European Journal of Surgical Oncology 45 (2019) 331–335

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

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

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ARTICLE INFO

Article history:
Received 27 August 2018
Received in revised form
14 November 2018
Accepted 18 November 2018
Available online 22 November 2018

Keywords:
Small bowel adenocarcinoma
Metastases resection
Hepatic metastases
Adjuvant chemotherapy

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.

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https://doi.org/10.1016/j.ejso.2018.11.012

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 Fig. 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

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)

(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; Fig. 1A) and the median OS was 28.6 months (95% CI 19–38.2; Fig. 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 (Fig. 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

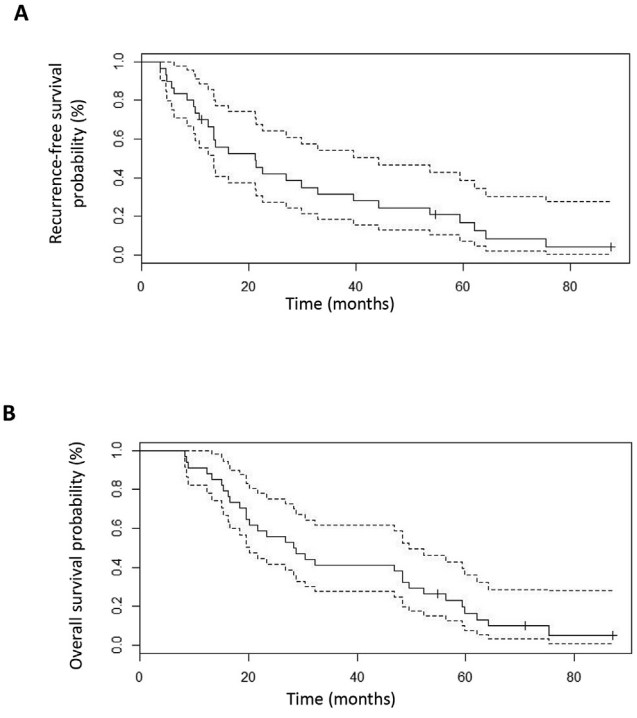

Fig. 1. Recurrence-free survival (A) and overall survival (B).

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

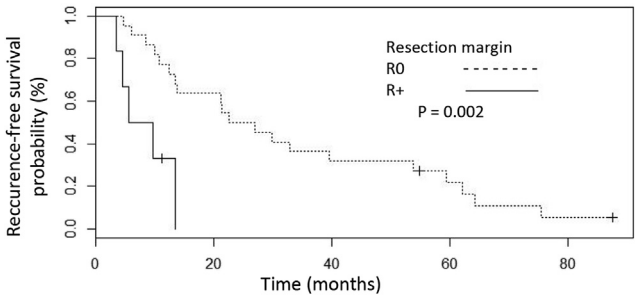

Fig. 2. Recurrence-free survival according to resection margin.

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 Fig. 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.

Disclosure

None.

Conflict of interest

None.

Funding

The ARCAD-NADEGE cohort received a grant from A.R.C.A.D. (Aide et Recherche en CAncérologie Digestive) fundation, grant n° NA2009.

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).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2018.11.012.

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