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ANGIOGENESIS INHIBITORS IN THE TREATMENT OF METASTATIC COLORECTAL CANCER

SUMMARY DOCTORAL THESIS

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I. INTRODUCTION

Colorectal cancer (CRC) is a cause of global mortality and morbidity and significant public health problem in Romania. According to GLOBOCAN in Romania CRC is the most common type of cancer. In contrast to the risk of CRC mortality in certain European countries in the last decade, the survival rates of patients with CRC in Romania are significantly lower.

Approximately 20%-25% of all CRC cases are metastatic at diagnosis, and approximately 30% of cancers diagnosed as stage II or III disease will develop recurrent metastatic disease after initial treatment.

Curative resections are only possible in a small percentage of patients with metastatic CRC with limited disease. Palliative systemic chemotherapy is the most common treatment modality to improve overall survival (OS) while maintaining quality of life. Various combinations of chemotherapies have been studied for the treatment of metastatic CRC and the addition of molecularly targeted therapies to chemotherapy and also the sequential use of different chemotherapy regimens available have contributed to improved survival, with a median OS that can reach approximately 30 months.

Treatment options include a triplet (FOLFIRINOX), a doublet (FOLFOX/CAPOX or FOLFIRI/CAPIRI), or fluoropyrimidine monotherapy (5-FU/Leucovorin or Capecitabine) in combination with a biologic agent targeted against vascular endothelial growth factor (VEGF) or against the epidermal growth factor receptor (EGFR) in patients with RAS wild-type tumors.

Anti-VEGF agents, such as Bevacizumab, Aflibercept, Regorafenib, and Ramucirumab, have proven effective in the treatment of metastatic CRC. Since the introduction of antiangiogenic agents, there has been great interest in identifying clinical or molecular markers to help predict which subgroup of patients will benefit from inhibition of the angiogenesis pathway.

In Romania, the first angiogenic agent approved since 2008 was Bevacizumab, a humanized monoclonal antibody (Ac) that acts by inhibiting vascular endothelial growth factor A (VEGF-A). The second agent approved in Romania in 2017 was Aflibercept, a recombinant fusion protein that acts as a soluble receptor that binds VEGF-A, vascular endothelial growth factor B (VEGF-B) and placental growth factor (PIGF).

Bevacizumab (Avastin) was approved in the treatment of metastatic CRC by the Food and Drug Administration (FDA) on February 26, 2004 in combination with intravenous (IV) 5-Fluorouracil-based chemotherapy; the approval recommendation was based on highly

statistically significant data showing improved overall survival with the addition of Bevacizumab in combination with Irinotecan, 5-Fluorouracil and Leucovorin. The **AVF2107g** trial was the first phase 3 trial to evaluate Bevacizumab in the first-line treatment of metastatic CRC in combination with IFL (bolus 5-FU, Leucovorin, and Irinotecan) and led to its approval. In the same month, the **BRiTE** trial, an observational study in the United States, was initiated to evaluate the safety and effectiveness of Bevacizumab in combination with chemotherapy in current medical practice in patients with previously untreated metastatic CRC. A few months later, the **BEAT** trial (Bevacizumab Expanded Access Trial) was initiated in Europe with the same aim. In both studies, combination chemotherapy was investigator's choice, being that used in current clinical practice. In January 2005, Bevacizumab received marketing authorization in the European Union, thus being approved by the EMA (European Medicines Agency) in the treatment of metastatic CRC. On June 20, 2006, the extension of the indication for treatment with Bevacizumab in the second-line treatment of metastatic CRC was approved in accordance with the results of the **E3200** study that demonstrated the safety and effectiveness of Bevacizumab in combination with FOLFOX4 (Oxaliplatin, Fluoruracil, Leucovorin) versus FOLFOX4 by improving significant global survival.

To address the French particularities of the use of Bevacizumab in metastatic CRC, in 2008 the **CONCERT** trial was initiated by Roche S.A.S. At the time of initiation of the **CONCERT** trial, Bevacizumab had been approved by the EMA for the treatment of colon and rectal cancer (regardless of the line of treatment) in combination with fluoropyrimidine-based chemotherapy. For this reason, unlike the **BRiTE** trial, the **BEAT** trial and the **CONCERT** trial were not limited to first-line treatment. The purpose of the **CONCERT** trial was to describe the characteristics of the patients, the characteristics of the use of Bevacizumab, its efficacy in terms of progression-free survival and overall survival, and also the safety of administration in patients with metastatic CRC that we care for in daily medical practice.

In January 2013, treatment with Bevacizumab beyond progression in combination with regimens based on 5-Fluorouracil and Irinotecan or 5-Fluorouracil and Oxaliplatin is approved for patients with metastatic CRC who have progressed after first-line treatment with Bevacizumab (**ML18147**). In 2008, Bevacizumab obtained reimbursement in Romania by being approved on the list of compensated medicines at the level of the National Health Insurance Agency (CNAS).

At the European level, the **ACORN** (Avastin ColORectal Non-interventional) trial was also carried out, which exclusively included the UK population and had as its objective to evaluate the effectiveness and safety of Bevacizumab administration in the first line of treatment, comparing chemotherapy regimens based on Capecitabine and Fluorouracil; the trial was initiated in July 2012, with data published in 2019. It is a phase 4 study that highlighted current medical practice in the UK and demonstrated that there are no significant differences between Capecitabine-based and Fluorouracil-based regimens, Capecitabine being used most frequently in the UK. There were also poor OS outcomes compared to other European states explained by the relatively short duration of Bevacizumab-based chemotherapy, less frequent use of Bevacizumab beyond progression, and a high rate of in-situ primary tumors.

The current state of knowledge comprises two large chapters, in the first, generalities about angiogenesis and its role in carcinogenesis, the VEGF signaling pathway, and the benefits of antiangiogenic agents in the treatment of metastatic CRC are presented. Also in the first chapter, data on colon cancer, epidemiology, risk factors, colon cancer diagnosis methods, colon cancer staging and surgical treatment of the primary tumor, surgical treatment of colon cancer complications and surgical treatment of various metastatic locations are presented. The second chapter focuses on the main angiogenesis inhibitor Bevacizumab, which is the main actor of the doctoral thesis. In the first part of the chapter, various first-line, second-line, beyond progression trials were exposed that led to the approval of Bevacizumab in the various treatment indications. There were phase 2 and phase 3 trials, but last but not least, phase 4 trials. In the second part, each indication was taken separately and the trials that justified the benefit of Bevacizumab were highlighted; thus for the first-line treatment, the **AVF2107g** phase 3 study that led to the initial approval of Bevacizumab by the FDA, the **BICC-C** phase 3 study clarified the optimal regimen based on Irinotecan in combination with Bevacizumab for the first-line treatment in metastatic CRC, the phase 3 study **NO16966**, the **BRiTE** study, **ARIES** and **BEAT**, the main studies with which the results obtained in our study were compared and also in first line was the phase 3 **TRIBE** study that evaluated the combination of Bevacizumab and FOLFIRINOX. For the second line of treatment, the **ECOG 3200** and **ML18147** trial for Bevacizumab, the **VELOUR** trial for Aflibercept and the **RAISE** trial for Ramucirumab were analyzed; the **BEVACOLOR** study was also presented for Bevacizumab. For treatment beyond progression, the **ML18147** trial (**TML**) and the **BRiTE** trial were presented. And for the maintenance treatment, several trials were presented: **OPTIMOX1** and **OPTIMOX2**, the

CONcePT trial, MACRO TTD, **CAIRO3**, **PRODIGE 9**, **AIO 0207**, **SAKK 41/06** and **STOP and GO**.

In the last part of the second chapter, some safety data related to the administration of Bevacizumab were presented, data that were extracted from the **BEAT** and **BRiTE** trial.

The current research has as its main subject Bevacizumab in the treatment of metastatic CRC and comprises a main study that includes the whole patient group and in which Bevacizumab was analyzed in the first and second line of treatment and two substudies derived from the same patient group, in the first, only patients who received treatment with FOLFOX or FOLFIRI plus Bevacizumab were selected, and in the second, the comparison was made between two time periods 2008-2012 and 2013-2018.

A second study carried out in collaboration with the surgery clinic of the Fundeni Clinical Institute includes patients who were treated with Bevacizumab, Aflibercept or Ramucirumab and who underwent hepatectomies for the resection of liver metastases with a curative purpose, the purpose of this study being to demonstrate the impact of localizations of primary tumor (of embryological origin) and RAS mutational status on OS, recurrence-free survival (RFS) and survival after recurrence (SAR) in patients who underwent resection of colorectal liver metastases.

In the last part of the thesis, several case reports are presented that aim to illustrate the complexity of the treatment of metastatic CRC and the importance of Bevacizumab in the treatment of metastatic CRC, the decisions being made in the multidisciplinary team and the treatment is personalized for each individual patient.

II. WORKING HYPOTHESIS AND GENERAL OBJECTIVES

Bevacizumab together with other angiogenesis inhibitors (Aflibercept, Ramucirumab and Regorafenib) has demonstrated efficacy over time alongside chemotherapy in the treatment of first-line, second-line metastatic CRC, as maintenance treatment and beyond progression. Our study aims to evaluate the efficacy and safety of Bevacizumab administration in the treatment of metastatic CRC in the first line, in the second line, as a maintenance treatment and beyond progression trying to identify certain factors that would favor the treatment with Bevacizumab.

GENERAL RESEARCH METHODOLOGY

We conducted a cohort, observational, retrospective, multicenter study conducted in Romania in which patients with metastatic CRC were included who were treated with

Bevacizumab in the Oncology Department of the National Gastroenterology Center of the Fundeni Clinical Institute, Bucharest and the Oncolab Hospital in Craiova in the period 2008-2018.

This is a retrospective observational study that spans over a 10-year period in which therapeutic advances in metastatic CRC have been very high. The study was conducted in two reference centers for digestive oncology, but approximately 90% of the patients come from the Medical Oncology Department of the Fundeni Clinical Institute, which, by being part of the Gastroenterology Section, gives it a special specificity for digestive oncology. The study recruited patients with metastatic colorectal cancer with approval from the National Health Insurance Company for Bevacizumab. It is desired to identify some temporal characteristics and the influence on the treatment effectiveness of the approval process of Bevacizumab files, somewhat dividing the 10-year period into two periods: 2008-2012 and 2013-2018, taking into account that since 2016 the approval commissions have been abolished from the Insurance House and the Bevacizumab file approval system was facilitated through electronic transmission and instant approval, leaving the decision and correctness of the approval to the attending physician.

Data collection and statistical analysis

The process of collecting the data required for the statistical analysis was difficult and lengthy, starting in 2016 the date of initiation of doctoral studies and ending in 2021 including a follow-up period after the end of Bevacizumab treatment until death from any cause or until at the last control in the clinic, it being necessary to return to the basic data of the patients obtained either from the observation sheets of the patients or from the electronic databases of the Fundeni Clinical Institute. The transition at the Fundeni Clinical Institute from one electronic database to another in 2011 led to the loss of essential information related to patients from the period 2008-2011. Patients from the Oncolab Clinic in Craiova were later added to the database after the completion of data collection from the institute. Of course, as the data was collected, the database underwent improvements, identifying certain factors that could contribute to the success of Bevacizumab treatment.

Access to patient data was approved by the local ethics committee of the Fundeni Clinical Institute. The data was collected and analyzed in compliance with GDPR data in complete anonymity. The study received the approval of the Ethics Council of the Fundeni Clinical Institute established on the basis of Ord. MS 1502 of 2016, which gave a favorable opinion for the conduct of the study in compliance with the criteria set forth in the General Data Protection Regulation (EU) 2016/679 regarding the respect of personal data personal,

no. 70204 of 30.12.2022. The study was conducted in accordance with the Declaration of Helsinki and its amendments.

Patient characteristics (age, sex), disease characteristics (date of diagnosis, location of tumor, location of metastases, stage and degree of tumor differentiation), data related to received treatment (date, dose, treatment changes, treatment interruption, reason for change and discontinuations, chemotherapy regimens in combination with Bevacizumab), disease progression (date) and death (date, cause) were collected. Safety data focused on the previously described adverse effects of Bevacizumab. Data collected also included Bevacizumab-related adverse events and serious adverse events.

After completing the data collection and arranging the database in the Microsoft Office - Excel program, the statistical analysis was performed using two programs GraphPad Prism 9.0.0 and IBM SPSS Statistic version 29.0.0.0. Percentages and total numbers were used to represent categorical variables and mean and median for continuous variables. Univariate and multivariate analysis was performed to identify prognostic factors for first-line and second-line Bevacizumab treatment. OS and progression-free survival (PFS) were compared using the log-rank test and the Kaplan-Meier curve.

The work included a main study on the entire patient group that included a number of 554 patients in which the comparison was made between the first line and the second line of treatment and two subgroup analysis; the first subgroup analysis selected only patients who underwent treatment with FOLFOX+Bevacizumab and FOLFIRI+Bevacizumab comparing the two chemotherapy regimens comprising a number of 250 patients; the second substudy was carried out on the same batch of 554 patients, but the comparison of the two periods 2008-2012 vs 2013-2018 is desired.

The diagram of the study is shown in the following figure:

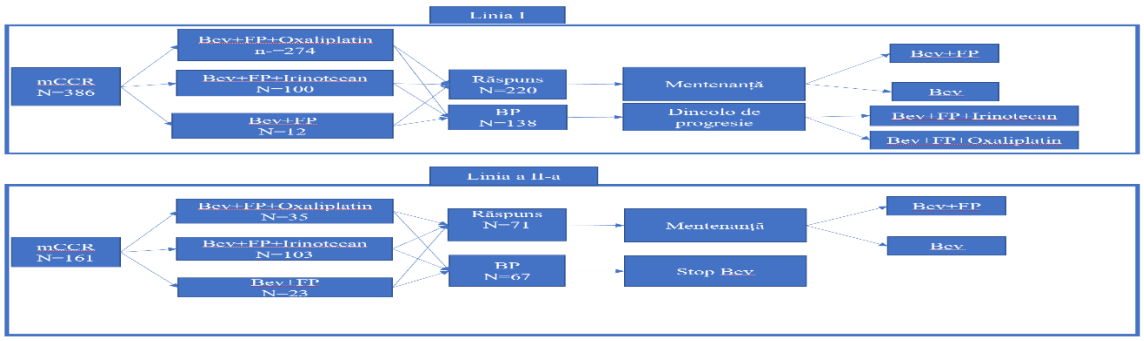


Figure 2.1: Diagram of the study

Results

In the main study, Bevacizumab „Treatment in metastatic CRC in current clinical practice", first-line PFS was 8.4 months (interquartile range [IQR], 4.5-15.1 months) and 6.6 months, respectively (IQR, 3.8-12.3 months) in the second line of treatment; OS was 17.7 months (IQR, 9.3-30.6 months) in first-line and 13.5 months (IQR, 6.7-25.2 months) in second-line treatment.

In the univariate analysis, no factors influencing the PFS in the first line of treatment were identified, instead the OS is statistically significantly influenced by the resection of the primary tumor, the location of the tumor on the left and the presence of metachronous metastases. In the second line of treatment, patients with resection of the primary tumor and mutant RAS status have a statistically significantly longer PFS; and those with resection of the primary tumor and RAS wild-type status have a statistically significant longer OS. In the multivariate analysis by Cox regression, no factors influencing PFS were identified, instead the age and laterality of the tumor seem to influence OS.

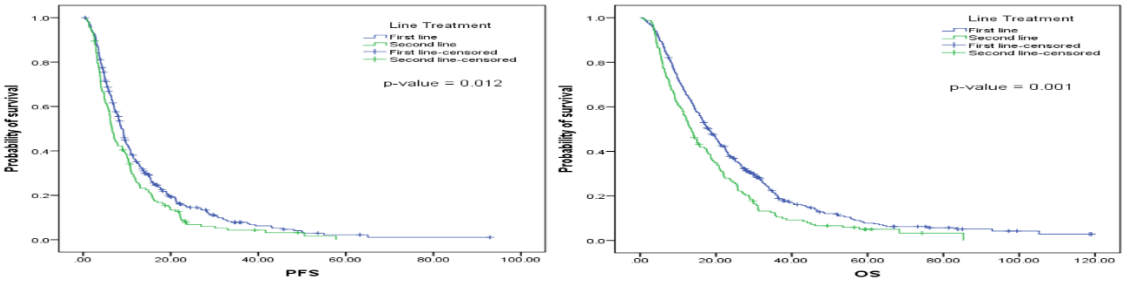


Figure 2.2: PFS and OS according to the line of treatment in which Bevacizumab was used (Log-rank)

Table 2.1: Univariate and multivariate analysis of prognostic factors for PFS with first-line Bevacizumab

Factors		**Univariate Analysis**		**Multivariate Analysis**	
		HR	***P***	**HR**	***p***
Age		1.001 (0.986-1.016)	0.883		
Cancer Grading	G1 vs G3 G2 vs G3	0.91 (0.45-1.81) 0.92 (0.48-1.77)	0.782 0.802		
Primary tumor resection	Yes vs No	0.84 (0.54-1.28)	0.407		
Location of metastases	liver vs other	1.089 (0.73-1.62)	0.673		

Sidedness of primary tumor	Right vs Left	1.13 (0.8-1.58)	0.499		
CHT Regimen	Irinotecan vs oxali FP vs oxali	0.92 (0.63-1.35) 1.11 (0.57-2.16)	0.666 0.759		
RAS Status		0.88 (0.75-1.04)	0.126		

Table 2.2: Univariate and multivariate analysis of prognostic factors for first-line Bevacizumab OS

Factors		**Univariate Analysis**		**Multivariate Analysis**	
		HR	***p***	**HR**	***p***
Age		1.02(1.003-1.03)	0.016	1.02 (1-1.03)	0.046
Cancer Grading	G1 vs G3 G2 vs G3	0.91(0.46-1.81) 1.09(0.57-2.09)	0.782 0.799		
Primary tumor resection	Yes vs No	0.77(0.51-1.18)	0.235		
Location of metastases	liver vs other	1.14(0.77-1.69)	0.524		
Sidedness of primary tumor	Right vs Left	1.54(1.09-2.16)	0.014	1.42 (1.0-2.02)	0.047
CHT Regimen	Iri vs Oxali FP vs Oxali	0.87(0.59-1.28) 1.34(0.69-2.61)	0.474 0.391		
RAS Status		0.88(0.75-1.03)	0.114		

OS was 23.9 months for RAS wild-type tumors with left sidedness (p=0.039) regardless of the treatment line, and in first line OS was 25.11 months for RAS wild-type tumors with left sidedness (p=0.028). Tumor sidedness and RAS status were shown to influence OS and PFS regardless of treatment line.

Table 2.3: OS according to RAS status and tumor sidedness

All RAS status/ Tumor Sidedness	Left (n,%) – 236 OS (months, 95%CI)	Right(n,%) - 84 OS (months, 95% CI)	p (Log-Rank)
Wild-type	115(48.7%)	39 (46.4%)	0.039
	23.967(19.400-28.534)	13.578(10.400-16.756)	
Mutant	121(51.3%)	45(53.6%)	
	17.556(12.681-22.432)	17.030(9.294-24.766)	

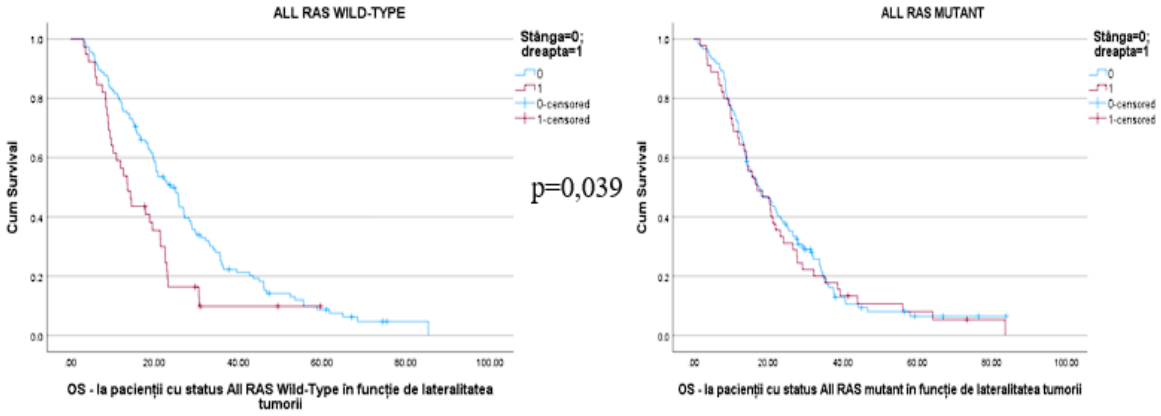


Figure 2.3 Comparative analysis of OS according to RAS status and tumor sidedness

Table 2.4: OS in first-line treatment with Bevacizumab according to RAS status and tumor sidedness

All RAS status/ Tumor sidedness	Left (n,%) – 164 OS (months, 95%CI)	Right(n,%) - 63 OS(months, 95% CI)	p (Log-Rank)
Wild-type	66(40.2%)	28 (44.4%)	0.028
	25.118(18.566-31.670)	13.479(7.811-19.148)	
Mutant	98(59.8%)	35(55.6%)	
	16.997(11.033-22.962)	18.510(12.832-24.187)	

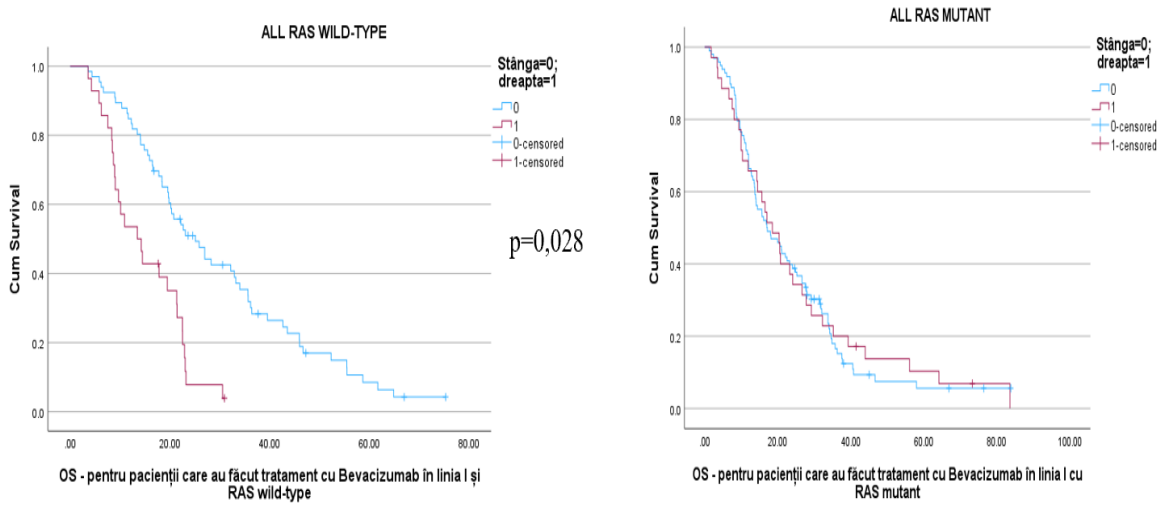


Figure 4: Comparative analysis of PFS and OS in first-line treatment with Bevacizumab according to RAS status and tumor sidedness

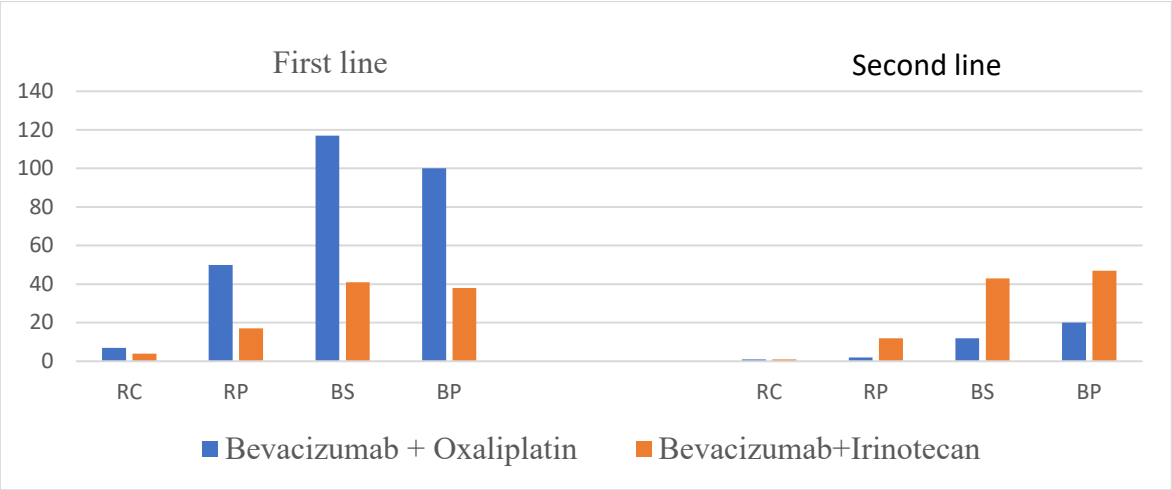


Figure 2.5: Distribution of responses to chemotherapy according to treatment line (RC – Complete response, RP – Partial response, BS – stable disease, BP – progressive disease)

Table 2.5: Response rates and disease control rate according to the chemotherapy regimen used in combination with Bevacizumab in the first line of treatment; N-number; RP- partial response; RC – complete response; BS- stable disease; BP – progressive disease; RR – response rate; DCR – disease control rate

CHT Type	Bevacizumab/ Oxaliplatin	Bevacizumab/ Irinotecan	P
First line treatment			
Pacients (N)	274	100	
Patients evaluable for response (N)	172	62	
RC(N)	7	4	
RP(N)	50	17	
BS(N)	117	41	
BP(N)	100	38	
RR(RC+RP)(%)	20.8%	21%	0.421
DCR(RC+RP+BS)(%)	63.5%	62%	0.979

The response rate for first-line Bevacizumab + Oxaliplatin chemotherapy was 20.8% and 21% for Bevacizumab + Irinotecan chemotherapy regimens, and the disease control rate was 63.5% for chemotherapy based on Bevacizumab+Oxaliplatin versus 62% for chemotherapy based on Bevacizumab+Irinotecan.

Table 2.6: Response rates and disease control rate according to the chemotherapy regimen used in combination with Bevacizumab in the second line of treatment; N-number; RP-partial response; RC – complete response; BS- stable disease; BP – progressive disease; RR – response rate; DCR – disease control rate

CHT Type	Bevacizumab/ Oxaliplatin	Bevacizumab/ Irinotecan	p
Second line treatment			
Pacients (N)	35	102	
Patients evaluable for response (N)	15	46	
RC(N)	1	1	
RP(N)	2	12	
BS(N)	12	43	
BP(N)	20	47	
RR(RC+RP)(%)	8.6%	12.6%	0.023
DCR(RC+RP+BS)(%)	42.9%	54.4%	0.530

In the second line, RR was 8.6% for chemotherapy based on Bevacizumab + Oxaliplatin and 12.6% for chemotherapy based on Bevacizumab + Irinotecan with a statistically significant difference (p=0.023), and DCR was 42.9% for the Bevacizumab+Oxaliplatin-based regimens and 54.4% for the Bevacizumab+Irinotecan-based regimens.

Treatment beyond progression and maintenance treatment influenced OS regardless of chemotherapy regimen.

In the 185 patients treated beyond progression it was observed that treatment beyond progression resulted in an additional survival of approximately 10.5 months with an OS of 23.112 months (95%CI 20.230-25.995) with a statistically significant $p < 0.001$.

Table 2.7: Comparative analysis of OS for patients treated beyond disease progression versus those not treated beyond disease progression

Bevacizumab beyond progression	OS (months, 95%CI)	p(log-rank)
Yes	23.112 (20.230-25.995)	<0,001
No	12.592(11.097-14.086)	

Maintenance treatment in the 140 patients resulted in a longer survival of 29.195 months compared to those who did not do maintenance treatment who only had an OS of 13.578 months with a statistically significant p <0.001.

Table 2.8: Comparative analysis of OS for patients who received Bevacizumab maintenance therapy versus those who did not receive maintenance therapy

Maintenance Bevacizumab	OS (months, 95%CI)	p(log-rank)
Yes	29.195 (24.177-34.212)	<0,001
No	13.578(12.145-15.011)	

A subgroup analysis was performed and from the 554 patients, only patients who received treatment with FOLFOX or FOLFIRI in combination with Bevacizumab in the first line or in the second line were selected. The aim of the analysis was to compare the efficacy of the two chemotherapy regimens in combination with Bevacizumab. A number of 250 patients underwent treatment with FOLFOX or FOLFIRI in combination with Bevacizumab, of which 173 p (69.2%) in the first line and 77 patients (30.8%) in the second line.

In the substudy FOLFOX vs FOLFIRI, in the first line of treatment the most frequent regimen used was FOLFOX 116 patients (67.1%), and in the second line of treatment the most frequent regimen used was FOLFIRI 59 patients (76.6%). In first-line treatment there is no difference in PFS between the two regimens, and overall survival was in favor of the FOLFIRI regimen; in second line there is a PFS in favor of the FOLFIRI regimen, and the OS is in favor of the FOLFOX regimen.

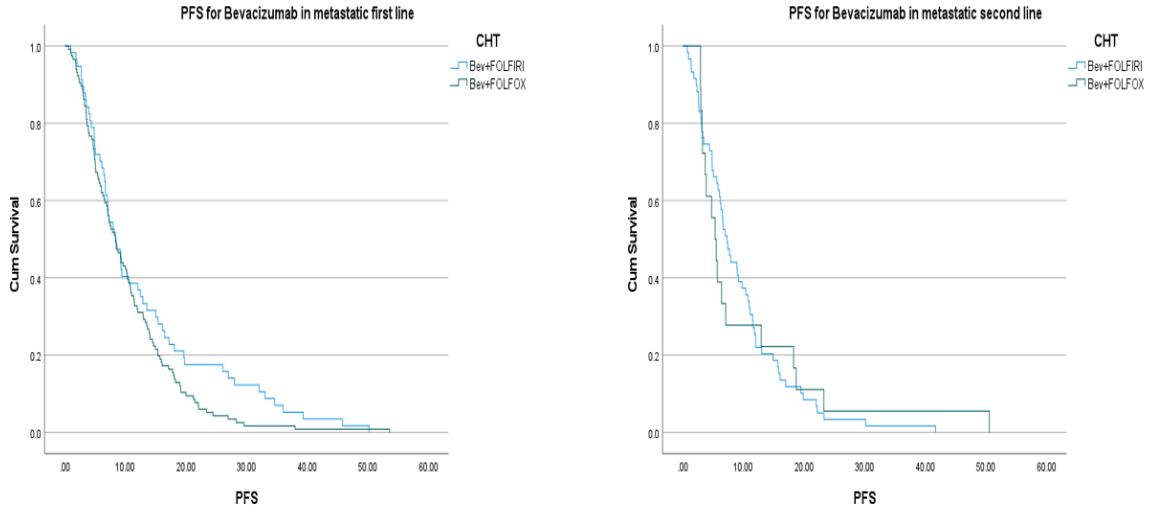


Figure 2.6: PFS curves in first-line or second-line treatment according to chemotherapy regimen

Table 2.9: PFS and OS by chemotherapy regimen and line of treatment.

Line of treatment	First line (n=173)		Second line (n=73)	
CHT regimen	Bev+ FOLFOX	Bev+ FOLFIRI	Bev+ FOLFOX	Bev+ FOLFIRI
PFS(months, 95% CI)	8.38 (6.65-10.12)	8.35 (6.19-10.50)	5.33 (3.75-6.89)	7.29 (5.81-8.78)
p (Log-Rank)	0.123		0.926	
SG(luni, 95% CI)	16.73 (14.11-19.36)	18.41 (13.06-23.76)	13.58 (4.08-23.08)	12.53 (9.24-15.81)
p (Log-Rank)	0.839			

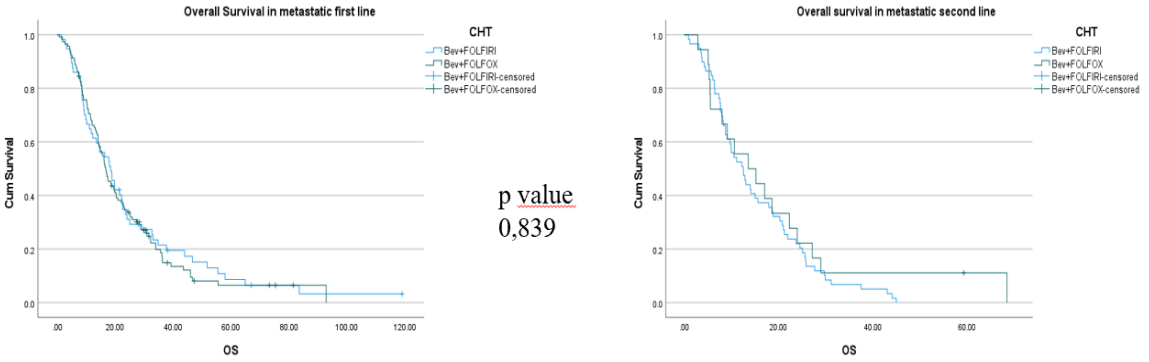


Figure 2.7: OS curve according to the chemotherapy regimen associated with Bevacizumab and according to the line of treatment (Log-rank)

When comparing the two periods 2008-2012 vs 2013-2018, both OS and PFS are in favor of the first time period 2008-2012, the explanation being that the selection of patients was much more correct in the second time period 2013-2018, the RAS status being carried out in a much higher percentage, and the number of patients was much lower in the first period of time.

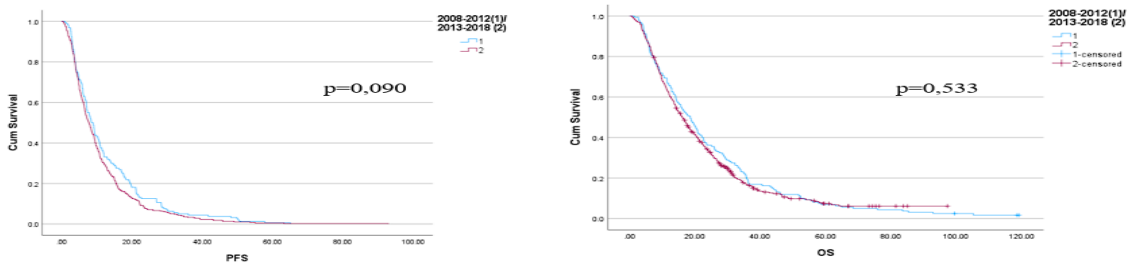


Figure 2.8: Comparative analysis of PFS and OS regardless of chemotherapy line and regardless of chemotherapy regimen in combination with Bevacizumab between 2008-2012 and 2013-2018.

PFS regardless of the chemotherapy regimen in combination with Bevacizumab and regardless of the line of treatment is 8.449 months (CI95% 6.870-10.029) in the period 2008-2012 versus 7.693 months (CI95% 6.742-8.645) in the period 2013-2018, with a overall PFS of 8.055 months (95% CI 7.190-8.920) over the entire period (Log-rank, p=0.090).

OS regardless of the regimen of chemotherapy in combination with Bevacizumab and regardless of the line of treatment in which Bevacizumab is used is 18.575 months (CI95% 15.060-22.090) in the period 2008-2012 versus 16.110 months (CI95% 14.214-18.005) in the period 2013 -2018, with an overall OS of 16.701 months (CI95% 14.900-18.503) over the entire period (Log-rank, p=0.533).

CONCLUSIONS:

The purpose of the study was to highlight the specificity of the routine use of Bevacizumab in Romania in patients with metastatic CRC in two reference centers. The safety profile of Bevacizumab was generally as expected. Overall survival was shorter although PFS was similar to that reported in other studies. Shorter patient survival is likely due to baseline patient characteristics and less frequent use of Bevacizumab beyond progression. There are differences in study design and population among studies, so a direct comparison of PFS and OS should be interpreted with caution. Other important findings of the study was that patients with metastatic CRC treated with Bevacizumab who underwent resection of the primary tumor had a longer overall survival compared to patients who did not have resection of the primary tumor. Most available data on the impact of primary tumor resection have come from subgroup analyzes or observational studies and thus need to be confirmed in randomized trials. It is important to emphasize that real-life data from studies using Bevacizumab in patients with mCCR may provide valuable insights into clinical oncology practice and aid in informed treatment decisions for patients with mCCR.

IMPORTANCE OF THE STUDY

Metastatic colorectal cancer represents a therapeutic challenge, and the number of patients is continuously increasing. Treatment with Bevacizumab in combination with chemotherapy is only one of the available treatment options, but it plays an important role in long-term disease control.

Although this study is an observational, retrospective study, it is one of the largest retrospective studies carried out in our country spanning a period of 10 years, in which an important evolution of treatments in metastatic CRC has occurred. This study attempted to highlight certain factors that may influence the decision to treat with Bevacizumab in metastatic colorectal cancer in first-line and second-line treatment. The study highlighted the current clinical practice and the evolution of Bevacizumab treatment in Romania.

The study included a number of 554 patients, which is comparable to that of large phase II and III clinical trials. This study was conducted in two reference centers for the treatment of metastatic colorectal cancer, but most of the patients came from the Fundeni Clinical Institute.

OS, PFS, and safety data are comparable to international randomized and non-randomized reference studies. The study demonstrated that regardless of the chemotherapy regimen used, Bevacizumab is effective in first-line, second-line, maintenance treatment and beyond disease progression with a tolerable safety profile. RAS status and tumor sidedness (left/right) are important factors in the treatment decision influencing overall survival and progression-free survival.

Randomized trials are needed to confirm the results obtained in this study.

III. The second study is called "Embryological origin of the primary tumor and RAS status and the impact on survival after resection of colorectal liver metastases" and aims to highlight the impact of the location of the primary tumor (LPT) on the long-term outcomes of patients with liver metastases resected from CRC, OS rates, recurrence-free survival (RFS) and survival after recurrence (SAR), long-term outcomes were compared between patients with RS tumors and patients with LS tumors according to their RAS status.

The study protocol was approved by the Ethics Council of the Fundeni Clinical Institute with number 6571/01.02.2022.

Material and method

All patients with known RAS status were selected from a prospectively maintained database that included all patients who underwent hepatectomy for liver metastases in the Surgery and Liver Transplant Clinic of the Fundeni Clinical Institute between 2006 and 2019. Patients who died within the first 30 days postoperatively (as their death was probably due to a cause other than cancer progression), patients with incomplete resections (R1/R2), and patients with incomplete follow-up data. RAS status was determined by NGS (next generation sequencing) on tissue from liver metastases or from the primary tumor. Only in

a small number of patients was the RAS status assessed immediately after liver resection (regardless of the development of recurrence).

This database also contained patients who received chemotherapy with Bevacizumab as neoadjuvant treatment before hepatectomy or as palliative treatment at recurrence after hepatectomy. Patients were also selected from the database of the main study, being chosen patients who underwent hepatectomies for liver metastases, with known RAS status and who received treatment with Bevacizumab, Aflibercept or Ramucirumab. The study was carried out through a collaboration between the surgery clinic and the oncology department.

Patients with primary colonic tumors located between the cecum and the splenic flexure (midgut) were included in the group of patients with RS tumors, and patients with primary colonic tumors located distal to the splenic flexure and those with rectal carcinomas (hindgut) were included in the group patients with LS tumors. Patients with carcinomas located at the level of the splenic flexure and also those with synchronous RCC located on the right and left were excluded from the analysis.

Postoperative chemotherapy was recommended for all patients. Monoclonal Ab treatment was associated, according to current guidelines, after disease recurrence. Patients enrolled in this study underwent specific oncological treatment for a long period of time (2006-2019). Chemotherapy consists of a combination of 5-FU or Capecitabine with Oxaliplatin or Irinotecan in combination with targeted therapies – anti-VEGF agents (Bevacizumab, Aflibercept or Ramucirumab) or anti-EGFR agents (Cetuximab or Panitumumab).

Long-term results

OS was calculated as the interval between liver resection and the date of patient death or the last follow-up date.

RFS was the interval between hepatectomy and the date of malignancy recurrence or the last follow-up date, if the patient was disease-free at that time.

SAR represents the interval between disease recurrence (after hepatectomy) and patient death or the last follow-up date (if the patient was alive at that time). Patients who did not develop recurrent disease by the last follow-up were not included in the analysis for SDR.

Statistical analysis

Categorical data are presented as numbers or percentages. The association between categorical variables was analyzed by the Fischer-exact test. Continuous data are presented as mean +/- standard deviations (SD) or as median and interquartile range [IQR25%-

IQR75%], according to tests used to assess normality of distribution. Normality of distribution was assessed by the Shapiro-Wilk test and subsequent comparisons were made with the t-test or the Mann Whitney test. Survival rates were estimated by the Kaplan-Meier method and compared between the different groups by the Log-rank test. In the univariate analysis, the impact of the previously mentioned parameters on OS, RFS and SAR was evaluated. Parameters that were associated with a p value of less than 0.1 in the univariate analysis were included in the multivariate analysis. Multivariate analysis was performed by the Cox regression method with a backward stepwise selection process that was used to identify independent prognostic factors associated with OS, RFS, and SAR. Hazard ratio (HR) was reported with 95% confidence interval (95%CI). A p-value less than 0.05 was considered significant. Statistical analysis was performed using IBM SPSS software, version 23 (SPSS Inc, Chicago, IL).

Results

There were 142 patients who met the inclusion criteria. Of these, 53 had RAS mutant liver metastases, while 89 had wild-type RAS metastases. Of the 142 patients, 55 patients received treatment with Bevacizumab, Ramucirumab or Aflibercept as antiangiogenic agents.

Mutant RAS

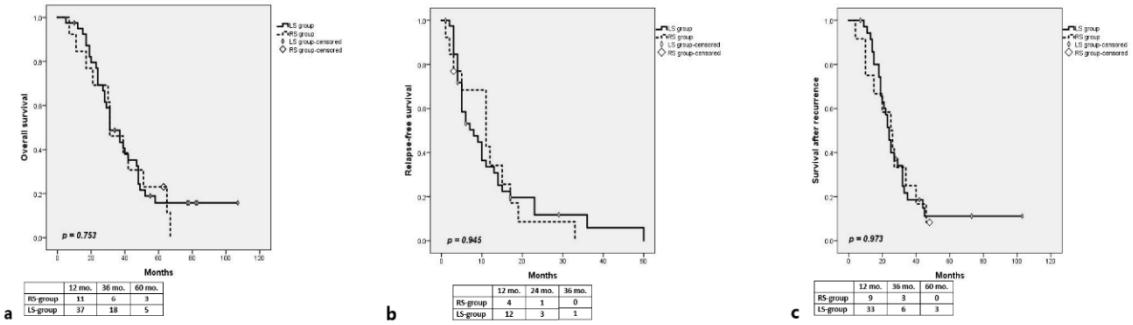
Long-term results

For the entire group, median OS was 31 months, with 1-, 3-, and 5-year OS rates of 92.4%, 48.1%, and 17.8%, respectively. The OS rates at 1-, 3- and 5-years were not significantly different (p=0.753) between primary tumor patients with LS (94.9%, 48.8% and 15.8%, respectively) and colorectal tumors with RS (84.6%, 46.2% and 23.1%, respectively) (Figure 3.1a).

After a median follow-up of 31 months, 48 patients developed recurrence: hepatic only - 23 patients, hepatic and extrahepatic - 10 patients, pulmonary - 7 patients, peritoneal - 2 patients, nodal - 2 patients, local recurrence - 2 patients , ovarian – 1 patient and bone – 1 patient. For the entire group, median RFS was 10 months, with 1- and 3-year RFS rates of 33.6% and 3.6%, respectively. RFS rates were not statistically significantly different between the group with LS tumors versus those with RS tumors (33.6% and 5.9% vs. 34.2% and 0% at 1- and 3-years, respectively, p =0.945) (Figure 3.1b).

For all patients who developed recurrence after initial resection of liver metastases, the 1-, 3-, and 5-year SAR rates were 89.4%, 20.4%, and 10.3%, respectively (median 24 months). The SAR rate was similar in the group with LS versus RS tumors. (94.3%, 18.6%

and 11.1% vs. 75%, 25% and 0% at 1-, 3- and 5-years, respectively, p=0.973) (Figure 3.1c).



a

	12 mo.	36 mo.	60 mo.
RS-group	11	6	3
LS-group	37	18	5

b

	12 mo.	24 mo.	36 mo.
RS-group	4	1	0
LS-group	12	3	1

c

	12 mo.	36 mo.	60 mo.
RS-group	9	3	0
LS-group	33	6	3

Figure 3.1 Comparative long-term results between the LS group and the RS group in patients with RAS mutant liver metastases (a) OS; (b) RFS; (c) SAR.

Wild-type RAS

Long-term results

For the entire group, median OS was 45 months, with 1-, 3-, and 5-year OS rates of 95.5%, 58.2%, and 26.6%, respectively. In patients with primary tumors with LS, the OS rates at 1-, 3- and 5-years (97.3%, 62.5%, and 28.4%, respectively) were significantly higher (p=0.007) than those achieved by liver resections in the group of tumors with RS (86.7%, 36.1%, and 10.8%, respectively (Figure 3.2a).

After a median follow-up of 39 months, 78 patients developed recurrence: only at the level of the liver - 42 patients, hepatic and extrahepatic - 15 patients, pulmonary - 8 patients, peritoneal - 4 patients, lymph nodes - 4 patients, pelvic recurrence - 3 patients, ovarian – 1 patient and bone – 1 patient. The recurrence rate was not significantly different between the group of patients with RS primary tumors (13/15) and those with LS primary tumors (65/74) (p=0.899). For the entire group, median RFS was 11 months, 1- and 3-year RFS rates of 38.6% and 12.7%, respectively. RFS rates were not statistically significantly different between groups of patients with primary tumors with LS versus those with RS (40.2% and 8.1% vs. 30% and 15% at 1- and 3-years, respectively, p=0.438) (Figure 3.2b).

Recurrent disease developed during the first year after initial resection of liver metastases in 52 patients (66.7%) and after more than 1 year in 26 patients (33.3%). Recurrence was resected in 27 patients (34.6%): liver re-resections – 17 patients, lung resections – 6 patients, hepatic and extrahepatic resections – 2 patients, oophorectomy – 1 patient and lymph node dissection in the hepatic pedicle – 1 patient. Although the recurrence resectability rate was higher in the LS primary tumor group (25/65 – 38.4%) than in the RS primary tumor group (2/13 – 15.3%), the differences were not statistically significant (p=0.199). For all patients who developed recurrence after initial resection of colorectal liver

metastases, the 1-, 3-, and 5-year SAR rates were 87.1%, 38.1%, and 10%, respectively (median 33 months). SAR rates were significantly higher in the group of patients with LS primary tumors vs those with RS (87.5%, 45.5% and 12% vs. 68.4%, 8.5% and 0% at 1- ,3- and 5-years respectively, p < 0.001) (Figure 3.2c).

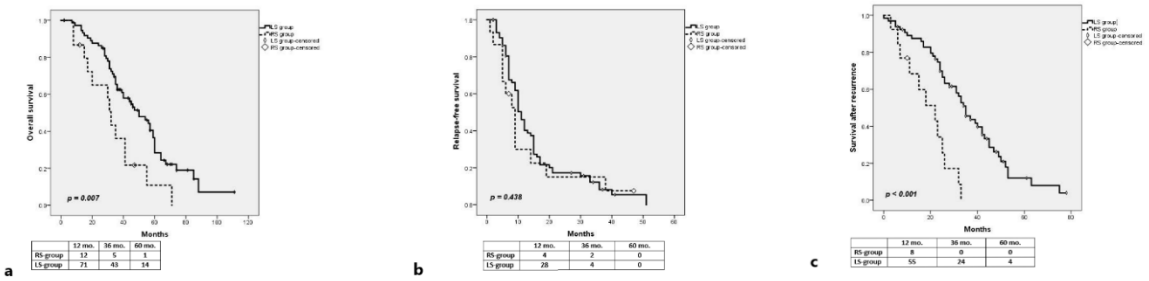


Figure 3.2 Long-term results comparing LS group and RS group in patients with RAS wild-type liver metastases (a) OS; (b) RFS; (c) SAR.

Univariate analysis

Factors associated with significantly worse OS in univariate analysis were right-sided primary tumor location (p=0.007), extrahepatic metastases (p=0.014), and abdominal lymph node metastases in addition to the primary tumor (N+) (p=0.004). Age greater than 65 years (p=0.095) and use of preoperative chemotherapy (p=0.084) were marginally associated with worse OS in univariate analysis.

The presence of postoperative complications (p=0.024), extrahepatic disease (p=0.003), and multiple liver metastases (p=0.026) were associated with significantly lower SFR rates in univariate analysis.

In univariate analysis, factors significantly associated with lower SAR rates were tumors with RS (p<0.001), N+ positive primary tumors (p=0.011), occurrence of recurrence during the first 12 months after resection of liver metastases (p=0.048) and resection of recurrence (p=0.007).

Multivariate analysis

To identify independent prognostic factors for poorer long-term outcomes, characteristics that were associated with a p value <0.01 in univariate analysis were included in multivariate analysis. Factors that were independently associated with poorer OS were right-sided LPT (p=0.009), extrahepatic metastases (p=0.001), N-positive primary tumor (p=0.014), age older than 65 years (p= 0.002) and the use of preoperative chemotherapy (p=0.004). For RFS, factors independently associated with poor prognosis were postoperative complications (p=0.024) and extrahepatic metastases (p=0.015). Primary

tumors with RS ($p<0.001$) and N-positive status of the primary tumor ($p=0.007$) were the only independent prognostic factors for worse SAR.

Conclusions

The effect of embryologic origin of colorectal cancers on long-term outcomes after resection of liver metastases depends on RAS status. In RAS mutant liver metastases, LTP has no impact on long-term outcomes, whereas in RAS wild-type patients with primary tumors with RS it was independently associated with worse OS and SAR. Worse OS rates were observed in patients with RS tumors with RAS wild-type liver metastases and this was mainly due to significantly lower SAR. The lower rates of SAR achieved by onco-surgical approach in patients with wild-type RAS tumors with RS suggest the reduced efficacy of current oncological therapies in these patients, underscoring the urgent need for more effective therapies in CRC patients with RS. Because RFS rates after hepatectomy are similar regardless of LPT, liver resections should not be discouraged even in patients with RS tumors. The different prognosis of patients with resected liver metastases according to LPT and RAS status may have therapeutic implications in the allocation of oncological treatment, especially after disease recurrence following resection of liver metastases.

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