Resection of the primary tumor versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectablemetastases (UICC stage IV)
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A randomized controlled multicenter trial (SYNCHRONOUS-Trial)

ISRCTN30964555

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Title of the study	Resection of the primary tumor versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV) - A randomized controlled multicenter trial (SYNCHRONOUS-Trial)
Trial registration	ISRCTN30964555
Condition	Patients with synchronous metastatic colon cancer not amenable for curative therapy.
Objectives	To investigate, whether resection of the primary tumor prolongs survival of patients with colon cancer and synchronous metastases not amenable for curative therapy. The primary hypothesis is that resection of the primary tumor prolongs survival from 20 to 26 months compared to systemic therapy without prior tumor resection.
Study arms	Experimental arm: Resection of the primary colon tumor followed by systemic therapy. Control arm: Systemic therapy without previous surgical resection of the primary colon tumor. Follow-up per patient: 36 months
Eligibility criteria	Key inclusion criteria: - Newly diagnosed, histologically confirmed colon cancer - Synchronous metastases not amenable for curative therapy - Resectable primary tumor - ECOG performance status of 0, 1, 2 - Patient considered to tolerate surgery and chemotherapy - ≥ 18 years of age - Written informed consent Key exclusion criteria: - Rectal cancer (tumor up to 12 cm from the anal verge) - Tumor-related symptoms or diagnostic findings requiring urgent surgery - Patients not eligible for surgery (ASA ≥ IV) - Unequivocal extensive peritoneal metastases - Chemo- and/or radiotherapy during the past 6 months - History of another primary cancer - Expected lack of compliance
Outcomes	Primary endpoint: - Overall survival Secondary endpoints: - Time-to-development of primary tumor related local symptoms (control arm) - Primary tumor complications (control arm) - Intervention due to primary tumor complication (control arm) - Administration of systemic therapy (experimental and control arm) - Peri-operative morbidity (experimental arm) - Peri-operative mortality (experimental arm) - Interventions with curative intent (experimental and control arm) - Course of tumor markers CEA and CA 19-9 (experimental and control arm) - Quality of Life (experimental and control arm) Assessment of safety: Rates of complications/ serious adverse events will be closely monitored.

Study design	Prospective randomized, controlled, open, multicenter trial with two parallel study groups.
Statistical analysis	Efficacy: Primary endpoint is overall survival. Description of the primary efficacy / test accuracy analysis and population: The confirmatory test for treatment group difference with respect to the primary endpoint will be done applying a Cox proportional hazard model that takes into account the covariates center, age and administered systemic therapy. The robust sandwich estimate of the covariance matrix proposed by Lin and Wei is used for the test for treatment effect. This test allows valid statistical inference also in situations where the proportional hazards assumption is violated, which may be the case in the current situation. The two-sided type I error rate is 5%. The corresponding two-sided 95% confidence interval for the hazard ratio is calculated. The primary analysis will be conducted for the intention-to-treat population of all randomized patients. Drop-out and lost-to-follow-up are treated as censoring events. Secondary endpoints: Descriptive analyses of differences between treatment groups, assessment of prognostic factors and comparison of interventions in appropriate subgroups. Safety: Calculation and descriptive comparison of the rates of complications and serious adverse events.
Sample size	To be assessed for eligibility. **(n = 900)** To be allocated to trial. **(n = 800)** To be analyzed. **(n = 800)**
Trial duration	First patient in to last patient out (months): 60 Duration of the entire trial (months): 72 Recruitment period (months): 24