

Original Research Article

Phase I and II trial on infusional 5-fluorouracil and gefitinib in combination with preoperative radiotherapy in rectal cancer: 10-years median follow-up



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ABSTRACT

Purpose: The aim of this study is to evaluate the long term survival of the addition of gefitinib to chemoradiotherapy (CRT) in locally advanced rectal cancer (LARC).

Methods and materials: This previously published multicentre, open-label, phase I-II study, enrolled patients (pts) with LARC to receive CRT with concurrent 5-fluorouracil continuous intravenous infusion and a dose escalation of orally administered gefitinib, followed 6–8 weeks later by surgery. An intra-operative radiotherapy boost of 10 Gy was planned. Adjuvant chemotherapy was administered in ypN1–2 pts. After a median f/u of >10 years, we analyzed Local Control (LC), Metastasis Free Survival (MFS), Disease Free Survival (DFS), Disease Specific Survival (DSS) and Overall Survival (OS). Predictive endpoints of clinical outcomes were tested by univariate and multivariate analysis. Variables analyzed included: age, gefitinib dose and interruptions, adjuvant CT, surgery type, ypT, ypN, and TRG grade. We have also analyzed late toxicity according to CTCAEv4.

Results: Of the 41 initially enrolled pts, 39 were evaluable (27M, 12F). With a median f/u of 133 months, LC, MFS, DFS, OS and DSS at 5 years were 84%; 71%; 64%; 87% and 92%, respectively. The OS and DSS at 10 years were 61.5% and 76%, respectively. Grade 3–4 late toxicity occurred in 38% of pts: sexual (28.2%) and gastrointestinal toxicities (10.2%).

Conclusion: Long term outcomes and late toxicity were similar to previously reported series. The addition of gefitinib did not improve outcomes in LARC. Gefitinib is not recommended for rectal cancer patients who received 5-FU based preoperative CRT. Further studies may identify if gefitinib is beneficial in selected group of patients.

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Introduction

The standard treatment for locally advanced rectal cancer (LARC) includes neoadjuvant chemoradiotherapy (CRT) followed by total mesorectal excision (TME) surgery.

In contrast to surgery alone, preoperative CRT improves local control (LC) of the disease and tumor down-staging, while the

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results in terms of overall survival (OS) and distance recurrences are very similar to those for surgery alone [1]. Currently the incidence of local recurrence (LR) is less than 10% while distance recurrence rate is as high as 26–28%.

The standard preoperative CRT regimen includes 5-fluorouracil (5FU) based chemotherapy. In recent years various studies have been undertaken to evaluate whether the integration of new chemotherapy or biological drugs into the standard treatments leads to an improved overall pathological response or survival outcomes, specifically disease free survival (DFS), disease specific survival (DSS) and OS [2–7].

In 2002 we started a multi-center Phase I-II study to evaluate the effectiveness of addition of the anti-epidermal growth factor receptor (EGFR) molecule gefitinib to 5-FU and preoperative radiotherapy in LARC. Our previously published early results have shown a high level of pathological complete response (pCR) (31%). Overall, 51.5% of patients had a favorable endpoint in terms of tumor down-staging, while 41% showed grade 3 gastrointestinal, skin and genitourinary toxicity [8]. The aim of this study is to report the long term results, including OS, DSS, DFS, LC and Metastasis free survival (MFS).

Methods and materials

Study design and participants

The study was a multicenter, open-label phase I-II trial in patients with clinical Stage III rectal carcinoma. Details of the study design and methods were previously published [8]. Eligible patients were Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, aged 18 years or older, with histologically confirmed rectal adenocarcinoma, clinical stage cT2N1-2M0 cT3N0-2M0 as assessed by digital examination, pelvic computed tomographic scan or magnetic resonance imaging (MRI), liver ultrasonography, chest X-rays, and barium enema. Patients with positive lymph nodes outside the mesorectum and distant metastases were excluded.

Treatment

Radiotherapy was delivered with a minimum energy of 6 MV photons. Patients were positioned prone on the up down table [9] (home-made belly board) and planned with three-dimensional treatment planning using a standard three-field box technique. A total dose of 50.4 Gy (1.8 Gy per day, five times per week) was delivered in 28 fractions, corresponding to 38 days of treatment. The Clinical Target Volume (CTV) 2 including the tumor, the entire mesorectum, the internal iliac, and the obturator nodes received a dose of 45 Gy. The CTV1 including the tumor, the corresponding mesorectum, plus 2 cm superiorly and inferiorly received a boost of 5.4 Gy. An intraoperative radiotherapy boost (IORT) of 10 Gy was delivered to the tumor bed plus a minimum 1 cm margin. 5-FU was administered by continuous intravenous infusion during the entire radiotherapy treatment period (225 mg/m² per day, 7 days a week). Gefitinib was administered orally once daily, every day. The dose was 250 mg and 500 mg in the phase I component of the study (6 patients) with dose-escalation, and 500 mg in phase II of the study (33 patients). The phase I component of the study served to determine the maximum tolerated dose of gefitinib, and the phase II, to evaluate response to treatment. Following radiological local restaging with the same diagnostic examination of the initial staging, surgery was performed about 6–8 weeks after completion of CRT. The choice of surgical procedure was discussed in a multidisciplinary meeting, however the final decision was at the surgeon's discretion. All patients underwent a TME with a tem-

porary colostomy. Patients with pathologically positive lymph nodes received 6 cycles of adjuvant chemotherapy with 5-FU and folic acid according to De Gramont regimen [10].

Pathological response criteria

All resection specimens were examined using a standardized protocol that included TNM classification, number of examined and involved lymph nodes, and status of resection margins. According to this classification, R0 defines negative resection margins, R1 defines microscopic involvement of margins, and R2 gross residual tumor. The tumor pathological response was based on the ypTNM version 5 score and Tumor Regression Grade (TRG) Mandard score [11].

Follow-up

Follow-up was performed every three to four months for the first year, every six months for the following five years, and thereafter annually, to detect any possible recurrence and to measure late toxicity. At every follow-up visit, both a digital examination of the rectum and a carcinoembryonic antigen test were performed. A hepatic ultrasound and chest X-ray alternated to an abdomino-pelvic CT scan with iv contrast every 6 months in the first year and every year thereafter. In addition, patients underwent their first colonoscopy 6–12 months following the surgery and every 3–5 years thereafter.

We evaluated the late toxicity in all patients including: gastrointestinal, renal-urinary, sexual, skin, neurological, cardiac and general. Late adverse events were recorded at 1, 3, 5 and 10 years after surgery and graded according to Common Terminology Criteria for Adverse Events score version 4 (CTCAE v4) [12].

Statistical analysis

Outcomes in term of LC, MFS, DFS, OS, DSS, were calculated using Kaplan-Meier curves [13,14]. LC was calculated from the time of surgery to the time of local recurrence or, if negative, last follow up. MFS was calculated from the time of surgery to the time of distant relapse or, if negative, last follow-up. DFS was calculated from the date of surgery to the date of the first recurrence of the disease (local and/or distant) or, if negative, last follow-up. OS was calculated from the date of diagnosis to the date of the final follow up or death. DSS was calculated from the date of diagnosis and the date of death from cancer.

Univariate and multivariate analysis were performed to predict outcomes with the Cox proportional hazard method. The univariate analysis was used to select the relevant features and these were inserted into the multivariate analysis. The variables were age, gefitinib dose level, interruption of gefitinib, type of surgery, ypT, ypN, TRG, and adjuvant chemotherapy. Both in the univariate and in the multivariate model the covariates with $p < 0.05$ were considered to be statistically significant. The statistical significance of the Cox model was verified through Likelihood and Wald Test and the performance of the multivariate model by the Area Under the Curve (AUC) of the Receiver Operating Characteristic (ROC). The statistical analysis was carried out using R-3.2 statistical software.

Results

Between 2002 and 2005, 41 patients were enrolled, of which 39 were evaluable since 2 withdrew from the study early on. The distribution of age, gender, tumor stage and localization is shown in Table 1.

Table 1
Patients characteristics.

Characteristic	N (%)
Sex	
M	27 (69%)
F	12 (31%)
Age	
Median	63.7
Range	40–75
Tumor location [#]	
0–30 mm	17 (44%)
>30 mm	22 (56%)
TNM stage	
cT2N1M0	1 (2.5%)
cT3N0M0	8 (20.5%)
cT3N1M0	17 (43.5%)
cT3N2M0	13 (33.5%)

*Years.

[#] From anal-rectal ring.

As previously reported, 62% of patients required a dose reduction of gefitinib from 500 to 250 mg due to acute, grade 3 toxicity and 15% had to stop receiving the drug altogether due to persistent grade 3 toxicities including skin rash, diarrhea, and other gastrointestinal problems [8].

Stage ypT0/TRG1 was seen in 12 patients (31%); TRG 1–2 was confirmed in 18 patients (46%), ypN0 was seen in 32 patients (82%). Twelve (31%) patients achieved a pCR (ypT0 ypN0).

Twenty-seven (69%) patients underwent a sphincter-saving surgery. Adjuvant chemotherapy was administered to 12 patients (31%) according to De Gramont regimen. All patients completed the expected cycles.

Local recurrence occurred in 6 patients; LC was 84% (95% CI: 73.5%–97%) at both 5 and 10 years. No covariates were significantly correlated to LC.

Distant metastasis occurred in 12 patients; MFS was 71% (95% CI: 58%–87%) at both 5 and 10 years. Three patients with lung metastases underwent salvage thoracotomy and are currently alive. The factors that influence MFS at univariate analysis were: ypT, ypN, TRG, and adjuvant chemotherapy (Table 2); at the multivariate analysis the covariate that remained significant was adjuvant chemotherapy.

Adjuvant chemotherapy was associated with lower MFS (Fig. 1). The rate of 5 year MFS was 88.7%, in patients who didn't receive chemotherapy compared with 33% in those who received chemotherapy.

Overall recurrence of the disease (local and distant) was seen in 15 patients (38.5%). DFS was 63.6% (95% CI: 50%–80%) at both 5 and 10 years.

The covariates that influence DFS at univariate analysis were: ypT, ypN, TRG and adjuvant chemotherapy (table 2), while at the multivariate analysis there was no one that remain significant.

Table 2
Univariate analysis.

Variable	p value			
	OS	DSS	MFS	DFS
Age at diagnosis	0.0289	0.3042	0.6457	0.8826
TRG	0.0735	0.0227	0.0137	0.0375
ypT	0.1077	0.0255	0.0025	0.0025
ypN	0.0091	0.0007	0.0002	0.0022
Surgery	0.5472	0.706	0.9262	0.6457
Decrease dose Gefitinib	0.257	0.659	0.2954	0.6436
Interruption Gefitinib	0.1334	0.4907	0.3547	0.4928
Adjuvant chemotherapy	0.032	0.0071	0.0019	0.0157

Statistical significant values are in bold.

OS: overall survival, DSS: disease specific survival, MFS: metastases free survival, DFS: disease free survival, TRG: tumor regression grade.

With a median f/u of 133 months (range: 26–158), 16 (41%) patients died. Of these, 10 (26%) were cancer related. OS at 5 and 10 years was 87% (95% CI: 77%–98%) and 61.5% (95% CI: 48%–79%), respectively. DSS at 5 and 10 years was 92% (95% CI: 84%–100%) and 76% (95% CI: 63%–90%), respectively.

Significant covariates at univariate analysis for OS were: age at diagnosis, ypN and adjuvant chemotherapy (table 2); at multivariate model the covariates that remained significant were: age at diagnosis and adjuvant CT. The factors that influenced DSS at the univariate were: ypT, ypN, TRG and adjuvant chemotherapy, while at the multivariate the only covariate that remained significant was ypN. Again, adjuvant chemotherapy (CT) was associated with worse outcomes (OS, DSS, MFS and DFS), whereas ypN0 influenced them positively. Patients with ypN0 had better OS and above all exhibited a better disease-specific survival compared to patients with pathological positive lymph nodes.

At 5 years OS was 87.5% and 85.7% (p = ns) in ypN0 and ypN1–2 patients, respectively. However, at 10 years OS was 69% and 28.5% (p < 0.0001), in pN0 and ypN1–2 patients respectively (Fig. 2). Furthermore, the 5 years DSS was 93.7% and 85.7% in ypN0 and pN1–2 patients respectively (p = ns), whereas 10 year DSS was and 87% and 28.5% in ypN0 and ypN1–2 patients respectively, (p < 0.0001) (Fig. 3).

Late toxicity

The incidence of late toxicity of all grades was 74%. The most common late toxicities affected the gastrointestinal system (56%), the reproductive system (49%) and the urinary system (28%).

The incidence of late grade 3+ toxicity was 38%. The most common late grade 3+ toxicities affected the reproductive system (28.2%) and the gastrointestinal tract (10.2%) (Table 3).

Discussion

We report the long-term results of a phase I-II study of gefitinib plus CRT in LARC after 10 years follow-up. Our goal was to determine if the high pCR rate (31%) previously reported with this approach (8) was associated with improved long-term outcome.

The present study shows the following 10 year outcomes: 84% LC, 71% MFS, 64% DFS, 61.5% OS and 76% DSS. These results are comparable to those reported in literature although the follow-up in our series is longer [15].

Our trial has a number of limitations. First, the number of patients are limited and second, the absence of molecular analysis which was not routinely performed at that time. These two factors limit the power of our analysis regarding the long-term benefit of gefitinib when added to CRT as well as the ability to identify those patients who may benefit from the addition of biologic drug.

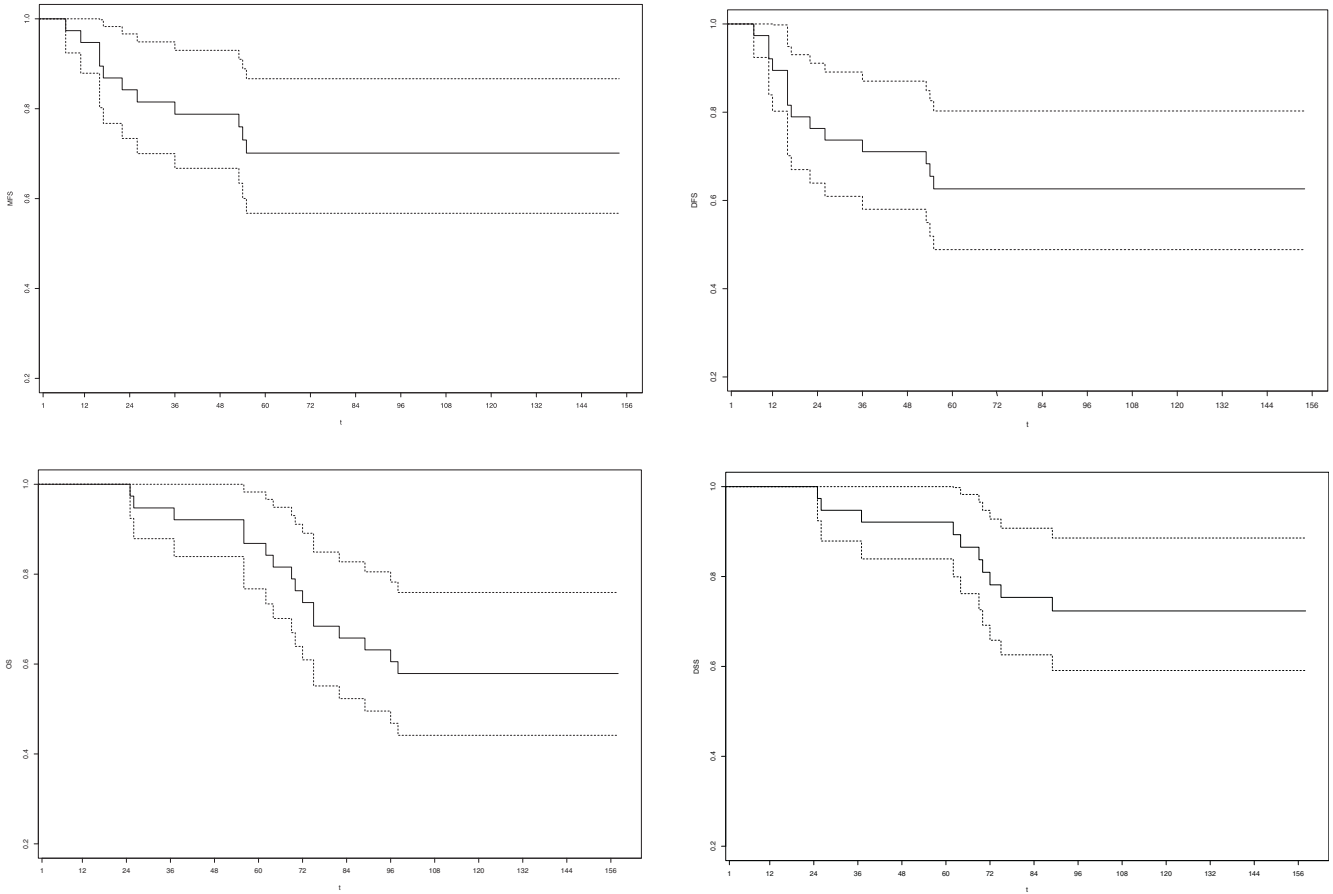


Fig. 1. Impact of adjuvant chemotherapy on MFS in months; discontinuous curve: patients who have made adjuvant chemotherapy; continuous curve: patients who have not made adjuvant chemotherapy.

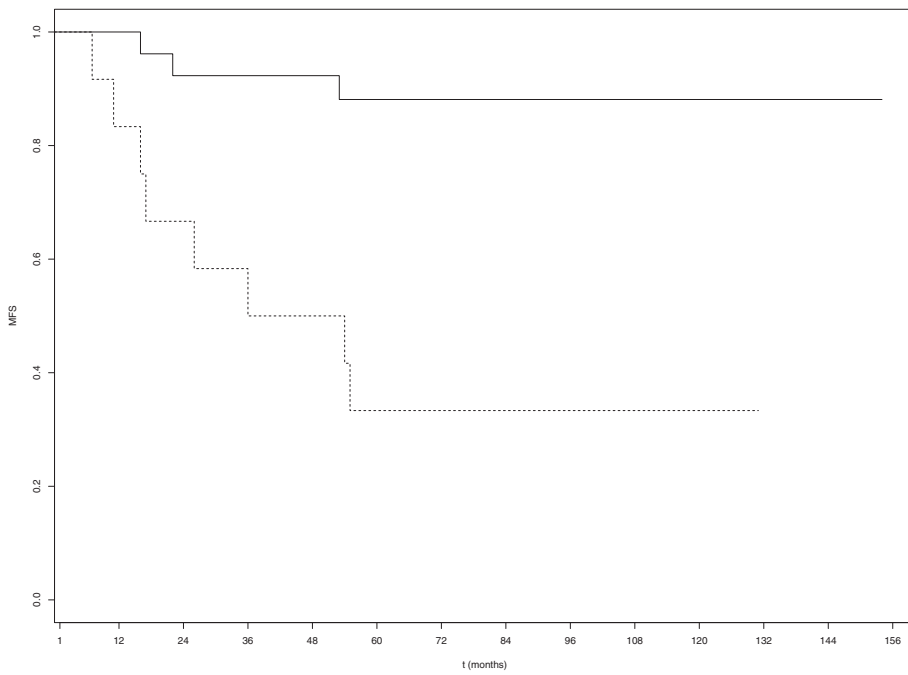


Fig. 2. Impact of ypN on OS in months; continuous curve: patients with ypN1-2; discontinuous curve: patients with ypN0.

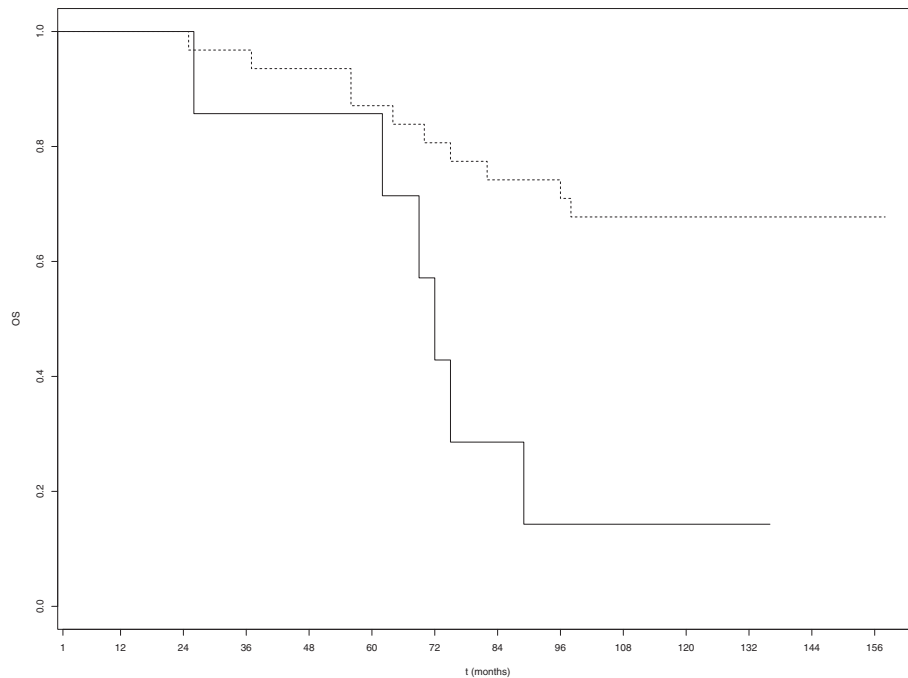


Fig. 3. Impact of ypN on DSS in months; continuous curve: patients with ypN1-2; discontinuous curve: patients with ypN0.

Table 3
Late toxicity.

Toxicity	Any Grade (%)	Grade > 3 (%)
Hematological	3 (7%)	0 (0%)
Gastrointestinal	22 (56%)	4 (10.2%)
Renal and urinary	11 (28%)	3 (7.7%)
Genital	19 (49%)	11 (28.2%)
Cutaneous	3 (7%)	0 (0%)
Neurological	1 (2.5%)	0 (0%)
Cardiac	1 (2.5%)	1 (2.5%)
General	10 (26%)	2 (5%)

However, this study does confirm that response to treatment as important prognosticator of most long-term outcomes. Specifically, the ypN stage predicted OS, DSS, MFS and DFS: ypN0 patients showed better outcomes compared to ypN+. In addition, tumor response measures, such as TRG and ypT affected DSS, MFS and DFS: patients with TRG 1-2 vs TRG 3-4 and also those with ypT0-2 vs ypT3-4 disease had better outcomes (Table 2).

These data suggest the importance of tumor down-staging and tumor response in order to improve survival outcomes. Intensification of systemic agents concomitant with radiotherapy is one of the strategies to increase tumor down-staging. The addition of molecular drugs to radiation is rationale given that EGFR inhibitors have demonstrated good results in colon cancer patients selected by a molecular profiles, and improve outcomes of radiotherapy in head and neck tumors [16,17]. From these observations, at that time, we decided to test a new anti-EGFR inhibitor as a radiosensitizer.

The high pCR rate (>30%) observed in our previous study is somewhat in contrast with clinical studies of other agents such as cetuximab when administered concomitant to CRT in LARC. The EXPERT-C Phase II randomized multi-center study, examining the addition of cetuximab to a capox-RT regimen, showed a significant increase in radiological response (capox-c 71% vs capox 51%, $p = 0.038$), however it did not translate into an increase of pCR (capox-c 11% vs capox 9%, $p = 1.0$) [18,19]. Similar results were

reported in a previous study comparing 5FU-based CRT versus the same regimen plus cetuximab from by Rodel et al. ($pCR = 9%$) [20]. The Authors attributed the negative results to the arrest of tumors cells in G1 when cells are less responsive to the effect of radiation therapy and anticancer drugs [21].

The high rate of pCR in our study, in contrast to other clinical studies using EGFR-inhibitors, may be related to the use of a different molecule: gefitinib a protein-kinase inhibitor is small molecule acting in the intracellular domain of the EGFR. This is only a theory and we do not have any other explanation to support this good result. Furthermore, there are no other clinical trials supporting our findings. There is phase I trial in which none of the 6 enrolled patients achieved a pCR [22]. Moreover the lack of molecular analysis, which was not common at the period of patient accrual, may have caused some bias in the patient selection.

The only data supporting our clinical finding is an in vitro study where gefitinib limited the proliferation rate of loVo cells surviving 5-FU and radiotherapy and increased their cytotoxicity [23].

In our long-term analysis, we also analyzed CTCAEv4 late toxicity. After 10 year follow-up, 30% of patients showed late grade 3+. The most common toxicities involved the gastrointestinal system (10.2%) and the reproductive system (28.2%). These toxicities may be a consequence of local treatment and are not related to systemic therapy, consistent with results of other studies [24–26]. For example, GI toxicity was primarily evacuation and continence problems rather than diarrhea. Surgery compromises the functions of the intestine due to the removal of rectum which acts as a reservoir. Moreover, preoperative radiotherapy increases fibrosis in the perirectal tissues and anal sphincter, decreases the capability of colon expansion and sphincter continence, causing an increase in involuntary release of feces and gas, which significantly compromises patients' quality of life.

Sexual problems are also very common following treatment for rectal cancer. In our experience 30% of all patients experienced G3+ sexual toxicity including the absence of ejaculation and/or erection problems. The erection dysfunction appeared immediately after surgery. Women rarely reported sexual problems since the

majority did not resume sexual activity after the diagnosis of rectal cancer. However, RT can cause irreversible vaginal dryness reducing sexual satisfaction.

Surgery, rather than radiation therapy, seems to be the main modality responsible of these disorders, while preoperative radiotherapy also contributes and increases the degree of dysfunction. Another important fact is that the sexual dysfunction appears to be irreversible. In our study 50% of patients experienced some degree of sexual toxicity.

The considerable late toxicity experienced by these patients combined with the fact that most of these long-term side effects are mainly attributable to surgery, leads to some important reflection. Patients who have a complete response to the CRT treatments could be, as various studies are now evaluating [27,28], candidates for conservative surgery or watch and wait policies. Both these approaches allow excellent sexual and gastro-intestinal functional results [27], however the good–excellent outcomes of this selected population of patients with complete response after CRT, need still to be confirmed with a longer follow-up of the ongoing and recently published studies [28].

The excellent rate of pCR of more than 30%, obtained in our study, may enhance the possibility of this subset of patients to avoid radical surgery and undergo a conservative approach. This would be associated with significantly less toxicity while still achieving good outcomes, given that TRG1-2 patients showed, in our analysis, excellent survival results (10 years DSS >90%).

In summary, this study suggests that the addition of gefitinib to standard treatment does not increase survival outcomes, which remain comparable to literature data. In contrast to cetuximab, the high rate of pCR with gefitinib may allow selection of patients for a less (or none) radical surgical approach reducing the late toxicity.

Assessing the molecular characteristics of this patient group may allow identification of a subgroup, which may benefit from the addition of gefitinib in future studies.

Disclosure

All authors individually contributed and approved the final article.

Conflicts of interest notification

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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