Chemotherapy of metastatic colon cancer in France: A population-based study

Léo Mas, Jean-Baptiste Bachet, Valérie Jooste, Côme Lepage, Anne-Marie Bouvier

Chemotherapy of metastatic colon cancer in France: A population-based study

Léo Mas[1] MD, Jean-Baptiste Bachet[1,2] Prof ,MD, Valérie Jooste [3,4] PhD, Côme Lepage[3,4] Prof, MD, Anne-Marie Bouvier[3,4] MD

[1] Department of Hepato-Gastroenterology and Digestive Oncology, Pitié Salpêtrière Hospital, APHP, 47-83 Boulevard de l'Hôpital, 75013 Paris, France

[2] Sorbonne University, UPMC University, 15-21 Rue de l'École de Médecine, 75006 Paris, France

[3] Digestive Cancer Registry of Burgundy, Dijon, France; Dijon University Hospital, 2 Boulevard du Maréchal de Lattre de Tassigny, 21000 Dijon, France

[4] INSERM UMR 1231, Dijon, France; University of Burgundy, Maison de l'Université, Espl. Erasme, 21078 Dijon, France

Funding: Study carried out with the support of Merck Serono.

Corresponding author:
Prof Jean-Baptiste Bachet, MD; Department of Hepato-Gastroenterology and Digestive Oncology, Pitié Salpêtrière Hospital, APHP; 47-83 Boulevard de l'Hôpital, 75013 Paris, France; Tel.: +33 (0)1 42 16 10 41, Fax: +33 (0)1 42 16 12 38, Email: jean-baptiste.bachet@aphp.frjean-baptiste.bachet@aphp.frjean-baptiste.bachet@aphp.fr

Words count: 3497
Abstract words count: 200
Tables: 4
Figures: 2

ABSTRACT

Aims: To describe, using data from a cancer registry in a well-defined French population, the therapeutic strategies and survival of patients with metastatic colon cancer (mCC).

Methods: All patients with synchronous mCC diagnosed within the 2005-2014 period recorded in the digestive cancers registry of Burgundy were included.

Results: 1,286 mCC patients were included (57% male), of which 34.5% did not receive any antitumor treatment. Both, advanced age (≥75 years) and the Charlson comorbidity score ≥2 were significantly associated with the absence of antitumor treatment. Among the patients treated with chemotherapy, 59% and 33% received at least two and three lines, respectively. Most patients treated with chemotherapy (68%) did not receive first-line targeted therapy. Of patients aged ≥75 years, 57% received no chemotherapy and 56% of treated patients had first-line treatment only.

Conclusion: This population-based study shows that more than one-third of patients with mCC receive no chemotherapy and that only 59% of treated patients receive treatment beyond the first line. This study also highlights the fact that more than half of patients ≥75 years do not get any antitumor treatment. In patients <75 years, the proportion of patients receiving chemotherapy and/or undergoing curative intent surgery tended to increase over time.

Key words: Metastatic colorectal cancer, chemotherapy, population-based

INTRODUCTION

Colorectal cancer (CRC) is the third most incident cancer (10%) and the second most deadly (9%) worldwide, with around 1,8 million new cases diagnosed and 881,000 death estimated in 2018 (1). In France, the incidence of CRC has remained relatively stable over the last ten years, while mortality is decreasing, probably in part due to screening programs and recent therapeutic developments (2–4). However, still about 20% of patients have metastatic disease present at the time of diagnosis (5,6). The management of metastatic CRC (mCRC) had evolved greatly in particular due to the improvement of surgical techniques and the diversity of available systemic and locoregional treatments resulting in improved survival in those who are likely to benefit from it (7–9). As a result of these improvements, but also of stricter selection criteria, the median survival of patients with mCRC in recent clinical trials has increased, reaching now 30-40 months (10–12) compared to only 12 months 20 years ago (13).

Numerous cytotoxic molecules (5-fluorouracil [5-FU], oxaliplatin, irinotecan), targeted therapies (anti-vascular endothelial growth factor [anti-VEGF], anti-epidermal growth factor receptor [anti-EGFR]), and oral treatments (trifluridine/tipiracil, regorafenib) are now validated for the management of mCRC patients. The current recommendations propose multi-line strategies based on the initial characteristics of the patient (age, performance index, comorbidities) and of the disease (resectability of metastases, tumor volume, metastatic sites, symptoms, the presence of *RAS* or *BRAF* mutation, a microsatellite stable [MSS]/microsatellite instability [MSI] phenotype) (14,15). These guidelines are based on the results of prospective clinical trials including highly selected patients treated mainly in specialized care centers. Besides, data, which is provided by specialized hospital units cannot be used as a reference due to inevitable selection bias. In particular, older patients are poorly

enrolled in clinical trials (16). Only limited population-based data on chemotherapy administration and prognosis of patients with mCRC are available.

The aim of this study was to describe chemotherapy management of patients with synchronous metastatic colon cancer (mCC) during the first year after diagnosis and to assess survival of these patients using population-based data from a specialized French digestive cancer registry.

PATIENTS AND METHODS

Patient population

The population-based digestive cancer registry includes all digestive tract cancers occurring in the resident population of two well-defined French areas (Côte d'Or, Saône-et-Loire Burgundy, 1,052,000 inhabitants). Information is collected from multiple sources: public and private pathology laboratories, university hospitals (including the Cancer Centre), general hospitals, private surgeons, gastroenterologists, radiotherapists, medical oncologists, surgeons, general practitioners, the hospital administrative database, the Regional Health Services database, and death certificates. Because death certificates are somewhat unreliable, they are only used to notify cases. Because of the multiplicity of information sources, we assumed that nearly all newly diagnosed cases were recorded. The quality and completeness of the registry is being certified every four years through an audit carried out by the National Institute for Health and Medical Research (INSERM), the French National Cancer Institute (INCa), and the French Public Health Agency (SPF). This study was therefore conducted without selection bias.

Registered cancers were classified using the International Classification of Diseases for Oncology (CIM-03). All patients with CRC located from the cecum to the rectosigmoid junction (C18.0 to C19.0), who were diagnosed with synchronous metastases between 2005 and 2014, were included. Location of the tumor was divided into right colon (cecum, ascending, hepatic flexure, and transverse) and left colon (splenic flexure, descending, sigmoid, and rectosigmoid junction). Patients with other synchronous associated cancer were excluded. Patients were grouped into two 5-year periods, 2005–2009 and 2010–2014.

Data collection

Clinical data collected included age, sex, date of diagnosis, tumor stage, primary tumor and metastasis location, comorbidities, and treatment (surgery for the primary tumor and metastatic site, chemotherapy drugs used). Comorbidity was measured according to the Charlson's comorbidity index (CCI). The CCI score was classified into three groups, irrespective of age: CCI score 0 = no comorbidity, CCI score 1 = low comorbidity and CCI score ≥2 = moderate to severe (17).

The lines of treatment given in the first year after diagnosis were defined as follows: i/ first line was defined as the first chemotherapeutic regimen administered to the patient, ii/ new line of chemotherapy was defined as the introduction of new molecules or a new targeted therapy with or without maintenance of other molecules. The addition of bevacizumab in the first 6 months of treatment without the modification of other molecules was not switching treatment to another line of therapy.

The follow-up period lasted at least 1 year for the entire population. This period extended to 3 years for all the patients who received at least one line of chemotherapy between 2011 and 2013.

Details on patient survival were ascertained from the National Register of French Residence (RNIPP), registers of place of birth and whenever necessary from practitioners. Life status at January 2017 was known for 99% of the cases.

Statistical analysis

Associations between categorical variables were assessed with the chi-square test. Net survival, defined as the survival that would be observed if cancer was the only possible cause of death, was calculated at 1 and 3 years using the Pohar-Perme estimator (18). Conditional survival is defined as the probability of surviving an additional *y* years on the condition that

the patient has already survived *x* years. It is calculated by dividing the net survival at (*x* + *y*) years after diagnosis by the net survival at *x* years after diagnosis. We calculated conditional 2 and 3-year net survival corresponding to the probability of surviving an additional 2 and 3 years on the condition that the patient has already survived 1 year considering death related to cancer only.

In order to have a homogeneous population of patients with unresected metastases, survival was calculated both on the entire population and in the subgroup of patients who did not undergo R0 surgical resection of the primary tumor and their metastases during follow-up.

Analyses were performed using STATA statistical software, version 14.0 (StataCorp, College Station, TX, USA).

RESULTS

Baseline characteristics

Between January 2005 and December 2014, 5,808 patients with colon adenocarcinoma were registered. Seventy-two patients with another synchronous cancer were excluded. Of the remaining, 1,286 had synchronous metastatic disease and were included in the present study. Patient and tumor characteristics according to the first line of treatment received in mCC patients during the 2005-2014 period are given in Table 1. The mean age at diagnosis was 70 years for men (standard deviation [SD]: 12 years) and 72 years for women (SD: 14 years; $p = 0.171$). Fifty-three percent of patients were younger than 75 years.

Pattern of first line treatment

Overall, 444 patients (34.5%) received best supportive care (BSC) only (Table 1). Patients with the CCI score ≥2 were given chemotherapy less frequently than patients with other scores (48 % vs 74% with the CCI score 0; $p < 0.001$), as well as patients aged ≥75 years than younger patients (43% vs 90% aged <65 years; $p < 0.001$). Primary tumor location was not associated with chemotherapy administration. The presence of isolated pulmonary metastases or peritoneal metastases was associated with decrease use of chemotherapy.

Overall, 9% of patients were given chemotherapy and underwent R0 resection of their primary and metastatic disease; these included mainly those with isolated liver metastases (15%) and younger (14% aged <75 years vs 3% aged ≥ 75 years).

Patients were grouped into two 5-year periods by date of initial diagnosis, 2005-2009 and 2010-2014. Overall, 32.5% of patients diagnosed between 2010 and 2014 received BSC only compared with 37% of patients diagnosed in the earlier 5-year period between 2005-2009 (Table 1bis A and B, additional data). This slight decrease was observed mainly among patients <75 years of age, 12.5% of whom had not received any antitumor treatment in the

most recently diagnosed group compared with 18% in the earlier diagnosed group. This proportion was more stable in patients aged ≥75 years with 55% in the 2010–2014 group and 58% in the 2005–2009 group. After 2010, the proportion of patients undergoing curative intent surgery increased in the group of patients younger than 75 years (from 12% to 16%), while this approach remained marginal in older patients (a total of 3% in the two 5-year period groups each). Among patients with isolated hepatic location, 18.5% had surgery in the 2010-2014 period compared with 11.5% over the 2005-2009 period.

First line regimens

Of the 842 treated patients, 80% received first-line combination treatments (Figure 1). The most common regimens were FOLFOX (56%), FOLFIRI (20%), and fluoropyrimidines (20%). A total of 32% of patients received first-line targeted therapy, mainly an anti-VEGF antibody (28%), with a minimal increase in the 2010-2014 group (33% vs 29% in the 2005-2009 group) (Figures 1bis, additional data). In the group of patients younger than 75 years, 93% had multidrug therapy and 38% first-line targeted therapy, while in the group of patients ≥75 years of age, 47% had fluoropyrimidine monotherapy and 16% targeted therapy (Figure 1ter, additional data).

Further lines regimens

Of the 273 patients who received first-line chemotherapy between 2011 and 2013 and who were followed for at least 3 years, 59% received second-line treatment, 33% third-line, and 14% four or more lines (Table 2). Age was the only factor associated with the number of lines administered ($p = 0.042$). No statistically significant association was found however with CCI and the primary and metastatic location at diagnosis.

FOLFIRI was the most prevalent second and third-line therapy (60% and 45%, respectively) while FOLFOX was less commonly used (35% and 37%, respectively; Figure 2). Sixty percent and 64% of patients received targeted therapy as part of their second and third-line treatment, respectively, with anti-VEGF being the most frequently used targeted therapy (40% and 42%; Figure 2).

Net and conditional survival

The net survival for 841 patients who received at least one line of chemotherapy was 70% at 1 year and 30% at 3 years. It was 95% and 83.5% for those who had R0 resection of the primary tumor and metastases, and 65.5% and 21% for those who did not undergo curative-intent surgery (Table 3). Younger age ($p < 0.001$), the CCI score <2 ($p = 0.034$), first-line multidrug therapy ($p < 0.001$), and R0 resection ($p < 0.001$) were associated with longer survival. Left tumor location ($p < 0.001$) and the presence of isolated liver metastases ($p <0.001$) were also associated with better outcomes. The latter association remained significant even after excluding patients who underwent curative-intent surgery ($p < 0.001$; Table 3bis, additional data).

The 2 and 3-year conditional survival was 62% and 42%, respectively, in patients who received first-line chemotherapy and were alive 1 year after diagnosis, 90.5% and 83% in those who underwent R0 resection and 55% and 32% in those who did not undergo curative-intent surgery, respectively (Table 6, additional data). Younger patients had better conditional survival, but the CCI score, as well as metastases location in patients without R0 resection, had no significant impact on outcomes (Table 6bis, additional data).

DISCUSSION

We report the French population-based study of 1,286 patients with synchronous mCC diagnosed between the years 2005 and 2014.

Therapeutic abstention and elderly population

This study shows that a high proportion of patients (34.5%) did not receive chemotherapy; with older patients (aged ≥75 years) at least two times less likely to receive chemotherapy than younger patients (aged <75 years; 43% vs 85%). Not surprisingly, age and comorbidities assessed by the CCI score were strongly associated with chemotherapy being administered. These results are well in line with those of previously published population-based or national administrative cohort studies, in which the proportions of treated patients ranged from 56% to 69% (Table 4) (5,6,19–21).

In terms of low number of elderly patients who received antitumor treatment, similar findings were reported in a previous study conducted in the same geographic area as our work between 1976 and 2009: while the proportion of elderly patients receiving chemotherapy increased sharply in the early 2000s, it was administered to only 36% of patients aged 75 years or older in the 2005-2009 period (compared to 29% and 5% during the 1997-2004 and 1976-1996 periods, respectively) (22). In our population, this proportion was relatively stable over the entire study period. Similar data have also been reported in other populations of French and Canadian patients (Table 4) (20,21).

On the contrary, a trend to higher rates of chemotherapy administration and curative intent surgical treatments was observed in younger patients treated after 2010. This was particularly noticeable in patients <75 years with isolated liver metastases, almost 20% of whom underwent resection in the recent time-period compared to just over 10% earlier.

Older patients often have more comorbidities and poorer general health than their younger counterparts, which can partially explain the lower use of chemotherapy. Nevertheless, the extent of the difference in treatment between these two groups suggests that older patients may be undertreated for their disease. This might be related to the low proportion of elderly patients enrolled in clinical trials, raising questions about the expected benefit in these patients. In a recent prospective cohort of older CRC patients, three quarters of them were ineligible for a clinical trial and one third of eligible patients were not invited to participate (16). Still, several pooled analyzes of randomized trials have demonstrated similar clinical benefit and safety between younger and older subgroups (23,24). Recently, the French recommendations specific to the management of mCRC in elderly patients have been proposed (25). These guidelines recommend palliative chemotherapy regardless of age, after performing a systematic screening for frailty using the G8 score and geriatric evaluation in the event of deterioration (25).

Multi-line therapeutic strategy in current practice

Results of our study show that less than two-thirds of treated patients were offered second-line chemotherapy (59%) and only 33% third-line. Others have also reported lower proportions of second and third lines (26,27). Moreover, a higher age was associated with the number of chemotherapy lines received. Only 44% and 20% of patients ≥75 years were given second and third-line of treatment compared with 66% and 39%, respectively, in patients <75 years. As expected, the proportions of patients receiving several lines of chemotherapy in our study was lower than that reported in the most recent phase III studies (second-line: 70 -75%, third-line: 40-50%) (28–30). However, this difference was particularly less pronounced for those aged <75 years in our population, more similar to patients included in the reported phase III trials. These findings highlight that more than one third of patients in total and more

than half of those aged ≥75 years do not receive second-line treatment. Although the interpretation of these results should be cautious considering the lack of survival comparisons, these data might question the relevance of step-up strategies in real-life practice. Indeed, the high proportion of patients who will not benefit from a second line chemotherapy might argue for the use, whenever possible, of the theoretically most effective regimen, consisting of multidrug therapy associated with targeted therapy, as first-line treatment. This choice should be adapted to the RAS status (29,31–33).

Chemotherapy regimens and targeted therapies

In our population, 80% of patients received first-line multidrug combination therapy, with FOLFOX being the most frequently used regimen. FOLFIRI was the most widely administered as a second and third-line treatment.

However, only 32% of patients received first-line targeted therapy, mainly an anti-VEGF antibody, with no clear difference between the two time periods (Figure 1bis, additional data). Moreover, targeted therapies were offered only to 16% of patients aged ≥75 years compared to 38% of younger patients (<75 years). These rates although lower than those reported by other population studies, particularly by these conducted in the United States with rates reaching 45%-55% of patients receiving first-line targeted therapies (mainly anti-VEGF-based) (table 4) (26,27,34), are similar to those (36%) reported in the ThInDiT French cohort (20).

The limited prescription of an anti-EGFR antibody as first-line treatment should be emphasized. Only 4% of the patients analyzed in our study were treated with an anti-EGFR antibody as part of their first-line protocol, which is similar to other studies (Table 4). Despite the demonstrated efficacy of anti-EGFR therapies in the first-line treatment of mCRC in 2009 (35,36), these were underused in the 2010-2014 period (5% versus 2% in the 2005-2009

period; figure 1bis, additional data). Noteworthy, 60% of patients were treated with second-line targeted therapy; including 20% receiving anti-EGFR-based therapy.

The delay for obtaining test results from routine *RAS/BRAF* mutational status assessment, up to 3 weeks in France (37), may have affected these results. Depending on the clinical situation, this delay may be too long and chemotherapy treatment may need to be started before determining eligibility for anti-EGFR therapy. In some patients this could be mitigated by initiating a therapeutic strategy with the chemotherapy backbone alone while awaiting the results of *RAS/BRAF* molecular testing in order to add an anti-VEGF or an anti-EGFR antibody treatment in a second step. This practice was evaluated retrospectively without showing any deleterious effect compared to treatment with anti-VEGF antibodies from the start (38). In that case, the approach that we applied to determine lines of chemotherapy might have biased our results with underestimation of the incorporation of anti-EGFR antibodies in first-line treatment. However, the low proportion of first-line targeted therapy in our study seems to be mainly due to a lower rate of patients receiving anti-VEGF antibodies as compared to other studies, while published data of first-line anti-EGFR antibodies are similar to ours (Table 4). Another possible explanation of our results could be the prescription of first-line treatments without targeted therapy in our population, again related to the delay to obtain molecular results, with the addition of a targeted therapy only as part of second line treatment after progression.

Survival and prognostic factors

In this study of mCC from a French registry data, 65% of patients received at least one line of chemotherapy. Among these, the net survival at 1 year was 70% and at 3 years 30%, while it was 65% and 21% in the patients who did not undergo curative-intent resection. Age and comorbidities (the CCI score 0-1 vs ≥2) were associated with poorer survival. Patients with

left colon tumors and those with isolated liver metastases had better outcomes, which is consistent with previous data in the literature (39–41). Patients with isolated liver metastases were the most likely to receive surgical treatment, with a gradual increase in the use of this type of strategy in the 2010-2014 period. The favorable prognostic impact associated with liver metastatic location remained significant in non-operated patients. An isolated pulmonary location appeared to be associated with a lower use of chemotherapy. However, these results should be viewed with caution given the small numbers involved. Still, we may assume that these results may be related to the fact that these patients with better prognosis and less symptomatic disease are more often abstain from treatment (40–42). Unfortunately, the small number of patients made it impossible to perform survival analysis in this subgroup. Finally, patients with peritoneal location of metastases were less frequently treated with chemotherapy, possibly due to an occlusive syndrome common in these patients. However, there was no statistically significant association between peritoneal location of metastases and differences in survival.

Strengths and limitations

The strength of this study lies in the high-quality population-based cancer registry from which our data are derived. Given the number and variety of information sources, it was assumed that nearly all newly diagnosed cases were recorded and that this study was performed without selection bias.

This population-based study has also some limitations. The 1 year follow-up period for the majority of patients limits the strength of our data according to the number of lines and chemotherapy regimens used beyond the first year. Methodology employed to define lines of chemotherapy was possibly a source of bias in the evaluation of the number of lines received and their composition in patients treated with an anti-EGFR antibody introduced on a delayed

basis. However, the proportion of patients who received first-line anti-EGFR therapy in our study was similar to that reported in the literature, thus we assumed that the impact of this potential bias was limited. Moreover, our analyses were restricted by the small number of patients in several subgroups according to the location of metastases, in particular concerning isolated pulmonary metastases.

CONCLUSION

In this French population-based study of patients who were diagnosed with synchronous mCC between 2005 and 2014, nearly a third of patients (34.5%) did not receive any antitumor treatment. A strong treatment disparity was observed especially between patients aged ≥75 years, 57% of whom did not receive chemotherapy compared to 15% of the younger patients, thus highlighting the limitations of current practice in older adults. In their younger counterparts, the proportion of patients receiving chemotherapy and/or undergoing curative intent surgery tended to increase over time.

More than a third (41%) of patients who received first-line treatment and majority of those aged ≥75 years (56%) did not receive second or subsequent lines of therapy, questioning the relevance of step-up strategies in current practice.

Conflict of interest

L. Mas declare no competing interests.

J.B. Bachet has received personal fees from Amgen, AstraZeneca, Bayer, Merck Serono, Pierre Fabre, Roche, Sanofi, Servier, Shire, and nonfinancial support from Amgen, Merck Serono, and Roche.

V. Jooste declare no competing interests.

C. Lepage has received personal fees from Advanced Accelerator Application, Merck Serono, and nonfinancial support from Amgen, Pierre Fabre, Merck Serono and Ipsen.

A.M. Bouvier declare no competing interests.

Funding

This study was supported by a grant from Merck Serono s.a.s. (France), an affiliate of Merck KGaA (Darmstadt, Germany). Merck Serono s.a.s. (France) had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Acknowledgements

The authors thank Magdalena Benetkiewicz for editorial assistance.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018 Nov;68(6):394–424.

2. Estimations nationales de l'incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018. Volume 1 – Tumeurs solides. :372.

3. Malvezzi M, Carioli G, Bertuccio P, Boffetta P, Levi F, La Vecchia C, et al. European cancer mortality predictions for the year 2018 with focus on colorectal cancer. Annals of Oncology. 2018 Apr;29(4):1016–22.

4. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017 Apr;66(4):683–91.

5. van der Geest LGM, Lam-Boer J, Koopman M, Verhoef C, Elferink MAG, de Wilt JHW. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. Clin Exp Metastasis. 2015 Jun;32(5):457–65.

6. van der Pool AEM, Damhuis RA, IJzermans JNM, de Wilt JHW, Eggermont AMM, Kranse R, et al. Trends in incidence, treatment and survival of patients with stage IV colorectal cancer: a population-based series: Trends in stage IV colorectal cancer. Colorectal Disease. 2012 Jan;14(1):56–61.

7. Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, et al. Improved Survival in Metastatic Colorectal Cancer Is Associated With Adoption of Hepatic Resection and Improved Chemotherapy. JCO. 2009 Aug 1;27(22):3677–83.

8. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier A-M. Epidemiology and Management of Liver Metastases From Colorectal Cancer: Annals of Surgery. 2006 Aug;244(2):254–9.

9. Tomita Y, Karapetis CS, Ullah S, Townsend AR, Roder D, Beeke C, et al. Survival improvements associated with access to biological agents: Results from the South Australian (SA) metastatic colorectal cancer (mCRC) registry. Acta Oncologica. 2016 Apr 2;55(4):480–5.

10. Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon J-L, Hecht JR, et al. PEAK: A Randomized, Multicenter Phase II Study of Panitumumab Plus Modified Fluorouracil, Leucovorin, and Oxaliplatin (mFOLFOX6) or Bevacizumab Plus mFOLFOX6 in Patients With Previously Untreated, Unresectable, Wild-Type *KRAS* Exon 2 Metastatic Colorectal Cancer. Journal of Clinical Oncology. 2014 Jul 20;32(21):2240–7.

11. Venook AP, Niedzwiecki D, Lenz H-J, Innocenti F, Fruth B, Meyerhardt JA, et al. Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With *KRAS* Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial. JAMA. 2017 Jun 20;317(23):2392.

12. Modest DP, Martens UM, Riera-Knorrenschild J, Greeve J, Florschütz A, Wessendorf S, et al. FOLFOXIRI Plus Panitumumab As First-Line Treatment of *RAS* Wild-Type Metastatic Colorectal Cancer: The Randomized, Open-Label, Phase II VOLFI Study (AIO KRK0109). JCO. 2019 Dec 10;37(35):3401–11.

13. Saltz LB, Moore MJ, Pirotta N. Irinotecan plus Fluorouracil and Leucovorin for Metastatic Colorectal Cancer. The New England Journal of Medicine. 2000;10.

14. Phelip JM, Tougeron D, Léonard D, Benhaim L, Desolneux G, Dupré A, et al. Metastatic colorectal cancer (mCRC): French intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR). Digestive and Liver Disease. 2019 Oct;51(10):1357–63.

15. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016 Aug;27(8):1386–422.

16. Canouï-Poitrine F, Lièvre A, Dayde F, Lopez-Trabada-Ataz D, Baumgaertner I, Dubreuil O, et al. Inclusion of Older Patients with Cancer in Clinical Trials: The SAGE Prospective Multicenter Cohort Survey. 2019;9.

17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases. 1987 Jan;40(5):373–83.

18. Perme MP, Stare J, Estève J. On Estimation in Relative Survival. Biometrics. 2012 Mar;68(1):113–20.

19. Renouf DJ, Lim HJ, Speers C, Villa D, Gill S, Blanke CD, et al. Survival for Metastatic Colorectal Cancer in the Bevacizumab Era: A Population-based Analysis. Clinical Colorectal Cancer. 2011 Jun;10(2):97–101.

20. Doat S, Thiébaut A, Samson S, Ricordeau P, Guillemot D, Mitry E. Elderly patients with colorectal cancer: Treatment modalities and survival in France. National data from the ThInDiT cohort study. European Journal of Cancer. 2014 May;50(7):1276–83.

21. Chan M, Hugh-Yeun K, Gresham G, Speers CH, Kennecke HF, Cheung WY. Population-Based Patterns and Factors Associated With Underuse of Palliative Systemic Therapy in Elderly Patients With Metastatic Colon Cancer. Clinical Colorectal Cancer. 2017 Jun;16(2):147–53.

22. Mitry E, Rollot F, Jooste V, Guiu B, Lepage C, Ghiringhelli F, et al. Improvement in survival of metastatic colorectal cancer: Are the benefits of clinical trials reproduced in population-based studies? European Journal of Cancer. 2013 Sep;49(13):2919–25.

23. Kabbinavar FF, Hurwitz HI, Yi J, Sarkar S, Rosen O. Addition of Bevacizumab to Fluorouracil-Based First-Line Treatment of Metastatic Colorectal Cancer: Pooled Analysis of Cohorts of Older Patients From Two Randomized Clinical Trials. JCO. 2009 Jan 10;27(2):199–205.

24. Kozloff MF, Berlin J, Flynn PJ, Kabbinavar F, Ashby M, Dong W, et al. Clinical Outcomes in Elderly Patients with Metastatic Colorectal Cancer Receiving Bevacizumab

and Chemotherapy: Results from the BRiTE Observational Cohort Study. Oncology. 2010;78(5–6):329–39.

25. Aparicio T, Canouï-Poitrine F, Caillet P, François E, Cudennec T, Carola E, et al. Treatment guidelines of metastatic colorectal cancer in older patients from the French Society of Geriatric Oncology (SoFOG). Digestive and Liver Disease. 2020 Feb;S1590865820300025.

26. Abrams TA, Meyer G, Schrag D, Meyerhardt JA, Moloney J, Fuchs CS. Chemotherapy Usage Patterns in a US-Wide Cohort of Patients With Metastatic Colorectal Cancer. JNCI Journal of the National Cancer Institute. 2014 Feb 7;106(2):djt371–djt371.

27. Hess GP, Wang PF, Quach D, Barber B, Zhao Z. Systemic Therapy for Metastatic Colorectal Cancer: Patterns of Chemotherapy and Biologic Therapy Use in US Medical Oncology Practice. JOP. 2010 Nov;6(6):301–7.

28. Ducreux M, Malka D, Mendiboure J, Etienne P-L, Texereau P, Auby D, et al. Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000–05): an open-label, randomised, phase 3 trial. 2011;12:13.

29. Cremolini C, Loupakis F, Antoniotti C, Lupi C, Sensi E, Lonardi S, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. The Lancet Oncology. 2015 Oct;16(13):1306–15.

30. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran S-E, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. The Lancet Oncology. 2014 Sep;15(10):1065–75.

31. Cremolini C, Loupakis F, Antoniotti C, Lonardi S, Masi G, Salvatore L, et al. Early tumor shrinkage and depth of response predict long-term outcome in metastatic colorectal cancer patients treated with first-line chemotherapy plus bevacizumab: results from phase III TRIBE trial by the Gruppo Oncologico del Nord Ovest. Annals of Oncology. 2015 Jun;26(6):1188–94.

32. Stintzing S, Modest DP, Rossius L, Lerch MM, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial. The Lancet Oncology. 2016 Oct;17(10):1426–34.

33. Modest DP, Fischer von Weikersthal L, Decker T, Vehling-Kaiser U, Uhlig J, Schenk M, et al. Sequential Versus Combination Therapy of Metastatic Colorectal Cancer Using Fluoropyrimidines, Irinotecan, and Bevacizumab: A Randomized, Controlled Study—XELAVIRI (AIO KRK0110). JCO. 2019 Jan 1;37(1):22–32.

34. McKibbin T, Frei CR, Greene RE, Kwan P, Simon J, Koeller JM. Disparities in the Use of Chemotherapy and Monoclonal Antibody Therapy for Elderly Advanced Colorectal Cancer Patients in the Community Oncology Setting. The Oncol. 2008 Aug;13(8):876–85.

35. Eric VC, Claus-Henning K, Erika H, Jerzy Z, Chung-Rong CC, Anatoly M, et al. Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer. n engl j med. 2009;10.

36. Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, et al. Fluorouracil, Leucovorin, and Oxaliplatin With and Without Cetuximab in the First-Line Treatment of Metastatic Colorectal Cancer. JCO. 2009 Feb 10;27(5):663–71.

37. Lièvre A, Merlin J-L, Sabourin J-C, Artru P, Tong S, Libert L, et al. RAS mutation testing in patients with metastatic colorectal cancer in French clinical practice: A status report in 2014. Digestive and Liver Disease. 2018 May;50(5):507–12.

38. Palmieri L, Mineur L, Tougeron D, Rousseau B, Granger V, Gornet J, et al. Withholding the Introduction of Anti- Epidermal Growth Factor Receptor: Impact on Outcomes in *RAS* Wild- Type Metastatic Colorectal Tumors: A Multicenter AGEO Study (the WAIT or ACT Study). The Oncol [Internet]. 2020 Feb [cited 2020 Sep 28];25(2). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1634/theoncologist.2019-0328

39. Arnold D, Lueza B, Douillard J-Y, Peeters M, Lenz H-J, Venook A, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Annals of Oncology. 2017 Aug;28(8):1713–29.

40. Prasanna T, Karapetis CS, Roder D, Tie J, Padbury R, Price T, et al. The survival outcome of patients with metastatic colorectal cancer based on the site of metastases and the impact of molecular markers and site of primary cancer on metastatic pattern. Acta Oncologica. 2018 Nov 2;57(11):1438–44.

41. Franko J, Shi Q, Meyers JP, Maughan TS, Adams RA, Seymour MT, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. The Lancet Oncology. 2016 Dec;17(12):1709–19.

42. Riihimäki M, Hemminki A, Sundquist J, Hemminki K. Patterns of metastasis in colon and rectal cancer. Sci Rep. 2016 Jul;6(1):29765.

Tables and figures

- **Table 1:** Patient and tumor characteristics according to the first line of treatment received in patients diagnosed with synchronous metastatic colon adenocarcinoma during the 2005-2014 period

- **Table 2:** Lines of chemotherapy received during the first three years following diagnosis in patients with metastatic colon adenocarcinomas diagnosed between 2011 and 2013

- **Table 3:** The 1 and 3-year net survival for patients with metastatic colon adenocarcinoma treated with chemotherapy between 2005 and 2014

- **Table 4:** Summary of main population-based studies evaluating systemic treatments and/or survival in mCRC.

- **Figure 1:** First-line chemotherapy regimens (A) and targeted therapies (B) administered within the first year after diagnosis over the period from 2005 to 2014

- **Figure 2:** Chemotherapy regimens (A) and targeted therapies (B) administered during the first 3 years after diagnosis over the period from 2011 to 2013 in first, second, and third line.

Table 1: Patient and tumor characteristics according to the first line of treatment received in patients diagnosed with synchronous metastatic colon adenocarcinoma during the 2005-2014 period

	Overall patients N (%)	Chemotherapy alone (n=727) %	Chemotherapy and R0 resection* (n=115) %	Best supportive care (n=444) %	P value
Total	1286 (100.0)	56.5	8.9	34.5	
Sex					0.891
Male	736 (57.2)	56.1	9.2	34.7	
Female	550 (42.8)	57.1	8.6	34.4	
Age at diagnosis					<0.001
<75	687 (53.4)	70.4	14.3	15.3	
<65	405 (31.5)	74.1	16.1	9.9	
65-69	132 (9.6)	68.2	11.4	20.5	
70-74	150 (11.7)	62.7	12.0	25.3	
≥75	599 (46.6)	40.6	2.8	56.6	
Charlson index score					<0.001
0	716 (55.7)	62.9	11.0	26.1	
1	303 (23.6)	52.8	9.2	38.0	
≥2	260 (20.2)	44.6	3.1	52.3	
Unknown	7				
Location					0.144
Colon right	564 (43.8)	55.9	7.8	36.4	
Colon left	686 (53.3)	57.4	10.4	32.2	
Unknown	36				
Metastatic sites					<0.001
Liver only	574 (44.6)	52.3	15.0	32.8	
Lung only	41 (3.2)	51.2	7.3	41.5	
Peritoneum	157 (12.2)	47.1	8.3	44.6	
Liver + lung	151 (11.7)	72.9	2.0	25.2	
Liver + peritoneum	139 (10.8)	59.7	0.7	39.6	
Multiples including liver	141 (11.0)	69.5	0.7	29.8	
Multiples without liver	50 (3.9)	62.0	8.0	30.0	
Other	33 (2.6)				

*R0 resection of primary tumor and metastasis

Table 2: Lines of chemotherapy received during the first three years following diagnosis in patients with metastatic colon adenocarcinoma diagnosed between 2011 and 2013

		Lines of therapy						
		1	2	3	4	5	6	
	N	%	%	%	%	%	%	P value
Total	273	41.0	26.4	18.3	10.3	2.6	1.5	
Sex								0.310
Male	153 (56.0)	46.4	22.2	17.7	9.2	3.3	1.3	
Female	120 (44.0)	34.2	31.7	19.2	11.7	1.7	1.7	
Age at diagnosis								0.042
<75	182 (66.7)	33.5	27.5	22.5	11	4	2.2	
<65	131 (48.0)	33.6	29.0	21.4	9.9	4.6	1.5	
65-69	25 (9.2)	28.0	28.0	32.0	8.0	0.0	4.0	
70-74	26 (9.5)	38.5	19.2	19.2	19.2	0.0	3.9	
≥75	91 (33.3)	56.0	24.2	9.9	8.8	1.1	0.0	
Charlson index score								0.714
0	181 (66.3)	38.7	26.0	21.0	9.9	2.2	2.2	
1	58 (21.2)	41.4	31.0	12.1	12.1	3.5	0.0	
≥2	34 (12.4)	52.9	20.6	14.7	8.8	2.9	0.0	
Location								0.517
Colon right	119 (43.6)	40.3	26.9	21.0	10.1	1.7	0.0	
Colon left	146 (53.5)	41.1	25.3	17.1	11.0	2.7	2.7	
Unknown	8							
Metastatic sites								0.177
Liver only	139 (50.9)	38.9	30.2	13.0	13.0	2.9	2.2	
Liver + other	85 (31.1)	41.2	23.5	23.5	10.6	1.2	0.0	
Other	49 (17.9)	46.9	20.4	24.5	2.0	4.1	2.0	
R0 resection								0.137
No	226 (82.8)	38.1	27.4	20.8	9.7	2.7	1.3	
Yes	47 (17.2)	55.3	21.3	6.4	12.8	2.1	2.1	

Table 3: The 1 and 3-year net survival for patients with metastatic colon adenocarcinoma treated with chemotherapy between 2005 and 2014

	Overall patients	**1 year**		**3 years**		**P value**
	N (%)	%	IC 95%	%	IC 95%	
Total	841 (100.0)	69.9	66.8-72.7	29.7	26.4-33.0	
Sexe						0.525
Male	480 (57.1)	70.5	66.9-73.7	30.5	26.3-34.8	
Female	361 (42.9)	69.1	65.1-72.7	28.6	24.0-33.3	
Age at diagnosis						<0.001
<65	364 (43.3)	75.0	71.4-78.2	36.5	31.5-41.4	
65-69	105 (12.5)	74.5	68.3-79.7	35.6	26.7-44.6	
70-74	112 (13.3)	72.3	65.8-77.8	32.0	23.5-40.9	
≥75	260 (30.9)	58.2	53.2-63.0	15.0	11.1-19.5	
Charlson index score						0.034
0	181 (21.5)	71.2	67.8-74.3	31.4	27.4-35.5	
1	58 (6.9)	70.4	65.2-75.0	30.3	23.8-37.0	
≥2	34 (4.0)	62.7	56.0-68.7	20.4	14.1-27.6	
Unknown	1					
Location						<0.001
Colon right	359 (42.7)	63.8	59.6-67.8	20.5	16.6-24.8	
Colon left	465 (55.3)	75.9	72.6-78.9	37.8	33.3-42.4	
Unknown	17					
Metastasis sites*						<0.001
Liver only	386 (45.9)	77.1	73.6-80.2	39.9	34.8-45.0	
Liver + other	295 (35.1)	60.3	55.6-64.7	16.8	12.9-21.2	
Lung only	24 (2.8)	NC		NC		
Peritoneum + Other	242 (28.8)	60.5	55.4-65.1	16.6	12.3-21.3	
Multiple without peritoneum	175 (20.8)	63.9	58.2-69	20.1	14.7-26.1	
R0 resection of primary tumor and metastasis						<0.001
No	726 (86.3)	65.5	62.2-68.6	20.7	17.7-23.9	
Yes	115 (13.7)	95.3	92.3-97.1	83.5	74.3-89.6	
First-line chemotherapy regimen**						<0.001
Fluoropyrimidine	165 (19.6)	56.0	49.7-61.8	13.3	8.9-18.5	
FOLFOX	463 (55.0)	73.2	69.7-76.3	33.8	29.3-38.2	
FOLFIRI	168 (20.0)	70.1	64.8-74.7	29.0	22.6-35.8	
Triplet regimen***	35 (4.2)	85.1	76.0-91.0	57.1	38.8-71.9	

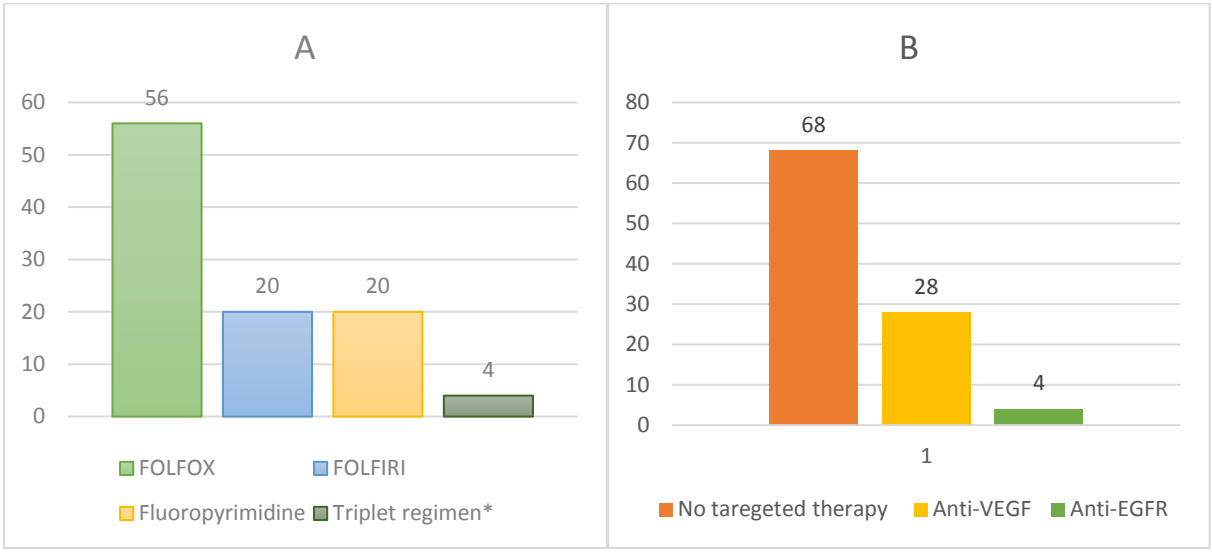
NC: not calculable; * Other locations (n=14); **With or without targeted therapy, Excluded cases treated with: anti-VEGF alone (n=4), Taxol + Carboplatin (n=3), with Taxol + anti-VEGF (n=1), and unknown molecule (n=2); *** FOLFOXIRI or FOLFIRINOX

Table 4: Summary of main population-based studies evaluating systemic treatments and/or survival in mCRC

Reference	Study Period	Population	Country	N	Inclusion criteria	Age, years (Median)	L1 (%)	L2* (%)	L3* (%)	Multi-chemotherapy +/- targeted therapy L1 (%)	L1 anti-VEGF / anti-EGFR (%)	Median overall survival, months (Treated vs Not treated)
Global population												
Van der pool et al. 2011	2005-2007	RCR	Netherlands	1036	NS	-	56	-	-	-	-	11.6
Renouf et al. 2011	2006	BCCA	Canada	448	NS	69	68	-	-	-	-	17.3 (23.6 vs 5.9)
Kumar et al. 2013	2006-2012	SACR	South Australia	2314	NS	<80 : 71% (67) >80 : 29% (85)	68 28	53 35	26 11	74 26	- -	19.2 (22.3 vs 2.7) 8.2 (19 vs 2.6)
Doat et al. 2014	2009	FHI	France	6312	NS	72	69	-	-	84	30 / 6.5	-
Van der Geest et al. 2015	2008-2011	NCR	Netherlands	10667	NS	69	60	-	-	-	-	12
Chan et al. 2016	2009-2010	BCCA	Canada	1013	NS	67 <70 : 58% >70 : 42%	65 77 48	- - -	- - -	- 81 47	- - -	- - (23.3 vs 5.7) - (21.2 vs 6.0)
Tomita et al. 2016	2009-2014	SAmCRC	South Australia	1844	NS	71.5	59	54	23	NA	41 / 2	17.1 (25.2 vs 3.1)
Treated population												
McKibbin et al. 2008	2003-2006	Community practices	US	520	Treated	66 <65 : 45% >65 : 55%	- 100 100	- 59 57	- 32 26	- 84 58	- 63 / - 44 / -	- 24.5 19.1
Hess et al. 2010	2004 – 2008	EMRs	US	1655	Treated	62	100	45	19	52	42 / 3	-
Abrams et al. 2014	2004 – 2011	IntelliDose	US	4877	Treated	-	100	53	28	83	51 / 4	-
Elderly population												
Reese et al. 2013	2003-2007	SEER	US	7951	> 65	-	41	44	19	-	-	-
Bikov et al. 2016	2003-2009	SEER	US	4545	Treated > 65	> 75 : 51%	100	42	-	69	40 / 3	-

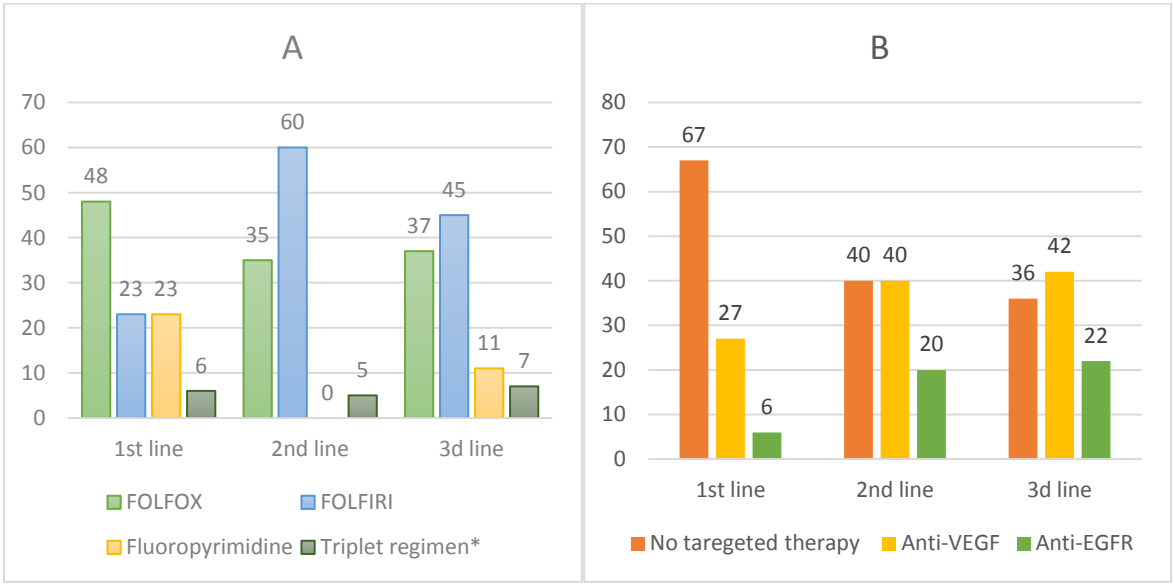
*expressed as % of patients treated in L1; RCR: Rotterdam Cancer Registry; BCCA: British Columbia Cancer Agency; SACR: South Australia Cancer Registry; FHI: French Health Insurance; NCR: Netherlands Cancer Registry; SAmCRC: South Australia metastatic Colorectal Cancer Registry; EMRs: Electronic Medical Records; SEER: Surveillance Epidemiology and End Results; NS: not selected

Figure 1. First-line chemotherapy regimens (A) and targeted therapies (B) administered within the first year after diagnosis over the period from 2005 to 2014



*Triplet regimen: FOLFOXIRI or FOLFIRINOX

Figure 2. Chemotherapy regimens (A) and targeted therapies (B) administered during the first 3 years after diagnosis over the period from 2011 to 2013 in first, second, and third line.



*Triplet regimen: FOLFOXIRI or FOLFIRINOX