formalin for 48 h; blocks of the tumour in relation to the inked CRM were collected; measurements of the margin were done microscopically. A specimen with tumour $\leq$1 mm from the inked margin was considered as having a positive CRM.

The median number of analysed lymph nodes per patient was 12 (range 10–14).

The pCR was defined as the absence of residual tumour cells in the surgical specimen regardless of the presence of mucine lakes.

Pathologic PR was defined as presence of few poorly differentiated pleomorphic tumour cells (pTmic if cellular aggregations were less than 5 mm in diameter). The specimen was deemed as pathologic SD in presence of extensive areas of tumour infiltration through the rectal wall or the perirectal tissue.

Endpoints and statistical analysis

The primary endpoints of the study were acute and late toxic effects of neo-adjuvant treatment (CRT and HT).

Secondary endpoints were rate of pCR and rate of sphincter-sparing surgery.

Follow-up visits were scheduled 1 month after treatment, then once every 3 months during the first 2 years, and every 4 to 6 months after. Patients were submitted to digital rectal examination at every visit; to proctoscopy 3 months after surgery and then every 6 months for the first 2 years, then once per year; to abdomino-pelvic Computed Tomography (CT) 6 months after surgery, then every 6 months for the first 2 years, then once per year.

Overall survival (OS) and DFS were measured from the date of surgery. DFS was defined as the time from surgery to the onset of local recurrence or metastatic disease. Statistical evaluations were performed using the software Intercooled Stata, version 9.0. We applied the Kaplan-Meyer method; the long-rank test and the Chi-square test were also performed. Student's *t*-test was performed to investigate the correlation between thermometry data and pCR status.

Results

Feasibility and toxicity

All patients completed HT plus CRT except one patient who stopped chemotherapy due to grade 3 neutropenia. All patients underwent surgery.

CRT and HT-related acute toxicities are shown in Table III.

The only dose-limiting toxicity was a grade 3 neutropenia in 1 in 76 patients (1.3%), who stopped chemotherapy and went on with radiotherapy only. OXA-related neurotoxicity was found in 4 out of 76 patients (5.2%); it consisted in peripheral sensitive neuropathy and/or reversible grade 2 cold-related paresthesias/dysesthesias. Diarrhoea was present in 12 out of 76 patients (15.7%). No cases of dermatitis were observed.

HT-related toxicity (registered according to the Berlin scoring system [29], shown in Table II) consisted in general discomfort (grade 0) due to bolus pressure in 7 of 76 patients (9.2%), local discomfort (hot-spot phenomena, grade 1) in 3 of 76 patients (4%), more severe discomfort which persisted after the end of the treatment (grade 2) in 2 out of 76 (2.6%). No patient had grade 3 toxicity. Subcutaneous burns (subcutaneous induration), grade 4 toxicity, occurred in 4 of 76 patients (5.2%) and disappeared spontaneously within two weeks. No patients developed skin burns. No one HT session had to be ended prematurely because of discomfort.

Late radiotherapy toxicity consisted in persistent diarrhoea in 2 patients (2.6%).

Table III. CRT – related acute toxicity according to RTOG – EORTC scoring criteria [35], observed in all patients ($n = 76$).

	Toxicity grade, %			
Toxicity	I	II	III	IV
Nausea	5.2 (4/76)	–	–	
Vomiting	–	–	–	–
Diarrhoea	5.2 (4/76)	9.2 (7/76)	1.3 (1/76)	–
Neurotoxicity	–	5.2 (4/76)	–	–
Dermatitis	–	–	–	–
Anemia	4 (3/76)	2.6 (2/76)	–	5.2 (4/76)
Thrombocytopenia	–	–	–	–
Neutropenia	–	–	1.3 (1/76)	–
Cistitis	1.3 (1/76)	2.6 (2/76)	–	–
Regional HT	4 (3/76)	2.6 (2/76)	–	5.2 (4/76)

Surgical complications occurred in 3 of 76 patients (4%); one patient developed a perianal abscess 7 days after surgery and 5 weeks after CRT; it required a surgical procedure and then healed. Another one, 8 days after surgery and 5 weeks after CRT, had a fistula which required surgical intervention. Another patient, soon after the intervention performed 4 weeks after CRT, had a delayed wound healing, which recovered after 2 months from TME. No cases of intestinal obstruction or severe faecal incontinence were observed.

Hyperthermia results

All patients were submitted to 5 HT sessions, once weekly.

T_{90} and T_{max} data for each patient, divided in pCR and no-pCR groups, are shown in Figure 2. Mean T_{90} was 40.8°C (95% confidence interval [CI] 40.6–41.0°C); mean T_{max} was 41.6°C (95% CI 41.4–41.8°C).

A correlation was found between higher T_{90} values and pCR status and it was statistically significant (Student's *t*-test: $p = 0.002$); a correlation (also statistically significant [Student's *t*-test: $p = 0.004$]) is also evident between T_{max} values and pCR. Poor correlation existed between T_{90} and T_{max}.

Among the study population, there was no significant difference in achieved temperatures between female and male patients, nor between old versus young ones, nor versus proximally or distally seated tumours.

Pathologic results

Among 76 patients 23 (30%) had metastatic lymph nodes at surgery (5 of 12 lymph nodes in one patient, 5 of 10 in two, 4 out of 14 in two, 4 out of 13 in two, 4 out of 11 in two, 3 out of 13 in one, 3 out of 12 in three, 2 out of 14 in one, 2 out of 13 in two, 2 out of 1 in two, 2 out of 11 in two, 1 out of 14 in one, 1 out of 12 in one, and 1 out of 11 in one).

Among the 56 out of 76 patients who underwent TME, 50 had negative CRM. In no patients was a macroscopic (R2) CRM noted. In six patients, a microscopic (R1) CRM was observed; in all these six cases TME specimens were intact, i.e. no specimen defects were noted.

Among the 20 out of 76 patients submitted to Miles procedure, no one showed positive CRM. So in summary we had 6 out of 76 R1 resections (7.9%) and no R2 resections.

Rate of pCR

Pathologic downstaging is shown in Table IV.

A pCR (ypT0 ypN0) was found in 18 out of 76 patients (23.6%) and they all underwent TME. After 2 years of follow-up, none of them developed local recurrences; only one patient developed distant metastases 31 months after surgery.

A PR was observed in 34 out of 76 cases (44.7%). Two patients developed a local recurrence plus distant metastases (lung in one case, liver in the other); they both underwent adjuvant chemotherapy with a FOLFOX scheme. Two other patients developed lung metastases and did not undergo chemotherapy due to the poor general conditions.

A SD was observed in 20 out of 76 cases (26.3%). Eighteen of them were initially cT3 N+, and two were cT3 N0. Ten among these 20 patients underwent adjuvant chemotherapy with a FOLFOX scheme. Two patients (not submitted to adjuvant chemotherapy) developed lung metastases after one year of follow-up.

There were 4 out of 76 cases of PD (5.2%): in two patients initially staged as cT3 N0 M0, liver metastases were found at surgery and a TME was

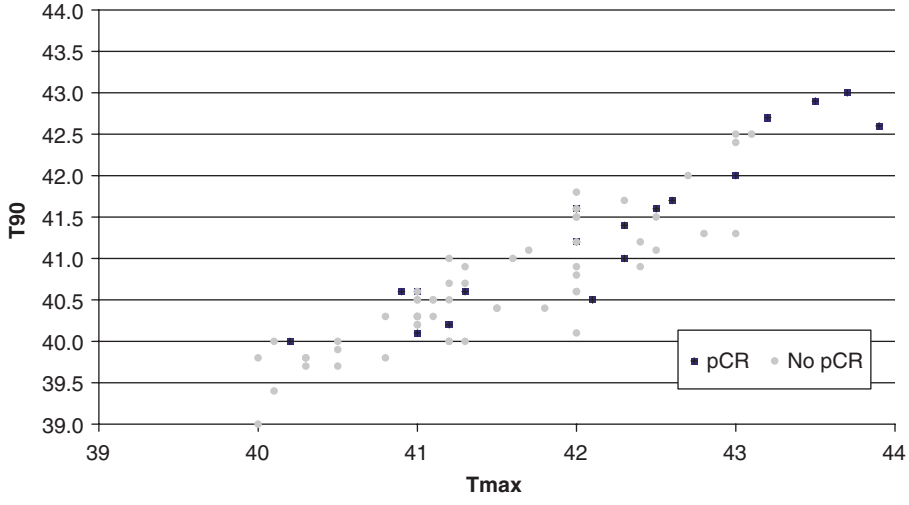

Figure 2. T_{max} and T_{90} values in patients who underwent pCR and in those who did not ($n = 76$).

performed due to the good down-staging (ypTmic ypN0); another two patients initially staged as cT3 N0 had a TME intervention and were found to be ypT3 ypN+; after 6 and 12 months from surgery respectively they developed liver metastases.

Type of surgery

Of 76 patients, 56 (73.7%) underwent TME. A Miles intervention was performed in the remaining 20 out of 76 patients (26.3%) in low-lying tumours or when at least a 2-cm distal margin of safety could not be obtained. Six out of 76 patients had a tumour initially sited at 5 cm from the anal verge (2 cm from dentate line); two of them had a down-staging at post-CRT examination, while the remaining four did not, nevertheless the surgeon decided to submit them all to a Miles intervention, as a free distal margin more than 1 cm could not be maintained.

Follow up

Median follow-up was 51 months (range 24–83). No patients were lost at follow-up. Five-year survival rate estimates +/− standard deviations were 86.5% +/−4.3% for OS; 74.5%+/−5% for DFS; 94.6% +/−2.6% for local recurrence-free survival; 73.2% +/−5.4% for metastases-free survival. Kaplan-Meyer OS estimates are shown in Figure 3; DFS estimates are shown in Figure 4.

Table IV. Clinical stage at diagnosis and subsequent pathological stage after neo – adjuvant HT plus CRT and surgery for all patients ($n=76$).

	n	(%)
cT3 N0		
ypT0 ypN0 (CR)	12	15,8
ypTmic ypN0 (PR)	2	2,6
ypTmic ypN0 M+ (PD)	2	2,6
ypT1 ypN0 (PR)	1	1,3
ypT2 ypN0 (PR)	8	10,5
ypT3 ypN0 (SD)	2	2,6
ypT3 ypN+(PD)	2	2,6
cT3 N+		
ypT0 ypN0 (CR)	5	6,6
ypTmic ypN0 (PR)	2	2,6
ypTmic ypN+ (SD)	2	2,6
ypT1 ypN0 (PR)	8	10,5
ypT1 ypN+ (PR)	2	2,6
ypT2 ypN0 (PR)	3	4,0
ypT2 ypN1 (PR)	1	1,3
ypT3 ypN+ (SD)	16	21,0
cT4 N0		
ypT0 ypN0 (CR)	1	1,3
ypTmic ypN0 (PR)	4	5,3
ypT3 ypN0 (PR)	1	1,3
cT4 N+		
ypT3 ypN0 (PR)	2	2,6

In Figure 5 a comparison is given between estimated DFS rates for patients with ypN0 and ypN+ status; a clear advantage is seen for ypN0 (estimated DFS at 5 years+/− standard deviation is 84.0%+/− 5.2% and 52.1%+/− 10.4% for ypN0 and

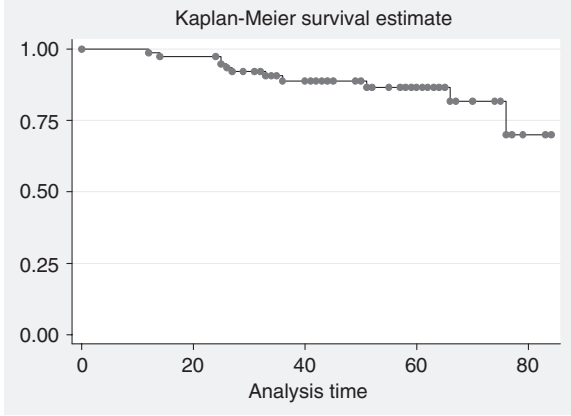

Figure 3. Kaplan-Meier OS estimates for all patients ($n=76$).

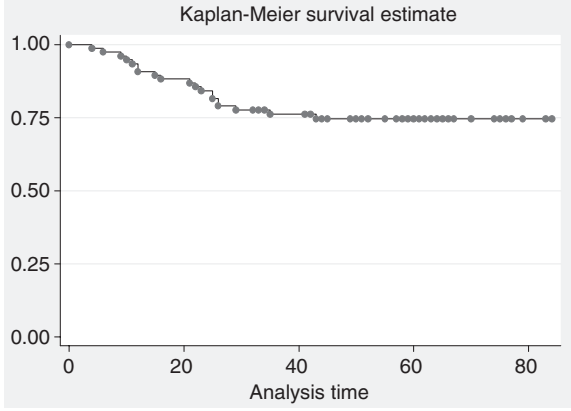

Figure 4. DFS estimates for all patients ($n=76$).

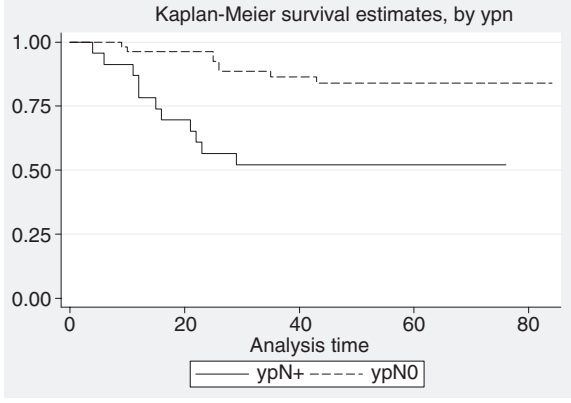

Figure 5. Comparison between DFS estimates for patients with ypN0 status ($n=53$) and patients with ypN+ status ($n=23$) (log-rank test: $p=0.0008$).

ypN+ patients, respectively) and it is statistically significant (log-rank test: $p = 0.0008$).

In Figure 6 we give a comparison between estimated DFS rates for pCR versus no pCR; also here a pCR yields a better DFS (94.4%+/− 5.4% and 68.3%+/− 6.2% estimated 5-year DFS+/− standard deviation for patients who achieved pCR and patients who did not), with statistical significance ($p = 0.03$).

Finally, a comparison between ypT0-2 and ypT3 patients is given in Figure 7, which shows an advantage for patients who achieved a ypT0-2 status (84.9%+/−4.9% and 52.2%+/−10.4% estimated 5-year DFS+/−standard deviation for ypT0-2 and ypT3 patients, respectively) ($p = 0.002$).

No patient missed the follow-up procedures. During the observation period, 11 out of 76 patients died (14.5%). Four patients (5.3%) developed a local recurrence, three of them together with distant metastases. Another 19 out of 76 patients (25%) had distant metastases during the follow-up period, so the whole number of patients with distant metastases was 22 out of 76 (29%).

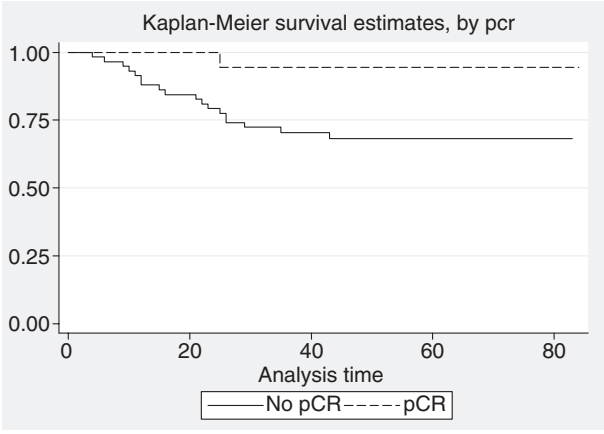

Figure 6. Comparison between DFS estimates for patients with pCR ($n = 18$) and patients with no pCR ($n = 58$) after neoadjuvant treatment (log-rank test: $p = 0.03$).

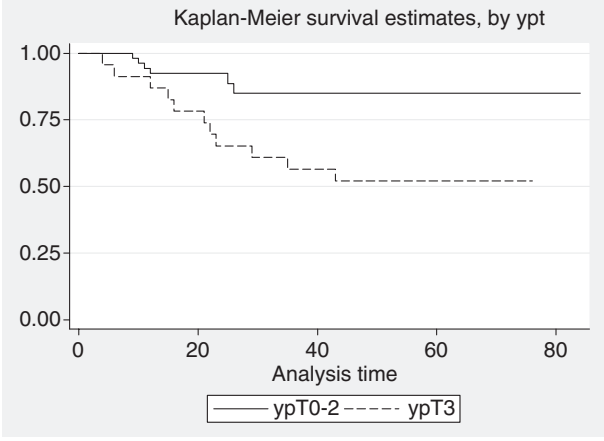

Figure 7. Comparison between DFS estimates for patients with ypT0-2 status ($n = 53$) and patients with ypT3 status ($n = 23$) after neoadjuvant treatment (log-rank test: $p = 0.002$).

Discussion

The rates of pCR after neoadjuvant treatment range from 15% to 25% in various series examined by Rödel in a recent review [13]. Larger series using CRT without HT have obtained rates of pCR of 8% ($n = 415$ patients) [37], 11.4% ($n = 375$ patients) [38], 16% ($n = 123$ patients) [39]. Another review [40] investigates the administration of neoadjuvant CRT with intensified chemotherapy, with the rationale that it can target potential micrometastases; pCR rates were 13–28% with 5FU or capecitabine plus OXA and radiotherapy doses of 45–50.4 Gy, 16–37% with 5FU or capecitabine plus irinotecan and the same doses of radiotherapy, 0–25% with 5FU or capecitabine plus molecularly targeted drugs (Cetuximab or Bevacizumab).

The rate of pCR (ypT0 ypN0) in our series (23.6%) was comparable to the ones of other series without HT; Rödel [20] achieved a 9% pCR with Xeloda-OXA (XELOX) and radiotherapy without cetuximab, but one should be cautious because this trial is not randomised. The pCR rates with XELOX and radiotherapy without cetuximab seem to be higher (nearly 15%) in two phase II trials [9,16]. In the EORTC Trial [27], pCR (pT0) was observed in 5.3% and 13.7% of patients in the radiotherapy and CRT arms, respectively; no significant difference was observed in terms of metastasis incidence at 5 years between the two arms (radiotherapy 38.2%; CRT 33.7%); in our series the incidence of metastases was 29% (22/76) in all our patients (follow-up period 24–83 months). However, the pCR rate is an early surrogate endpoint that may not necessarily translate into improved long-term outcomes [12]; in our series, among the 18 patients who had a pCR, no one developed a pelvic recurrence and only one patient had distant metastases. A French multi-centric phase II trial is ongoing, evaluating the effect of XELOX plus cetuximab plus radiotherapy followed by post-operative XELOX plus cetuximab in patients with locally advanced rectal cancer with synchronous operable metastases according to tumour molecular status.

Down-staging in our series was also a good predictor of outcome, as ypN0 and ypT0 – 2 patients had better DFS estimates than ypN+ and ypT3 ones; the data were statistically significant at log-rank test. These findings fit quite well with the ones of Rödel et al. [7], who had (among 385 patients) a DFS at 5

years of 86% for patients with tumour regression grade (TRG) 4 (pCR), 75% for TRG of 2–3 (PR) and 63% for TRG of 0-1 (SD); these differences were not statistically significant ($p = 0.11$). Also in our series, like in the one of Rödel [7], ypN positive was the strongest prognostic factor (log-rank test: $p = 0.0008$ in our series). Also, CRM status is a good predictor of prognosis [41]; in our series, all but six patients submitted to TME had negative CRM at pathological examination.

The benefits of the addition of chemotherapy to radiotherapy in a neoadjuvant setting are definitively demonstrated by a Cochrane metanalysis [42]. 5FU, when added to radiation, appears to enhance apoptotic response significantly in p53 mutant cells, which often exhibit increased radiation resistance. While the mechanism of 5FU and radiation interaction is not fully understood, the absence of a G1/S block in mutant p53 cells following radiation may allow cells to progress to S phase where 5FU may be incorporated into the DNA resulting in cell killing. Besides, weekly OXA administration potentially allows optimised inhibition of radiation-induced, sub-lethal DNA damage repair.

The rationale for addition of HT to 5FU has been reviewed in detail. Combination of low-dose long-exposure 5FU prior to 2 h of heating at 42°C lead to a ten-fold reduction in cell survival compared to either treatment alone; cell cycle analysis with flow cytometry demonstrates that the effect is likely due to an accumulation of cells in S-phase, which are known to be particularly sensitive to heat cytotoxicity [43,44]. These results provide a rationale for using 5FU as a continuous infusion in combination with HT. The effects of HT at various temperatures on intracellular uptake of 5FU and its conversion to active metabolites were also examined [45]; it was found that temperatures ranging from 39° to 42°C are effective in increasing the rate of intracellular uptake of 5FU (two- to five-fold increase in intracellular concentrations compared to 37°C); the greatest enhancement is seen at 39°C; rates of production of active metabolites are also enhanced by heating, again with the greatest effect at 39°C.

The efficacy of HT in the treatment of rectal cancer is still a matter of debate. The only randomised phase III trial is the Rotterdam one, which compared radiotherapy versus radiotherapy plus HT in 143 patients with rectal cancer, mostly with unresectable tumours [46]; the results were defined disappointing by the authors, and according to them this was due to the low doses of radiotherapy used (mean dose 56 Gy).

One important question about this study is whether intraluminal thermometry was sufficient or an invasive thermometry was needed. A reason for using invasive thermometry is the possibility of improving the temperature distribution or minimizing side effects by varying the adjustment parameters of the heating system. Nevertheless, invasive thermometry is expensive and represents a burden for the patient, with possible side effects or even complications, such as infections. Many surgeons are also sceptical about penetrating the tumour, particularly during preoperative treatment. Besides, in regional hyperthermia of the pelvis, various non-invasive endoluminal temperature measuring tracks are available, such as rectum, vagina, bladder, and urethra. In a paper published by the Berlin group [47], for pelvic tumours, the authors pointed out that invasive measurements can be replaced by minimally-invasive or non-invasive techniques, which provide equivalent or even more complete information.

We found a correlation (statistically significant) between some thermal parameters (T_{90} and T_{max}) and response to neoadjuvant treatment; for rectal cancer, this correlation has already been proved by the study of B. Rau et al. [29]. This relationship is also established for superficial tumours [48] and prostate cancer [49].

The percentage of sphincter preservation in our series was 73.7% (56 out of 76). Comparing this data with other series, in the German Rectal Cancer Trial (CAO/ARO/AIO-94) [37] the rate of sphincter-sparing surgery was 69% (286 out of 415 patients); in the Lyon R0-04 phase II trial [9], it was 62.5 (25 out of 40 patients); finally, in the EORTC Radiotherapy Group Trial 22921 [50], sphincter-sparing resection was performed in 255 patients who were assigned to preoperative radiotherapy (50.5%) and in 267 patients assigned to preoperative CRT (52.8%). About the studies with HT, in the one of Rau [29], conservative surgery was performed in 86.5% of patients (32 out of 36).

The results of our study were encouraging in terms of rate of pCR and conservative surgery. The good results of our study may be due not only to HT but also to the relatively high dose of radiotherapy delivered (60 Gy/30 fractions). The most important studies with preoperative CRT delivered a dose of 45 Gy/25 fractions [9, 27], or 50.4 Gy/28 fractions [37]. Despite the fact that some institutions are investigating dose-escalating chemotherapy schedules [8] or new biologic agents [18–23], regional HT in a preoperative setting should be considered in the new rectal-cancer trials.

Conclusion

Preoperative CRT combined with regional HT resulted in acceptable toxicity. Although pCR rates seem encouraging, the efficacy of adding HT to the neoadjuvant CRT on long-term outcome (especially

metastatic disease) is still to be determined in larger studies.

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