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Direktor: Prof. Dr. Jens Ricke

Computed tomography in metastatic colorectal cancer under combination-therapy: Exploration of qualitative and quantitative image parameters for risk and response assessment

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Berichterstatter:	Prof. Dr. med. Wieland H. Sommer, MPH
Mitberichterstatter:	PD Dr. med. Enrico De Toni Prof. Dr. med. Jens Ricke Prof. Dr. med. Martina Rudelius
Mitbetreuung durch den promovierten Mitarbeiter:	Dr. med. Melvin D'Anastasi
Dekan:	Prof. Dr. med. dent. Reinhard Hickel
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Publication list

Cumulative dissertation

Towards volumetric thresholds in RECIST 1.1: Therapeutic response assessment in hepatic metastases

K.S. Winter¶, **F.O. Hofmann¶**, K.M. Thierfelder, J.W. Holch, N. Hesse, A.B. Baumann, D.P. Modest, S. Stintzing, V. Heinemann, J. Ricke, W.H. Sommer, M. D'Anastasi

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¶ These authors contributed equally.

Prognostic value of radiologically enlarged lymph nodes in patients with metastatic colorectal cancer: Subgroup findings of the randomized, open-label FIRE-3/AIO KRK0306 trial

F.O. Hofmann¶, J.W. Holch¶, V. Heinemann, I. Ricard, M.F. Reiser, A.B. Baumann, N. Hesse, M. D'Anastasi, D.P. Modest, S. Stintzing, W.H. Sommer

Eur J Radiol 2018; **100:** 124-9. doi: 10.1016/j.ejrad.2018.01.006.

¶ These authors contributed equally.

Further publications and presentations

CT attenuation of liver metastases before targeted therapy is a prognostic factor of overall survival in colorectal cancer patients. Results from the randomised, open-label FIRE-3/AIO KRK0306 trial.

M.F. Froelich, V. Heinemann, W.H. Sommer, J.W. Holch, F. Schöppe, N. Hesse, A.B. Baumann, W.G. Kunz, M.F. Reiser, J. Ricke, M. D'Anastasi, S. Stintzing, D.P. Modest, P.M. Kazmierczak, **F.O. Hofmann**

Eur Radiol 2018. doi: 10.1007/s00330-018-5454-7. [Epub ahead of print]

Automatic Liver and Lesion Segmentation in CT Using Cascaded Fully Convolutional Neural Networks and 3D Conditional Random Fields

P.F. Christ, M.E.A. Elshaer, F. Ettlinger, S. Tatavarty, M. Bickel, P. Bilic, M. Rempfler, M. Armbruster, **F. Hofmann**, M. D'Anastasi, W.H. Sommer, S.A. Ahmadi, B.H. Menze

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Automatic liver and tumor segmentation of CT and MRI volumes using cascaded fully convolutional neural networks

P.F. Christ, F. Ettlinger, F. Grün, M.E.A. Elshaera, J. Lipkova, S. Schlecht, F. Ahmaddy, S. Tatavarty, M. Bickel, P. Bilic, M. Rempfler, **F. Hofmann**, M.D'Anastasi, S.A. Ahmadi, G. Kaissis, J. Holch, W. Sommer, R. Braren, V. Heinemann, B. Menze

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Change of liver metastases under therapy: do target lesions represent the changes in the hepatic tumour burden?

F.O. Hofmann, V. Heinemann, J. Holch, A. Baumann, N. Hesse, M. D'Anastasi, W.H. Sommer

European Congress of Radiology 2016; Session B-0189. doi: 10.1007/s13244-016-0475-8.

Predicting the real volume of liver metastases from diameter-based measurements and the lesions' shape

F.O. Hofmann, V. Heinemann, J. Holch, N. Hesse, A. Baumann, M. D'Anastasi, W.H. Sommer

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Measuring two target lesions: how representative are selected target lesions of all liver metastases?

F.O. Hofmann, V. Heinemann, J. Holch, A. Baumann, N. Hesse, M. D'Anastasi, W.H. Sommer

European Congress of Radiology 2016; Student Session.

Abbreviations

AJCC, American Joint Committee on Cancer; **AP**, alkaline phosphatase; **APC**, adenomatous polyposis coli gene; **ASS**, acetylsalicylic acid; **BRAF**, v-Raf murine sarcoma viral oncogene homolog B; **CAPOX**, capecitabine and oxaliplatin; **CI**, confidence interval; **CPH**, Cox proportional hazard; **CRC**, colorectal cancer; **CT**, computed tomography; **CR**, complete response; **ECOG**, Eastern Cooperative Oncology Group scale of performance score; **EGFR**, epidermal growth factor receptor; **FIT**, fecal immunochemical test; **FLOX**, fluorouracil / folinic acid and oxaliplatin; **FOBT**, fecal occult blood test; **FOLFIRI**, 5-fluoururacil / folinic acid and irinotecan; **FOLFOX**, 5-fluoururacil / folinic acid and oxaliplatin; **FOLFOXIRI**, 5-fluoururacil / folinic acid and oxaliplatin and irinotecan; **HR**, hazard rate ratio; **KRAS**, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; **LDH**, lactate dehydrogenase; **LN**, lymph nodes; **mCRC**, metastatic colorectal cancer; **MRI**, magnetic resonance imaging; **NE**, not evaluable; **NRAS**, neuroblastoma rat sarcoma viral oncogene homolog; **NTL**, non-target lesion; **OS**, overall survival; **PC**, peritoneal carcinomatosis; **PET/CT**, positron emission tomography / computed tomography; **PIK3CA**, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; **PFS**, progression-free survival; **PD**, progressive disease; **PR**, partial response; **RAS**, rat sarcoma gene family; **RECIST**, response evaluation criteria in solid tumors; **RFA**, radiofrequency ablation; **SD**, stable disease; **TACE**, transarterial chemoembolization; **TGF-β/SMAD**, transforming growth factor beta receptor family; **TL**, target lesion; **TNM**, tumor (T), nodes (N) and metastases (M) staging system; **TP53**, tumor protein p53; **UICC**, Union internationale contre le cancer; **VEGF**, vascular endothelial growth factor; **VOI**, volume of interest; **w**, with; **WBC**, white blood cell count; **w/o**, without; **XELOX**, capecitabine and oxaliplatin.

1 Introduction

1.1 Colorectal cancer

Colorectal cancer is among the most frequently diagnosed cancers worldwide.[1,2] In Europe, it is the second most common cancer in women (205 200 new cases in 2012, 12.7 % of all cancer cases) and the third most common cancer in men (241 600 new cases in 2012, 13.2 % of all cancer cases).[2] It caused 12.2 % (214 700 / 1 754 600) of all cancer related deaths in 2012.[2] In 2009, health-care costs caused by colorectal cancer were estimated at € 5.57 billion (11 % of all cancer related health care costs) and productivity losses due to morbidity and mortality at € 4.69 billion within the European Union.[3]

The incidence of colorectal cancer is higher for older and male individuals. Median age at the time of diagnosis is 66 years for males and 69 years for females, and median lifetime risk of the diagnosis is 4.42 % for males and 4.06 % for females.[4] Table 1 provides an overview of established risk and preventive factors. However, especially the lifestyle factors often occur collinearly, hampering independent analyses.[24]

Factors	Risk	Reference
Sociodemographic		
Older age	↑	4
Male sex	↑	4
Medical		
Positive family history	↑	5,6
Hereditary syndromes	↑	7,8
Inflammatory bowel diseases	↑	9-11
Diabetes	↑	12,13
ASS	↓	14,15
Postmenopausal hormones	↓	16,17
Lifestyle		
Smoking	↑	18,19
Obesity	↑	20,21
↑ Consumption of alcohol	↑	22,23
↑ Consumption of red or processed meat	↑	24,25
↑ Physical activity	↓	26
↑ Consumption of fiber	↓	27
↑ Consumption of calcium	↓	28-30
↑ Consumption of milk	↓	30,31

Table 1: Risk factors. Parameters increasing (↑) or decreasing (↓) the risk to develop colorectal cancer. ASS, acetylsalicylic acid.

'Classic' tumorigenesis of colorectal cancer follows the adenoma-carcinoma-sequence[32]: Loss of the tumor-suppressing 'gatekeeping' APC pathway initiates the development of early adenomas.[33-35] Additional mutations, often activating the KRAS / BRAF pathway, cause further tumor growth.[32,35,36] The accumulation of additional mutations in other genes or pathways (e. g., PIK3CA[37,38], TP53[39-41], TGF-β / SMAD[42-44]) results in the progression to adenocarcinomas.[32,45]

The progression of an adenoma to a carcinoma takes several years[45,46]. The long asymptomatic course of disease, the high incidence, and the availability of often curative treatment allow efficient screening.[47,48] The fecal occult blood test (FOBT)[49,50] and the fecal immunochemical test (FIT)[51] are suitable for first-round screening; positive patients should be further examined in colonoscopy.[52] Other countries adapted colonoscopy for first-round screening.[52] Altogether, colonoscopy allows immediate – and potentially

curative – polypectomy, histopathological evaluation, and reduces colorectal cancer's incidence[53] and mortality[54].

Colorectal cancer is diagnosed in screening or in the assessment of symptomatic patients having e. g. blood in stool, abdominal pain, changed bowel habits, anemia, fatigue, or weight loss.[55,56] The diagnostic procedures include physical examination, imaging, endoscopy, or surgical exploration.[52,56,57] Tissue for histopathological reviews is usually obtained in endoscopic polypectomy or biopsy and may confirm the diagnosis.[56,58,59] The tumor's depth of infiltration, its dissemination to regional lymph nodes, and its dissemination to distant lymph node regions or other organs determine the TNM-stage (Table 2).[57,58,60] The TNM-stage enters the UICC / AJCC staging (Table 3)[57,61] that helps to standardize reports and the selection of optimal treatment[59,62] and is associated with the prognosis[57].

	Definition
Tis	Carcinoma in situ, Infiltration lamina propria
T stage	
T1	Infiltration submucosa
T2	Infiltration muscularis propria
T3	Infiltration subserosa / pericolic & perirectal tissue
T4a	Infiltration serosa
T4b	Infiltration neighboring organs / tissue
N stage	
N1a	1 regional lymph node metastasis
N1b	2 – 3 regional lymph node metastases
N1c	Satellite tumor deposits in subserosa / pericolic & perirectal tissue *w/o* regional lymph node metastasis
N2a	4 – 6 regional lymph node metastases
N2b	≥ 7 regional lymph node metastases
M stage	
M1a	Distant metastasis to 1 organ or distant lymph node region *w/o* peritoneal metastases
M1b	Distant metastasis to ≥ 1 organ or distant lymph node regions *w/o* peritoneal metastases
M1c	Peritoneal metastases *w or w/o* distant metastases to other organs or distant lymph node regions

Table 2: TNM-Classification. Classification of colorectal cancer regarding its depth of infiltration (T stage), the involvement of regional lymph nodes (N stage) and the involvement of other organs, distant lymph node regions or the peritoneum (M stage). Adapted from Brierley et al.[57] Abbreviations: w, with; w/o, without.

Stage	T	N	M
0	Tis	N0	M0
I	T1/T2	N0	M0
II	T3/T4	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
III	any T	N1/N2	M0
IIIA	T1/T2	N1	M0
	T1	N2a	M0
IIIB	T3/T4a	N1	M0
	T2/T3	N2a	M0
	T1/T2	N2b	M0
IIIC	T4a	N2a	M0
	T3/T4a	N2b	M0
	T4b	N1/N2	M0
IV	any T	any N	M1
IVA	any T	any N	M1a
IVB	any T	any N	M1b
IVC	any T	any N	M1c

Table 3: UICC-Classification. Union Internationale Contre le Cancer (UICC) / American Joint Committee on Cancer (AJCC) classification of colorectal cancer. Adapted from Brierley et al.[57]

In patients with malignant polyps that were completely resected and revealed favorable histopathology, endoscopic polypectomy is usually considered as curative, and surgery is not necessary.[63-65] Patients with malignant polyps that were incompletely resected or revealed unfavorable histopathology[63,64,66], or patients with non-metastasized colorectal cancer (stage I – III) in general, should usually undergo surgery in curative intention:

In colon cancer, complete mesocolic excision includes the resection of the affected bowel segment and its mesocolon containing the regional lymph nodes.[67,68] For patients

with stage II disease, adjuvant chemotherapy is optional and should be considered especially in high-risk situations.[69-72] For patients with stage III disease, adjuvant chemotherapy is recommended.[60,72,73]

In rectal cancer, selected patients (very early cT1N0, low grade G1/G2, etc.) may be treated by transanal excision or transanal endoscopic microsurgery[74-77]. Other patients should undergo transabdominal surgery with total mesorectal excision (en bloc resection of mesorectum, mesorectal fat and mesorectal fascia).[78,79] Proximal tumors may be approachable by lower anterior resection of the rectum, distal tumors can require abdominal perineal resection.[77,79,80] Guidelines recommend differently scheduled protocols combining pre- and postoperative chemo- and radiotherapy for patients with stage II or III rectal cancer.[81,82]

Preferred first-line adjuvant chemotherapy in non-metastatic colorectal cancer is a cytotoxic doublet with a fluoropyrimidine and oxaliplatin such as 5-fluoururacil/folinic acid and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (XELOX or CAPOX).[83-88] Alternatives are bolus fluorouracil/folinic acid and oxaliplatin (FLOX), and in certain situations monotherapy with capecitabine or 5-fluoururacil/folinic acid.[89-92] The combination with targeted agents did not improve outcomes in non-metastasized colorectal cancer.[93-97]

The prognosis of patients with colorectal cancer highly depends on the stage: The 5-year relative survival rate for patients with localized cancer is about 90 % but clearly reduced for patients with regional-stage disease (stage II & III, ~70 %).[4,99,100] However, patients with metastatic colorectal cancer (stage IV) have the worst prognosis, despite significant therapeutic improvements in the last decades.[101] Table 4 provides detailed 5-year relative survival rates for colon and rectal cancer.

Stage	5-year relative survival rate	
	Colon cancer	Rectal cancer
I	92%	88%
II		
IIA	87%	81%
IIB	65%	50%
III		
IIIA	90%	83%
IIIB	72%	72%
IIIC	53%	58%
IV	12%	13%

Table 4: 5-year relative survival rate by stage. 5-year relative survival rate by UICC / AJCC stage for colon and rectal cancer according to and adapted from cancer.org[98]. Note that numbers are based on a previous version of the TNM staging system.

1.2 Metastatic colorectal cancer

Half of all patients with colorectal cancer develop metastases: About 20 % present synchronous metastases at the time of the diagnosis[102,103], and 20 – 30 % develop metachronous metastases later in their course of disease[104,105]. Colorectal cancer metastasizes

most commonly to liver, lungs, peritoneum, and lymph nodes, and less frequently to bones, brain, or other organs.[102,105,106]

Diagnostic procedures include physical examination, imaging, endoscopy, or surgical exploration similarly to non-metastasized colorectal cancer.[56,57] Additionally, tissue from the primary tumor or metastases[107-109] should be genotyped for RAS and BRAF,[110,111] as patients harboring these mutations do not benefit or benefit less from therapy with antibodies targeting the epidermal growth factor receptor (EGFR, cetuximab and panitumumab).[112-116]

The evaluation of distant metastases relies heavily on imaging. Computed tomography (CT) is the most commonly used standard (also see 1.3 Computed tomography).[117-119] Magnetic resonance imaging (MRI) should be considered in patients with rectal carcinoma prior resection[120,121] or if the abdominal or pelvic CT is inadequate[122,123]. PET/CT may be considered if the dignity of a suspect structure is unclear, yet crucial for the decision whether curative surgery is technically feasible.[124,125]

Patients with limited liver or lung metastases may benefit from R0-resection.[126-129] If R0-resection is technically feasible, primary tumor and metastases can be resected simultaneously (synchronously) or successively (staged).[130-133] In selected patients, alternatively non-resectable metastases can be approached with local therapies such as radioembolization[134-136], transcatheter arterial chemoembolization (TACE)[134,137], or radiofrequency ablation (RFA)[138,139].[140] Chemotherapy should be administered adjuvantly, neoadjuvantly or between the resection of the primary tumor and the metastases.[141-145]

However, most patients have initially unresectable disease[146] and combination-therapy is the treatment of choice: In patients with limited disease, downsizing may enable secondary surgery with curative intention.[146-149] In patients with metastases that are unlikely to become resectable, the treatment intention might be disease control and preventing progression.[59,111]

For stage IV disease, preferred combination-therapy includes a chemotherapeutical backbone aligned with a targeted agent. The specific treatment strategy and drug selection depends on the patient's health status, risk factors, clinical and molecular predictive parameters (e.g., tumor sidedness, mutational status), the treatment goal (e.g., downsizing *vs* disease control), the drug's side effects and the patient's preferences.[59,111,150]

Preferred first-line chemotherapies consist of the cytotoxic doublets 5-fluoururacil/folinic acid and irinotecan (FOLFIRI)[151-153] or 5-fluoururacil/folinic acid and oxaliplatin (FOLFOX)[152-154] or capecitabine and oxaliplatin (XELOX or CAPOX)[155-157]. Alternatives

are the combination of 5-fluoururacil / folinic acid, irinotecan and oxaliplatin (FOLFOXIRI)[158,159] or the less intensive monotherapy with infusional 5-fluoururacil / folinic acid[160-162] or capecitabine[163-165].

The combination of chemotherapy with antibodies targeting the epidermal growth factor receptor (EGFR, cetuximab and panitumumab) or the vascular endothelial growth factor (VEGF, bevacizumab) increases overall survival and progression-free survival.[112,166-169] EGFR-antibodies are ineffective in presence of RAS mutations, and therefore only patients with RAS wild-type gene may receive cetuximab or panitumumab.[110-114] Also, the effectiveness of EGFR-antibodies is smaller in patients with right-sided tumors.[170-174]

Combination-therapy prolongs the median overall survival of patients with metastatic colorectal cancer up to 30 months in current phase 3 trials and observational registries.[101,111]

1.3 Computed tomography

Computed tomography (CT) is an established standard for diagnosis and monitoring of metastases in colorectal cancer.[59,111,117-119,175] Scans should include the chest, the abdomen and the pelvis to cover the most common metastatic sites (liver, lungs, peritoneum, and lymph nodes).[59,111,119,175]

Details of the CT scanner settings and imaging protocols might vary. However, the optimal evaluation of the liver and hepatic metastases requires an abdominal scan in portal venous phase after applying intravenous iodinated contrast agent.[176,177] Furthermore, all series should be reconstructed with a slice-thickness of 5 mm or smaller to ensure accurate lesion measurements and reliable detection of new metastases.[175]

1.4 RECIST 1.1

The assessment of radiological treatment outcomes of metastatic colorectal cancer patients relies mostly on RECIST 1.1 (Response Evaluation Criteria in Solid Tumors, version 1.1). Based on quantitative and qualitative evaluations, these criteria allow an objective and reproducible assessment of radiological response and progress.[175]

Up to two representative and measurable metastases per organ and up to five metastases in total are selected as target lesions and their longest diameters are measured. The evaluation of lymph nodes is different as their size is measured along the shortest axis and only nodes ≥ 10 mm are considered as suspect. All measured diameters are summed up, its change is calculated relative to the baseline or the 'nadir' (smallest sum during treatment), and the response is categorized according to the criteria presented in Table 5. Altogether, partial response (PR) is significant shrinkage of target lesions ≥ 30 %

without achieving complete response (CR), and progressive disease (PD) is significant growth of target lesions ≥ 20 %.[175]

Tumor response		Target lesions
CR	Complete Response	All TL disappeared and all lymph nodes < 10 mm
PR	Partial Response	≥ 30 % decrease in diameter sum, reference baseline
SD	Stable Disease	Neither CR, PR, nor PD
PD	Progressive Disease	≥ 20 % increase in diameter sum (min. 5 mm), reference nadir

Table 5: Objective tumor response of target lesions. Categories of tumor response of target lesions according to RECIST 1.1 (adapted from Eisenhauer et al.[175]). Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; TL, target lesions.

Tumor response		Non-target lesions
CR	Complete Response	All NTL disappeared and all lymph nodes < 10 mm and normalized tumor marker level
Non-CR / Non-PD		Persistence of ≥ 1 NTL and / or maintenance of tumor marker above normal level
PD	Progressive Disease	Unequivocal progression of existing NTL

Table 6: Tumor response of non-target lesions. Categories of tumor response of non-target lesions according to RECIST 1.1 (adapted from Eisenhauer et al.[175]). Abbreviations: CR, complete response; NTL, non-target lesions; PD, progressive disease; PR, partial response.

All metastases not measured or not measurable are qualitatively evaluated as non-target lesions and the tumor response is categorized as described in Table 6.[175]

The evaluation of the overall tumor response at a specific time point respects target lesions and non-target lesions (Table 7): Altogether, complete response (CR) is the disappearance of all metastases, partial response (PR) is a significant but incomplete response, and progressive disease (PD) is a significant growth of any target-lesion, any non-target lesion or the appearance of any new metastases. Insignificant size changes in patients with target lesions are considered as stable disease (SD), in patients without target lesions as non-CR / non-PD.[175]

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
—	CR	No	CR
CR	Non-CR / non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
—	Non-CR / non-PD	No	Non-CR / non-PD
SD	Non-PD or not all evaluated	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
—	PD	Yes or no	PD
—	Any	Yes	PD
Not all evaluated	Non-PD	No	NE
—	Not all evaluated	No	NE

Table 7: Overall tumor response at specific time point. Evaluation of the tumor response depending on target lesions, non-target lesions and new lesions at a specific time point according to RECIST 1.1 (adapted from Eisenhauer et al.[175]). Abbreviations: CR, complete response; NE, not evaluable; NTL, non-target lesions; PD, progressive disease; PR, partial response; SD, stable disease.

1.5 Volumetric thresholds according to RECIST 1.1

RECIST simplifies the measurement of target lesions by focusing on the metastases' longest diameter.[175] This reflects the real size change accurately as long as the diameter's change equals the average change in all directions.

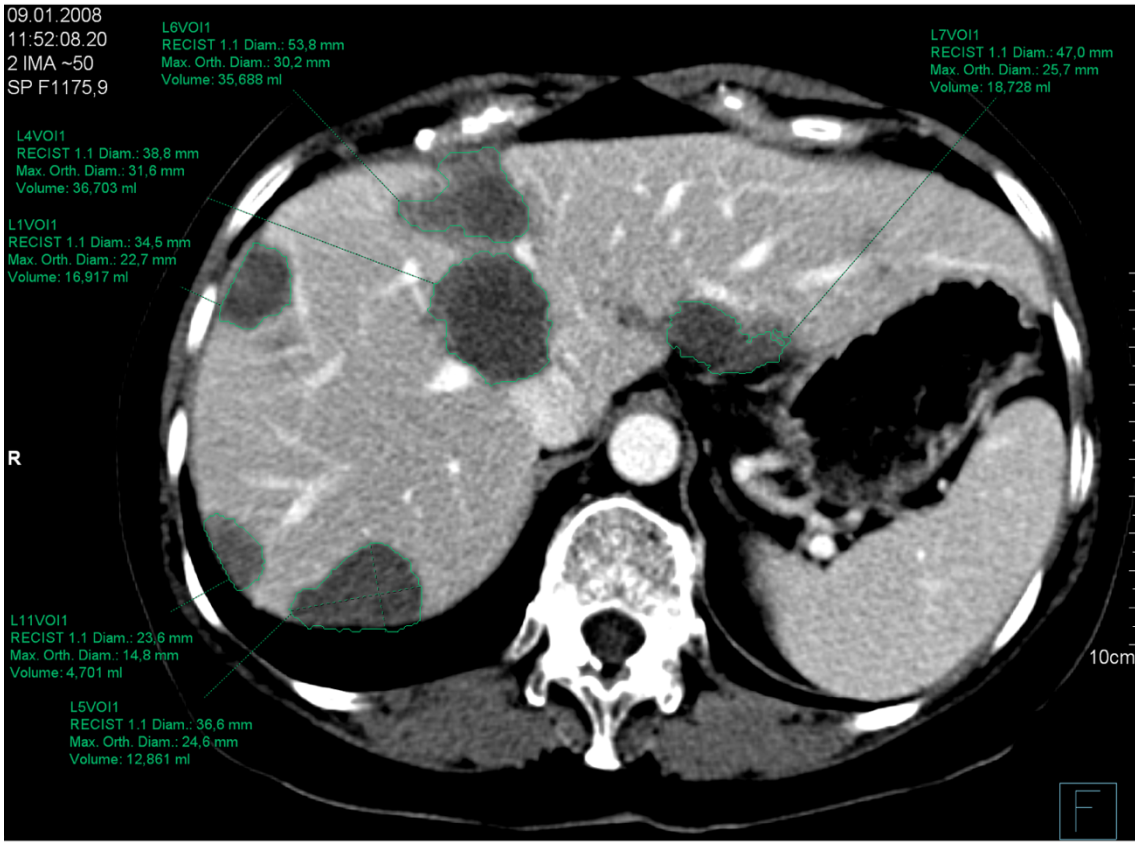

Figure 1: Volumetric segmentation. Semi-automated volumetric segmentation of hepatic metastases of a 62-year-old female with metastatic colorectal cancer who received FOLFIRI plus bevacizumab. Segmentation was performed in the image postprocessing software syngo.via, MM Oncology, Siemens Healthineers, Siemens Healthcare GmbH, Erlangen.

Improved image postprocessing techniques allow three-dimensional, volumetric tumor measurements[178,179]: In semi-automated volumetry, the lesions' diameter is manually marked, and the software automatically suggests a volumetric segmentation that, if necessary, can be corrected manually (Figure 1). All voxels comprising the metastasis are included into the volume of interest (VOI). Thus, the calculated volume might represent the size of the whole lesion more accurately than its longest diameter.[180] Therefore, and as prior studies suggest[181], volume changes could correlate better with treatment response and outcomes.

Volumetric segmentation is technically feasible.[178] However, the application of volumetric criteria is hampered by the lack of thresholds defining response and progress.[182,183] In prior studies, volumetric thresholds equivalent to the established RECIST thresholds (-30 %, +20 %) were interpolated by using the volume-formula of perfect spheres.[183-186] This assumes that the change of the measured diameter represents the

change in all directions accurately. However, especially in asymmetric or large lesions, variations occur.

The aim of the published study (publication I) was to empirically identify volumetric thresholds corresponding to the established diametric RECIST 1.1 thresholds. The author (F.O.H.) contributed significantly to conception and design of the study, acquisition and assembly of the data, statistical analysis and interpretation of the data, and the writing of the manuscript.[187]

1.6 Radiologically enlarged lymph nodes

CT is fundamental for diagnosis, treatment planning, and response assessment in patients with metastatic colorectal cancer. Therefore, most of the patients undergo baseline CT. Many of the findings (e.g., TNM-stage, number of metastatic sites) influence treatment decisions and the patients' prognosis.[57,188] However, baseline CT often also reveals findings with unclear prognostic relevance such as the presence of radiologically enlarged lymph nodes.

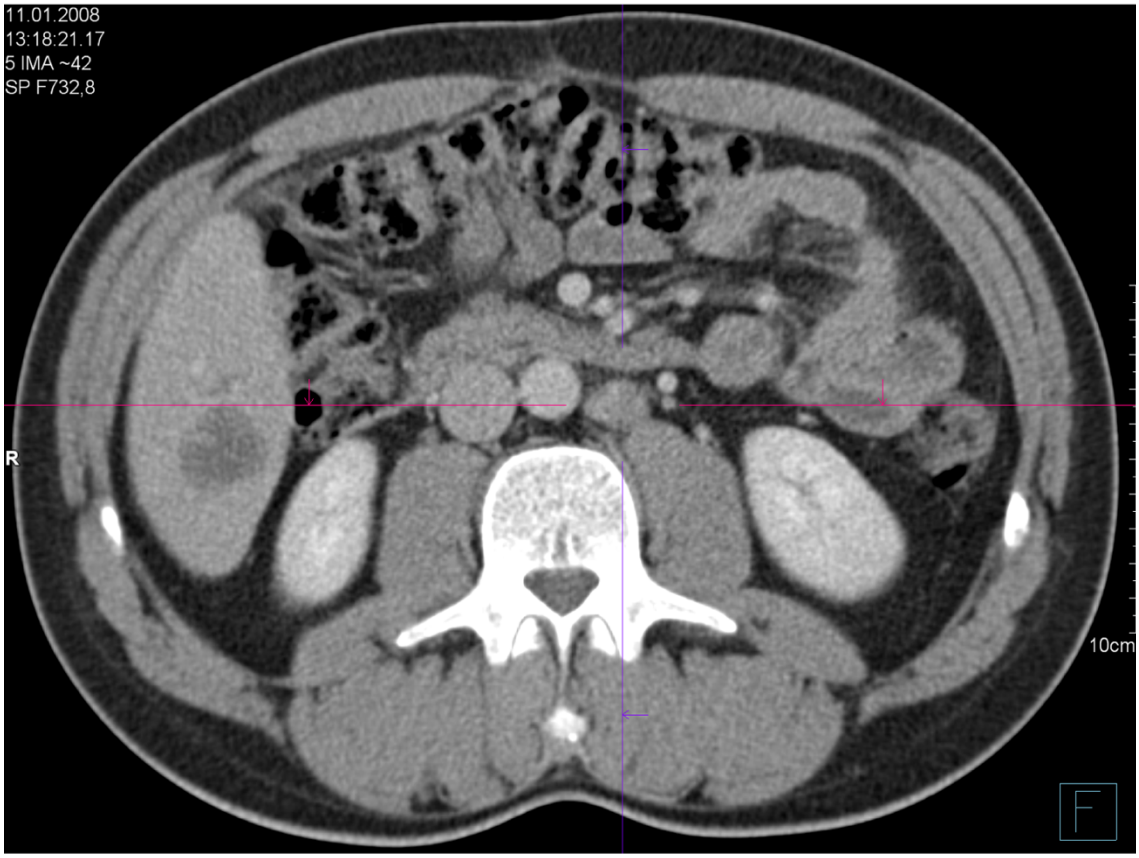

Figure 2: Radiologically enlarged lymph node. Radiologically enlarged, paraaortic lymph node of a 43-year-old male with metastatic colorectal cancer. Evaluation was performed in the image postprocessing software syngo.via, MM Oncology, Siemens Healthineers, Siemens Healthcare GmbH, Erlangen.

Colorectal cancer tumor cells disseminate through blood and lymphatic vessels.[189-193] The metastatic spread through the lymphovascular system is highly relevant and reflected by the metastatic affection of lymph nodes.[192,194,195]

Lymph node metastases influence the prognosis and the optimal treatment regimen in colorectal cancer: For instance, regional lymph node metastases (stage III disease) are associated with a reduced overall survival[57] and chemotherapy is recommended[60,72,73]. In patients with stage IV disease, regional and distant lymph node metastases are also associated with a reduced overall survival.[196-198]

The histopathology of radiologically enlarged lymph nodes at baseline often remains unclear and its evaluation is limited to morphological properties. In RECIST 1.1, lymph nodes with the shortest diameter ≥ 10 mm are considered as suspect (Figure 2).[175] However, its prognostic relevance beyond other prognostic parameters remains unclear in stage IV disease patients receiving combination-therapy.

The aim of the published study (publication II) was to determine the prognostic relevance of radiologically enlarged lymph nodes in baseline computed tomography beyond established and potential prognostic parameters. The author (F.O.H.) contributed significantly to conception and design of the study, acquisition and assembly of the data, statistical analysis and interpretation of the data, and the writing of the manuscript.[199]

2 Summary

2.1 Purpose

The aim of the published studies was

I to determine volumetric thresholds corresponding to the established diametric RECIST thresholds defining response and progress of target lesions and

II to investigate the prognostic relevance of radiologically enlarged lymph nodes in baseline computed tomography (CT) of patients with metastatic colorectal cancer prior first-line combination-therapy.

2.2 Materials & Methods

The published studies are retrospective analyses of the prospective clinical phase 3 trial FIRE-3 that included 592 patients with initially unresectable, histologically confirmed metastatic colorectal adenocarcinoma (ClinicalTrials.gov, number NCT00433927). FIRE-3 compared first-line combination-therapy with FOLFIRI aligned with either EGFR-antibody cetuximab or VEGF-antibody bevacizumab.[200,201]

In total, 2535 CT of 506 patients were retrospectively evaluated regarding radiological response and progress. Therefore, diameters and volumes of 1659 target lesions in liver (1224), lungs (282) and lymph nodes (153) were measured in 9226 single semi-automated volumetric segmentations. Additionally, non-target lesions were evaluated according to RECIST 1.1. Based on the acquired data multiple analyses were performed, among these the following:

I Relative diametric and volumetric size changes of the same hepatic target lesions were calculated. Based on this, volumetric thresholds corresponding to the established diametric RECIST thresholds were determined with loess-regression. The implications on the categorization regarding response and progress were further investigated.

II The prognostic relevance of radiologically enlarged regional and distant lymph nodes was investigated in univariable Cox proportional hazard regression and Kaplan Meier analysis. The influence of enlarged lymph nodes on survival beyond established prognostic parameters was further analyzed in multivariable Cox proportional hazard regression.

2.3 Results

I The volumetric threshold indicating response ranged between - 63.6 % and - 65.3 %, depending on whether one, the sum of up to two or the sum of up to five target lesions was considered. Likewise, the volumetric threshold indicating progress

ranged between +61.7 % and +64.6 %. To provide a uniform and memorable threshold we proposed -65 % and +65 % as equivalents to the established RECIST thresholds -30 % and +20 %. In sensitivity analysis, the deviation from the regression results only marginally influenced the categorization of cases concordantly or discordantly to RECIST. For the sum of up to two metastases, 85.0% of all weighted cases categorized as responsive according to volumetry were also responsive according to RECIST. 91.2 % of all weighted cases without significant volumetric size change also had no significant change according to RECIST. 88.3% of all weighted cases categorized as progressive according to volumetry were also progressive according to RECIST.

II Of 339 analyzed patients, 178 (52.5 %) had radiologically enlarged lymph nodes at baseline CT prior first-line combination-therapy. For these, overall survival (OS) was significantly shorter (median OS 21.7 [95 % CI, 18.8 – 24.7] months *vs* 33.2 [95 % CI, 28.8 – 38.3] months; HR, 1.61 [95 % CI, 1.23 – 2.09], $P < .001$). Progression-free survival (PFS) however was only insignificantly shorter (median PFS 9.9 [95 % CI, 8.8 – 10.8] months *vs* 11.1 [95 % CI, 10.1 – 12.3] months; HR, 1.23 [95 % CI, 0.98 – 1.54], $P = .072$). Multivariable regression confirmed the negative prognostic implication of radiologically enlarged lymph nodes on OS beyond established prognostic parameters (HR, 1.37 [95 % CI, 1.02 – 1.83], $P = .036$). Furthermore, peritoneal carcinomatosis, elevated alkaline phosphatase, BRAF mutations and the treatment with bevacizumab (instead of cetuximab) were associated with a reduced OS.

2.4 Conclusion

Volumetric thresholds of -65 % and +65 % are corresponding to the established diametric RECIST thresholds of -30 % and +20 % indicating response and progress of target lesions. Radiologically enlarged lymph nodes at baseline prior combination-therapy are associated with a reduced OS beyond established prognostic parameters.

3 Zusammenfassung

3.1 Ziel

Das Ziel der publizierten Studien war

I volumetrische Grenzwerte zu bestimmen, die den etablierten, Durchmesser-basierten Grenzwerten nach RECIST entsprechen, welche das Ansprechen und den Progress von „Target Lesions“ definieren, und

II die prognostische Relevanz von radiologisch vergrößerten Lymphknoten in Baseline-Computertomographien (CT) von Patienten mit metastasiertem kolorektalem Karzinom vor Erstlinien-Kombinationstherapie zu untersuchen.

3.2 Material & Methoden

Die publizierten Studien sind retrospektive Analysen der prospektiven klinischen Phase 3 Studie FIRE-3, die 592 Patienten mit initial nicht resektablen, histologisch gesichertem, metastasiertem kolorektalem Adenokarzinom einschloss (ClinicalTrials.gov, Nummer NCT00433927). FIRE-3 verglich die Erstlinien-Kombinationstherapie mit FOLFIRI kombiniert entweder mit dem EGFR-Antikörper Cetuximab oder mit dem VEGF-Antikörper Bevacizumab.[200,201]

Insgesamt wurden 2535 CT von 506 Patienten retrospektiv hinsichtlich des radiologischen Ansprechens und Progresses ausgewertet. Dazu wurden Durchmesser und Volumina von 1659 „Target Lesions“ in Leber (1224), Lunge (282) und Lymphknoten (153) in 9226 einzelnen, semi-automatischen, volumetrischen Segmentierungen vermessen. Weiterhin wurden „Non-target Lesions“ nach den RECIST 1.1 Kriterien evaluiert. Auf Basis der akquirierten Daten erfolgten unter anderem die folgenden Analysen:

I Die relativen Änderungen der Durchmesser und Volumina der gleichen „Target Lesions“ in der Leber wurden berechnet. Basierend darauf wurden volumetrische Grenzwerte, die den etablierten Durchmesser-Grenzwerten der RECIST-Kriterien entsprechen, mittels loess-Regression bestimmt. Die Auswirkung auf die Kategorisierung in größenregrediente und größenprogrediente Metastasen wurde weiter untersucht.

II Die prognostische Relevanz radiologisch vergrößerter regionaler und ferner Lymphknoten wurde in univariabler Cox proportional hazard Regression und Kaplan Meier Analyse analysiert. Der Einfluss auf das Überleben über etablierte Prognosefaktoren hinaus wurde in multivariabler Cox proportional hazard Regression untersucht.

3.3 Ergebnisse

I Der volumetrische Grenzwert, ab welchem Läsionen als ansprechend kategorisiert wurden, rangierte zwischen - 63.6 % und - 65.3 %, abhängig davon, ob eine, die Summe von bis zu zwei oder die Summe von bis zu fünf Metastasen zur Berechnung herangezogen wurde. Der volumetrische Grenzwert, ab welchem Läsionen als progressiv kategorisiert wurden, rangierte zwischen + 61.7 % und + 64.6 %. Der Einheitlichkeit und Eingängigkeit wegen schlugen wir - 65 % und + 65 % als Äquivalente zu den etablierten RECIST-Grenzwerten - 30 % und + 20 % vor. In Sensitivitätsanalysen beeinflusste die Abweichung von den Ergebnissen der Regressionen nur minimal, ob die Kategorisierung mit RECIST übereinstimmte oder davon abwich. In der Untersuchung der Summe von bis zu zwei Metastasen, waren 85.0 % der gewichteten, nach Volumetrie signifikant größenregredienten Fälle auch nach den RECIST größenregredient. 91.2 % der gewichteten Fälle ohne signifikante volumetrische Größenänderung hatten auch nach RECIST keine signifikante Größenänderung. Ebenso waren 88.3 % der gewichteten, nach Volumetrie größenprogredienten Fälle nach RECIST ebenfalls größenprogredient.

II Von 339 analysierten Patienten hatten 178 (52.5 %) radiologisch vergrößerte Lymphknoten in der Baseline-CT vor Erstlinien-Kombinationstherapie. Ihr Gesamtüberleben (OS) war signifikant kürzer (medianes OS 21.7 [95 % CI, 18.8 – 24.7] Monate *vs* 33.2 [95 % CI, 28.8 – 38.3] Monate; HR, 1.61 [95 % CI, 1.23 – 2.09], $P < .001$). Das progressionsfreie Überleben (PFS) hingegen war nur insignifikant kürzer (medianes PFS 9.9 [95 % CI, 8.8 – 10.8] Monate *vs* 11.1 [95 % CI, 10.1 – 12.3] Monate; HR, 1.23 [95 % CI, 0.98 – 1.54], $P = .072$). Die multivariable Regression bestätigte den negativen prognostischen Einfluss radiologisch vergrößerter Lymphknoten auf das Gesamtüberleben über etablierte prognostische Parameter hinaus (HR, 1.37 [95 % CI, 1.02 – 1.83], $P = .036$). Weiterhin waren Peritonealkarzinose, erhöhte alkalische Phosphatase, Mutation des BRAF-Gens sowie die Behandlung mit Bevacizumab (anstelle von Cetuximab) mit kürzerem Gesamtüberleben assoziiert.

3.4 Schlussfolgerung

Volumetrische Grenzwerte von - 65 % und + 65 % entsprachen den etablierten Durchmesser-basierten Grenzwerten der RECIST-Kriterien von - 30 % und + 20 %, die das Ansprechen und den Progress von „Target Lesions“ definieren. Radiologisch vergrößerte Lymphknoten in der Baseline-Computertomographie vor Kombinationstherapie sind über die etablierten prognostischen Parameter hinaus mit einem reduziertem Gesamtüberleben assoziiert.

4 Publication I

Towards volumetric thresholds in RECIST 1.1: Therapeutic response assessment in hepatic metastases

K.S. Winter¶, **F.O. Hofmann¶**, K.M. Thierfelder, J.W. Holch, N. Hesse, A.B. Baumann, D.P. Modest, S. Stintzing, V. Heinemann, J. Ricke, W.H. Sommer, M. D'Anastasi

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¶ These authors contributed equally.

5 Publication II

Prognostic value of radiologically enlarged lymph nodes in patients with metastatic colorectal cancer: Subgroup findings of the randomized, open-label FIRE-3/AIO KRK0306 trial

F.O. Hofmann¶, J.W. Holch¶, V. Heinemann, I. Ricard, M.F. Reiser, A.B. Baumann, N. Hesse, M. D'Anastasi, D.P. Modest, S. Stintzing, W.H. Sommer

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¶ These authors contributed equally.

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8 Affidavit

I, Felix O. Hofmann (* July 31, 1992), hereby declare, that the submitted thesis entitled

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Exploration of qualitative and quantitative image parameters
for risk and response assessment

is my own work. I have only used the sources indicated and have not made unauthorized use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

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November 14, 2019
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