COLORECTAL CANCER: 10-YEAR RESULT OF A PERSONALIZED CARE AT THE PLATFORM OF ONCOLOGY

Joseba Rebollo MD, Pedro Bretcha MD, Manuel Sureda MD, Ignacio Azinovic MD, José Farre MD, Aurora Crespo MD, Ramón González-Manzano MD, Francisco García-Cases MD, Francisco José Fernández Morejón MD, Belén Valenzuela MD, Carlos Dussan MD, Rosa Cañón MD, Begoña Vázquez MD, Elena Martínez-Navarro MD, Francisco José Pena MD, Carmen Redal MD, Maritza Duarte MD, Nuria Javaloyes MD and Antonio Brugarolas MD.

Plataforma de Oncología, USP-Hospital San Jaime, Torrevieja, Alicante, Spain.

Corresponding author:

Joseba Rebollo, MD. Plataforma de Oncología. USP-Hospital San Jaime. c/ Partida la Loma s/n. 03184-Torrevieja, Alicante, Spain.
Phone number: 0031-966922313
Fax: 0031-966922441
E-mail: joseba.rebollo@usphospitales.com

Conception and design: Antonio Brugarolas, Joseba Rebollo

Provision of study materials or patients: Joseba Rebollo, Manuel Sureda, Ignacio Azinovic, José Farre, Aurora Crespo, Ramón González-Manzano, Francisco García-Cases, Francisco José Fernández -Morejón, Carlos Dussan, Rosa Cañón, Begoña Vázquez, Francisco José Pena, Carmen Redal, Maritza Duarte, Nuria Javaloyes.

Collection and assembly of data: Antonio Brugarolas, Joseba Rebollo

Data analysis and interpretation: Belén Valenzuela, Ramón González-Manzano, Elena Martínez-Navarro, Antonio Brugarolas, Joseba Rebollo

Manuscript writing: Antonio Brugarolas, Joseba Rebollo, Manuel Sureda.

Final approval of manuscript: Ignacio Azinovic, José Farre, Joseba Rebollo, Antonio Brugarolas

SUMMARY

PURPOSE: The Platform of Oncology is a multidisciplinary organization aimed to the integral diagnosis and treatment of cancer patients in a personalized manner. This report is the 10-year analysis of the outcome in patients with colorectal carcinoma (CRC).

MATERIALS AND METHODS: All unselected patients treated at the Platform of Oncology have been divided in three groups: Patients with localized CRC (group A), those with metastatic recurrent CRC (group B) and those with initially metastatic CRC (group C). All patients have been treated using standardized criteria with a personalized definition of patient and tumor characteristics to get the optimal clinical benefit. Survival has been calculated using the estimation method of Kaplan-Meier.

RESULTS: From September 2000, 209 consecutive patients have been treated. Sixty-eight patients in group A, 66 in group B and 82 in group C. Patients have had a median age of 69, 64.5 and 58 years. Patients had a high rate of severe co-morbidity in all subgroups. Median follow-up has been 81 months. **Group A:** There have been 6.9% stage I patients, 46.5% stage II, and 46.5% stage III. Median survival has not been reached and 73.5% of patients are currently alive without recurrence. Two patients (4.2%) that received adjuvant chemotherapy have been toxic deaths. **Group B:** After a median of 17 months of time to interval recurrence (most considered unresectable), were treated with chemotherapy (average regimens per patient including adjuvant, 3.1) and with other local consolidation and rescue techniques (average per patient 1.9). Estimated median survival has been 28 months since recurrence date. 66.7% have died from CRC and 6.1% were toxic deaths. **Group C:** The average chemotherapeutic regimens per patient have been 2.2 and average surgical and local techniques per patient were 2.1. Fifteen patients (18.3%) have received palliative chemotherapy only. Estimated median survival has been 27 months, with 65.9% of patient's dead from CRC and 8.5% toxic deaths. Overall, 13.4% of metastatic patients are alive without disease recurrence.

CONCLUSION: Despite the unfavorable characteristics of the patients (age, co-morbidities), clinical outcomes have been favorable. In a time in which personalized therapy is mandatory because of the genomic approach to tumor therapy, the interdisciplinary approach reveals itself as a major contributor to the individual cancer care approach and it might lead to an enhanced cure and survival rates.

INTRODUCTION

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in western countries (1).

CRC survival has improved during the last decades. Five-year survival rates in local CRC ranges from 30% to 80% depending on the tumor staging (2-8). In advanced CRC, median survival time has doubled from 11 months in the 90's to 23 months at present. This improvement is due to the addition of new active drugs, more aggressive salvage surgical procedures and a strict selection of patients in the trials.

Surgery, radiotherapy and chemotherapy are well-established therapeutic approaches (9-15). Newly developed procedures include minimally invasive approaches (laparoscopy)(16, 17), or salvage hepatic(18-23), lung (24) or peritoneal (with hyperthermic peritoneal chemotherapy, HIPEC) resections (25), as well as the use in combinations of target therapies such as anti-EGFR (26-28) and antiangiogenic drugs(29-31) are becoming widely implemented.

A number of other techniques are available in some specialized centers, such as intraoperative radiotherapy (IORT) (32-33) or hepatic intraarterial approach for chemotherapy (34) or radionuclide therapies (35).

The Oncology Platform at the USP-Hospital San Jaime begun to work with cancer patients in September 2000 with an integrated multispecialty organization centered in the patient, to provide a rapid implementation of the clinical and technological advances under a personalized program. It was proposed that this approach would offer the maximal benefit to each patient and therefore it might impact favorably on the survival.

This first 10-years results on the treatment of CRC patients treated at the Oncology Platform represents the proof-of-concept of this particular management strategy.

MATERIALS AND METHODS

Characteristics of the patients

The present study analyzes all patients included in the USP-Hospital San Jaime Platform of Oncology Tumor Registry from September 2000 to March 2010. There have been no exclusion criteria.

The whole group of CRC patients have been divided in three groups: Patients with localized CRC (Group A), patients with recurrent metastatic CRC after therapy for localized cancer (i.e. with a free disease interval) (Group B) and patients with initially metastatic CRC (Group C).

All patients have been studied and treated according to standardized criteria. However, every patient has received a personalized therapy in order to obtain the maximal therapeutic benefit.

Therapeutic methods

Treatments have evolved during the 10 years of the study due to the appearance of new drugs and also the development of new procedures.

Systemic therapy has included the combination of all active drugs available, including Fluorouracil or analogs (capecitabine, UFT), Oxaliplatin, Irinotecan, Mitomycin C, Raltitrexed, Pemetrexed, as well as monoclonal antibodies such as Cetuximab, Panitumomab and Bevacizumab. Bevacizumab has been omitted when a surgical procedure was considered as a consolidation procedure. Chemotherapy has been administered occasionally by hepatic intraarterial approach.

UGT1A polymorphisms related to Irinotecan pharmacogenomics, and sequencing of k-ras to select anti-EGFR monoclonal therapies has been determined systematically when the techniques became available. Pharmacokinetically-guided dosing of drugs also became a routine when available. Finally, some patients with high-risk of disease recurrence (completely eradicated macroscopic disease after successful therapy) have been treated with Interleukin-2 and Retinoic Acid according to the protocol described by Dr F. Recchia (36).

Tumor resection has been performed according to standardized criteria. When possible, minimal invasive (laparoscopic) and sphincter sparing procedures have been selected. If appropriate, as a part of multimodal program, salvage surgery has been done, including lung and hepatic (with or without radiofrequency ablation) resection of metastases and abdomino-pelvic surgery, hyperthermic peritoneal chemotherapy (HIPEC) after peritoneal cytoreductive surgery as described by P Sugarbaker (25).

To increase loco-regional tumor control or to increase resectability of the tumor, surgery has been combined with radiotherapy (preoperative, postoperative or intraoperative), when indicated, technically feasible and tolerable. In a few patients palliative radiotherapy was also administered.

A number of other techniques have been used in some situations, like hepatic embolization with Yttrium^{90} charged microspheres (SYR-Spheres), Photodynamic therapy with Photofrin, and transarterial chemoembolization (TACE) with irinotecan-eluted beads, representing very few procedures in these series.

Statistical analysis

Chi-square test has been used to compare frequencies. Overall survival has been calculated using Kaplan-Meier estimation from diagnosis (Groups A and B) and from recurrence date (Groups B and C) to death or last follow up. Disease free interval (Group B) has been estimated from the end of local therapy to recurrence date.

Since the goal of the study is to evaluate the survival impact of personalized multimodal therapy in patients with CRC, no single therapies have been analyzed.

In order to evaluate the impact of salvage multimodality programs on survival, a ‘clinical benefit’ concept has been introduced and it is defined as a time interval longer than 12 months from the beginning of an interdisciplinary treatment until the next episode of progression of the disease in patients with metastatic CRC (Groups B and C).

RESULTS

A total of 209 patients with CRC have been treated at the Platform of Oncology from September 2000 to March 2010. Additionally, during this period 36 patients have been referred for surgical resection only and 82 patients have been referred for adjuvant Radiotherapy (preoperative or postoperative) only. These 118 patients have not been included in the analysis, because these patients continued follow up and therapy in their referral centers.

Median follow up of the whole series of 209 patients has been 81 months, with 129 out of 209 (61.7%) followed up more than five years, 38.3% less than five years and 8.6% less than two years.

Local CRC group (Group A)

Sixty eight patients are included in this group (Table 1). Median age has been 69 years (range 24-79 years), with 35.3% of patients older than 70 years. Table shows sex and age distribution, the place of origin as well as the co-morbidity of the patients, with an associated pathology present in 64.7% of the patients (considered severe in 42.6%).

In table 2, location, and staging of the tumors in this groups are shown. Rectal location was present in 36.7% (7 patients had the tumor less than 5 cm form de anal margin). Stage I had 6.9% of patients, 46.5% had stage II and 46.5% stage III. Ten patients with rectal cancer were considered to have an incomplete pathological tumor staging due to down staging after preoperative chemo-radiotherapy.

In table 3, the type of surgical resection is shown. In addition, some special techniques have been used such as laparoscopic resection in 6 patients. Intraoperative radiotherapy was given in 2 patients. Multiple organ resections were needed because of locally advanced tumors in 3 patients. Seventeen patients were treated preoperatively with concomitant chemotherapy and radiotherapy.

Twenty one patients (30.9%) did not receive adjuvant chemotherapy (Table 4) because of tumor stage or location, age of the patients or because of the patients' preferences. Five of the untreated patients (23.8%) have had tumor recurrence and three have died because of CRC, while two patients have been surgically rescued. On the other hand, 47 patients (69.1%) have been treated with adjuvant chemotherapy. Almost half of the regimens have been single drug therapy 5-Fluorouracil or analogs, while 27.6% received fluoropyrimidines in combination with Oxaliplatin or Irinotecan and an additional 27.6% were treated with a combination of all of them (FLOFOXIRI). Toxic deaths occurred in 2 patients.

Estimated median overall survival (Kaplan-Meier method) is above 52 months (figure 1, Table 5), with 50 patients (73.5%) alive free of recurrence, 31 of them with a longer than 5-years survival, and 1 patient alive with disease. Five patients (17.4%) have died because of disease and 4 patients have died because a second primary cancer. There are 6 patients (8.8%) lost to follow up.

Metastatic CRC "with interval" group (Group B)

Sixty six patients are included in this group. Seven patients belonged to the Group A and were included in Group B because of metastatic recurrence. The rest of patients have been initially treated elsewhere.

Tables 1and 2 show the characteristics of the patients and their tumors. Median age was 64.5 years with 22.7% older than 70 years. Forty two patients (63.6%) had a concomitant pathology that could be considered severe in 14 (21.1%). A lower proportion of patients lived close to the hospital compared to those of the group A.

Thirty one patients (47%) had had rectal primaries, and 20.9% had had stage III primary tumors. Median interval time to recurrence has been 17 months. Twenty three patients (43.8%) had not received adjuvant chemotherapy and their median interval time to recurrence has been 16 months (range 3 to 20 months), most of them (65.2%) with less than 18 months interval and only six patients with an interval longer than 2 years. In the other hand 43 patients (65.2%) had received adjuvant chemotherapy and their median interval time to recurrence has been 20 months (range 3 to 56 months), 48.8% of patients with an interval shorter than 18 months and 39.5% longer than 2 years.

One organ site recurrence was present in 68.1% of patients: Peritoneal cavity and pelvis in 31.8% of patients, liver in 19.7% and lung in 13.6% of patients. Most of the hepatic (53.8%) and lung recurrences (77.7%) were considered unresectable. Multiple sites of recurrence (M1b) have occurred in 31.8% of the patients.

The initial surgical procedures before the recurrence are shown in Table 3.

The initial therapy for recurrent metastatic disease has usually been chemotherapy and, in cases of favorable clinical response, a consolidation or salvage treatment has been considered. The table also shows different chemotherapy regimens employed. Usually a doublet combination (FOLFOX or FOLFIRI or similar) has been used in 90.9% of patients, and a triplet combination (FOLFOXIRI) in 39.4% of patients. Salvage combination chemotherapy with Irinotecan, Mitomycin C and Raltitrexed combination has been used in 24.2%. A significant number of patients (42.4%) have been treated with monoclonal antibodies added to chemotherapy. Bevacizumab has been avoided in case of a programmed salvage surgery after response to chemotherapy.

When available, UGT1A polymorphisms were studied and pharmacokinetically-guided chemotherapy was used to adjust drug dosing.

A total of 202 systemic chemotherapy regimens have been administered. It represents an average of 3.1 regimens per patient. The initial adjuvant chemotherapy is included in these series to have a better definition of the complete approach.

In addition 127 localized procedures have also been used: Salvage pelvic resection in 22.7% of patients, hepatic resection (with or without Radiofrequency ablation) in 30.3%, lung resection in 20.2%, and radical peritonectomy plus HIPEC in 7.6% of patients. External beam radiotherapy has been used in 39.4% of patients and intraoperative radiotherapy in 6%. The total number of procedures has been 127, an average of 1.9 procedures per patient.

Estimated median overall survivals have been 47.5 and 28 months since diagnosis and recurrence dates, respectively. Eighteen patients (29%) have not had therapeutic benefit while 66.7% had a therapeutic benefit, with median survivals of 12 and 32 months, respectively. Furthermore, only 33.4% of patients without therapeutic benefit have had the opportunity of salvage surgery, compared to 79.5% of patients with therapeutic benefit. Seven patients (10.6%) are alive free of disease, 31 to 108 months of survival, and two patients alive with disease 35 and 39 months since recurrence date. Four patients (6.1%) have had toxic death, 66.7% died because of CRC and 6.1% because of a second malignancy. Seven patients (10.6%) were lost to follow up.

Initial metastatic CRC group (Group C).

Eighty-two patients have been included in this group (Table 1). Median age was 58 years (range 29 to 77 years), with only 2.4% of patients older than 70 years. The highest proportion of patients with a residency far from the hospital appears in this group. Table also shows the concomitant pathology that was present in 63.4% of patients (severe in 13.4%).

Primary cancer characteristics are shown in Table 2. Fifty-seven patients (69.5%) had single organ metastasis: peritoneal in 25.6%, liver in 37.8%, and lung in 6.1%. Multiple organ recurrence occurred in 25 patients (30.5%). Patients considered potentially resectable were 63.1% in liver disease and 33.3% of patients with lung disease.

Patients were initially treated with chemotherapy (Table 3), most commonly with FOLFOXIRI regimen (50%) or Irinotecan, Mitomycin C, Raltitrexed combination in 31.7%. Doublets such as FOLFOX or FOLFIRI have been used in 35.4% and 17.1% of patients, respectively, and monoclonal antibodies in combination with chemotherapy in 35.4%. Hepatic intra-arterial chemotherapy, before or after hepatic surgery, has been used in 23.2% of patients. Finally, 17.1% of patients have received immunotherapy after optimal eradication of macroscopic disease. Total number of regimens has been 183, an average of 2.2 regimens per patient.

In case of a favorable response to induction chemotherapy, salvage surgery of primary and metastatic disease has been considered. Preoperative radiotherapy has been added to chemotherapy in primary rectal cancer or locally advanced unresectable primary colon tumors.

Salvage resection of metastatic cancer in the liver, with or without Radiofrequency ablation, has been performed in 43.9% of patients, lung salvage surgery in 28% and peritonectomy with HIPEC in 20.7%. Total number of procedures has been 171, an average of 2.1 procedures per patient.

Forty-nine patients (65.3%) have shown clinical benefit (Table 5) and their estimated median overall survival has been 40 months, while 34.7% of patients have not shown the benefit and their median overall survival has been 14 months.

Multimodality salvage program has been used in 61.5% of patients that did not achieve clinical benefit, while has been used in 85.7% of patients with benefit. On the other hand, palliative chemotherapy as a single treatment modality was used in 34.6% of patients in the former group compared to only 12.2% of patients in the latter group.

There are 11 patients (13.4%) alive without any evidence of disease between 16+ and 116+ months of follow up and 3 additional patients (3.7%) alive with disease. Toxic deaths have been 8.5%, 7 patients (8.5%) were lost to follow up and 65.9% have died of CRC.

Median estimated survival of the Group C is 27 months (range 2 to 120 months). Figure 2 shows the estimated survivals of metastatic CRC groups (Groups B and C), which do not show statistically significant differences.

DISCUSSION

This report evaluates the 10-year analysis of the outcome of CRC patients treated in the Platform of Oncology to evaluate the effect on survival of a multidisciplinary personalized approach.

CRC patients have been divided in three groups according to the usual presentation of the disease in an oncology unit: localized CRC (Group A), interval recurrent metastatic CRC (Group B) and initially metastatic (Group C). The series presented in this report include all treated patients and therefore include unselected patients, with unfavorable prognostic factors such as advanced age, high co-morbidity rate in the medical history, and second malignancies.

The referral pattern confirms this aspect and indicates that the distance from the patient residence to the hospital varied according to the severity of the prognosis. In the localized CRC a home distance of more than 100 Km was observed in 13.3% of the patients, while in the interval metastatic CRC this figure was 31.8% and in simultaneously metastatic CRC it was 46.4%.

Similarly, the co-morbidity pattern rate for severe concurrent and associated past medical illnesses in these series is elevated, ranging from 42.6% in localized CRC, mainly related to the old age of this group, to 21.1% and 13.4% in the interval and synchronous metastatic series which contain younger patients. In most phase II-III studies co-morbidities are considered exclusion criteria. These results suggest that CRC patients are frequently affected by interacting chronic diseases and this population is often misrepresented in the published clinical trials.

Another interesting finding in these series is the high incidence of multiple adenomatous polyps, second CRC diagnosis and familial syndromes (Lynch, HNPCC, FAP), as a ’field cancerization effect’. This indicates the need for well designed follow-up studies to detect a second or third CRC during the lifetime period of the patient cured from CRC.

In the other hand the incidence of second non-CRC primaries has also been very high in these series. In the localized CRC series there were 14 patients with multiple cancer including breast (4), H&N (3), prostate (4), NSCLC (2), pancreas (1), sarcoma (1) and endometrial cancer 1. In the interval metastatic patients second non-CRC cancers were present in 8 patients including breast (1), prostate (2), urinary bladder (1), seminoma (1), parotid gland cancer (1), melanoma (1) and medullary tumor of the thyroid (1). Finally in the series of simultaneous metastatic CRC the presence of multiple non-CRC neoplasias occurred in 6 patients, including breast cancer (3), cervix cancer (2) and NHL (1). The spectrum of second cancer shown in these series indicate that in addition to a familial genetic or environmental risk profile, it might also exist a general cancer

syndrome in which the presence of a prior cancer history is by itself a risk for a subsequent diagnosis of a second primary tumor.

These series confirm that CRC is a heterogeneous disease with different outcomes reflecting in survival curves that stabilize only after a 10 year interval, requiring a prolonged follow-up. A 5 year recurrence free interval is usually considered a hall mark of cure, but recent series indicate the need of a more prolonged follow up as a result of better adjuvant therapies which may modify the course of the disease.

Personalized care is reflected in the variety of the procedures. Conservative surgical procedures include efforts for sphincter preservation, laparoscopic excisions, preoperative chemo-radiotherapy and other rescue surgical approaches after an effective systemic therapy. The patients are willing to participate in the decision of the therapeutic plan and indicate always the preferences when different alternatives are considered. As a consequence the Miles abdominoperineal resection rate (9%) is very low. At the same time multiorgan resection due to local abdominal extension of the disease was performed in 4.4% of the patients. Availability of the different techniques is a condition necessary for a personalized care and possibly a limitation to highly specialized units.

For localized CRC the cure rate has been very high, even in presence of metastatic regional disease. The results of these series support curative surgery, even in the presence of health related problems or advancing age. Adjuvant chemotherapy has been avoided in 30% of local CRC patients due to patients' preferences, stage II disease and advanced age, but the recurrence rate has been 23% in this group of untreated patients. In the other hand recurrence rate have been low (4%) in treated patients in spite that they had more adverse factors. The availability of less aggressive chemotherapies (i.e. oral UFT) makes possible the administration of adjuvant therapy to virtually every patient and therefore is also strongly recommended. With a commensurate adjuvant chemotherapy, including combination chemotherapy programs in high risk extensive nodal disease excellent survival rates are obtained. In this report, the 73.5% free of recurrence survival for all locoregional CRC (group A series) obtained compare favorably with the expected results of the SEER data for a more limited disease stages (2, 3).

The distinction of metastatic patients in two different groups according to the presentation interval from the primary tumor until the development of metastasis as done in this report indicate differences in age of presentation, family history of disease, and spread of the disease, but the survival curves from the diagnosis of metastatic disease are remarkably similar. For this reason it appears to be acceptable to include metastatic patients with and without interval diagnosis in advanced stage clinical trials.

The series of interval metastasis show that administration of adjuvant chemotherapy correlate with disease free survival. Median free recurrence intervals have been 16 months and 20 months, and 2-year disease free survival 26% and 39% respectively, for patients with and without adjuvant chemotherapy. In the interval group median overall survival has been 41.5 months from diagnostic date and 28 months from recurrence with a median disease free interval of 17 months.

In advanced unresectable disease the choice of chemotherapy might depend on the projected salvage procedure in case that a conversion to resectable disease occurs after presenting a response to chemotherapy. In this case chemotherapy is selected towards obtaining maximal activity and tolerable toxicity, avoiding drugs such Bevacizumab when surgery is planned as a consolidation therapy. In the other hand, if palliation is the goal the emphasis should be on maximal tolerance and prolongation of progression free survival, and the less aggressive protocols are preferred.

Advanced stage Phase III trials, based in a strict patient selection criteria, project the results of single or at the most double modality therapies but fail to introduce personalized interdisciplinary protocols involving different approaches for residual or metastatic disease. In these cases interdisciplinary approach is contemplated as exceptional means, probably unavoidable, very difficult to evaluate.

From this point of view the evaluation of these series is very complex because there are no exclusions and the hallmark of the Platform of Oncology is precisely to find the best therapeutic option introducing in each patient the possibility of a salvage individualized program.

During study period of 10 years a number of relevant therapeutic advances have occurred. Most relevant ones are based on genomics (k-ras mutation for the treatment with Cetuximab or Panitumomab), UGT1A1 polymorphisms for the treatment with Irinotecan, gene-based predictors of response (Tymidylate synthase), pharmacokinetically-based drug dosing(for Oxaliplatin, Irinotecan and 5-Fluorouracil), new drug combinations or biological therapies such as Retinoic acid and Interleukin-2 combination. The application of these therapeutic advances has been gradual and can not be assessed in this report, owing to a more detailed analysis. The addition of monoclonal antibodies, which has been associated with a significant prolongation of survival in metastatic patients, had a small influence in the results observed because it occurred in the last 3 years of the analyzed period of time.

The number of local procedures in the series of metastatic patients averaged 1.9 and 2.1 per patient, respectively in the interval and simultaneous metastatic CRC. The total number of procedures is higher in the interval metastatic group because all of the initial surgery (with additional radiotherapy in certain cases) for the treatment of the primary tumor, while in the simultaneous metastatic group the resection of the primary tumor was frequently performed together with the metastatic rescue procedure.

Similarly, the average of systemic therapies ranged from 3.1 to 2.2 respectively for interval and simultaneous metastases, also reflecting the initial adjuvant therapy.

Most of the primary tumors in the initially metastatic group have been resected (92.7%) as a component of a multidisciplinary program that has been included an effective chemotherapy regimen, and the possibility of a consolidation treatment with surgery and radiotherapy. Some of the multidisciplinary approaches used are available in most centers but a number of techniques such as IORT, hepatic intraarterial chemotherapy, surgery and radiofrequency ablation of metastases, and peritonectomy with HIPEC are available in some specialized centers with experienced and integrated teams.

For the metastatic groups (groups B and C) a new concept of therapeutic benefit (more than 12 months interval between consecutive progression episodes) has been created in order to evaluate the impact of a combined interdisciplinary program of induction chemotherapy followed by a locoregional consolidation approach. According to this definition one third of metastatic patients do not benefit from therapy and two thirds of patients benefit with a prolonged survival. These figures indicate a need for further progress in systemic therapy.

Median overall survivals of metastatic CRC groups have been 27 months, 3 to 5 months above that currently achieved with the advent of active systemic therapies, and it is possibly due to the contribution of loco-regional consolidation therapies. In addition, 18 patients in groups B and C are alive free of recurrence, 5 of them less than five years and 9 patients more than 5 years of follow up. Five of these patients had initially a potentially resectable recurrent disease, i.e. less than 5 lung or hepatic metastases, while 14 patients had multiorgan unresectable recurrences. Potential curability has been 12.2%, a modest but solid contribution of the personalized multidisciplinary therapy. Interdisciplinarity probably contributed to the results obtained by personalizing surgical and locoregional techniques, performing wide organ resections and offering additional adjuvant radiotherapy and or chemotherapy according to the tumor and patient risk characteristics.

The small but consistent long term survivor rate in the range of 12% in the metastatic series attest to the efficacy of current salvage interdisciplinary approaches in advanced CRC.

Toxic death rate has been 6.1% in group B and 6.5% in group C, higher than expected for current chemotherapy and surgical procedures, and definitely occurring as a result of the multimodality approach. Although these figures are unsatisfactory, nutritional, infectious or vascular complications make a baseline 5% toxic death rate almost unavoidable in this patient population and for this reason the final overall 6.3% toxic death rate can be considered acceptable in this unselected patient series. In these series toxic deaths have been of cardiopulmonary origin (3 patients), postoperative complications (4 patients) and neutropenic sepsis (6 patients).

In a time in which personalized therapy is mandatory because of the genomic approach to tumor therapy, the interdisciplinary approach reveals itself as a major contributor to the individual cancer care approach and it might lead to an enhanced cure and survival rates.

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Table 1. Characteristics of the patients

		Group A	Group B	Group C
Total		68 (100%)	66 (100%)	82 (100%)
Sex Male		46 (67.6%)	35 (52.3%)	44 (53.7%)
Female		22 (32.4%)	31 (47.7%)	38 (46.3%)
Age Median (range)				
Global		69 (24-79)	64.5(24-81)	58 (29-77)
Male		70 (24-78)	66 (24-81)	59.5 (29-77)
Female		59 (33-79)	58 (32-77)	57 (34-74)
>70 y		24 (35.3%)	15 (22.7%)	2 (2.4%)
Place of origin				
<100 km		59 (86.7%)	45 (68.2%)	44 (53.7%)
>100km		9 (13.2%)	21 (31.8%)	38 (46.3%)
Metabolic syndrome		14 (20.6%)	8 (12.1%)	28 (34.1%)
Cardiopathy	Acute MI	2 (2.9%)	3 (4.5%)	5 (6.1%)
	Arrhythmia	6 (8.8%)	1 (1.5%)	-
Stroke		4 (5.9%)	1 (1.5%)	1 (1.2%)
Severe vascular disease (by-pass, resected aneurysm)		2 (2.9%)	2 (3%)	4 (4.9%)
Severe arthrosis, Ankylosing spondylitis		7 (10.3%)	5 (7.6%)	-
Severe chronic renal disease (dialysis)		-	3 (4.5%)	1 (1.2%)
Hepatic disease: CVH, BVH, alcohol		3 (4.4%)	2 (3%)	3 (3.7%)
Chronic obstructive lung disease		-	1 (1.5%)	-
ASA/NSAI Allergy		-	-	6 (7.3%)
Psychotic depression/Alzheimer		2 (2.9%)	2 (3%)	2 (2.4%)
Hirschprung disease /previous colectomy		-	-	1 (1.2%)
Endometriosis (blocked pelvis)		-	-	1 (1.2%)
Autoimmune disorders		-	-	3 (3.7%)
Gastritis (gastrectomy)		-	-	5 (6.1%)
Others*		-	-	5 (6.1%)
FAP/CRC family history		-	2 (3%)	6 (7.3%)
Multiple dysplastic polyps		2 (2.9%)	2 (3%)	3 (3.7%)
Second primary CRC		1 (1.5%)	2 (3%)	4 (4.9%)
Second cancer		9 (13.2%)	8 (12.1%)	6 (7.3%)
Triple cancer		5 (7.4%)	1 (1.5%)	-
Unconfirmed metastases (PET, CT)		3 (4.4%)	-	-
Total associated pathology		44/68 (64,7%)	42/66 (63.6%)	52/82 (63.4%)
Severe pathology		29/68 (42,6%)	14/66 (21.1%)	11/82 (13.4%)
Mild/moderate pathology		15/68 (22,1%)	28/66 (42.4%)	41/82 (50%)
No associated disease		24/68 (35.3%)	24/66 (36.4%)	24/82 (29.3%)

Table 2. Characteristics of tumors.

		Group A	Group B	Group C
LOCATION	Rectal	25 (36.7%)	31 (47%)	18 (22%)
	< 5 cm	7 (28%)	7 (32.2%)	2 (11.1%)
	Sigma	20 (29.4%)	21(31.8%)	26 (31.7%)
	Left colon	8 (11.8%)	7 (10.6%)	12 (14.6%)
	Right colon	14 (20.6%)	7 (10.6%)	22 (26.8%)
	Multiple	1 (1.5%)	-	-
	Oculto	-	-	1 (1.2%)
TNM	T x	10 (14.7%)	10 (15.1%)	20 (24.3%)
	T1	1 (1.5%)	-	-
	T2	6 (8.8%)	10 (15.1%)	-
	T3	40 (58.8%)	36 (54.5%)	36 (43.9%)
	T4	11 (16.2%)	10 (15.1%)	26 (31.7%)
	Nx	9 (13.2%)	10 (15.1%)	33 (40.2%)
	N0	32 (47.1%)	28 (42.4%)	9 (10.9%)
	N1	18 (26.5%)	14 (21.2%)	10 (12.2%)
	N2	9 (13.2%)	14 (21.2%)	30 (36.6%)
STAGING (PRIMARY TUMOR)	Rectal cancer (incomplete)	10 (14.7%)	12 (18.2%)	-
	Stage I	4 (6.9%)	9 (16.3%)	-
	Stage IIa	21 (36.2%)	15 (27.3%)	-
	Stage IIb	6 (10.3%)	2 (3.6%)	-
	Stage IIIa	3 (5.2%)	-	-
	Stage IIIb	18 (31%)	15 (27.3%)	-
	Stage IIIc	6 (10.3%)	13 (23.6%)	-
TIME TO RECURRENCE (Group B)	Median 17 m	-		
No adjuvant Chemotherapy	Median 16 m (r 3-20)	-		
N 23 (34.8%)	Interval < 12 m	-	7 (30.4%)	-
Adjuvant chemotherapy	Median 20 m (r 3-56)	-		
N 43 (65.2%)	Interval < 12 m	-	15 (34.9%)	-
Chemotherapy regimens	5FU/Analog	-	28 (42.5%)	-
	2 agents*	-	9 (13.6%)	-
	3 agents**	-	6 9.1%)	-
METASTATIC SITES		-		
Liver (<5/>5 = 6/7)		-	13 (19.7%)	31 (37.8%)
Lung (<5/>5 = 2/7)		-	9 (13.6%)	5 (6.1%)
Abdomen/peritoneum		-	23 (34.8%)	21 (25.6%)
Multiple (M1b)		-	21 (31.8%)	25 (30.5%)

*FU-Ox or similar

**FU-Ox-Iri

Table 3. Therapeutic procedures.

	Group A	Group B	Group C
SURGICAL PROCEDURES			
Anterior resection and t-t anastomoses	35 (51.4%)	39 (59.1%)	32 (39%)
Abdomino-perineal resection	7 (10.3%)	8 (12.1%)	5 (6.1%)
Left hemicolectomy	10 (14.7%)	11 (16.7%)	15 (18.3%)
Rigt hemicolectomy	14 (20.6%)	6 (9.1%)	21 (25.6%)
Subtotal colectomy	2 (2.9%)	1 (1.5%)	3 (3.7%)
Not operated	-	1 (1.5%)	6 (7.3%)
ASSOCIATED TECHNIQUES			
Laparoscopic resection	6 (8.9%)	2 (3.1%)	4 (4.9%)
Intraoperative radiotherapy	2 (2.9%)	-	1 (1.2%)
Multiple organ resection (T4)*	3 (4.4%)	4 (6.1%)	10 (12.2%)
Neodjuvant chemotherapy (QT+RT)	17 (25%)	8 (12.1%)	-
Adjuvant Therapy	-	4 (6.1%)	-
ADDITIONAL PROCEDURES			
Fistula/Douglas abscess/Acute abdomen	5 (7.3%)	3 (4.5%)	-
Salvage pelvic surgery	2 (3%)	15 (22.7%)	-
Lung nodule resection	1 (1.5%)	14 (21.2%)	14 (17.1%)
Abdominal surgery	-	23 (34.8%)	23 (34.8%)
HIPEC/Sugarbaker	-	5 (7.6%)	17 (20.7%)
Hepatic resection/RFA	-	20 (30.3%)	36 (43.9%)
Other resections (abdominal wall/bones)	-	10 (15.1%)	4 (4.9%)
ERCP/biliary reconstruction	-	2 (3%)	3 (2.4%)
Nephrostomy, double J catheterization	-	3 (4.5%)	-
Pelvic radiotherapy	-	26 (39.4%)	10 (12.2%)
Other external RT (brain, bones)	-	4 (6%)	4 (4.9%)
Intraoperative Radiotherapy	-	4 (6%)	1 (1.2%)
Others (SYR-Y90, FDT)	-	3 (4.5%)	1 (1.2%)
Average procedures/patient	**-**	**1.9**	**2.1**
CHEMOTHERAPY			
Double FU/FC-Ox	-	40 (60.6%)	29 (35.4%)
Double FU/FC-Iri	-	20 (30.3%)	14 (17.1%)
Triple FOLFOXIRI	-	26 (39.4%)	41 (50%)
CMT	-	16 (24.2%)	26 (31.7%)
Bevacizumab/Cetuximab + Cht	-	28 (42.4%)	29 (35.4%)
Other associations	-	50 (75.7%)	14 (17.1%)
Hepatic intraarterial chemotherapy	-	8 (12.1%)	19 (23.2%)
Immunotherapy (IL-2/Dr Recchia)	-	14 (21.2%)	14 (17.1%)
Average regimens/patient	**-**	**3.1**	**2.2**

*Uterus, ovary, bladder, intestine.

Table 4. Adjuvant treatment. Group A.

		No adjuvant therapy		Adjuvant therapy
Total		21 (30.9%)		47 (69.1%)
	Recurrence/metastases	5 (23.8%)		2 (4.2%)
	Salvage recurrence	2 (9.5%)		----
	CRC deaths	3 (14.3%)	Toxic deaths	2 (4.2%)
Patients profiling	>70 y	10 (47.6%)		19 (40.4%)
	Rectal cancer	1 (4.7%)		22 (46.8%)
	N0	15 (71.4%)		25 (53.2%)
	N1	4 (19%)		13 (27.6%)
	N2	2 (9.5%)		9 (19.1%)
	Second CRC*	4 (19.2%)		2 (4.2%)
Chemotherapy regimens			5FU/analog	21 (44.6%)
			2 drugs**	13 (27.6%)
			3 drugs***	13 (27.6%)

* Endometrial, prostate, lung, breast, pancreas and cervical cancers.
** FOLFOX, FOLFIRI, XELOX or similar.
*** FOLFOXIRI

Table 5. Survival analysis. Comparison between groups.

	GROUP A	GROUP B	GROUP C
Survival since diagnostic date			
Median	52 m	47.5 m	27 m
Interval	2-120	14-330	2-120
Survival since recurrence	NA	28 m	27 m
TUMOR STATUS LAST FOLLOW-UP			
FREE OF DISEASE	50 (73.5%)	7 (10.6%)	11 (13.4%)
ALIVE WITH DISEASE	1 (1.5%)	2 (3%)	3 (3.7%)
DEATH CCR	5 (7.3%)	44 (66.7%)	54 (65.9%)
DEATH 2nd TUMOR	4 (5.9%)	2 (3%)	-
TOXIC DEATH	2 (2.9%)	4 (6.1%)	7 (8.5%)
LOST FOLLOW-UP	6 (8.8%)	7 (10.6%)	7 (8.5%)
Survival according to therapeutic benefit*			
NO BENEFIT	NA	18 (29%)	26 (34.7%)
Median survival (m)	-	12	14
Therapeutic modality			
Chemotherapy only	-	9 (50%)	9 (34.6%)
ChT + RT	-	3 (16.7%)	1 (3.8%)
ChT + Surgery	-	3 (16.7%)	13 (50%)
ChT + RT + Surgery	-	3 (16.7%)	3 (11.5%)
WITH BENEFIT	NA	44 (66.7%)	49 (65.3%)
Median survival (m)	-	32	40
Therapeutic modality			
Chemotherapy only	-	8 (18.2%)	6 (12.2%)
ChT + RT	-	1 (2.3%)	1 (2%)
ChT + Surgery	-	26 (59.1%)	36 (73.5%)
ChT + RT + Surgery	-	9 (20.4%)	6 (12.2%)

*Defined as progression free interval longer than 12 months

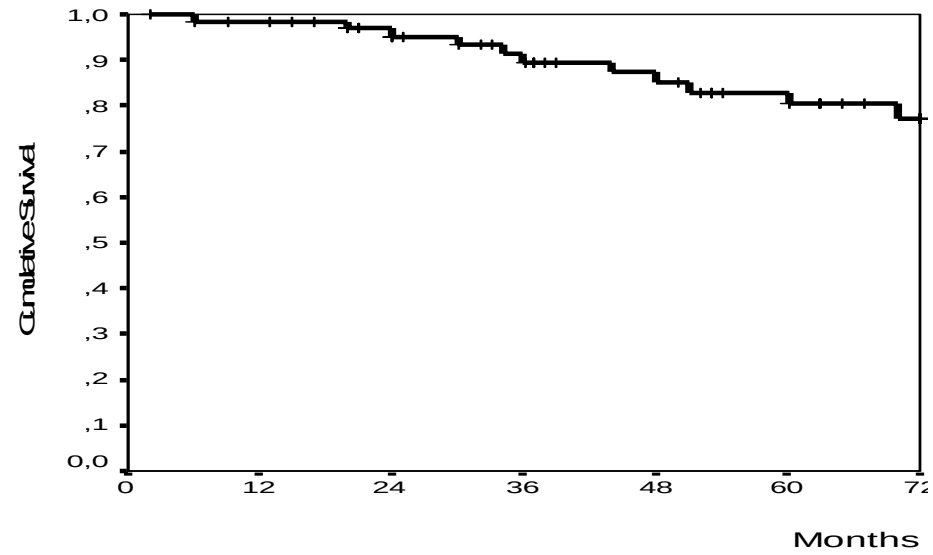

Figure 1. Estimated survival according to Kaplan-Meier for Group A.

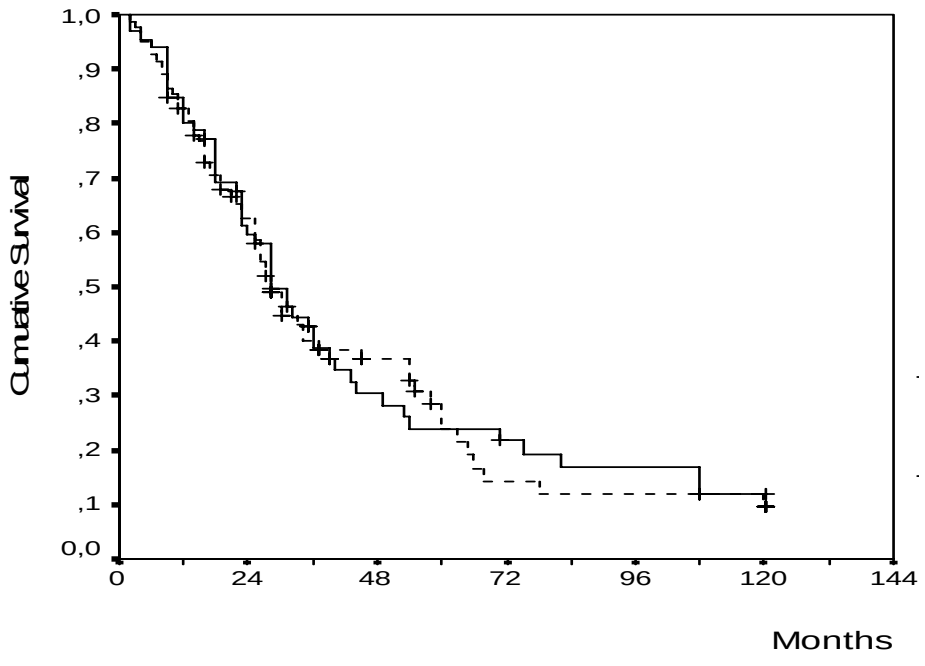

Figure 2. Estimated survival plot (Kaplan-Meier) of Goups B (solid line) and C (dotted line).