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1 **Impact of recommendations and new therapies on the prognosis**
2 **of colon cancer with synchronous liver metastasis.**

3

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1 **Summary**

2

3 **Objective:** To assess the prognostic impact of the new therapies
4 recommended over the past twenty years for colonic cancers with
5 synchronous hepatic metastasis (hmCC).

6

7 **Methods:** From 1995 to 2016, 802 hmCC were identified in a tumor
8 registry. An univariate and multivariate analysis looked for the impact of
9 the different recommendations over three periods: chemotherapy without
10 targeted therapy (p1CH), chemotherapy with targeted agent in 2nd line
11 (p2TA2), chemotherapy with TA in 1st line (p3TA1) depending on
12 anatomoclinical criteria and therapeutic sequences: chemotherapy then
13 resection of the primary tumor (CR) (n = 100), resection of the primary
14 tumor then chemotherapy (RC) (n = 541), chemotherapy alone with or
15 without TC (onlyCH) (n = 161).

16

17 **Results:** The rates of onlyCH, CR and RC had varied respectively during
18 these 3 periods from 12% to 26%, 6% to 21% and from 82% to 53% (p =
19 0.001). The medians of p1CH, p2TA2 and p3TA1 survival were 20.2, 22.7
20 and 23.6 months, respectively (p = 0.12). The independent factors of poor
21 prognosis were age \geq 75 years (1.6 [1.35; 1.9] p=0.0001), chemotherapy
22 only 2.3 [1.6; 3.5] p=0.0001), p1CH 1.7 [1.4; 2.1] p<0.0001), p2TA2 1.2
23 [1.02;1.6] p=0.04. The p2TA2 period had a worse prognosis than p3TA1
24 (1.25 [1.01; 1.5] p =0.03).

25 **Conclusion:** In public health point of view, the recommendation of first-
26 line TA improved survival and increased rate of primary tumor resection
27 after chemotherapy.

28

29 **Key words :**

30 recommendations, prognosis, colon, cancer, liver, metastasis

31 Colonic cancer (CC) is the second most commonly diagnosed cancer in Europe and
32 a leading cause of death both in Europe and worldwide (1,2).

33 Over the last 20 years, the clinical outcome for patients with metastatic CC has
34 improved. This is due to several reasons, mainly:1) a rising surgical procedures
35 with curative intents, 2) a closer follow-up after resection of the primary tumour
36 and earlier detection of metastatic disease, 3) an improvements in the efficacy of
37 systemic therapies, 4) a better understanding of biological behavior of the tumor
38 cells.

39

40 New treatments named targeted agents (TA) exist. Whereas fluoropyrimidines,
41 irinotecan, and oxaliplatin mainly target RNA and DNA, the activity of TA is based
42 upon perturbation of cell surface receptor–ligand interactions resulting in inhibition
43 of the signal transduction. Signaletic pathways of Epidermal growth factor (EGF)
44 and VasculoEndothelial Growth Factor (VEGF) are the primary focus of the TA.

45 The purpose of this study was to assess the prognostic impact of targeted
46 agents recommended over the past twenty years in patients with a colonic cancer
47 and synchronous hepatic metastasis (hmCC).

48 **Methods**

49 1-Population

50 From 1995 to 2016, the Hérault tumor register has collected a prospective
51 tumor database of incident cases in both public and private establishments: 8
52 private hospitals, 2 nonspecialized and 2 specialized hospitals in the
53 department of the Herault. Among 2,080 incident cases of mCRC from 1995 to
54 2016, data of a total of 802 patients with a colonic cancer and synchronous
55 hepatic metastasis (hmCC) were completed for analysis. Epidemiological
56 data, colic tumor topography, mode of diagnosis, histopathologic analysis and
57 treatment modalities were collected retrospectively by the Hérault tumor
58 register.

59

60 2-Definitions

61 Pathological staging was based on the Dukes and UICC/TNM classification
62 (3).

63 Tumors were defined as expanding or infiltrating and histologically classified
64 according to World Health Organization criteria (4): well differentiated,
65 moderately differentiated, undifferentiated, or independent cells

66 Treatment modalities were divided in three groups: chemotherapy followed
67 by resection (CR) of the primary tumor (n=100), surgery of the primary site
68 followed by chemotherapy (RC) (n=541) and only chemotherapy with or
69 without TA (onlyCH) (n=161).

70 Postoperative mortality was defined as the occurrence of death within 30
71 days following surgery.

72 French consensus guidelines on the management of colonic (5) and rectal
73 cancer (6) and ESMO consensus guidelines (7) were the reference for

74 chemotherapy settings (8). These recommendations allowed to define three
75 periods: 1- chemotherapy without TA (p1CH) from 1995 to 2004. 2-
76 chemotherapy with second-line TA (p2TA2) from 2005 to 2009. 3-
77 chemotherapy with first-line TA (p3TA1) from 2010 to 2016.

78

79 3- Variables studied

80 Managements and survival rates of patients suffering from hmCC were
81 compared taking into account the periods.

82

83 4- Statistical analysis

84 Clinicopathological parameters (gender, age, tumor localisation, TNM
85 classification, chemotherapy, radiotherapy, surgery, targeted agents, site of
86 treatment, therapeutic sequence, period of treatment and survival) were included
87 in the statistical analysis. Chi2 test, t-test and Kruskal-Wallis test for non-
88 parametric variables were used. Data are shown as the prevalence, mean
89 (standard deviation), or median (range).

90 Data related to the following clinicopathological features were compared in a
91 univariate analysis (Chi-squared test for discrete parameters and t-test for
92 continuous parameters). The comparative analysis of survival of all variables was
93 performed in univariate mode by comparing the medians of survival by considering
94 all the deaths linked to the disease including the deaths of the postoperative
95 period.

96 The evaluation of survival was done on an intention-to-treat basis and therefore
97 included all the results of the proposed medical and surgical treatments. Survival
98 curves were calculated by the Kaplan-Meier method. The overall survival rate
99 (overall mortality including postoperative deaths) was calculated. To assess the

100 relationship between survival time and a range of pathologic variables plus age
101 and gender, separate Cox regression models were fitted for each variable.
102 Significance levels for variables entry and stay in the model were 10%.
103 Postoperative deaths were included. The factors associated with mortality were
104 defined as independent factors of poor prognosis. The SAS version 6, statistical
105 software (SAS Institute, Cary, NC) was used for statistical evaluation. The
106 accepted level of significance was set at $p < 0.05$.

107

108

109

110 **Results**

111 Clinicopathological parameters included in the univariate analysis are summarised
112 in Table 1 and 2. Over p1CH, p2TA2 and p3TA1, the mean ages were 65,5 years
113 (SD 11), 66,5 years (SD 10) and 68 years (SD 11) respectively (p=0.01). The sex
114 ratio increased respectively during these 3 periods from 1,45 to 2.2 (p=0.02).
115 Over p1CH, p2TA2 and p3TA1, the rates of onlyCH, CR and RC have switched from
116 12% to 26%, 6% to 21% and from 82% to 53% respectively (p=0.001). The rates
117 of patients with hmCC treated with targeted agents were 4.9% during p2TA2 and
118 31.2% during p3TA1 (p=0.001). Over p2TA2 (n=161), 4 patients (12%) in onlyCH
119 group and 4 patients (3,3%) in RC group have been treated by target agents
120 (p=0.1). Over p3TA1 (n=358), 34 patients (37%) in onlyCH group, 51 patients
121 (27%) in RC group and 30 patients (39,5%) in CR group have been treated by
122 target agents (p=0.07).

123 ***-Survival analysis***

124 Because of large standard deviation, median survival was used instead of mean of
125 overall survival period. The overall median survival of p1CH, p2TA2 and p3TA1
126 were 20.2, 22.7 and 23.6 months respectively (p=0.12) (Table 3).

127 The cumulative 3-year survival rate of p1CH, p2TA2 and p3TA1 were 27%, 30%
128 and 37% respectively (p=0.03).

129 Univariate analysis (table 4) of the different parameters showed a significant
130 pejorative prognosis for age \geq 75 years (p=0.001), TNM classification T3-4
131 (p=0.001) and N+, chemotherapy only (p=0.001), targeted agents (p=0.03), and
132 therapeutic sequence (p=0.001).

133 In multivariate analysis (table 5), the factors associated with mortality were:
134 age \geq 75 years (1.6 [1.35; 1.9] p=0.0001), chemotherapy only 2.3 [1.6; 3.5]
135 p=0.0001), p1CH 1.7 [1.4; 2.1] p=0.0001), p2TA2 1.2 [1.02;1.6] p=0.04.

136 The period using TA as a second-line regimen (p2TA2) had a poorer prognostic
137 than the period using TA as a front-line regimen (p3TA1) (1.25 [1.01; 1.5]
138 $p < 0.03$).

139 **Discussion**

140

141 The objective of our population study was to assess the place and impact of
142 recommendations on incident cases of hmCC in a population over the past 20
143 years. This study showed a change in therapeutic practices with the progressive
144 use of targeted agents in patients with hmCC with improving survival over 20 years
145 even though the population with hmCC aged over the years.

146 The indications for chemotherapy have evolved over the last 20 years in the light
147 of the first recommendations (5). Our study showed an increase in chemotherapy
148 alone in parallel with the increase in the use of targeted agents. This attitude is
149 justified by the results of several randomized studies. In the CRYSTAL study, the
150 addition of cetuximab, immunoglobulin G1 monoclonal antibodies against
151 epidermal growth factor receptor (EGFR) to irinotecan, fluorouracil and leucovorin
152 (FOLFIRI) as first-line treatment for metastatic CRC reduces the risk of disease
153 progression by 15% (hazard ratio, 0.85; $p = 0.048$) (9). Another randomised
154 controlled trial (PRIME study) showed the benefit of adding Panitumumab, an all-
155 human anti-EGFR monoclonal antibody to fluorouracil, leucovorin and oxaliplatin
156 (FOLFOX4) as a first-line treatment. In contrast, adding panitumumab as a
157 second-line diet did not improve outcomes (10).

158 However, these targeted agents have limitations. In our studies, the use of
159 targeted agents regardless of mCC did not improve survival in univariate analysis
160 showing that it was necessary to respect the indications and combine them with
161 other therapies which will potentiate the effectiveness. The PRIME (11) and
162 CRYSTAL (12) studies and other studies of EGFR monoclonal antibody therapies
163 have shown that mutations other than those of KRAS exon 2 (i.e. KRAS exons 3
164 and 4 and NRAS exons 2,3 and 4 (expanded KRAS analysis)) also predicted a lack

165 of response to monoclonal antibodies targeting EGFR. Therefore, molecular
166 testing of tumors for all activating RAS mutations is essential before considering
167 anti-EGFR therapy (7).

168 It is the combination of medical-surgical care that has an impact on survival as
169 our study has shown. First, in the combination of chemotherapies where studies
170 have shown that FOLFOX and FOLFIRI are active in combination with EGFR
171 inhibitors in patients with a wild-type KRAS disease (13-15).

172 Although our study did not include information on the type of liver surgery
173 performed, the combination of surgery with pre- or post-operative chemotherapy
174 had a favorable impact on survival. Over the past 20 years, preoperative
175 chemotherapy has progressed in contrast to postoperative chemotherapy with no
176 impact on survival. In the literature, the combination of chemotherapy and
177 surgery improves the prognosis of patients with metastatic colorectal cancer that
178 is potentially resectable or initially resectable. For potentially resectable patients,
179 two randomized phase II trials in patients with unresectable disease showed that
180 intensification of treatment led to increased resection rates with a consequent
181 increase in R0 resection rates and improved survival (15,16). Similarly, Folfoxiri
182 with or without bevacizumab was found to be superior to FOLFOX or FOLFIRI
183 regimens and its activity was independent of tumor RAS and BRAF mutation status
184 (16-19). For patients with resectable metastases, perioperative chemotherapy
185 should be the therapeutic approach of choice (7). The proposed chemotherapy
186 should be FOLFOX [or alternatively capecitabine with oxaliplatin (CAPOX)] as
187 reported for the EPOC trial (20,21). Monoclonal antibodies targeting EGFR should
188 not be used in this context, based on data from the New EPOC trial (22). No data
189 on bevacizumab are available for this specific patient group; therefore,
190 bevacizumab should not be used.

191 The strength of this study was the high number of incident cases of targeted
192 patients (colon cancer with synchronous liver metastases) in a population, the
193 hindsight and the multicenter data collection. On the other hand, Tumor registry
194 data collection did not identify the type of surgical resection on liver metastases,
195 type of targeted therapy, and KRAS status. This lack of information limits the
196 interpretation of the results on the place of the evolution of liver surgery of
197 synchronous metastases of colon cancer.

198 In conclusion, our population study showed the favorable impact on the survival
199 of target agents and especially in the first line in patients with colon cancer with
200 synchronous liver metastases.

201

202 **References**

203

204 1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW,
205 Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates
206 for 40 countries in 2012. *Eur J Cancer Oxf Engl 1990*. 2013 Apr;49(6):1374–
207 403.

208 2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al.
209 Cancer incidence and mortality worldwide: sources, methods and major
210 patterns in GLOBOCAN 2012. *Int J Cancer*. 2015 Mar 1;136(5):E359-386.

211 3. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th
212 edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg*
213 *Oncol*. 2010 Jun;17(6):1471–4.

214 4. Jass JR, Atkin WS, Cuzick J, Bussey HJ, Morson BC, Northover JM, and al. The
215 grading of rectal cancer: historical perspectives and a multivariate analysis of
216 447 cases. *Histopathology* 1986; 10:437-59.

217 5. [Consensus conference: Prevention Screening and Management of the Colonic
218 Cancers. Paris, France, January 29-30, 1998. Proceedings]. *Gastroenterol Clin*
219 *Biol*. 1998 Mar;22(3 Suppl):S1-295.

220 6. [Choice of treatment in rectal cancer. Consensus Conference, Chamber of
221 Commerce and Industry, Paris, December 1-2, 1994]. *Ann Gastroenterol*
222 *Hepatol (Paris)*. 1995 Sep;31(4):226–30, 233–6.

223 7. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D,
224 et al. ESMO consensus guidelines for the management of patients with
225 metastatic colorectal cancer. *Ann Oncol Off J Eur Soc Med Oncol*. 2016
226 Aug;27(8):1386–422.

227 8. Borie F, El Nasser M, Herrero A, Gras-Aygon C, Daures J-P, Tretarre B, et al.
228 [Impact of the French consensus guidelines on the management of colonic
229 and rectal cancer: a population-based study]. *J Chir (Paris)*. 2008
230 Jun;145(3):247–51.

- 231 9. Van Cutsem E, Köhne C-H, Hitre E, Zaluski J, Chang Chien C-R, Makhson A,
232 et al. Cetuximab and chemotherapy as initial treatment for metastatic
233 colorectal cancer. *N Engl J Med*. 2009 Apr 2;360(14):1408–17.
- 234 10. Douillard J-Y, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al.
235 Randomized, phase III trial of panitumumab with infusional fluorouracil,
236 leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line
237 treatment in patients with previously untreated metastatic colorectal cancer:
238 the PRIME study. *J Clin Oncol Off J Am Soc Clin Oncol*. 2010 Nov
239 1;28(31):4697–705.
- 240 11. Douillard J-Y, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, et al.
241 Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N*
242 *Engl J Med*. 2013 Sep 12;369(11):1023–34.
- 243 12. Van Cutsem E, Lenz H-J, Köhne C-H, Heinemann V, Tejpar S, Melezínek I, et
244 al. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS
245 mutations in colorectal cancer. *J Clin Oncol Off J Am Soc Clin Oncol*. 2015 Mar
246 1;33(7):692–700.
- 247 13. Folprecht G, Gruenberger T, Bechstein WO, Raab H-R, Lordick F, Hartmann
248 JT, et al. Tumour response and secondary resectability of colorectal liver
249 metastases following neoadjuvant chemotherapy with cetuximab: the CELIM
250 randomised phase 2 trial. *Lancet Oncol*. 2010 Jan;11(1):38–47.
- 251 14. Folprecht G, Gruenberger T, Bechstein W, Raab H-R, Weitz J, Lordick F, et al.
252 Survival of patients with initially unresectable colorectal liver metastases
253 treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary
254 concept (CELIM study). *Ann Oncol Off J Eur Soc Med Oncol*. 2014
255 May;25(5):1018–25.
- 256 15. Ye L-C, Liu T-S, Ren L, Wei Y, Zhu D-X, Zai S-Y, et al. Randomized controlled
257 trial of cetuximab plus chemotherapy for patients with KRAS wild-type
258 unresectable colorectal liver-limited metastases. *J Clin Oncol Off J Am Soc Clin*
259 *Oncol*. 2013 Jun 1;31(16):1931–8.
- 260 16. Gruenberger T, Bridgewater J, Chau I, García Alfonso P, Rivoire M, Mudan S,
261 et al. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially

- 262 unresectable liver metastases from colorectal cancer: the OLIVIA
263 multinational randomised phase II trial. *Ann Oncol Off J Eur Soc Med Oncol.*
264 2015 Apr;26(4):702–8.
- 265 17. Cremolini C, Loupakis F, Antoniotti C, Lupi C, Sensi E, Lonardi S, et al.
266 FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line
267 treatment of patients with metastatic colorectal cancer: updated overall
268 survival and molecular subgroup analyses of the open-label, phase 3 TRIBE
269 study. *Lancet Oncol.* 2015 Oct;16(13):1306–15.
- 270 18. Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, et al. Phase
271 III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan
272 (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan
273 (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo
274 Oncologico Nord Ovest. *J Clin Oncol Off J Am Soc Clin Oncol.* 2007 May
275 1;25(13):1670–6.
- 276 19. Loupakis F, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, et al.
277 Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal
278 cancer. *N Engl J Med.* 2014 Oct 23;371(17):1609–18.
- 279 20. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al.
280 Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone
281 for resectable liver metastases from colorectal cancer (EORTC Intergroup trial
282 40983): a randomised controlled trial. *Lancet Lond Engl.* 2008 Mar
283 22;371(9617):1007–16.
- 284 21. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al.
285 Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for
286 resectable liver metastases from colorectal cancer (EORTC 40983): long-term
287 results of a randomised, controlled, phase 3 trial. *Lancet Oncol.* 2013
288 Nov;14(12):1208–15.
- 289 22. Primrose J, Falk S, Finch-Jones M, Valle J, O'Reilly D, Siriwardena A, et al.
290 Systemic chemotherapy with or without cetuximab in patients with resectable
291 colorectal liver metastasis: the New EPOC randomised controlled trial. *Lancet*
292 *Oncol.* 2014 May;15(6):601–11.

Table 1: Clinicopathological parameters of patients according to the period

Variables	p1CH* n=282		p2TA2* n=162		p3TA1* n=358		Total n=802		p
Gender									
Female	125	44,3%	51	31,5%	151	42,2%	327	40,8%	0,02
Male	157	55,7%	111	68,5%	207	57,8%	475	59,2%	
Age <75	231	81,9%	118	72,8%	248	69,3%	597	74,4%	0,002
≥ 75	51	18,1%	44	27,2%	110	30,7%	205	25,6%	
Histologic Tumor Grading									0,004
Well differentiated	80	28,4%	44	27,2%	159	44,4%	283	35,3%	
Moderately differentiated	78	27,7%	70	43,2%	122	34,1%	270	33,7%	
undifferentiated,- independent cells	20	7,1%	10	6,2%	16	4,5%	46	5,7%	
X	104	36,9%	38	23,5%	61	17,0%	203	25,3%	
pT									0,001
1	2	0,7%	1	0,6%	3	0,8%	6	0,7%	
2	9	3,2%	8	4,9%	11	3,1%	28	3,5%	
3	158	56,0%	75	46,3%	189	52,8%	422	52,6%	
4	57	20,2%	33	20,4%	51	14,2%	141	17,6%	
X	56	19,9%	45	27,8%	104	29,1%	205	25,6%	
pN									0,001
0	38	13,5%	25	15,4%	67	18,7%	130	16,2%	
1	184	65,2%	93	57,4%	193	53,9%	470	58,6%	
X	60	21,3%	44	27,2%	98	27,4%	202	25,2%	
Colon	251	89,0%	134	82,7%	302	84,4%	687	85,7%	0,12
Colorectal Junction	31	11,0%	28	17,3%	56	15,6%	115	14,3%	
Diagnosis modalities									0,008
Metastasis sample	4	1,4%	5	3,1%	24	6,7%	33	4,1%	
Tumor sample	277	98,2%	155	95,7%	333	93,0%	765	95,4%	
Imagery	1	0,4%	2	1,2%	1	0,3%	4	0,5%	
Radiotherapy									0,004
no	272	96,5%	161	99,4%	358	100%	791	98,6%	
yes	10	3,5%	1	0,6%			11	1,4%	
targeted agents									0,001
No	282	100%	154	95,1%	243	67,9%	679	84,7%	
Yes			8	4,9%	115	32,1%	123	15,3%	
Treatment schedule									0,001
onlyCH*	35	12,4%	34	21,0%	92	25,7%	161	20,1%	
RC*	230	81,6%	121	74,7%	190	53,1%	541	67,5%	
CR*	17	6,0%	7	4,3%	76	21,2%	100	12,5%	

294 CR = chemotherapy followed by resection of the primary tumor ; RC = surgery of the primary site

295 followed by chemotherapy ; onlyCH = only chemotherapy with or without TA ; p1CH = chemotherapy

296 without TA ; p2TA2 = chemotherapy with second-line TA ; p3TA1 = chemotherapy with first-line TA.

297

298

299
300
301**Table 2:**

Variables	onlyCH*		RC*		CR*		Total		p
Gender									
Female	75	46,6%	209	38,6%	43	43,0%	327	40,8%	0,17
Male	86	53,4%	332	61,4%	57	57,0%	475	59,2%	
Age <75	105	65,2%	406	75,0%	86	86,0%	597	74,4%	0,008
≥ 75	56	34,8%	135	25,0%	14	14,0%	205	25,6%	
Histologic Tumor Grading									
Well differentiated	1	54	33,5%	189	34,9%	40	40,0%	283	0,04
Moderately differentiated	2	44	27,3%	187	34,6%	39	39,0%	270	
undifferentiated,- independent cells	3	12	7,5%	32	5,9%	2	2,0%	46	
X	X	51	31,7%	133	24,6%	19	19,0%	203	
pT									
1			5	0,9%	1	1%	6	0,7%	0,001
2			20	3,7%	8	8%	28	3,5%	
3			362	66,9%	60	60%	422	52,6%	
4			124	22,9%	17	17%	141	17,6%	
X	161	100%	30	5,5%	14	14%	205	25,6%	
pN									
0			101	18,7%	29	29%	130	16,2%	0,001
1			410	75,8%	60	60%	470	58,6%	
X	161	100%	30	5,5%	11	11%	202	25,2%	
Colon	141	87,6%	468	86,5%	78	78,0%	687	85,7%	0,06
Colorectal Jonction	20	12,4%	73	13,5%	22	22,0%	115	14,3%	
Diagnosis modalities									
Metastasis sample	32	19,9%	1	0,2%			33	4,1%	0,001
Tumor sample	125	77,6%	540	99,8%	100	100%	765	95,4%	
Imagery	4	2,5%		0,0%			4	0,5%	
Radiotherapy									
no	159	98,8%	536	99,1%	96	96%	791	98,6%	0,1
yes	2	1,2%	5	0,9%	4	4%	11	1,4%	
targeted agents									
No	123	76,4%	486	89,8%	70	70%	679	84,7%	0,1
Yes	38	23,6%	55	10,2%	30	30%	123	15,3%	

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CR = chemotherapy followed by resection of the primary tumor ; RC = surgery of the primary site followed by chemotherapy ; onlyCH = only chemotherapy with or without TA

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Table 3: The overall median survival (months) according to the period of targeted agents using.

	p1CH	p2TA2	p3TA1	p p1CH vs p2TA2	p p1CH vs p3TA1	p p2TA2 vs p3TA1
Survival median <i>(months)</i>	20.2	22.7	23.6	0.36	0.03	317
Min <i>(months)</i>	0.3	0.6	0.03			0.6
Max <i>(months)</i>	258.7	163.3	110.0			321

322 p1CH = chemotherapy without TA ; p2TA2 = chemotherapy with second-line TA ; p3TA1 =
323 chemotherapy with first-line TA.

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Table 4 Survival rates in univariate analysis

	n	2 years	3 years	p ³⁰
Gender				
Female	327	46,2%	33%	0,5
Male	475	48%	31,4%	
Age <75	597	51%	36,4%	0,001
≥ 75	205	36,5%	19,1%	
Histologic Tumor Grading				0,02
Well differentiated	283	54%	38,4%	
Moderately differentiated	270	49%	32%	
undifferentiated,- independent cells	46	30%	23,6%	
X	203	38%	25%	
pT				0,001
1	6	83%	62%	
2	28	68%	47%	
3	422	60,8%	43,6%	
4	141	40,7 %	26%	
X	205	19,6%	8,5%	
pN				0,001
0	130	76%	55%	
1	470	52%	36%	
X	202	18,4%	8%	
Colon	687	46,6%	32,2%	0,5
Colorectal Jonction	115	51,2%	32%	
targeted agents				0,03
No	679	48,2%	34%	
Yes	123	43%	22%	
Treatment schedule				0,001
CR*	161	54,8%	39%	
RC*	541	60,8%	37,9%	
onlyCH*	100	10,6%	4,2%	
Period				0,03
p1CH*	282	42%	27%	
p2TA2*	162	44%	30%	
p3TA1*	358	52%	37%	

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332 **CR = chemotherapy followed by resection of the primary tumor ; RC = surgery of the**
 333 **primary site followed by chemotherapy ; onlyCH = only chemotherapy with or without TA**
 334 **; p1CH = chemotherapy without TA ; p2TA2 = chemotherapy with second-line TA ; p3TA1**
 335 **= chemotherapy with first-line TA.**

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Table 5: Multivariate analysis of prognostic factors.

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	OR	95% Inf	95% Sup	P
Age ≥ 75 years	1,6	1,35	1,9	0.0001
p1CH	1.7	1.4	2.1	0.0001
p2TA2	1.2	1.02	1.6	0.04
OnlyCH	2.3	1.6	3.5	0.0001

338 p1CH = chemotherapy without TA ; p2TA2 = chemotherapy with second-line TA ; onlyCH = only

339 chemotherapy with or without TA ; RC = surgery of the primary site followed by chemotherapy

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