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Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer
The AIO-FLOT3 Trial

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IMPORTANCE Surgical resection has a potential benefit for patients with metastatic adenocarcinoma of the stomach and gastroesophageal junction.

OBJECTIVE To evaluate outcome in patients with limited metastatic disease who receive chemotherapy first and proceed to surgical resection.

DESIGN, SETTING, AND PARTICIPANTS The AIO-FLOT3 (Arbeitsgemeinschaft Internistische Onkologie–fluorouracil, leucovorin, oxaliplatin, and docetaxel) trial is a prospective, phase 2 trial of 252 patients with resectable or metastatic gastric or gastroesophageal junction adenocarcinoma. Patients were enrolled from 52 cancer care centers in Germany between February 1, 2009, and January 31, 2010, and stratified to 1 of 3 groups: resectable (arm A), limited metastatic (arm B), or extensive metastatic (arm C). Data cutoff was January 2012, and the analysis was performed in March 2013.

INTERVENTIONS Patients in arm A received 4 preoperative cycles of fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) followed by surgery and 4 postoperative cycles. Patients in arm B received at least 4 cycles of neoadjuvant FLOT and proceeded to surgical resection if restaging (using computed tomography and magnetic resonance imaging) showed a chance of margin-free (R0) resection of the primary tumor and at least a macroscopic complete resection of the metastatic lesions. Patients in arm C were offered FLOT chemotherapy and surgery only if required for palliation. Patients received a median (range) of 8 (1-15) cycles of FLOT.

MAIN OUTCOMES AND MEASURES The primary end point was overall survival.

RESULTS In total, 238 of 252 patients (94.4%) were eligible to participate. The median (range) age of participants was 66 (36-79) years in arm A (n = 51), 63 (28-79) years in arm B (n = 60), and 65 (23-83) years in arm C (n = 127). Patients in arm B (n = 60) had only retroperitoneal lymph node involvement (27 patients [45%]), liver involvement (11 [18.3%]), lung involvement (10 [16.7%]), localized peritoneal involvement (4 [6.7%]), or other (8 [13.3%]) incurable sites. Median overall survival was 22.9 months (95% CI, 16.5 to upper level not achieved) for arm B, compared with 10.7 months (95% CI, 9.1-12.8) for arm C (hazard ratio, 0.37; 95% CI, 0.25-0.55) ($P < .001$). The response rate for arm B was 60% (complete, 10%; partial, 50%), which is higher than the 43.3% for arm C. In arm B, 36 of 60 patients (60%) proceeded to surgery. The median overall survival was 31.3 months (95% CI, 18.9-upper level not achieved) for patients who proceeded to surgery and 15.9 months (95% CI, 7.1-22.9) for the other patients.

CONCLUSIONS AND RELEVANCE Patients with limited metastatic disease who received neoadjuvant chemotherapy and proceeded to surgery showed a favorable survival. The AIO-FLOT3 trial provides a rationale for further randomized clinical trials.

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Gastric cancer is often diagnosed in locally advanced or metastatic stage and, therefore, has a poor prognosis. Systemic chemotherapy is recommended for patients with stage II or III disease as neoadjuvant or perioperative treatment and for patients with stage IV as a single-modality treatment. In the latter case, only 10% of the patients survive longer than 2 years. Unlike with other tumor entities, such as colon and ovarian cancer, in which multimodality approaches are frequently used for select patients in stage IV, patients with metastatic gastric cancer generally receive only palliative chemotherapy.

A number of retrospective analyses examined the role of surgery of the primary tumor and/or metastases for patients with stage IV gastric cancer and suggested that surgery might be associated with prolonged survival in select patients, such as those 70 years or younger who had 1 metastatic site,[1] those with 1 incurable site and excellent response to systemic preoperative chemotherapy,[2,3] and those with liver metastases in whom complete resection was possible.[4] However, the role of surgical intervention for metastatic gastric cancer remains an open question. A recent trial in Asia (REGATTA) randomized 175 patients with gastric cancer and a single noncurable site to chemotherapy alone or to initial gastrectomy (without resection of the metastases) followed by chemotherapy. That trial failed to show improvements in survival.[5]

In the debate on how to conduct further studies in this field, we consider 3 theoretical aspects to be important: (1) the proper selection of suitable candidates for surgery, (2) the clear definition of the goal of the surgery (eg, palliative or curative), and (3) the necessity to administer effective systemic chemotherapy prior to surgery.

Here, we report on the feasibility and efficacy of using induction chemotherapy with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) followed by surgical resection with curative or life-prolonging intent for select patients with limited metastatic gastric cancer. We chose FLOT treatment because of its confirmed tolerability[6,7] and ability to induce considerable rates (up to 20%) of complete pathological regression.[8-10]

Key Points

Question Is there a survival benefit for patients with limited metastatic gastric or gastroesophageal junction cancer who receive neoadjuvant chemotherapy followed by surgical resection?

Findings In this phase 2 trial that enrolled 252 patients with resectable or metastatic gastric or gastroesophageal junction adenocarcinoma, 60 of the 238 eligible patients were classified as having limited metastatic stage and 36 of these 60 patients had surgery, including resection of the primary tumor and metastases. The median overall survival was 31.3 months for patients who underwent surgery and 15.9 months for the other patients.

Meaning Patients with limited metastatic gastric or gastroesophageal junction cancer may benefit from neoadjuvant chemotherapy followed by surgical resection.

Methods

Patient Eligibility

Patients with histologically confirmed, previously untreated, nonmetastatic, operable (>T2, N any, and M0 or any T, N+, and M0) or metastatic (T any, N any, and M1) adenocarcinoma of the stomach or esophagogastric junction were eligible to participate in this AIO-FLOT3 (Arbeitsgemeinschaft Internistische Onkologie-fluorouracil, leucovorin, oxaliplatin, and docetaxel) trial (NCT00849615). Patients with recurrent disease were not. An Eastern Cooperative Oncology Group performance status of 0 to 2, sufficient bone marrow and kidney function, and no concurrent, uncontrolled medical illness were required of trial participants. The protocol (available in Supplement 1) and the patient informed consent form were approved by the ethics committees of all participating cancer care centers (eAppendix 1 in Supplement 2). Participants provided written informed consent.

Clinical Staging and Group Stratification

Patients underwent preoperative staging that consisted of endoscopy, endoscopic ultrasonography, and computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. Patients who were potentially resectable or had limited metastases were recommended to undergo diagnostic laparoscopy. In case of suspected bone lesions on CT scans, additional bone scans were required.

After pretreatment staging, patients were stratified by the investigator into 1 of 3 groups—resectable (arm A), limited metastatic (arm B), or extensive metastatic (arm C)—using the following criteria:

- Arm A, resectable tumors without distant metastases (cM0).
- Arm B, metastatic tumors (cM1) with all of the following criteria fulfilled:
  - abdominal, retroperitoneal lymph node metastases only (eg, para-aortic, intra-aortic-caval, peripancreatic, or mesenterial lymph nodes) or 1 incurable organ site with or without retroperitoneal lymph node metastases;
  - no clinically visible (on CT scans or because of ascites) or symptomatic carcinomatosis of peritoneum or pleura and no diffuse (>P2 score; eAppendix 2 in Supplement 2) peritoneal carcinomatosis on diagnostic laparoscopy;
  - fewer than 5 liver metastases, if the single organ site is the liver;
  - Eastern Cooperative Oncology Group performance status of 0 or 1; and
  - normal serum alkaline phosphatase levels.
  - Furthermore, the following specific cases were predefined in the study protocol: localized peritoneal carcinomatosis (P1 or P2 score), according to the classification of the Japanese Research Society for Gastric Cancer, was allowed and considered 1 incurable organ site. Bilateral or unilateral Krukenberg tumors were allowed and considered 1 incurable organ site. Unilateral or bilateral adrenal gland metastases were also considered 1 incurable organ site. Extra-abdominal lymph node metastases, such as supraclavicular lymph node involvement, were allowed and considered 1 incurable organ site.
- Arm C, metastatic patients who did not fulfill the criteria of arm B.

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Retroperitoneal lymph node involvement was defined as an abnormally increased number of retroperitoneal lymph nodes measuring more than 1 cm in the short-axis diameter or a single lymph node measuring more than 2 cm in the short-axis diameter. The stratification was confirmed by central review (S.-E.A.-B.). If necessary, central review requested additional information and documents or contacted the investigator to achieve consensus.

Treatment Plan

The FLOT chemotherapy consisted of oxaliplatin, 85 mg/m^2; leucovorin, 200 mg/m^2; and docetaxel, 50 mg/m^2. Each is an intravenous infusion followed by fluorouracil, 2600 mg/m^2, as a 24-hour continuous intravenous infusion on day 1, repeated every 2 weeks.[6] (FLOT is a 2-week regimen.)

Patients in arm A received 4 cycles of preoperative FLOT followed by surgery and 4 postoperative cycles. Patients in arm B received 4 cycles of FLOT and proceeded to surgery if restaging showed a realistic chance for margin-free (R0) resection of the primary tumor and at least a "macroscopic complete resection" of the metastatic lesions. For final decision, we took into consideration the current patient's Eastern Cooperative Oncology Group performance status, comorbidity, organ function, and response to FLOT treatment. After surgery, patients in arm B received 4 additional postoperative cycles of FLOT (8 cycles in total). Patients who did not proceed to surgery after the fourth cycle continued to receive 4 additional cycles (8 cycles in total). Patients in arm C received 8 cycles, and surgical interventions were allowed for palliative reasons. In treatment arms B and C, the maximum duration of FLOT treatment could be extended to a maximum of 12 cycles at the investigator's discretion.

Surgery

Restaging through CT or MRI scans and endoscopy of the upper gastrointestinal tract was repeated after 4 cycles prior to surgical treatment, which was 3 weeks after the last cycle of preoperative chemotherapy. Surgery was performed according to German standards: the AIO-FLOT3 trial protocol suggested transthoracic esophagectomy with resection of the proximal stomach (Ivor-Lewis procedure) and 2-field lymphadenectomy for type I gastroesophageal junction cancers and gastrectomy with transhiatal distal esophagectomy plus D2 lymphadenectomy for types II and III gastroesophageal junction cancers. For gastric cancer, total or subtotal distal gastrectomy with D2 lymphadenectomy was recommended. The study protocol provided recommendations on surgical intervention for these specific situations in arm B: para-aortic involvement, peripheral or central liver metastases, localized peritoneal carcinomatosis, and metastases to adrenal glands (eAppendix 2 in Supplement 2).

Toxicity Assessment

Toxic effects were graded according to the National Cancer Institute's Common Toxicity Criteria, version 3.0.[11] Postoperative morbidity and mortality were recorded.

Evaluation of Efficacy Outcomes

Response in the metastatic groups (arms B and C) was classified according to RECIST (Response Evaluation Criteria in Solid Tumors), version 1.0.[12] Tumor assessment through CT or MRI scans was carried out every 8 weeks during and after the end of the study treatment (for patients who discontinued the study without disease progression). *R0 resection* was defined as no tumor identified on microscopic examination of proximal, distal, or circumferential margins.

End Points and Statistical Analysis

We assumed that if patients in arm B (independent of whether patients had an operation) showed a better outcome than did patients in arm C, we could justify the further evaluation of neoadjuvant chemotherapy followed by surgical resection in the patient group of arm B. Therefore, the primary end point was overall survival (OS), and the study had 80% power to detect a 45% risk reduction of death in arm B compared with arm C (hazard ratio [HR], 0.55), with $P < .05$ in the 2-tailed log-rank test indicating statistical significance. Assuming that approximately 30% of metastatic patients in the study group would match the criteria for arm B (did not reflect the natural prevalence of this group), we calculated the sample size to be 192 (arm B, 64; arm C, 128). Arm A did not have an effect on sample size calculation and was capped at 50 patients. Progression-free survival was measured from the date of arm assignment until disease progression or death of any cause. Similarly, OS was measured from the date of arm assignment until death of any cause. Data cutoff was January 2012, and the analysis was performed in March 2013. Patients were analyzed in the arm to which they were assigned.

Results

Patient Characteristics

Between February 1, 2009, and January 31, 2010, we enrolled 252 patients (and stratified them to arm A, 52; arm B, 67; and arm C, 133) in 52 centers in Germany (eAppendix 1 in Supplement 2). Of the 252 patients, 14 (5.6%) were excluded from the efficacy analysis for these reasons: 10 had recurrent disease, 2 had ineligible underlying disease (ie, breast cancer, hepatocellular carcinoma), 1 had received prior chemotherapy, and 1 was stratified into arm B but was confirmed having M0 disease at on-site monitoring. Therefore, 238 patients (94.4%) were eligible for the efficacy analysis (arm A, 51 patients; arm B, 60; arm C, 127). Details are shown in **Figure 1**. The median (range) age of participants was 66 (36-79) years in arm A, was 63 (28-79) years in arm B, and was 65 (23-83) years in arm C. The majority of patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. Pretreatment patient characteristics are shown in eTable 1 in Supplement 2. Patients in arm B were more likely to have their primary tumor in the gastroesophageal junction. All other differences between the 3 arms were attributable to trial protocol definitions. The largest subgroup of arm B comprised patients with only retroperitoneal lymph node metastases, accounting for

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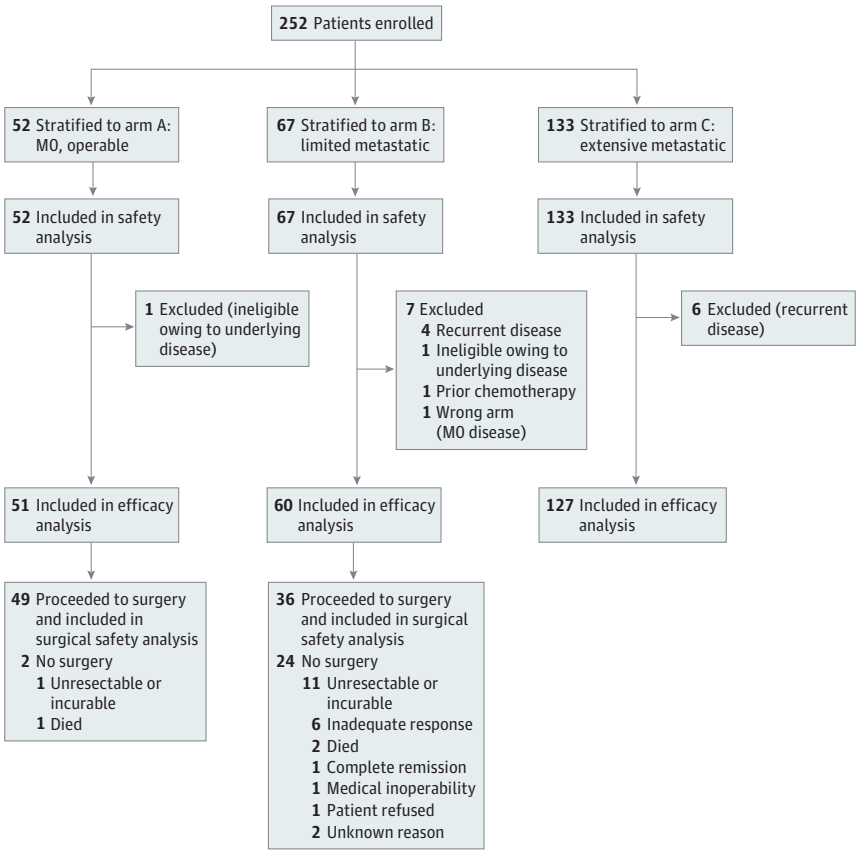
Figure 1. CONSORT Diagram



27 of 60 patients (45%), followed by patients with liver metastases (11 [18.3%]).

Chemotherapy and Surgical Treatment

Patients received a median (range) of 8 (1-15) cycles of FLOT. The median (range) numbers of preoperative and postoperative cycles were 4 (preoperative, 3-15; postoperative, 1-7) for each arms of A and B. Forty-nine patients (96.1%) in arm A, 36 (60%) in arm B, and 15 (11.8%) in arm C proceeded to any surgical resection. R0 resections of the primary tumor were achieved in 40 patients (81.6%) in arm A, 29 (80.6%) in arm B, and 5 (33.3%) in arm C. As shown in eTable 2 in Supplement 2, fewer patients in arm B than in arm A had a right transthoracic esophagectomy with 2-field lymph node dissection despite the fact that junctional tumors were more frequent in arm B.

In arm B, surgery was performed in 18 of 27 patients (66.7%) with retroperitoneal lymph node metastases, 6 of 11 (54.5%) with liver metastases, 6 of 10 (60%) with lung metastases, 2 of 4 (50%) with local peritoneal carcinomatosis, and 4 of 8 (50%) with other metastases. Metastasectomy of at least 1 metastatic lesion was performed in 17 of the 36 patients (47.2%) who were assigned to surgery in arm B. These surgical procedures included D3 lymphadenectomy in 7 patients, peritonectomy in 3, multivisceral resections in 3, hepatectomy in 3, and adrenalectomy in 1. Among the 18 patients with retroperitoneal lymph node metastases who underwent a resection, metastatic lymph node involvement could be confirmed in 11 patients but was not assessable in 3 patients who had complete pathological regression and could not be confirmed in the other 4 patients. Complete pathological regression (stage of T0) was reported in 6 of 36 patients (16.7%) of arm B who underwent resection. Complete regression in resected metastatic lesions, as indicated by fibrotic changes and the absence of malignant cells, was noticed in 3 patients (retroperitoneal lymph nodes in 2 patients and liver lesions in 1 patient). The reasons for not assigning patients to surgery in arm B were unresectable or incurable metastatic lesions in 11 of 60 patients (18.3%), inadequate response in 6 (10%), death in 2 (3.3%), complete response in 1 (1.7%), medical inoperability in 1 (1.7%), patient refusal in 1 (1.7%), and unknown in 2 (3.3%), as reported by the investigator.

Efficacy Outcomes

Median follow-up for surviving patients was 28.6 months (arm A, 30.3 months; arm B, 27.5 months; arm C, 24.4 months). Median OS was 22.9 (95% CI, 16.5-upper level not achieved) months in arm B and 10.7 (95% CI, 9.1-12.8) months in arm C (HR, 0.37; 95% CI, 0.25-0.55; $P < .001$). Median OS in arm A was not achieved and compared favorably with the median OS in arm B. The analysis of progression-free survival among the arms revealed distributions similar to OS distributions (**Figure 2**).

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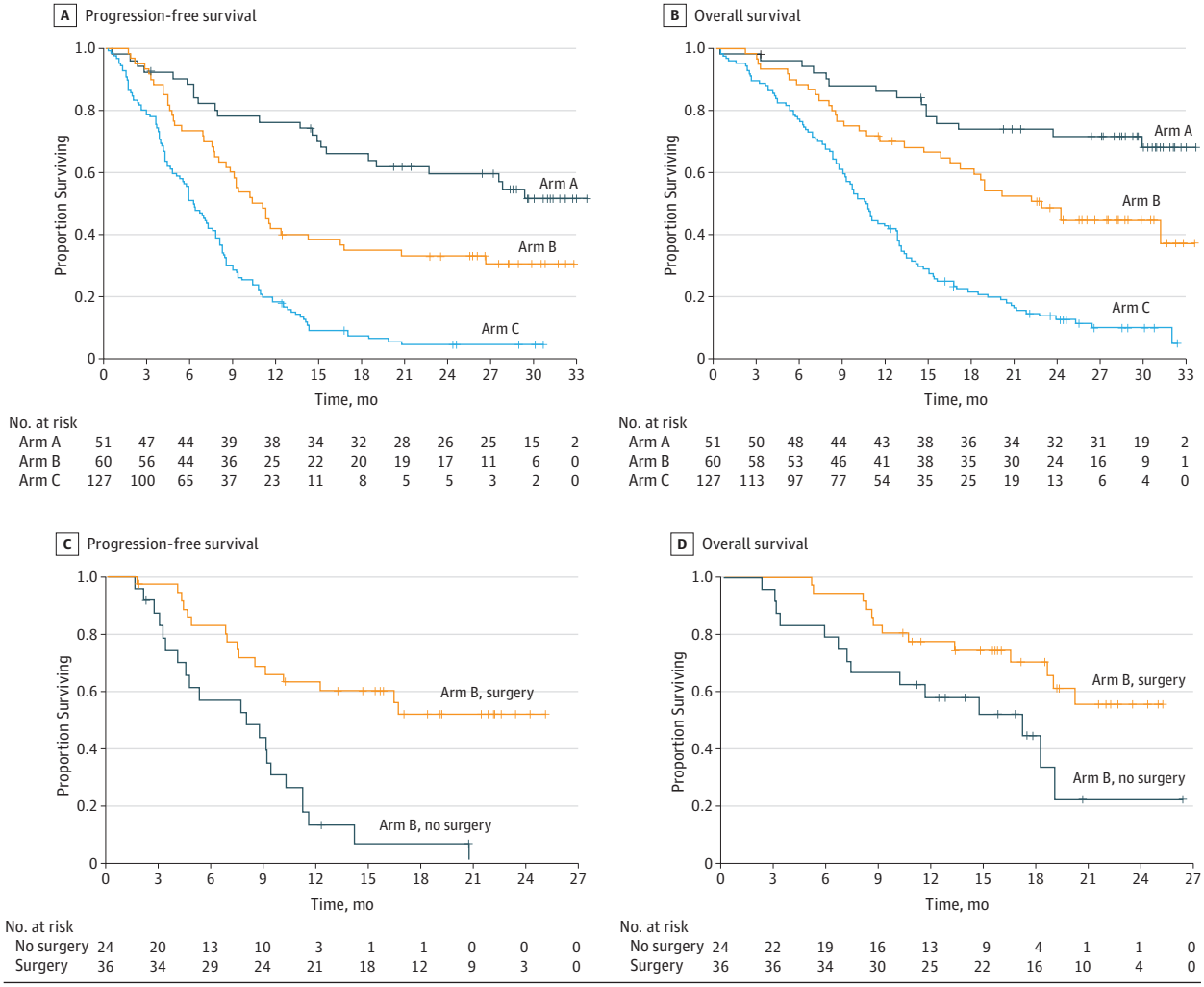
Figure 2. Survival Analyses



Kaplan-Meier analysis of progression-free survival (A) and overall survival (B) in patients with resectable (arm A), limited metastatic (arm B), or extensive metastatic (arm C) disease as well as progression-free survival (C) and overall survival (D) in patients with limited metastatic disease (arm B) who underwent surgery and no surgery. Crosshatching indicates censored data.

Within arm B, patients who proceeded to surgery had more favorable median OS (31.3 months [95% CI, 18.9-upper level not achieved] vs 15.9 months [95% CI, 7.1-22.9]) and progression-free survival (26.7 months [95% CI, 9.1-upper level not achieved] vs 8.4 months [95% CI, 4.1-10.4]) than the other patients in arm B (Figure 2). Outcomes with 95% CIs are shown in **Table 1**. Among the subgroups of arm B, only patients with retroperitoneal lymph node metastases had the best prognosis, whereas patients with liver metastases showed a less favorable survival (eFigure in Supplement 2). The overall response rate (complete and partial response) to chemotherapy was higher in arm B patients than in arm C patients (60.0% vs 43.3%; $P = .04$). Response rates are shown in **Table 2**.

We compared the baseline characteristics and comorbidities of patients who proceeded to surgery with those who did not within arm B. No differences in age, sex, location of the primary tumor, histological type, type of metastases, and other characteristics were found. However, patients who did not undergo surgery had significantly more active comorbidities than patients who had surgery (20 of 24 [83.3%] vs 18 of 36 [50.0%]; $P = .009$), particularly of the cardiovascular type (15 of 24 [62.5%] vs 10 of 36 [27.8%]; $P = .008$), and less complete responses (1 of 24 [4.2%] vs 5 of 36 [13.9%]; Table 2) during chemotherapy.

Safety

The safety analysis comprised all 252 patients. The safety profile of FLOT was in line with the profile of previous studies.[6,7,10,13] Patients in arm C had significantly more Common Toxicity Criteria all-grades anemia, pain, and elevated alkaline phosphatase levels, most likely correlated with the high tumor burden (eTable 3 in Supplement 2). Severe postsurgical morbidity (fulfilling the criteria of a serious adverse event) affected 5 patients (10.2%) in arm A and 3 patients (8.3%) in arm B (eTable 4 in Supplement 2). Numbers do not

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represent the overall postsurgical morbidity because only those that resulted in serious adverse events are reported. In-hospital mortality after surgery occurred in 1 patient in arm A.

Discussion

The AIO-FLOT3 trial was an exploratory, phase 2 study that prospectively evaluated the feasibility and efficacy of induction chemotherapy followed by surgery for patients with limited metastatic gastric cancer who had additional favorable prognostic factors. Sixty patients had limited metastatic disease (arm B), and they had a considerable median OS of 22.9 months. Of the 60 patients, 36 (60%) proceeded to surgery. The median OS was 31.3 months for patients who underwent surgery and 15.9 months for the other patients. Both groups had survival rates that were markedly better than the expected survival for metastatic disease, which were generally accepted to be 9 to 11 months in recent trials. The important question is to what extent surgery contributed to the favorable outcome of the resected group. Because of the lack of randomization, relevant selection bias may exist. For instance, a difference in comorbidity was observed between the groups. Patients assigned to surgery had less active comorbidity than the patients who did not have surgery (50.0% vs 83.3%). The most common reason for not assigning patients to surgery was the investigator's decision that metastatic lesions were unresectable or incurable after neoadjuvant chemotherapy. Conversely, this means that patients assigned to surgery were superselected. Nevertheless, within these limitations, the considerable survival in the surgical group of arm B remains promising. A median survival of 31 months is more than we would expect in a superselected group of patients with metastatic disease.

Patients with retroperitoneal lymph node metastases or liver metastases represented the 2 largest subgroups of arm B. Patients with retroperitoneal lymph node metastases showed the best survival. This patient group may be of a particular interest for such a bimodality therapy approach.[14-18] One important point is whether CT or MRI was sufficient to determine retroperitoneal involvement. The accuracy of CT or MRI for defining lymph node involvement is dependent on the anatomical location. In the abdomen, the upper limit of the short-axis diameter of normal nodes varies from 6 to 10 mm.[19] The study protocol went beyond these definitions, requiring either too many lymph nodes (lymph node clusters) greater than 1 cm in the short axis or single lymph nodes greater than 2 cm. Therefore, we do not believe that arm B was inflated by patients with nonmetastatic lymphatic hyperplasia. The less favorable outcome of patients with liver metastases leads us to recommend to either exclude this group in future trials or limit the group to patients in whom complete (R0) resection is judged possible at initial evaluation. Nevertheless, few patients with metastatic gastric cancer will have initially resectable liver disease.[4,20]

The REGATTA trial[5] randomized 175 patients with gastric cancer and a single noncurable site confined to liver, peritoneum, or para-aortic lymph nodes to chemotherapy alone or gastrectomy followed by chemotherapy. The study did not show any improvement of OS by gastrectomy (median OS, 16.6 months without gastrectomy and 14.3 months with gastrectomy).[5] The concept of the REGATTA trial differs from the concept of the AIO-FLOT3 trial in 2 important ways. First, patients in the REGATTA trial did not receive neoadjuvant chemotherapy. Second, the surgical intervention was restricted to only gastrectomy with D1 lymphadenectomy without any resection of metastatic lesions, making the study palliative rather than curative. As mentioned in the Introduc-

Table 1. Median Overall Survival and Progression-Free Survival by Arm

	Survival	
Study Arm	Median OS (95% CI), mo	Median PFS (95% CI), mo
Arm A	NA	NA
Arm B		
All	22.9 (16.5-NA)	10.7 (8.0-16.5)
With surgery	31.3 (18.9-NA)	26.7 (9.1-NA)
Without surgery	15.9 (7.1-22.9)	8.4 (4.1-10.4)
Arm C	10.7 (9.1-12.8)	6.3 (5.0-7.6)

Abbreviations: NA, not achieved; OS, overall survival; PFS, progression-free survival.

Table 2. Response Rates According to RECIST for Patients With Limited (Arm B) and Extensive (Arm C) Metastatic Disease

	Best Response[a]				
Study Arm	Complete Response, No. (%) [95% CI]	Partial Response, No. (%) [95% CI]	Overall Response, Complete + Partial, No. (%) [95% CI][b]	Stable Disease, No. (%) [95% CI]	Progressive Disease/ Not Evaluable, No. (%) [95% CI]
Arm B					
All (n = 60)	6 (10.0) [4.3-20.5]	30 (50.0) [37.7-62.3]	36 (60.0) [47.4-71.4]	18 (30.0) [19.8-42.6]	5 (8.3) [3.2-18.5]
With surgery (n = 36)	5 (13.9) [5.6-29.1]	15 (41.7) [27.1-57.8]	20 (55.6) [39.6-70.5]	14 (38.9) [24.8-55.2]	1 (2.8) [<0.01-15.4]
Without surgery (n = 24)	1 (4.2) [<0.01-21.9]	15 (62.5) [42.6-78.9]	16 (66.7) [46.6-82.2]	4 (16.7) [6.1-36.5]	4 (16.7) [6.1-36.5]
Arm C (n = 127)	5 (3.9) [1.5-9.1]	50 (39.4) [31.3-48.1]	55 (43.3) [35-52]	44 (34.6) [26.9-43.3]	23 (18.1) [12.3-25.8]

[a] *Best response* refers to the best response achieved as evaluated by comparison of baseline tumor assessment with all available, subsequent tumor assessments until surgical resection was conducted, if applicable. Tumor assessments performed after surgery were not relevant for response.

[b] $P = .04$ for the numbers of patients with overall response (complete + partial) in arm B compared with those in arm C, using 2-sided Fisher exact test. The P value is presented only if $P < .05$.

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tion, we believe the use of neoadjuvant therapy and the pursuit of a potentially curative surgery are 2 crucial factors in a multimodality approach to a biologically aggressive disease such as metastatic gastric cancer. Administering chemotherapy first helps prevent a delay in administration of the systemic treatment component, which has been proven to be effective. Moreover, administering chemotherapy first provides a tool for selecting patients with the highest likelihood to benefit from additional surgery, on the basis of their response to treatment and other factors.

Limitations

The main limitation of the AIO-FLOT3 trial was the lack of randomization. Another limitation was the use of CT or MRI to determine retroperitoneal involvement. Both of these topics were addressed in the discussion.

Conclusions

To our knowledge, the AIO-FLOT3 trial is the first prospective study to evaluate neoadjuvant chemotherapy followed by surgery in patients with metastatic gastric and gastroesophageal junction cancer. Within the limitations of a nonrandomized phase 2 study, the results reported here showed that the concept was feasible and provided a rationale for an ongoing, randomized, phase 3 trial[21] funded by the German Research Foundation Deutsche Forschungsgemeinschaft.

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