Evaluation of Histopathological Heterogeneity After Preoperative Chemotherapy in Patients With Liver Metastases from Colorectal Cancer

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**Research**

**Keywords:** Histopathological, heterogeneity, colorectal cancer, liver, metastasis.

**DOI:** [https://doi.org/10.21203/rs.3.rs-192547/v1](https://doi.org/10.21203/rs.3.rs-192547/v1)

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Abstract

Background: Patients with liver metastases from colorectal cancer (CRLMs) frequently receive chemotherapy prior to liver resection. Histopathological assessment of the resected specimen can evaluate the response to chemotherapy. This study analyzed the correlation between histopathological changes in the primary site and liver metastases.

Patients and Methods: This study comprised 45 patients with resectable CRLMs at the Surgical Oncology Department of Gifu University School of Medicine from January 2006 to August 2015.

Results: The study included 24 men and 21 women. The primary colonic tumor was located in the right side in 13 (28.9%) patients and the left side in 32 (71.9%) patients. We evaluated patients with metastatic colorectal cancer (31/45) after excluding those in whom histopathological heterogeneity between the primary and liver metastasis changed to grade 3 after chemotherapy. We compared the group which underwent hepatectomy after chemotherapy (n=25) with that underwent hepatectomy alone (n=6). In 16 (53.3%) out of 25 patients, histopathological heterogeneity of the liver metastasis was lost (p=0.04).

Conclusion: Chemotherapy appears to change histopathological heterogeneity. Our study suggests that the change of intratumoral heterogeneity reflects the response of chemotherapy.

Background

Colorectal cancer is the third most common human malignant tumor and is one of the major causes of cancer mortality in the Western world. Metastatic tumors account for 40% to 50% of malignancies in newly diagnosed patients (1). The prognosis of metastatic colorectal cancer (mCRC) remains poor. Among the treatment options for colorectal liver metastases (CRLM), liver resection is the most conducive to a cure, with 5-year overall survival rates of 29-48%. Even for initially unresectable CRLM, effective chemotherapy, along with targeted therapy, sometimes enables their resection (2, 3). Promising treatments for CRLM include chemotherapy and molecular agents that target epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF). These reports suggest that the combination of targeted agents and chemotherapy can increase rates of liver resection and response, thus improving progression-free and overall survival of patients with CRLM. However, no studies have compared histopathological type by treatment with anti-VEGF agents and anti-EGFR agents for wild-type RAS liver-limited CRLM (4, 5).

Patients And Methods

This study included 45 patients with CRLM confirmed to be resectable following neoadjuvant chemotherapy (NACT). Patients were treated with surgery alone or with surgery following FOLFOX alone or FOLFOX plus anti-EGFR (cetuximab or panitumumab) FOLFOX plus anti-VEGF (bevacizumab) as first-line treatment at the Surgical Oncology Department of Gifu University School of Medicine from January 2006 to August 2015.
Because an important consequence of intratumoral heterogeneity is potential differences in histopathology between primary tumors and their liver metastases, the histopathological profile of the primary colorectal tumors prior to and after chemotherapy and that of the CRLMs resected post-chemotherapy were assessed to investigate the changes between them (Figures 1 and 2).

In accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (6), the same methods were used to perform tumor assessment at baseline and subsequently every 8-12 weeks using torso contrast-enhanced computed tomography and liver contrast-enhanced magnetic resonance imaging. The tumor histopathological response rate was defined as the proportion of patients with grade Ib or more necrosis in accordance with the following definition: Grade 0: No necrosis in the tumor; grade 1a: necrosis in <33.3% of the tumor; grade 1b: necrosis in 33.3-66.6% of the tumor; grade 2: necrosis in 66.6-<100% of the tumor; and grade 3: necrosis in 100% of the tumor. Patients underwent liver resections if their CRLMs were considered resectable, based on tumor assessments performed after receiving at least six cycles of treatment. Liver resection was performed at least 42 days after the last dose of bevacizumab.

We obtained written informed consent from all patients enrolled in this study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and the guidelines of the regional ethical committees of Zurich and Basel, Switzerland, and was approved by the Institutional Review Board of the Gifu University Graduate School of Medicine (Approval number: 28-508; March 23, 2017).

The slice revisions of primary tumor and matched CRLMs were performed by experienced pathologists (Figure 3).

Statistical analysis. For continuous variables, the data are summarized as the median with range and were compared using the non-parametric Mann–Whitney U test, Kruskal–Wallis tests or the chi-square test. A p-value of less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed using JMP12 software (SAS Institute Inc., Cary, NC, USA).

Results

The study comprised 45 patients with mCRC (24 men, 21 women; mean age = 61.9±9.4 years). Locations of primary tumor in the 45 patients were the right-sided colon in 13 (28.9%) patients and the left-sided colon in 32 (71.9%) patients. The group treated with surgery alone included nine patients, whilst those treated with surgery after FOLFOX alone or plus anti-VEGF or anti-EGFR included 12 patients each (Table I). The heterogeneity of the histopathology between the primary site and the liver metastasis was significantly different in the group treated with surgery alone compared with the other groups (p = 0.04). However, there were no significant differences between the three groups. In addition, tub2 histopathology of appeared to be a predictive marker between primary site and posttreatment liver metastasis specimens from patients with CRLM because the histopathology forms disappeared after each chemotherapy treatment, except for tub2 (Figures 4–6). Though this study didn’t showed data, we assume that Histopathological change greatly influence long-term survival. We also evaluated patients with CRLM
after excluding the patients in whom histopathological heterogeneity changed to grade 3 in the liver metastasis after chemotherapy. This study compared the group which underwent hepatectomy after chemotherapy (n = 25) with that which underwent hepatectomy alone (n = 6). In all six of the latter patients, histopathological heterogeneity at the liver metastasis was maintained after therapy. However, in 16 out of the 25 patients (53.3%) who underwent hepatectomy after chemotherapy, histopathological heterogeneity of liver metastases was lost. We confirmed the loss of neoplastic cells by chemotherapy and homogeneity in liver metastases ($p = 0.04$).

**Discussion**

The present study describes the histopathological patterns of response of CRLMs to preoperative NACT followed by liver resection. To our knowledge, this is the first report to focus on change of histopathological heterogeneity comparing between primary tumor sites and CRLMs.

Over the past decade, NACT has been widely recommended for the management of initially resectable CRLMs with the aim of inducing tumor shrinkage to identify optimal candidates for subsequent surgical removal. The assessment of tumor regression has been gradually used to quantify the histopathological response to NACT and has served as an early parameter predicting prognosis (7, 8).

Discrepancies in the tumor regression patterns in response to different chemotherapy regimens have been revealed in previous literature. Rubbia-Brandt *et al.* reported that an oxaliplatin-based regimen improved histopathological response compared with 5-fluorouracil-, and irinotecan-based regimens (9, 10). In terms of monoclonal antibodies, a bevacizumab-containing regimen provided a better histopathological response than chemotherapy alone or in combination with cetuximab (11, 12).

Poultsides *et al.* published a large retrospective analysis of 366 patients (68% treated preoperatively and 32% not) who underwent CRLM resection. In that study there was no increase in the degree of necrosis after chemotherapy (13). Nevertheless, it should be noted that only 69 out of 249 (28%) patients received bevacizumab as part of the preoperative treatment, and the results in terms of necrosis for that subgroup were not reported. In other experience, increase in necrosis seemed to be due to a bevacizumab-related effect (14, 15). Additionally, the tumor histopathological response rate was defined as the proportion of patients with grade $\geq$Ib.

Taken together, all of the above-reported observations of reduced viable cells, fibrosis, and necrosis from a pathological perspective explained the typical pattern of CLMs detected using computed tomography scanning in patients receiving chemotherapy and bevacizumab. Before treatment, the lesions showed different types of enhancement, a heterogeneous degree of attenuation, and ill-defined borders that were transformed into hypo-attenuated and homogeneous metastases with well-defined borders after treatment (16). Such histological and morphological characteristics strengthen the hypothesis that the RECIST criteria are not completely adequate for evaluating response in patients receiving bevacizumab (17).
In contrast, the anti-EGFR agent cetuximab in combination with chemotherapy has been reported to increase the response rate and yield a good curative hepatectomy. In the PEAK (18), FIRE–3 (19) and CALGB/SWOG 80405 (20) randomized controlled trials performed to compare bevacizumab and anti-EGFR therapy for the progression of recurrent CRC, anti-EGFR was also confirmed to have a positive effect on survival extension in the presence of wild-type RAS.

Recently, the multicenter, randomized, phase II ATOM trial from Japan was designed to evaluate the efficacy and safety of mFOLFOX6 plus bevacizumab and mFOLFOX6 plus cetuximab in patients with liver-limited metastasis from wild-type all-RAS CRC. After study treatment followed by surgical resection of tumors with R0/R1 status, the median progression-free survival of the bevacizumab-treated arm was 6.5 months [95% confidence interval (CI) = 4.0–13.6 months], whereas that of the cetuximab-treated arm was 13.8 months (95% CI = 8.4 months-not reached; hazard ratio = 0.610, 95% CI = 0.298–1.245). Of the 57 tumors for which the histopathological analysis was assessable, the histopathological response rate (grade 1b/2/3) was 66.6% (20/30) in the bevacizumab-treated arm and 92.6% (25/27) in the cetuximab-treated arm \((p = 0.0229)\) (16), indicating that the rate tended to be better in the cetuximab-treated arm (21).

Falcão et al. reported three categories of tumor growth: (a) Replacement growth pattern, in which the tumor permeates between the liver hepatocytes without disrupting the normal architecture; (b) desmoplastic growth pattern, in which the tumor is separated from the liver parenchyma by a band of fibrous tissue that contains tumor-infiltrating lymphocytes; and (c) pushing growth pattern, in which the tumor expands and compresses the surrounding hepatocytes. They reported the pushing growth pattern to be an independent risk factor for reduced survival (22).

Recently, a tumor-heterogeneity concept that considers a single tumor to consist of many tumor cell sub-clones has become an important topic in cancer genomics (23). It is hypothesized to play a critical role in the progression of many cancer types and is a major obstacle to precision cancer therapy. During this process, sub-clones continuously arise via genomic mutation. The presence of sub-clones has been shown to adversely affect outcome in chronic lymphocytic leukaemia, head and neck cancer, and lung adenocarcinoma. However, the full complement of factors that lead to tumor heterogeneity during CRC progression is unknown.

Several promising CRLM treatments have been reported, including chemotherapy and molecular agents that target EGFR and VEGF. Anti-EGFR drugs resulted in high response and resection rates in the CELIM phase II trial and other studies for initially unresectable CRLM with wild-type \(KRAS\) (24;25). Anti-VEGF regimens, such as mFOLFOX6 or CAPEOX plus bevacizumab, have also shown high response and resection rates in phase II studies (26). These reports suggest that the combination of targeted agents and chemotherapy can increase the response rate.

A previous study reported a higher pathological response rate to bevacizumab than for cetuximab. This study suggested that the loss of intratumoral heterogeneity markedly affects the response to chemotherapy.
Conclusion

In conclusion, the present study highlighted marked differences between pre and posttreatment specimens from sites in patients with mCRC. Histopathology appeared to be a predictive marker in specimens comparing primary site and CRLMs posttreatment because histopathology types other than tub2 disappeared after chemotherapy treatment. Each NACT agent had an acceptable safety profile. In the near future, we expect results from further study to expand the indication for NACT.

Abbreviations

mCRC: metastatic colorectal cancer, CRLM: colorectal liver metastases. EGFR: epidermal growth factor receptor. VEGF: vascular endothelial growth factor. NACT: neoadjuvant chemotherapy, RECIST: the Response Evaluation Criteria in Solid Tumors

Declarations

Acknowledgments

The authors thank the medical staff of the Department of Surgical Oncology at Gifu University Hospital for their participation in this study. We could not have completed this study without their diligence and support.

Authors’ Contributions

NM, HT and TK conceived the study and its design. NM, HT, TK, TT, YI, MF, IY, TS, TI, RM, HI, YT, NO, AH and KYo acquired the data. NM, HT and TK analyzed and interpreted the data and drafted the article. NM, TT and KYo performed critical revision of the article. AH and KYo supervised the study. All Authors read and approved the final article.

Funding

None declared.

Availability of data and materials

The datasets used during this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The present study was conducted in accordance with the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee of Gifu University (Approval number: 28-508; March 23, 2017). As this study was a retrospective study and did not include any potentially identifiable patient data, informed consent was not obtained from the enrolled patients. The institutional review board gave the ethics approval for this retrospective study.
Consent for publication

Not applicable

Competing interests

K. Yoshida has received honoraria for lectures from Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Eli Lilly and Company, Daiichi Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Merck Serono Co., Ltd., Novartis Pharma K.K., and Sanofi K.K.; and research funding from Ajinomoto Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Taiho Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., and Yakult Honsha Co., Ltd. outside the submitted work.

T. Takahashi has received honoraria for lectures from Takeda Pharmaceutical Co., Ltd. All remaining Authors declare that they have no conflicts of interest.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. Nov;68(6):394-424.2018 PMID: 30207593 DOI: 3322/caac.21492

2. Cancer Statistics in Japan -2018
https://ganjoho.jp/reg_stat/statistics/brochure/backnumber/2018_jp.html

3. NCCN GUIDELINES FOR PATIENTS 2018
https://www.nccn.org/patients/guidelines/content/PDF/colon-patient.pdf

4. Saltz LB¹, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F and Cassidy J. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol.26(12):2013-2019. 2008.PMID: 18421054 DOI: 1200/JCO.2007.14.9930

5. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. Jan;45(2):228-247.2009.PMID: 19097774 DOI: 1016/j.ejca.2008.10.026

6. Van Cutsem E¹, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D’Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Teijpar S, Schlichting M, Nippgen J and Rougier P.
Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 360(14):1408-1417.2009. PMID: 19339720. DOI: 1056/NEJMoa0805019

7. Chua TC, Saxena A, Liauw W, Kokandi A and Morris DL. Systematic review of randomized and nonrandomized trials of the clinical response and outcomes of neoadjuvant systemic chemotherapy for resectable colorectal liver metastases. Ann Surg Oncol. 17(2):492-501, 2010. PMID: 19856028. DOI: 1245/s10434-009-0781-1

8. Nordlinger B, Van Cutsem E, Gruenberger T, Glimelius B, Poston G, Rougier P, Sobrero A, Ychou M; European Colorectal Metastases Treatment Group; Sixth International Colorectal Liver Metastases Workshop. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: recommendations from an expert panel. Ann Oncol. 20(6):985-992.2009. PMID: 19153115. DOI: 1093/annonc/mdn735

9. Rubbia-Brandt L. Hepatic lesions induced by systemic chemotherapy for digestive cancer. Ann Pathol. Dec;30(6):421-425.2010. PMID: DOI: 10.1016/j.annpat.2010.09.008

10. Rubbia-Brandt L, Giostra E, Brezault C, Roth AD, Andres A, Audard V, Sartoretti P, Dousset B, Majno PE, Soubrane O, Chaussade S, Mentha G, Terris B. Importance of histological tumor response assessment in predicting the outcome in patients with colorectal liver metastases treated with neo-adjuvant chemotherapy followed by liver surgery. Ann Oncol 18: 299-304.2007. PMID: 17060484. DOI: 1093/annonc/mdl386

11. Gruenberger B, Tamandl D, Schueller J, Scheithauer W, Zielinski C, Herbst F, Gruenberger T. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. J Clin Oncol. Apr 10;26(11):1830-1835.2008. PMID: 18398148. DOI: 1200/JCO.2007.13.7679

12. Gruenberger B, Schueller J, Heubrandtner U, Wrba F, Tamandl D, Kaczirek K, Roka R, Freimann-Pircher S and Gruenberger T. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. Lancet Oncol. Dec;11(12):1142-1148.2010. PMID: 21071270. DOI: 1016/S1470-2045(10)70247-3

13. Poultides GA, Bao F, Servais EL, Hernandez-Boussard T, Dematteo RP, Allen PJ, Fong Y, Kemeny NE, Saltz LB, Klimstra DS, Jarnagin WR, Shia J and D’Angelica MI Pathologic response to preoperative chemotherapy in colorectal liver metastases: fibrosis, not necrosis, predicts outcome. Ann Surg Oncol .19: 2797-2804.2012. PMID: 22476753. DOI: 1245/s10434-012-2335-1

14. Klinger M, Tamandl D, Eipeldauer S, Hacker S, Herberger B, Kaczirek K, Dorfmeister M, Gruenberger B and Gruenberger T. Bevacizumab improves pathological response of colorectal cancer liver metastases treated with XELOX/FOLFOX. Ann Surg Oncol.17: 2059-2065.2010. PMID: 20177795. DOI: 1245/s10434-010-0972-9

15. Wicherts DA, de Haas RJ, Sebagh M, Saenz Corrales E, Gorden DL, Levi F, Paule B, Azoulay D, Castaing D and Adam R. Impact of bevacizumab on functional recovery and histology of the liver after resection of colorectal metastases. Br J Surg.98: 399-407.2011. PMID: 21254017. DOI: 1002/bjs.7368
16. Chun YS, Vauthey JN, Boonsirikamchai P, Maru DM, Kopetz S, Palavecino M, Curley SA, Abdalla EK, Kaur H, Charmsangavej C and Loyer EM. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. JAMA.302: 2338-2344.2009.PMID: 19952320 PMCID: PMC4139149 DOI: 1001/jama.2009.1755

17. Gruenberger T, Arnold D and Rubbia-Brandt L :Pathologic response to bevacizumab-containing chemotherapy in patients with colorectal liver metastases and its correlation with survival. Surg Oncol.21: 309-315.2012. PMID: 22884035 DOI: 1016/j.suronc.2012.07.003

18. Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, Yu H, Oliner KS and Go WY. 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. J. Clin. Oncol.32, 2240-2247.2014.PMID: 24687833 DOI: 1200/JCO.2013.53.2473

19. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Stauh M, Scheithauer W, Hiescher J, Scholz M, Müller S, Link H, Niederle N, Rost A, Höffkes HG, Moeher M, Lindig RU, Modest DP, Rossius L, Kirchner T and Jung A, Stintzing S.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. Lancet Oncol.15, 1065-1075.2014. PMID: 25088940 DOI: 1016/S1470-2045(14)70330-4

20. Venook AP, Niedzwiecki D, Lenz HJ, Innocenti F, Fruth B, Meyerhardt JA, Schrag D, Greene C, O’Neil BH, Atkins JN, Berry S, Polite BN, O'Reilly EM, Goldberg RM, Hochster HS, Schilsky RL, Bertagnolli MM, El-Khoueiry AB, Watson P, Benson AB 3rd, Mulkerin DL, Mayer RJ and Blanke C..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 317, 2392-2401.2017.PMID: 28632865. PMCID: PMC5545896 DOI: 1001/jama.2017.7105

21. Oki E, Emi Y, Yamanaka T, Uetake H, Muro K, Takahashi T, Nasagasa T, Hatano E, Ojima H, Manaka D, Kusumoto T, Katayose Y, Fujiiwa T, Yoshida K, Unno M, Hyodo I, Tomita N, Sugihara K and Maehara Y. Randomised phase II trial of mFOLFOX6 plus bevacizumab versus mFOLFOX6 plus cetuximab as first-line treatment for colorectal liver metastasis (ATOM trial).Br J Cancer.121(3):222-229.2019.PMID: 31285591 PMCID: PMC6738101 DOI: 1038/s41416-019-0518-2

22. Falcão D, Alexandrino H, Caetano Oliveira R, Martins J, Ferreira L, Martins R, Serôdio M, Martins M and Tralhão JG, Cipriano MA, Castro E Sousa F. Histopathologic patterns as markers of prognosis in patients undergoing hepatectomy for colorectal cancer liver metastases - Pushing growth as an independent risk factor for decreased survival. Eur J Surg Oncol.Aug;44(8):1212-1219.2018.PMID: 29691114 DOI: 1016/j.ejso.2018.03.023

23. Li H, Courtois ET, Sengupta D, Tan Y, Chen KH, Goh JYL, Kong SL, Chua C, Hon JK, Tan WS, Wong M, Choi PJ, Wee LJ, Hillmer AM, Tan IB, Robson P and Prabhakar S. Reference component analysis of single-cell transcriptomes elucidates cellular heterogeneity in human colorectal tumors. Nat Genet. ;49(5):708-718.2017.PMID: 28319088 DOI: 1038/ng.3818
24. Folprecht G, Gruenberger T, Bechstein WO, Raab HR, Lordick F, Hartmann JT, Lang H, Frilling A, Stoehlmacher J, Weitz J, Konopke R, Stroszczynski C, Liersch T, Ockert D, Herrmann T, Goekkurt E, Parisi F and Köhne CH. Tumor response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol.;11(1):38-47.2010. PMID: 19942479 DOI: 1016/S1470-2045(09)70330-4

25. Rivera F, Karthaus M, Hecht JR, Sevilla I, Forget F, Fasola G, Canon JL, Guan X, Demonty G and Schwartzberg LS. Final analysis of the randomised PEAK trial: overall survival and tumor responses during first-line treatment with mFOLFOX6 plus either panitumumab or bevacizumab in patients with metastatic colorectal Int J Colorectal Dis.;32(8):1179-1190.2017. PMID: 28424871 PMCID: PMC5522523 DOI: 10.1007/s00384-017-2800-1

26. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmüller C, Kahl C, Seipel G, Kullmann F, Stauch M, Scheithauer W, Hielscher J, Scholz M, Müller S, Link H, Niederle N, Rost A, Höffkes HG, Moehler M, Lindig RU, Modest DP, Rossius L, Kirchner T, Jung A and Stintzing S. 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. Lancet Oncol 15(10):1065-1075.2014 PMID: 25088940 DOI: 1016/S1470-2045(14)70330-4

Tables

Table I. Patient characteristics. Heterogeneity of differences in pathology between the colorectal primary tumors and the colorectal liver metastases after surgery only, and chemotherapy with FOLFOX alone and with antibody to vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR).
| Characteristic       | Subgroup | Surgery only (N=9) | FOLFOX (N=12) | Anti-EGFR+FOLFOX (N=12) | Anti-VEGF+FOLFOX (N=12) | P-value |
|----------------------|----------|-------------------|---------------|-------------------------|-------------------------|---------|
|                      |          |                   |               |                         |                         |         |
| Sex, n               | Male     | 3                 | 10            | 5                       | 6                       | 0.08    |
|                      | Female   | 6                 | 2             | 7                       | 6                       |         |
| Age, years           | Median (range) | 62 (50-81)     | 64.5 (49-83)  | 63 (49-68)              | 58.5 (40-68)            | 0.45    |
| Location, n          | Right side | 2                 | 3             | 3                       | 5                       | 0.78    |
|                      | Left side | 7                 | 9             | 9                       | 7                       |         |
| RECIST, n            | SD       | -                 | 3             | 2                       | 4                       | 0.27    |
|                      | PR       | -                 | 9             | 10                      | 8                       |         |
|                      | CR       | -                 | 0             | 0                       | 0                       |         |
| Grade*, n            | 1a/1b    | 3                 | 2             | 2                       | 2                       | 0.37    |
|                      | 2        | 9                 | 8             | 8                       |                         |         |
|                      | 3        | 0                 | 2             | 2                       |                         |         |
| Histopathology, n Primary | Heterogenous | 6            | 7             | 11                      | 12                      | 0.036   |
|                      | Homogenous | 3               | 5             | 1                       | 0                       |         |
| Liver                | Heterogenous | 6               | 4             | 6                       | 5                       | 0.17    |
|                      | Homogenous | 3               | 8             | 6                       | 7                       |         |

CR: Complete response; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors (5); SD: stable disease. *Of metastases only.