Resection of small bowel adenocarcinoma metastases: Results of the ARCAD-NADEGE cohort study

Pierre Rompteaux, Johan Gagniere, Jean-Marc Gornet, Romain Coriat, Isabelle Baumgaertner, Thierry Lecomte, Pauline Afchain, Aziz Zaanan, Marc Pocard, Jean-Baptiste Bachet, et al.

Resection of small bowel adenocarcinoma metastases: Results of the ARCAD-NADEGE cohort study

Pierre Rompteaux[1], Johan Gagnière[2], Jean-Marc Gornet[3], Romain Coriat[4], Isabelle Baumgaertner[5], Thierry Lecomte[6], Pauline Afchain[7], Aziz Zaanan[8], Marc Pocard[9], Jean-Baptiste Bachet[10], Nathalie Bonichon-Lamichhane[11], Olivier Bouché[12], Jean-Luc Faucheron[13], Julien Forestier[14], Cedric Lecaille[15], Sylvain Manfredi[16], David Tougeron[17], Eric Terrebonne[18], Mohamed Chehimi[19], Anne-Laure Villing[20], Corinne Sarda[21], Jean-Louis Legoux[22], Robert Benamouzig[1], Thomas Aparicio[3]

[1] Department of Gastroenterology and Digestive Oncology, CHU Avicenne, APHP, Bobigny, France

[2] Department of Digestive and Hepatobiliary Surgery, University Hospital of Clermont-Ferrand, U1071 INSERM, Clermont-Auvergne University, Clermont-Ferrand, France

[3] Department of Gastroenterology and Digestive Oncology, CHU Saint Louis, APHP, Denis Diderot University, Sorbonne Paris Cité, Paris, France

[4] Department of Gastroenterology, CHU Cochin, APHP, Paris, France

[5] Department of Gastroenterology, CHU Henri Mondor, APHP, Créteil, France

[6] Department of Hepato-Gastroenterology and Digestive Oncology, Trousseau Hospital, CHU Tours, Tours, France

[7] Department of Oncology, CHU Saint-Antoine, APHP, Paris, France

[8] Department of Digestive Oncology, CHU Georges Pompidou, APHP, Paris, France

[9] Department of Digestive Surgery, CHU Lariboisière, APHP, Paris, France

[10] Sorbonne University, UPMC, Department of Hepato-Gastroenterology, CHU Pitié-Salpétrière, APH, Paris, France

[11] Department of Oncology and Radiotherapy, Clinic Tivoli, Bordeaux, France

[12] Department of Gastroenterology, CHU Robert Debré, Reims, France

[13] Department of Surgery, Grenoble University Hospital, Grenoble, France

[14] Department of Gastroenterology, CHU Edouard Herriot, HCL, Lyon, France

[15] Department of Gastroenterology, Polyclinic Bordeaux Nord, Bordeaux, France

[16] Department of Gastroenterology, CHU Dijon, University of Bourgogne-Franche Comté, INSERM U1231, Dijon, France

[17] Department of Gastroenterology, CHU Poitiers, Poitiers, France

[18] Department of Gastroenterology, CHU Haut-Lévêque, Pessac, France

[19] Department of Oncology, Saint Quentin Hospital, Saint Quentin, France

[20] Department of Oncology, Auxerre Hospital, Auxerre, France

[21] Department of Oncology, Castres Hospital, Castres, France

[22] Department of Hepato-Gastroenterology and Digestive Oncology, CHR La Source, Orléans, France

Corresponding author: Thomas Aparicio, MD PhD

Department of Gastroenterology and Digestive Oncology, Saint Louis Hospital, AP-HP, Denis Diderot University, Sorbonne Paris Cité, 1 avenue Claude Vellefaux, 75010 Paris, France; Tel: 33 (0) 1 42 49 95 97, Fax: 33 (0) 1 42 49 91 68; E-mail: thomas.aparicio@aphp.fr

Keywords: small bowel adenocarcinoma, metastases resection, hepatic metastases, adjuvant chemotherapy

Funding: The A.R.CA.D. Foundation and GERCOR.

Disclosure: None.

Word count text (max 3000 words): 1916

Word count abstract (max 250 words): 204

ABSTRACT

Introduction: Data are lacking with regard to curative resection of metastasis from small bowel adenocarcinoma (SBA). This study evaluated outcomes and prognostic factors in patients with curatively resected metastatic SBA.

Methods: A series of 34 patients undergoing resection of metastatic SBA from January 2009 to November 2014 at French centers were included into this cohort study. The primary endpoint was overall survival (OS). Secondary endpoints were recurrence-free survival (RFS) and prognostic factors. Univariate analyses were performed to determine prognostic risk factors.

Results: The sites of SBA metastases were peritoneal (29.4%), liver (26.5%), lymph nodes (11.8%), lung (2.9%), multiple (14.7%), and other (14.7%). Thirty (88.2%) patients received adjuvant or perioperative chemotherapy, mainly was oxaliplatin-based (76.5%). The median OS was 28.6 months and RFS was 18.7 months. Fourteen (41.2%) patients survived for more than 36 months. In univariate analysis, poor differentiation ($P = 0.006$), invaded margins ($P = 0.003$), and lymphatic invasion in the primary tumor ($P = 0.039$) were associated with decreased OS.

Conclusion: Overall survival of patients after resection of metastatic SBA remains poor, but long-term survivors are observed. Resection of metastatic SBA should be consider if patients are expected to be operated on with curative intent and have moderately or well-differentiated tumors.

INTRODUCTION

Small bowel adenocarcinoma (SBA) is a rare tumor, representing less than 5% of digestive cancers.[1] In the United States, the annual incidence rate of SBA is estimated to be 7 cases per million persons.[2] Similar incidence rate is observed in Europe, with an increasing rate trend seen between 1999 and 2013.[3]

Around 30% of patients have their disease diagnosed at a later metastatic stage.[4] Surgical resection of the primary tumor is the only curative treatment for localized SBA, however the recurrence rate remains high (40%).[5] Although benefit of adjuvant chemotherapy after curative resection relies on a low level of evidence in this setting, the recent French guidelines recommend fluoropyrimidine and oxaliplatin-based adjuvant chemotherapy for patients with T4 and/or N+ tumors.[6] Metastatic SBA have a poor prognosis, with a median overall survival (OS) of patients with metastatic disease ranging between 8 and 22 months in small retrospective series.[7-11] An international randomized phase III study is ongoing to assess the efficacy of chemotherapy after resection of localized SBA.[12]

There is a paucity of data regarding patient's outcome after surgical resection of metastatic SBA. We conducted a nationwide prospective cohort study (ARCAD-NADEGE) to determine outcomes and prognostic factors of patients with SBA.

MATERIAL AND METHODS

Study design and patient selection

Patients with SBA were selected from the prospective cohort ARCAD-NADEGE study enrolling patients between January 2009 and December 2012 in 74 French hospitals and from the French Association of Gastroenterologist and Oncologist (AGEO) network enrolling patients between December 2012 and November 2014 in French centers. All patients who

underwent resection of metastatic SBA were included in the current study. Patients with adenocarcinoma of the ampulla of Vater were not included. Clinical and demographic data of patients who underwent curative resection of metastatic SBA were prospectively reviewed. The following parameters were collected: gender, age at diagnosis, risk factors (Crohn's disease, Lynch syndrome, Familial Adenomatous Polyposis, celiac disease, Peutz-Jeghers syndrome), characteristics of the primary tumor (grade, resection margin, lymph node involvement), characteristics of the metastases (site, number, synchronous/metachronous, margin resection, and pathological differentiation), chemotherapy regimens and type of treatments received (adjuvant chemotherapy after metastasis resection, hyperthermic intraperitoneal chemotherapy [HIPEC]), or neoadjuvant chemotherapy). Patients with R1 and R2 resections were pooled (R+ group) due to the small sample size and analyzed together. Follow-up ended on May 31, 2015 and survival data were censored on October 1, 2018. All the patients gave their consent for inclusion in the cohort. This study was authorized by the ethics committee "Ile de France II" No. ID-RCB: 2008-A01058-47".

Endpoints

The primary endpoint was OS, defined as the time from metastases curative resection (synchronous or metachronous) to the date of death (from any cause) or of the last date the patient was known to be alive. Secondary endpoints were recurrence-free survival (RFS) and prognostic factors for survival. RFS was defined as the time from metastases curative resection to the date of recurrence observed on computed tomography scan, magnetic resonance imaging, or positron-emission tomography scan or to the date of censoring (recurrence-free or alive).

Statistical analyses

Survivals were estimated using the Kaplan Meier method and prognostic factors analyzed by the log-rank test. No multivariate analysis was performed due to the small sample size. *P*-values < 0.05 were considered statistically significant. All analyses were performed using R Software version 3.2.2 (R Development Core Team, 2005) and BiostaTGV Software (BiostaTGV, Jussieu, France).

RESULTS

Patient characteristics

A total of 343 patients with SBA were included in the NADEGE study in the given period. After selection for metastatic SBA and for curative surgery, a total cohort of 27 patients was included. Seven patients with metastatic SBA after curative resection from the AGEO network were also selected, providing a total of 34 patients included in the current study (Supplementary Figure S1). The median enrolment was one patient per center. Patient clinical and pathological features are summarized in Table 1. The tumors were mainly located in the duodenum. Five (14.7%) patients were diagnosed with Crohn's disease and two (5.9%) with Lynch syndrome. The median time to recurrence for patients with metachronous metastases was 25.2 months (95% CI 8.8-41.6). A total of 29 patients had one metastatic site; four had two and one had three. Metastases from SBA were mainly peritoneal and hepatic. The types of surgical procedures performed and chemotherapy received are presented in Table 2.

Surgery

Patients with synchronous metastases (n = 25) were treated by single-stage surgery with or without neo-adjuvant chemotherapy. Two (5.9%) patients had radiofrequency for hepatic metastases during surgery of the primary tumor. Of the ten (29.4%) patients who underwent

peritoneal tumor resection, two received oxaliplatin-based HIPEC and one patient mitomycin C-based HIPEC. Nine (26.5%) patients underwent surgery for metachronous metastasis.

Adjuvant chemotherapy

Twenty-four patients with synchronous metastases received adjuvant and/or neo-adjuvant chemotherapy: 5-fluorouracil [5-FU] with oxaliplatin (n=16), 5-FU with oxaliplatin and bevacizumab (n=3), capecitabine with oxaliplatin (n=1), 5-FU with irinotecan (n=2), 5-FU with irinotecan and cetuximab (n=1), or 5-FU alone (n=1). Two patients received perioperative chemotherapy and one patient received only neo-adjuvant chemotherapy. Following surgery, one patient (82 years of age) was kept under observation alone.

Of the nine (26.4%) patients with metachronous metastases, six received adjuvant chemotherapy: 5-FU with oxaliplatin (n=5) or gemcitabine with oxaliplatin (n=1). Only one patient in this group received both neo-adjuvant and adjuvant chemotherapy.

Survival

After a median follow-up of 38.2 months (95% CI 25.2-50.8), 25 (73.5%) patients had recurrence and 21 (61.8%) died during the follow-up period. Of those who died, 16 died within the first 3 years of follow-up and 21 died within the first 5 years. The median RFS was 18.7 months (95% CI 12.0-25.4; Figure 1A) and the median OS was 28.6 months (95% CI 19-38.2; Figure 1B). Fourteen (41.2%) patients survived for more than 36 months. Five patients were lost to follow-up before progression at 12.4, 59.4, 62.1 and 75.4 months. Overall, 3 (8.8%) patients were alive and without relapse at the end of data collection.

Prognostic factors

In the exploratory univariate Cox analysis (Table 3), the only prognostic factor of shorter RFS was positive surgical margin (Figure 2). There was a non-significant trend for longer RFS in patients receiving oxaliplatin-based adjuvant chemotherapy.

Eight (23.5%) patients had a RFS beyond 36 months (extreme 39.5–87.1). All of these patients had a margin-negative resection (R0), a well to moderately differentiated tumor, and received oxaliplatin-based adjuvant chemotherapy. Of these patients, seven had synchronous metastases (n = 2, peritoneal; n = 3, liver; n = 1, lymph node metastasis; n = 1, liver plus peritoneal) and one had metachronous peritoneal recurrence at anastomotic site 2.9 years after the primary surgery. Of the seven patients with synchronous metastases, two were in remission at the end of the study (RFS: 87.1 and 54.8 months), five were lost to follow-up without relapse (RFS: 64.2, 59.4, 75.4, 62.1 months), and one recurred after 53.8 months. The latter patient had also received oxaliplatin-based adjuvant chemotherapy and was lost of follow-up 59.8 months after the first metastasis resection. The patient with metachronous peritoneal recurrence at anastomotic site had a second recurrence 39.5 months after the first metastasis resection. This patient had received palliative 5-FU plus irinotecan-based chemotherapy and achieved long median OS (49.5 months).

The univariate analysis identified three prognostic factors associated with an increased risk of death: poor differentiation, resection margin, and lymph node involvement at surgery of the primary tumor (Supplementary Figure S2). Treatment with oxaliplatin was associated with better prognosis in patients who received adjuvant chemotherapy (Table 4).

DISCUSSION

In the present multicenter French series of patients, we have analyzed the clinical outcomes relevant prognostic factors of patients with different sites of metastatic SBA after curative-

intent resection. Patients were treated in a short period of time, in different centers, and in the recent past, which illustrates the current state of the global medical care.

The median OS for patients undergoing curative intent resection of SBA metastasis was 28.6 months in our study; 41.2% of patients had OS of 36 months or longer. The median survival observed for SBA patients with metastatic disease in the whole NADEGE cohort was 12.7 months.[13] Moreover, survival of patients with resected metastasis observed in our study compare favorably to those recently reported in retrospective or prospective studies of patients treated with palliative chemotherapies (median OS ranging from 8 to 22 months).[7-11] In a multicenter retrospective observational study by Sakae et al., a median OS was 36.9 months for patients treated with the combined modality therapy, but 12 months for those treated with palliative chemotherapy alone.[14] Another recent large multi-institutional study of series of patients with SBA, reported a median OS of 32 months after HIPEC.[15] Altogether these results and our findings are in favor of metastases resection. However, these survival data are disappointing given that a median OS for colorectal patients undergoing liver resection or HIPEC is 54-61 or 63 months, respectively.[16, 17] This suggests that patients who undergo resection of SBA metastases have worse prognosis than those who undergo resection of metastases from colorectal carcinoma. This observation is consistent with the result from the large US database showing that patients with SBA have worse prognosis than those with colon cancer across all stages.[4]

We found that invaded margins, poor differentiation, and lymph node metastasis from the primary tumor were poor prognostic factors for OS after metastasis resection. This finding is consistent with the published data. Invaded margin has been previously identified as a pejorative prognostic factor after the primary SBA resection [2, 18] and margins status as a determinant of survival after hepatic resection from metastatic colorectal cancer.[19-21] This suggests that expected R0 resection margin should be considered before surgery.

Poor differentiation has been reported as negative independent prognostic indicator for survival after primary tumor resection alone and with HIPEC.[18, 22, 23] Interestingly, it is also inconstantly found as a prognostic factor after resection of colorectal liver metastases.[20, 24] In our study, the median OS of patients who underwent resection of metastases from poorly differentiated tumors is close to that observed in patients treated by palliative chemotherapy in previous studies.[9, 11, 14] Thus, resection of metastases from poorly differentiated tumor seems not appropriate for this group of patients.

Lymph node metastasis is the main prognostic factor after resection of localized SBA [18, 25] and has been reported as independent prognostic factor after resection of peritoneal metastasis.[15] Similarly, the presence of positive lymph node at primary metastatic colorectal cancer resection is also independent predictor of worst survival.[20]

In our cohort, adjuvant chemotherapy after metastasis resection was not associated with a better prognosis, most likely due to the small sample size. This finding opposes the results from retrospective analysis in localized SBA,[18] and the only prospective trial in this setting is still ongoing.[12] Our subgroup analysis showed improved OS in patients treated with oxaliplatin-based adjuvant chemotherapy, which is consistent with previous results observed in the metastatic setting. This observation suggests that patients receiving oxaliplatin-containing chemotherapy regimens benefit more than those treated with other regimens.[9, 11] Nevertheless, the reason to choose oxaliplatin or not in adjuvant treatment is unclear in our study and may have bias the results. Moreover, because of the small sample size of the non-oxaliplatin group (only four patients), we did not seek to determine prognostic factors using multivariate methods. Therefore, all the prognostic factors analysis should be taken with caution.

CONCLUSIONS

In conclusion, our study suggests that surgical resection of SBA metastases should be considered in patients who are expected to be operated on with curative intent and have well-differentiated tumors. These results warrant further larger studies.

Conflict of interest: None.

Funding: The NADEGE cohort study received a grant from A.R.CA.D. Foundation and GERCOR.

Acknowledgment: We thank GERCOR for providing access to the NADEGE database. We thank Ines Bacha (GERCOR, Paris) and Vanessa Le Berre (CHU Poitiers, Poitiers). We would like to acknowledge the editorial assistance of Magdalena Benetkiewicz (PhD, GERCOR).

REFERENCES

1. Aparicio T, et al. Small bowel adenocarcinoma: epidemiology, risk factors, diagnosis and treatment. Dig Liver Dis 2014;46:97-104.

2. Bilimoria KY, et al. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg 2009;249:63-71.

3. Legue LM, et al. Trends in incidence, treatment and survival of small bowel adenocarcinomas between 1999 and 2013: a population-based study in The Netherlands. Acta Oncol 2016;55:1183-9.

4. Overman MJ, et al. A population-based comparison of adenocarcinoma of the large and small intestine: insights into a rare disease. Ann Surg Oncol 2012;19:1439-45.

5. Talamonti MS, et al. Primary cancers of the small bowel: analysis of prognostic factors and results of surgical management. Arch Surg 2002;137:564-70; discussion 70-1.

6. Locher C, et al. Small bowel adenocarcinoma: French intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO). Dig Liver Dis 2018;50:15-9.

7. Overman MJ, et al. Chemotherapy with 5-fluorouracil and a platinum compound improves outcomes in metastatic small bowel adenocarcinoma. Cancer 2008;113:2038-45.

8. Overman MJ, et al. Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of Vater. J Clin Oncol 2009;27:2598-603.

9. Tsushima T, et al. Multicenter retrospective study of 132 patients with unresectable small bowel adenocarcinoma treated with chemotherapy. Oncologist 2012;17:1163-70.

10. Xiang XJ, et al. A phase II study of modified FOLFOX as first-line chemotherapy in advanced small bowel adenocarcinoma. Anticancer Drugs 2012;23:561-6.

11. Zaanan A, et al. Chemotherapy of advanced small-bowel adenocarcinoma: a multicenter AGEO study. Ann Oncol 2010;21:1786-93.

12. Evans TRJ, et al. GLOBAL BALLAD: An International Rare Cancers Initiative trial to evaluate the potential benefit of adjuvant chemotherapy for small bowel adenocarcinoma (IRCI 002). J Clin Oncol 2016;34, no. 15_suppl. TPS4154.

13. Aparicio T, et al. ARCAD-NADEGE cohort: Result of a small bowel adenocarcinomas prospective cohort. Annals of Oncol 2018;29 (suppl_8): viii205-viii270.

14. Sakae H, et al. The characteristics and outcomes of small bowel adenocarcinoma: a multicentre retrospective observational study. Br J Cancer 2017;117:1607-13.

15. Liu Y, et al. Cytoreductive Surgery Plus Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Metastases From a Small Bowel Adenocarcinoma: Multi-Institutional Experience. Ann Surg Oncol 2018;25:1184-92.

16. Nordlinger B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013;14:1208-15.

17. Elias D, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol 2009;27:681-5.

18. Ecker BL, et al. Efficacy of adjuvant chemotherapy for small bowel adenocarcinoma: A propensity score-matched analysis. Cancer 2016;122:693-701.

19. Andreou A, et al. Margin status remains an important determinant of survival after surgical resection of colorectal liver metastases in the era of modern chemotherapy. Ann Surg 2013;257:1079-88.

20. Rees M, et al. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg 2008;247:125-35.

21. Vigano L, et al. Early recurrence after liver resection for colorectal metastases: risk factors, prognosis, and treatment. A LiverMetSurvey-based study of 6,025 patients. Ann Surg Oncol 2014;21:1276-86.

22. Liu Y, et al. Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Dissemination from Small Bowel Malignancy: Results from a Single Specialized Center. Ann Surg Oncol 2016;23:1625-31.

23. Saxena A, et al. Recurrence and Survival Outcomes After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Small Bowel Adenocarcinoma. Anticancer Res 2017;37:5737-42.

24. John SK, et al. Prognostic factors and survival after resection of colorectal liver metastasis in the era of preoperative chemotherapy: an 11-year single-centre study. Dig Surg 2013;30:293-301.

25. Overman MJ, et al. Prognostic value of lymph node evaluation in small bowel adenocarcinoma: analysis of the surveillance, epidemiology, and end results database. Cancer 2010;116:5374-82.

Figure and Table Legends

Figure 1. Recurrence-free survival (A) and overall survival (B)

Figure 2. Recurrence-free survival according to resection margin

Table 1. Patient and tumors characteristics

Table 2. The types of surgical procedures performed and chemotherapies received

Table 3. Univariate analysis of prognostic factors for recurrence-free survival

Table 4. Univariate analysis of prognostic factors for overall survival

Supplementary files

Figure A.1 Flow chart of the cohort study

Figure A.2 Overall survival (OS) according to tumor differentiation (A), resection margins (B), and node status at primary tumor site (C)

Table 1. Patient and tumor characteristics

	Total ***N* = 34** **n (%)**
Gender	
Male	24 (70.6)
Female	10 (29.4)
Median age (range)	60 (37–82)
Primary tumor	
Duodenum	14 (41.2)
Jejunum	8 (23.5)
Ileum	10 (29.4)
Undetermined	2 (5.9)
Node status at primary tumor site	
N0	8 (23.5)
N+	21 (61.8)
Undetermined	5 (14.7)
Delay of metastases	
Synchronous	25 (73.5)
Metachronous	9 (26.5)
Metastatic site	
Peritoneum alone	10 (29.4)
Liver alone	9 (2.5)
Lymph node alone	4 (11.8)
Lung alone	1 (2.9)
Other	5 (14.7)

Multiple	5 (14.7)
Resection margin status	
R0	24 (70.6)
R1	4 (11.8)
R2	3 (8.8)
Unknown	3 (8.8)
Tumor grade (differentiation)	
Well	14 (41.2)
Moderately	10 (29.4)
Poorly	5 (14.7)
Unknown	5 (14.7)

Table 2. The types of surgical procedures performed and chemotherapies received

	Total ***N* = 34** **n (%)**
Metastases surgery	
Peritoneal	
Without HIPEC	7 (20.6)
With HIPEC	3 (8.8)
Liver	
Lobectomy	4 (11.8)
Segmentectomy	1 (2.9)
Radiofrequency ablation	2 (5.9)
Unknown	2 (5.9)
Lymph node resection	4 (11.8)
Lung lobectomy	1 (2.9)
Surgery of two metastatic sites	5 (14.7)
Others	5 (14.7)
Chemotherapy schedule	
Adjuvant chemotherapy alone	26 (76.5)
Neo-adjuvant +/- adjuvant chemotherapy	4 (11.8)
No chemotherapy	4 (11.8)
Chemotherapy regimen	
Oxaliplatin	26 (76.5)
No oxaliplatin	4 (11.8)

Table 3. Univariate analysis of prognostic factors for recurrence-free survival

	Number of patients ***N* = 30**	**Median RFS (months)**	***P*-value**
Gender			
Male	20	21.3	
Female	10	14.9	0.78
Age (years)			
< 65	20	27.0	
≥ 65	10	12.1	0.55
Location of primary			
Duodenum	11	21.3	
Jejunum	8	20.3	0.91
Ileum	9	21.2	0.90
Node status at primary tumor site			
N0	7	21.2	
N+	19	13.5	0.11
Delay of metastases			
Synchronous	23	13.7	
Metachronous	7	21.3	0.73
Metastatic site			
Peritoneum alone	8	13.6	
Liver alone	9	21.2	0.36
Other	8	10.7	0.64

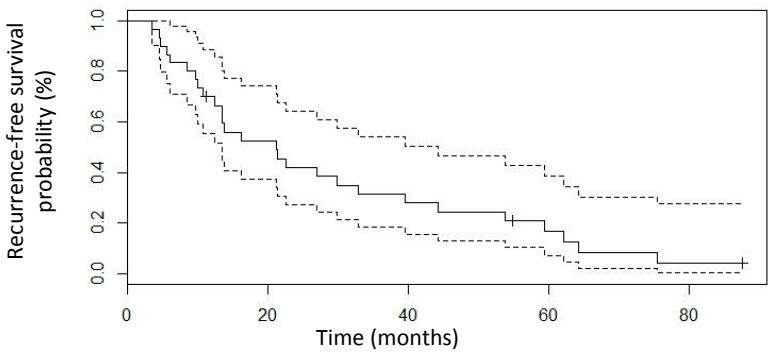
Multiple	5	25.5	0.67
Tumor grade			
Well or moderately	22	21.3	
Poorly	3	7.3	0.074
Resection margins			
R0	22	24.8	
R1-2	6	7.6	0.002
Adjuvant chemotherapy			
With oxaliplatin	22	21.9	
Without oxaliplatin	4	7.8	0.074

Table 4. Univariate analysis of prognostic factors for overall survival

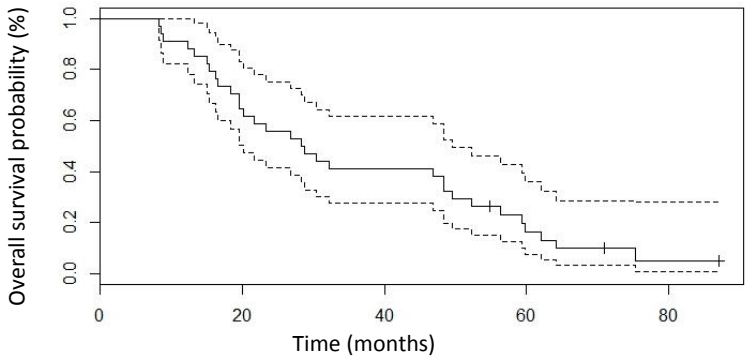
	Number of patients *N* **= 34**	**Median OS (months)**	***P*-value**
Gender			
Men	24	27.6	
Women	10	40.0	0.28
Age (years)			
< 65	24	38.6	
≥ 65	10	20.6	0.42
Location of primary tumor			
Duodenum	14	27.6	
Jejunum	8	53.5	0.16
Ileum	10	38.6	0.96
Node status at primary tumor site			
N0	8	56.1	
N+	21	23.3	0.039
Delay of metastases			
Synchronous	25	23.3	
Metachronous	9	30.4	0.63
Metastatic site			
Peritoneum alone	10	19.9	
Liver alone	9	46.9	0.59
Other	10	21.7	0.52
Multiple	5	39.4	0.54
Tumor differentiation			

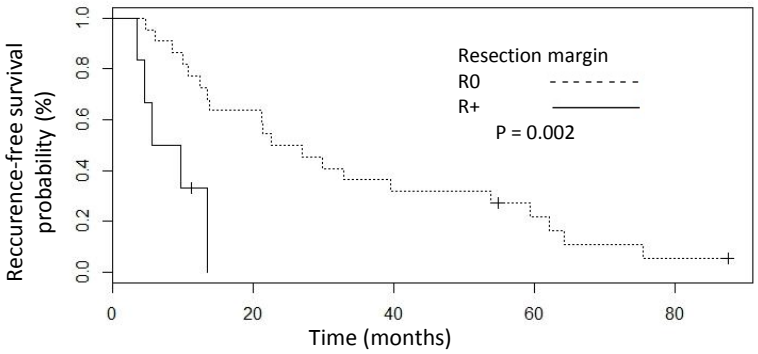
Well or moderately	24	40.3	
Poorly	5	15.1	0.006
Resection margin			
R0	24	48.4	
R1-2	7	16.6	0.003
Adjuvant chemotherapy			
With oxaliplatin	25	46.9	
Without oxaliplatin	4	16.0	0.038

A


Recurrence-free survival probability (%)
0.0
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
Time (months)

B


Overall survival probability (%)
0.0
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
Time (months)


Reccurence-free survival probability (%)
0.0
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
Time (months)
Resection margin
R0
R+
P = 0.002