

Perioperative FLOT Chemotherapy Plus Surgery for Oligometastatic Esophagogastric Adenocarcinoma: Surgical Outcome and Overall Survival

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Abstract

Background:

Guidelines do not recommend surgery for patients with oligometastatic disease from esophagogastric adenocarcinoma (EGAC), although some studies suggest a more favourable survival. We analyzed the outcome of oligometastatic EGAC receiving FLOT chemotherapy followed by surgery.

Methods:

The data of patients with either pre-therapeutic, post-neoadjuvant or intraoperative clinical diagnosis of oligometastatic EGAC were extracted from a prospective database of the 2009-2018 treatment period. 48 consecutive patients were identified with oligometastatic disease, who underwent perioperative chemotherapy plus surgery. We retrospectively analyzed surgical outcome and overall survival.

Results:

The overall 5-year survival was 18 %. 12 patients with pre-therapeutic oligometastatic EGAC, who had no histologic vital tumor evidence of metastases after surgery had a survival rate of 48 % compared to an 11 % 5-year survival rate of 36 patients, who had histologic vital tumor metastatic evidence after FLOT chemotherapy and surgical resection ($p=0.012$). The survival rates after R0, R1 and R2 (non-resected metastases) resection were 21 % ($n=33$), 0 % ($n=4$) and 17 % ($n=11$), respectively ($p=0.273$).

Conclusion:

Oligometastatic EGAC is associated with poor overall survival even after complete resection of all tumor manifestations. The subgroup of patients with a complete pathohistologic response of metastatic lesions to neoadjuvant FLOT shows 5-year survival rates similar to non-metastatic EGAC.

Trial registration:

Not applicable

Background

Different randomized controlled trials (RCT) have demonstrated superior results of perioperative chemotherapy plus surgery for non-metastatic esophagogastric cancers (EAGC) compared to surgery alone [1–4]. The chemotherapy of choice in Europe is the FLOT regime, consisting of Docetaxel 50 mg/m², Oxaliplatin 85 mg/m², Leucovorin 200 mg/m² and 5FU 2600 mg/m². FLOT is associated with overall better survival compared to ECF/ECX regimes [5]. One RCT showed survival rates of 50 months for perioperative FLOT therapy vs 35 months for patients receiving ECF/ECX regimes [5]. Perioperative chemotherapy has been adopted by national and international guidelines for locally advanced but not for metastatic EGAC [3, 6] for which palliative chemotherapy is recommended. There is, however, great

uncertainty about the best management for patients with oligometastatic EGAC. Oligometastatic disease is defined as less than five distant, potentially resectable metastases, eg liver metastases and limited peritoneal carcinomatosis. It is used to describe a state between limited and disseminated metastatic disease, with the potential intention of curative treatment [7]. The evidence is low with some retrospective studies suggesting prolonged survival after surgical resection of metastases from EGAC tumors [8–10]. The ongoing RENAISSANCE trial, a multicenter RCT, comparing the effect of chemotherapy alone vs chemotherapy followed by surgery for patients with oligometastatic EGAC is anticipated to shed light on the best treatment modality [10]. As we await the results, we conducted an analysis of our prospective database, evaluating the outcome and 5-year survival of patients with oligometastatic EGAC, who received perioperative FLOT chemotherapy plus surgery of the primary tumor and its metastases.

Methods

Between June 2009 and April 2018 277 patients had locally advanced EGAC, who were treated with FLOT chemotherapy and subsequent surgery at the Medical Center of the University of Freiburg. Out of these 277 patients, 48 patients with oligometastatic disease, including potentially resectable peritoneal carcinomatosis, underwent perioperative FLOT chemotherapy followed by surgery. The majority of patients with metastatic disease received palliative chemotherapy alone. The metastases were found either at the time of initial diagnosis (cM1), during post-neoadjuvant staging investigations (ycM1), or found intraoperatively. As 9 patients were lost to follow up, a total of 220 patients showed no metastases at time of diagnosis (cM0). Data had been prospectively collected and retrospectively analyzed in this study. Patient demographics, pre- and postoperative tumor stages, histopathological regression (HPR), perioperative complications and administration of perioperative chemotherapy were correlated with overall survival of the patients.

Complications were classified according to Clavien Dindo [11] and tumor regression according to Becker et al [12]. Survival data was obtained from the cancer registry of the Cancer Centre of our Medical Center. Inclusion in the cancer registry required informed consent, which was obtained from all patients. The study was approved by the Medical Ethics Committee of the University of Freiburg (File number 253/19).

Diagnostic work up and Staging

All patients with symptoms suggesting the presence of esophageal or gastric cancers were taken through diagnostic and staging work up according to German S3 guidelines [6]. This includes a thorough medical history and physical exam, as well as upper GI endoscopy with several biopsies, endoscopic ultrasound if technically possible and a CT Thorax/Abdomen to exclude distant metastases. Diagnostic laparoscopy with peritoneal biopsies and PET-CT scans were added in selected cases of suspected peritoneal carcinomatosis or distant metastases, otherwise distant metastases were diagnosed by staging CT. The management pathway was chosen according to TNM staging. For patients with locally advanced EGAC

(pT3 or pT4), re-staging was carried out after the completion of neoadjuvant chemotherapy, in order to plan surgical management. Figure 1 shows the flowchart of diagnosis and staging (Fig. 1).

Chemotherapy and surgical resection

Perioperative chemotherapy consists of four cycles prior to surgery (over 8 weeks) and further four cycles post-surgery, with each cycle lasting 2 weeks. The FLOT regime consists of infusions of 5-FU 2600 mg/m² (24 h), leucovorin 200 mg/m² (2 h), oxaliplatin 85 mg/m² (2 h) and docetaxel 50 mg/m² (1 h) every 2 weeks [5].

Surgery was usually carried out between 4–6 weeks after the completion of the neoadjuvant cycles of chemotherapy, with few selected patients undergoing surgery at a later point in time. Surgery was chosen according to tumor location and size. Routinely esophagectomy plus proximal gastrectomy with two-field lymphadenectomy was performed for esophageal or junctional adenocarcinoma (AEG I + II), whilst patients with AEG III tumors (in some selected cases also AEG II underwent transhiatal extended gastrectomy with lower mediastinal and modified DII-lymphadenectomy. Total or subtotal gastrectomy plus modified DII-lymphadenectomy was performed for patients with gastric cancer. In extended tumors, the surgical approach was adapted as necessary. Resectability of the primary and metastases depended on the location and was determined by an interdisciplinary team. It was then carried out accordingly e.g. as liver resection, adrenalectomy or peritonectomy for peritoneal carcinomatosis. Hyperthermic intraperitoneal chemotherapy (HIPEC) was additionally performed for patients with limited peritoneal metastases using Cisplatin (75 mg/m²) and Doxorubicin (15 mg/m²). Routine postoperative standard histopathological workup and staging was performed.

Statistical Analysis

Statistical analysis was performed using IBM SPSS statistics, Version 23. Categorical variables were put in absolute and relative frequencies; differences were evaluated by Chi-Square or Fisher's exact test as appropriate. Quantitative values were expressed as medians with range and differences were measured using the Mann-Whitney-U test. The Kaplan-Meier method was used to evaluate survival, with a long-rank test for the comparison of subgroups. Relative risks and 95% confidence intervals were reported. A p-value < 0.05 was considered statistically significant.

Results

Early results

Median follow up was 13 months (11 months for deceased patients and 17 months for all others). Out of 48 patients, 31 patients (64%) were diagnosed with gastric cancer and 17 patients (35%) with esophageal adenocarcinoma. All patients, except for one (pT2), had pT3 or pT4 tumors at initial staging. Comorbidities, including cardiac, pulmonary, renal and hepatic disease were present in 64% of patients. Patients' characteristics are summarized in Table 1. 83% of patients completed four cycles of

neoadjuvant FLOT chemotherapy (n = 40), whereas the adherence to postoperative chemotherapy was less, with only 31 patients (65%) completing their adjuvant treatment. Metastases were present in all patients either at the time of initial diagnosis or during preoperative staging (Fig. 1). Sixty two percent of patients (n = 30) had peritoneal carcinomatosis, from which 83% arose from gastric cancer. Distant lymph node metastases (lymph nodes outside of D1-II resection area) were found in seven patients, other distant metastases sites were hepatic (n = 7), adrenal (n = 3) and pulmonary (n = 1). Complete remission of metastasis was found in 25% of patients (ypM0) (n = 12), after resection. Resection of metastases was performed if distant metastases could be detected intraoperatively and surgical resection seemed feasible. Thus, in 68% of patients (n = 33) simultaneous resection of metastases was performed with resection of the primary tumor. 11 patients did not undergo resection of the metastatic lesion and were defined as R2. HIPEC was additionally carried out in 15 patients with peritoneal metastases, when cytoreductive surgery was completed.

Table 1
Patients demographics

	Gastric carcinoma (n = 31)	Esophageal carcinoma (n = 17)	Total (n = 48)
Sex			
Female	11 (35%)	4 (23%)	15 (31%)
Male	20 (64%)	13 (76%)	33 (69%)
Age in years*	55.1 (33.6–81.1)	58.3 (30.2–80)	56.8 (30.2–81.2)
ASA classification			
ASA 1–2	17 (55%)	12 (70%)	29 (60%)
ASA 3–4	14 (45%)	5 (29%)	19 (39%)
BMI in kg/m ² *	26.3 (18.0-41.7)	24.5 (20.5–38.1)	25.3 (18.0-41.7)

Complications and length of stay

Postoperative complications occurred in 48% of patients (42% after gastrectomy and 59% after esophagectomy). Surgical complications include anastomotic leaks (n = 2) wound infection (n = 5), chylothorax (n = 3) and haemorrhage (n = 2), whilst medical complications were mainly pulmonary, such as pleural effusions (n = 4), pneumonia (n = 8) and the need for reintubation (n = 2). 16 patients experienced complications of grade I-II and seven patients had major complications of grade III-V. Two patients died after esophagectomy: one patient due to postoperative erosive bleeding from the splenic artery and one due to rapid progressive pleural carcinomatosis, and one patient after gastrectomy, due to

an anastomotic leak followed by septic shock. Average length of hospital stay was 12 days (range 7–94), with an average length of stay on ICU/IMC of 4 days (range 2–22 days). Treatment data is summarized in Table 2.

Table 2
 Perioperative treatment data

	Gastric carcinoma (n = 31)	Esophageal carcinoma (n = 17)	Total (n = 48)
Type of surgery			
Esophagectomy	1 (3%)	15 (88%)	16 (33%)
Gastrectomy	30 (97%)	2 (12%)	32 (66%)
HIPEC	14 (45%)	1 (6%)	15 (31%)
Additional resection			
None	10 (32%)	5 (29%)	15 (31%)
Peritoneum	16 (51%)	2 (12%)	18 (37%)
Distant lymph nodes	1 (3%)	3 (18%)	4 (8%)
Liver	1 (3%)	3 (18%)	4 (8%)
Adrenal	3 (10%)	0	3 (6%)
Multivisceral resection	0	4 (24%)	4 (8%)
Perioperative in-patient stay in days	11 (8–23)	14 (7–94)	12 (7–94)
Perioperative in intensive care in days	4 (2–11)	5 (3–22)	4 (2–22)
Perioperative complications			
Clavien Dindo	13 (42%)	10 (59%)	23 (48%)
I/ii	9 (29%)	7 (41%)	16 (33%)
III/IV	3 (10%)	1 (6%)	4 (8%)
V	1 (3%)	2 (12%)	3 (6%)
Resection margin			
R0	21 (68%)	12 (70%)	33 (69%)
R1 (primary tumor)	3 (9%)	1 (6%)	4 (8%)
R2 (non-resected metastases)	7 (22%)	4 (23%)	11 (23%)

	Gastric carcinoma (n = 31)	Esophageal carcinoma (n = 17)	Total (n = 48)
Postoperative residual tumor			
Local	3 (10%)	1 (6%)	4 (8%)
Peritoneal carcinomatosis	3 (10%)	2 (12%)	5 (10%)
Lymph nodes	1 (3%)	2 (12%)	3 (6%)
Distant metastasis	3 (10%)	0	3 (6%)
Recurrence	12 (39%)	7 (41%)	19 (40%)
Time of recurrence after surgery in months*	5,5 (1–15)	6,5 (1–10)	6 (1–15)
Type of recurrence			
Local	1 (8%)	0	1 (5%)
Local and distant	2 (17%)	2 (29%)	4 (21%)
Peritoneal carcinomatosis	4 (33%)	1 (14%)	5 (26%)
Hepatic metastasis	3 (25%)	3 (43%)	6 (32%)
Other type of metastasis	1 (8%)	1 (14%)	2 (11%)

Overall survival

Overall 5- year survival of patients with oligometastatic EGAC was 18%, with a median survival of 15 months after surgery. Tumor recurrence occurred in 19 of 37 patients without residual macroscopic tumor after surgery, in a median time interval of 6 months (1–15). Most recurrences were distant metastases (peritoneal carcinomatosis n = 5, hepatic n = 6, multiple distant n = 1). Post-recurrence treatment was individualized to the patient and included surgery, radiotherapy, palliative chemotherapy or best supportive care. According to the treatment used, the rate of overall survival will differ. Patients with gastric cancer and esophageal adenocarcinoma had comparable 5-year survival rates (25% and 10%, respectively p = 0.213). The location of metastases had no significant correlation for 5-year survival (p = 0.945). Independent predictors of 5-year survival were tumor regression (p = 0.012) grading and postoperative T-stage (p = 0.047). Tumor regression grading according to Becker et al [12], showed that with 1a regression (no residual tumor), patients had a 60% survival at 5 years, median survival was not reached. Patients with regression grades of 1b and 2 only had 11% and grade 3 and above only 12% of 5-year survival (Fig. 2). Median survival was 21 months and 9 months, respectively. Furthermore, postoperative T-staging of tumors produced similar results with a survival rate 60% for patients with T0 staging, compared to 27% for T1/T2 and 0% for T3/T4 tumors (n = 6, n = 15, n = 27, respectively, p =

0.047). The most significant finding was demonstrated by the difference in 5-year survival rate between patients with non-detectable tumor postoperatively (ypM0) and patients with detectable metastases. Here, patients with postoperative ypM0 (n = 12) had a 48% 5-year survival rate, with a median survival of 47 months, in contrast to only 11% at 5 years for patients with detectable tumor cells (ypM1, n = 36), with a median of 12 months (p = 0.012). Furthermore, the overall survival of patients with ypM0 is comparable to patients without metastatic disease at primary diagnosis (cM0), with 48% and 51% respectively (p < 0.001; Fig. 3). There is no significant difference in overall survival between patients with resected metastases, and those without resection (9% vs 17% p = 0.427; Fig. 4). Other factors that did not show any significant influence on overall survival are resection rates, nodal status (Fig. 5), the type of metastases or preoperative M-staging, with p levels of p = 0.273, p = 0.922 and p = 0.945, respectively. Results are summarized in Table 3.

Table 3
Univariate Analysis of survival

	n	5-year-survival	Median survival in years	p=
Total	48	18%	1.3	
Sex				
Female	15	26%	2.8	0.195
Male	33	16%	1.0	
Age				
< 65	35	10%	1.2	0.596
≥ 65	13	26%	1.4	
ASA classification				
ASA 1–2	29	20%	1.3	0.405
ASA 3–4	19	16%	1.0	
Type of carcinoma				
Esophageal carcinoma	17	10%	1.0	0.213
Gastric carcinoma	31	24%	1.3	
Preoperative T stage				
T2	1	0%	0.5	0.338
T3	29	14%	1.2	
T4	5	0%	3.9	
Type of surgery				
Esophagectomy	16	0%	1.0	0.099
Gastrectomy	32	30%	1.3	
Resection margin				
R0	33	21%	1.4	0.273
R1 (primary tumor)	4	0%	0.4	
R2 (non-resected metastases)	11	17%	1.3	

	n	5-year-survival	Median survival in years	p=
Tumor regression grading				
1a	6	60%	Not reached	0.012
1b-2	22	11%	1.8	
3-4	20	12%	0.9	
Postop. pathologic T stage				
T0	6	60%	Not reached	0.047
T1-T2	15	27%	1.3	
T3-T4	27	0%	1.0	
Postop. pathologic N stage				
N0	17	31%	2.9	0.062
N+	31	11%	1.2	
Type of metastasis				
Peritoneal carcinomatosis	30	11%	1.0	0.945
Lymph nodes	7	43%	1.3	
Hepatic	7	40%	2.9	
Adrenal	3	0%	0.9	
Pulmonary	1	0%	1.7	
Preoperative M stage				
M0	8	22%	1.4	0.922
M1	40	17%	1.3	
Postoperative M stage				
ypM0	12	48%	3.9	0.427
ypM1 and resection of metastasis	25	9%	1.0	
ypM1 and no resection of metastasis	11	17%	1.3	
ypM0				
Yes	12	48%	3.9	0.012
No	36	11%	1.0	

	n	5-year-survival	Median survival in years	p=
Adjuvant chemotherapy				
Yes	31	21%	1.7	0.182
No	9	30%	0.5	

Discussion

Multimodal treatment strategies have significantly improved the long-term results in the treatment of non-metastatic EGAC. Up to date, there is an ongoing debate about the best treatment option for EGAC with oligometastatic disease. Synchronous metastatic disease is seen in up to 14% of cases [13, 14]. Up to date, guidelines across Europe do not recommend multimodal treatment including surgery for patients with distant metastases, but rather recommend palliative chemotherapy [6, 15, 16]. The value of surgery for metastases, especially for liver metastases originating from colorectal cancer, has evolved over the last few years as it has been shown to improve long-term and disease-free survival, with 5 year survival rates of 25% – 40% [17, 18]. Thus, the option of surgery as a potential curative treatment is standardly offered to patients with hepatic metastatic colorectal disease. Furthermore, even though the addition of treatment modalities like cytoreductive surgery and HIPEC have been shown to prolong survival in selected patients with gastrointestinal and gynecological tumors there is in an ongoing debate about the best management of patients with metastatic disease [19–21]. Although some retrospective studies suggest an improved survival of patients with surgical resection of metastases for EGAC [22, 23], there is a lack of prospective, randomized evidence. There is currently an ongoing RCT comparing surgical intervention for oligometastatic disease to the effectiveness of palliative chemotherapy [10].

Comparing our survival data with the existing literature, certain consistencies can be identified. The median survival of all patients included in this study was 15 months, the data in the literature ranges from 13–31 months [9, 10, 13]. Most definitions of oligometastatic disease, however, do not include peritoneal carcinomatosis. A difference in 5-year survival is shown between lymphatic and hepatic metastases (43% and 40%) compared to peritoneal carcinomatosis of 11%, suggesting that results might differ according to which definition of oligometastases was used. Patients with peritoneal carcinomatosis are often only treated with best supportive care or palliative chemotherapy, with a median survival of 4 and 7 months, respectively [24]. Our data suggests median survival rates of 13 months for patients with peritoneal carcinomatosis and perioperative chemotherapy followed by surgery, with 15 patients receiving additional HIPEC. The median survival correlates with data found in the literature regarding HIPEC and gastric cancers quoting median survival of between 10 and 21 months [25–27]. Although some authors suggest an improved overall survival for patients with limited peritoneal metastatic disease and HIPEC, it is not introduced in national and international treatment guidelines for patients with EGAC [25, 26, 28–30].

Different studies suggest a significantly improved overall survival of patients with surgical resection of the primary EGAC and metastases [8–10, 13, 14, 31], although results from RCTs are still anticipated. Patients without any detectable metastases after perioperative chemotherapy and surgical resection (ypM0) had a similar overall survival to patients without any metastatic disease at primary diagnosis (48% and 52% at 5 years, respectively), demonstrating the effectiveness of good response to neoadjuvant chemotherapy. Similar survival benefits could not be established with chemotherapy alone. Median survival for patients with ypM0 of 47 months compares to median survival quoted in the literature for patients after FLOT therapy for locally advanced tumors of 50 months [5]. The phase 2 AIO-FLOT3 trial suggests better overall survival after resection compared to chemotherapy alone, quoting almost double the median survival (31.3 months vs 15.9 months) [31]. Patients selected for surgery of metastases had to show a chance of R0 resection of the primary and metastatic lesion at restaging, assuming a good response to preoperative chemotherapy. Metastases found intraoperatively suggest either progress of disease or lack of sensitivity of staging diagnostics.

Although results in the literature suggest a favorable outcome for patients with perioperative FLOT chemotherapy and surgery of the primary and metastases, we could not directly reproduce these results in our analysis. Similar to our results, a large retrospective analysis of 5185 patients did not show a survival benefit of simultaneous resection of metastases compared to resection of the primary alone [32]. Prognostic factors were pT- staging, regression grading and type of recurrence. Although some studies suggest significant influence of age, gender, sex, tumor location and nodal stage [2, 8, 13, 33] a significance could not be reproduced for patients with oligometastatic disease from EGAC.

Limitations of this study included foremost the sample size of 48 heterogenous patients and the retrospective, non-randomized nature of this study. The patients analyzed in this manuscript are a highly selected collective of patients with metastasized EGAC, who underwent surgical resection. The majority of patients with metastatic disease received palliative chemotherapy only. Secondly, all types of metastases were included in our study, with some patients receiving additional HIPEC. In single cases a misdiagnosis of preoperative cM1 status in patients with postoperative ypM0 status is possible and may thus create a bias. Furthermore, a multidisciplinary tumor board only selected patients with a good response to chemotherapy to proceed to surgery, for a potential cure of malignant disease.

Conclusions

Comparing our results to the existing data, we could not establish a significant benefit for survival for patients undergoing additional resection of metastases compared to those, where only the primary tumor was resected. Oligometastatic EGAC is associated with overall poor survival rates, despite complete resection of all tumor manifestations. Survival rates for patients with complete response after FLOT and resection match survival rates of patients without any metastatic disease at primary diagnosis. However, the results from RCTs are needed to evaluate the significance of additional surgery for metastases, in order to define the best option for patients with oligometastatic disease in the era of multimodal treatment of EGAC.

Abbreviations

FLOT- Chemotherapy consisting of Docetaxel, Oxaliplatin, Leucovorin and 5FU

EGAC- Esophagogastric adenocarcinoma

RCT- randomized controlled trial

ECF- Chemotherapy consisting of Epirubicin, Cisplatin and 5FU

ECX- Chemotherapy consisting of Epirubicin, Cisplatin and Capecitabin

HPR- histopathological regression

GI- gastrointestinal

CT- computer tomography

PET-CT- positron emission tomography

AEG- Esophagogastric junction cancers

HIPEC- Hyperthermic intraperitoneal chemotherapy

Declarations

Ethics approval and consent to participate: The study was approved by the Medical Ethics Committee of the University of Freiburg (File number 253/19).

Consent for publication: Not applicable

Availability of data and materials: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions:

- Conceptualization: MR, TG, JH, RV
- Methodology: RV, MR, TG,
- Formal analysis: RV, MR, TG
- Writing—original draft preparation: MR
- Writing—review and editing: JS, TG, JH, SFF

- Supervision: TG, JH, SFF
- All authors have read and agreed to the published version of the manuscript

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References

1. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ *et al*: **Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer**. *The New England journal of medicine* 2006, **355**(1):11-20.
2. Wang K, Ren Y, Ma Z, Li F, Cheng X, Xiao J, Zhang S, Yu Z, Yang H, Zhou H *et al*: **Docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil (FLOT) as preoperative and postoperative chemotherapy compared with surgery followed by chemotherapy for patients with locally advanced gastric cancer: a propensity score-based analysis**. *Cancer Manag Res* 2019, **11**:3009-3020.
3. Moehler M, Baltin CT, Ebert M, Fischbach W, Gockel I, Grenacher L, Holscher AH, Lordick F, Malfertheiner P, Messmann H *et al*: **International comparison of the German evidence-based S3-guidelines on the diagnosis and multimodal treatment of early and locally advanced gastric cancer, including adenocarcinoma of the lower esophagus**. *Gastric cancer : official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association* 2015, **18**(3):550-563.
4. Boige V, Pignon J, Saint-Aubert B, Lasser P, Conroy T, Bouché O, Segol P, Bedenne L, Rougier P, Ychou M: **Final results of a randomized trial comparing preoperative 5-fluorouracil (F)/cisplatin (P) to surgery alone in adenocarcinoma of stomach and lower esophagus (ASLE): FNLCC ACCORD07-FFCD 9703 trial**. *Journal of Clinical Oncology* 2007, **25**(18_suppl):4510-4510.
5. Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, Kopp HG, Mayer F, Haag GM, Luley K *et al*: **Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial**. *Lancet* 2019, **393**(10184):1948-1957.
6. Moehler M *et al*: **S3-Leitlinie "Magenkarzinom"—Diagnostik und Therapie der Adenokarzinome des Magens und Ösophagogastralen Übergangs** In.: *Z Gastroenterol*; 2001: 461–531.
7. Chiapponi C, Berlth F, Plum PS, Betzler C, Stippel DL, Popp F, Bruns CJ: **Oligometastatic Disease in Upper Gastrointestinal Cancer - How to Proceed?** *Visceral medicine* 2017, **33**(1):31-34.
8. Beckert S, Königsrainer A: **Oligometastasierung beim Magen- und Ösophaguskarzinom**. *Der Chirurg* 2018, **89**(7):505-509.
9. Carmona-Bayonas A, Jimenez-Fonseca P, Echavarria I, Sanchez Canovas M, Aguado G, Gallego J, Custodio A, Hernandez R, Viudez A, Cano JM *et al*: **Surgery for metastases for esophageal-gastric cancer in the real world: Data from the AGAMENON national registry**. *European journal of surgical*

oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 2018, **44**(8):1191-1198.

10. Al-Batran SE, Goetze TO, Mueller DW, Vogel A, Winkler M, Lorenzen S, Novotny A, Pauligk C, Homann N, Jungbluth T *et al*: **The RENAISSANCE (AIO-FLOT5) trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III trial of the German AIO/CAO-V/CAOGI.** *BMC cancer* 2017, **17**(1):893.
11. Dindo D, Demartines N, Clavien PA: **Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey.** *Annals of surgery* 2004, **240**(2):205-213.
12. Becker K, Mueller JD, Schulmacher C, Ott K, Fink U, Busch R, Bottcher K, Siewert JR, Hofler H: **Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy.** *Cancer* 2003, **98**(7):1521-1530.
13. Markar SR, Mikhail S, Malietzis G, Athanasiou T, Mariette C, Sasako M, Hanna GB: **Influence of Surgical Resection of Hepatic Metastases From Gastric Adenocarcinoma on Long-term Survival: Systematic Review and Pooled Analysis.** *Annals of surgery* 2016, **263**(6):1092-1101.
14. Song A, Zhang X, Yu F, Li D, Shao W, Zhou Y: **Surgical resection for hepatic metastasis from gastric cancer: a multi- institution study.** *Oncotarget* 2017, **8**(41):71147-71153.
15. Alderson D: **Scottish Intercollegiate Guidelines Network (SIGN) 87 — the Management of Oesophageal and Gastric Cancer.** *Clinical Oncology* 2008, **20**(7):530-531.
16. Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R: **Guidelines for the management of oesophageal and gastric cancer.** *Gut* 2011, **60**(11):1449-1472.
17. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E *et al*: **Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer.** *New England Journal of Medicine* 2004, **350**(23):2335-2342.
18. Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, Kemeny N, Brennan MF, Blumgart LH, D'Angelica M: **Actual 10-Year Survival After Resection of Colorectal Liver Metastases Defines Cure.** *Journal of Clinical Oncology* 2007, **25**(29):4575-4580.
19. Teo MCC, Tan GHC: **Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in gastrointestinal cancers: fad or standard of care?** *Singapore Med J* 2018, **59**(3):116-120.
20. Morris EJ, Forman D, Thomas JD, Quirke P, Taylor EF, Fairley L, Cottier B, Poston G: **Surgical management and outcomes of colorectal cancer liver metastases.** *The British journal of surgery* 2010, **97**(7):1110-1118.
21. Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG: **Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients.** *Annals of surgery* 2008, **247**(1):125-135.
22. Hartgrink HH, Putter H, Klein Kranenbarg E, Bonenkamp JJ, van de Velde CJ: **Value of palliative resection in gastric cancer.** *The British journal of surgery* 2002, **89**(11):1438-1443.

23. Cheon SH, Rha SY, Jeung H-C, Im C-K, Kim SH, Kim HR, Ahn JB, Roh JK, Noh SH, Chung HC: **Survival benefit of combined curative resection of the stomach (D2 resection) and liver in gastric cancer patients with liver metastases.** *Annals of Oncology* 2008, **19**(6):1146-1153.
24. Johnston FM, Beckman M: **Updates on Management of Gastric Cancer.** *Current oncology reports* 2019, **21**(8):67.
25. Rau B, Brandl A, Piso P, Pelz J, Busch P, Demtröder C, Schüle S, Schlitt H-J, Roitman M, Tepel J *et al*: **Peritoneal metastasis in gastric cancer: results from the German database.** *Gastric cancer : official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association* 2019.
26. Manzanedo I, Pereira F, Rihuete Caro C, Pérez-Viejo E, Serrano Á, Gutiérrez Calvo A, Regueira FM, Casado-Adam Á, Cascales-Campos PA, Arteaga X *et al*: **Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Gastric Cancer with Peritoneal Carcinomatosis: Multicenter Study of Spanish Group of Peritoneal Oncologic Surgery (GECOP).** *Annals of Surgical Oncology* 2019, **26**(8):2615-2621.
27. Rau B, Brandl A, Thuss-Patience P, Bergner F, Raue W, Arnold A, Horst D, Pratschke J, Biebl M: **The efficacy of treatment options for patients with gastric cancer and peritoneal metastasis.** *Gastric cancer : official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association* 2019.
28. Feingold PL, Kwong MLM, Sabesan A, Sorber R, Rudloff U: **Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for gastric cancer and other less common disease histologies: is it time?** *Journal of gastrointestinal oncology* 2016, **7**(1):87-98.
29. Koemans WJ, van der Kaaij RT, Boot H, Buffart T, Veenhof A, Hartemink KJ, Grootsholten C, Snaebjornsson P, Retel VP, van Tinteren H *et al*: **Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy versus palliative systemic chemotherapy in stomach cancer patients with peritoneal dissemination, the study protocol of a multicentre randomised controlled trial (PERISCOPE II).** *BMC cancer* 2019, **19**(1):420.
30. Yarema R, Mielko J, Fetsych T, Ohorchak M, Skorzewska M, Rawicz-Pruszyński K, Mashukov A, Maksimovsky V, Jastrzebski T, Polkowski W *et al*: **Hyperthermic intraperitoneal chemotherapy (HIPEC) in combined treatment of locally advanced and intraperitoneally disseminated gastric cancer: A retrospective cooperative Central-Eastern European study.** *Cancer medicine* 2019, **8**(6):2877-2885.
31. Al-Batran SE, Homann N, Pauligk C, Illerhaus G, Martens UM, Stoehlmacher J, Schmalenberg H, Luley KB, Prasnikar N, Egger M *et al*: **Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer: The AIO-FLOT3 Trial.** *JAMA oncology* 2017, **3**(9):1237-1244.
32. Chen J, Kong Y, Weng S, Dong C, Zhu L, Yang Z, Zhong J, Yuan Y: **Outcomes of surgery for gastric cancer with distant metastases: a retrospective study from the SEER database.** *Oncotarget* 2017, **8**(3):4342-4351.

33. Yang D, Hendifar A, Lenz C, Togawa K, Lenz F, Lurje G, Pohl A, Winder T, Ning Y, Groshen S *et al*:
Survival of metastatic gastric cancer: Significance of age, sex and race/ethnicity. *J Gastrointest Oncol* 2011, **2**(2):77-84.

Figures

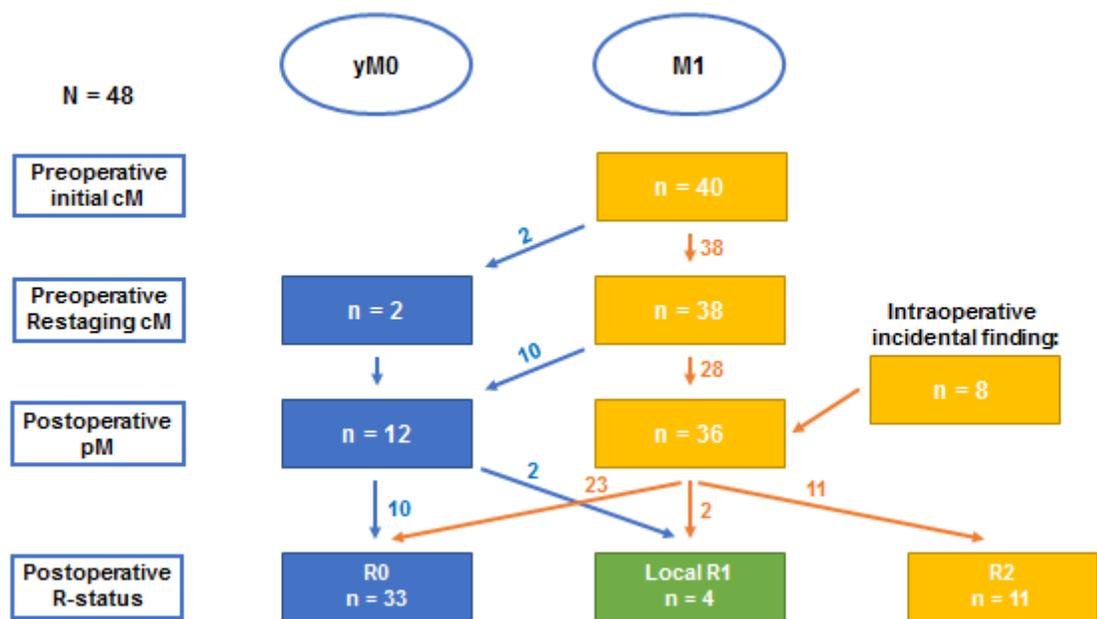


Figure 1

Flowchart of diagnosis and staging

Tumor regression grading

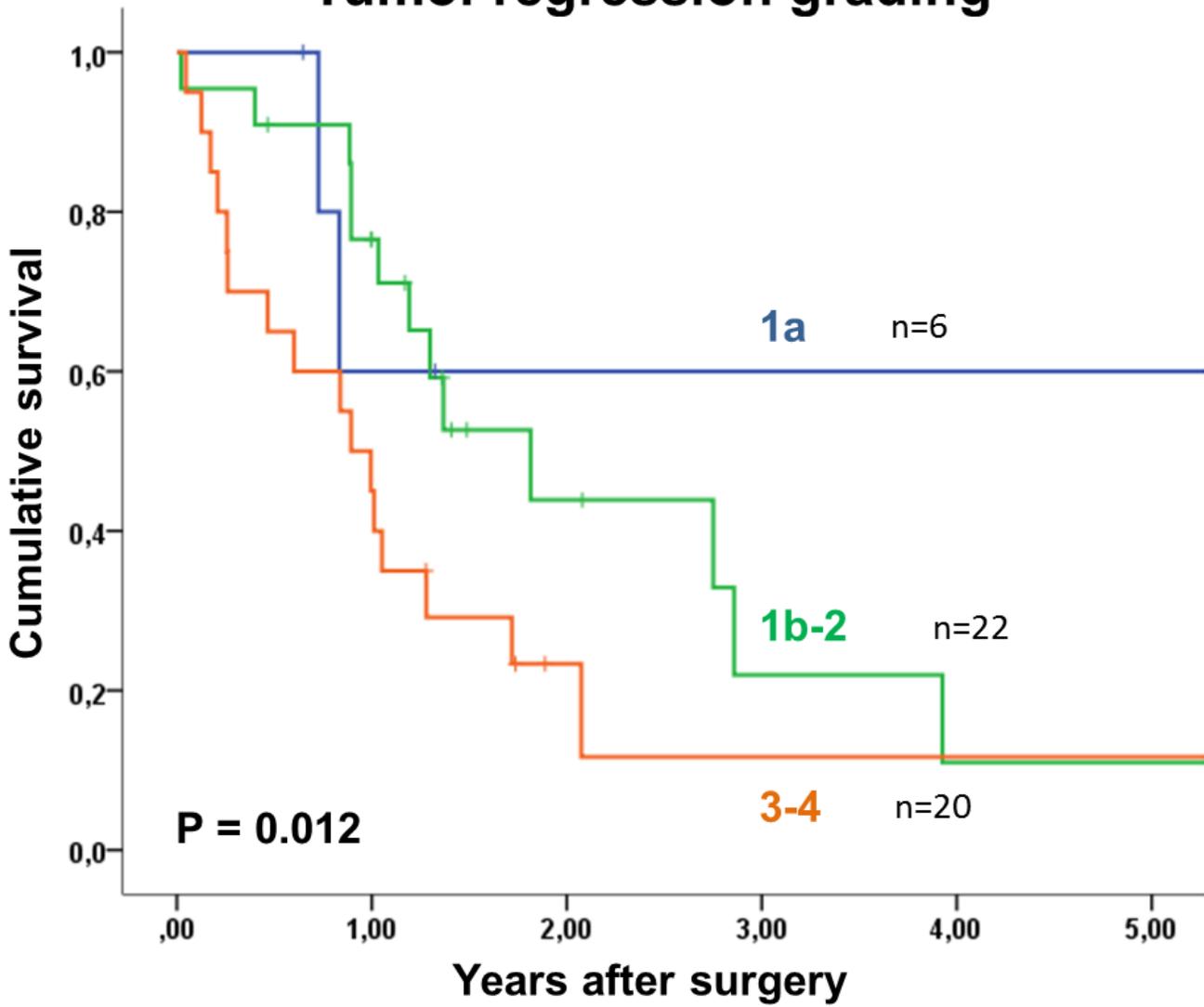


Figure 2

Kaplan Meier 5- year survival depending on tumor regression grading

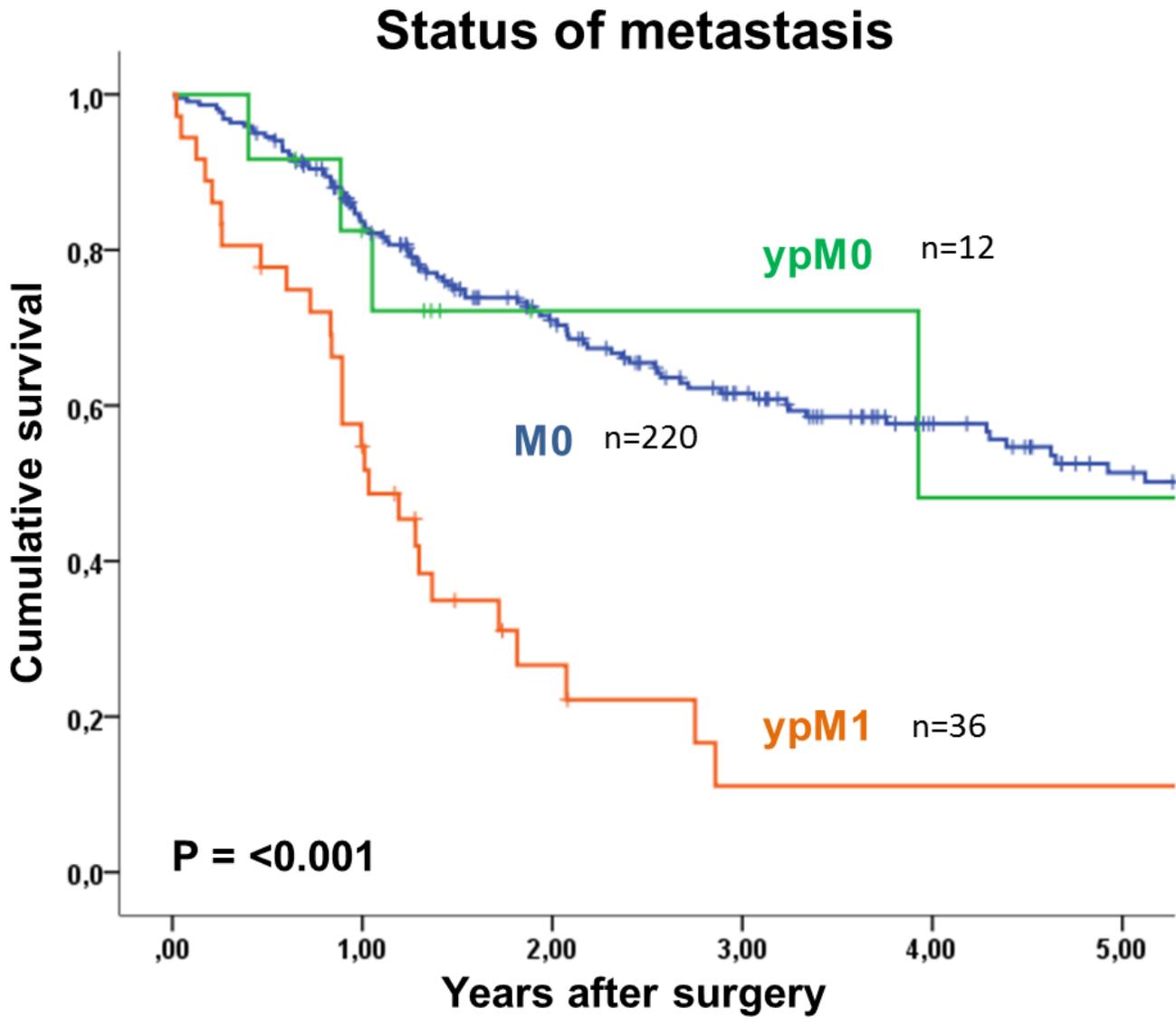


Figure 3

Kaplan Meier 5- year survival depending on status of metastases

Postoperative M stage

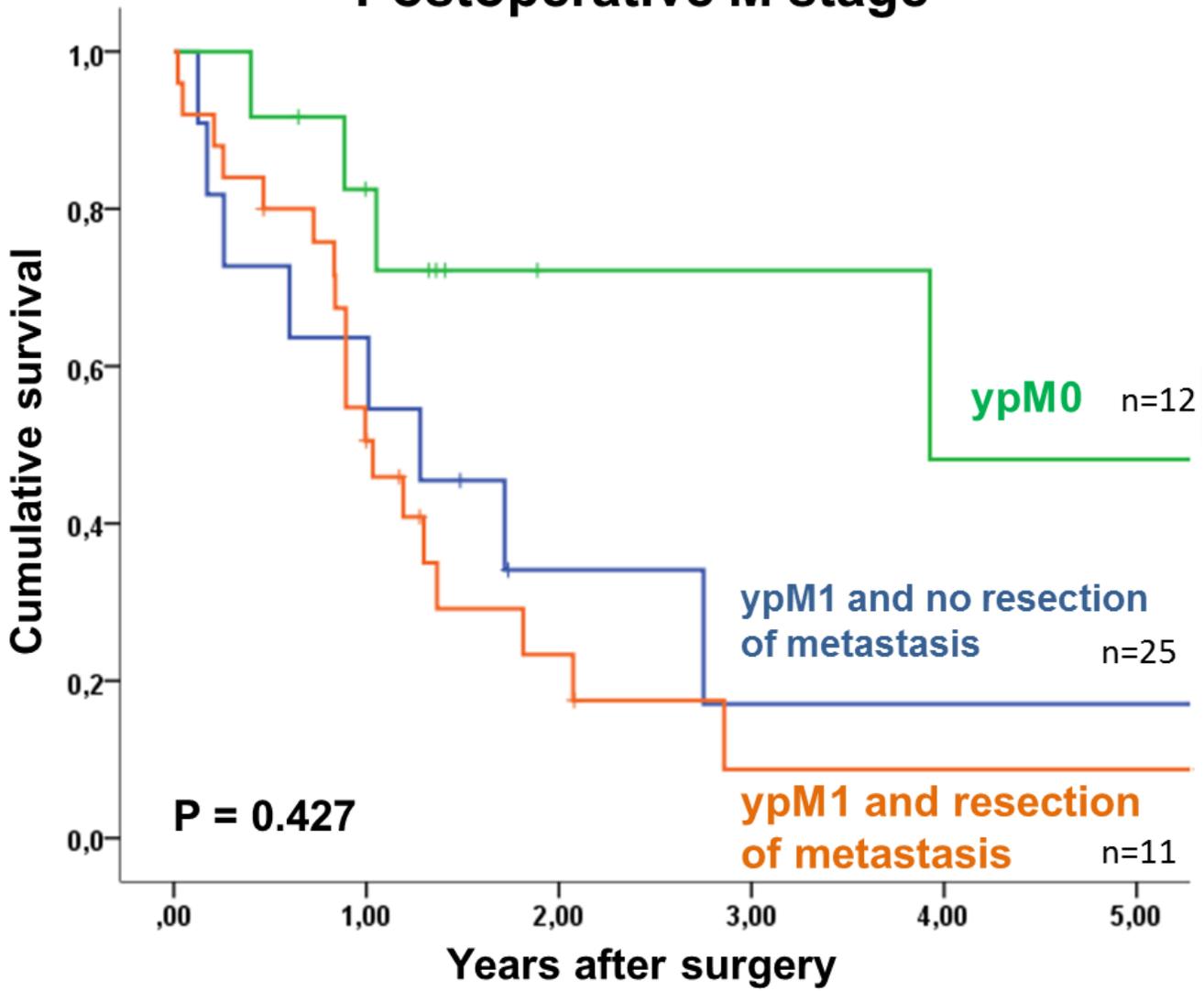


Figure 4

Kaplan Meier 5-year survival depending on postoperative M-stage

Postoperative pathologic N stage

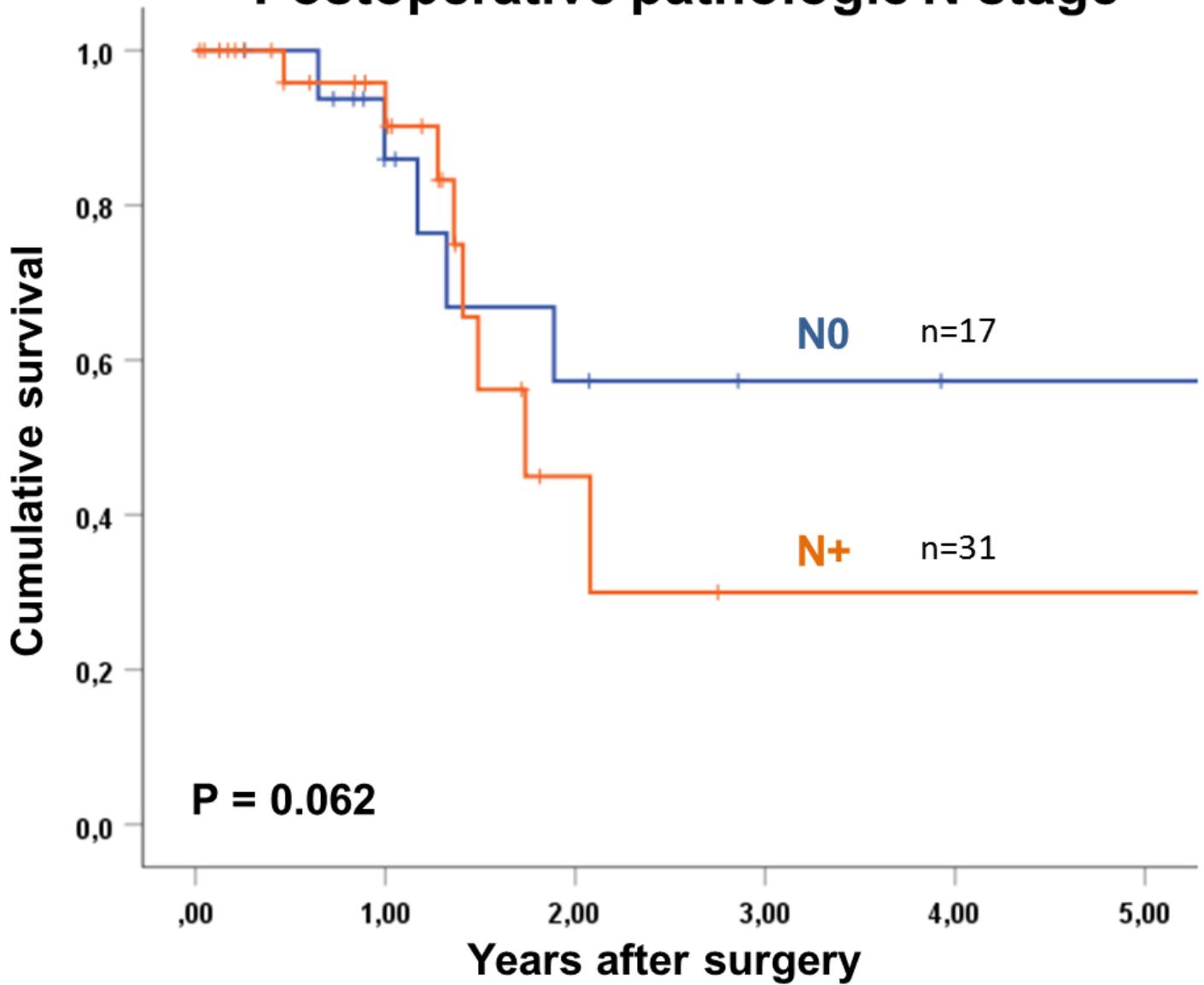


Figure 5

Kaplan Meier 5- year survival depending on postoperative pathologic N-staging