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ORIGINAL ARTICLE

Adjuvant systemic chemotherapy with or without bevacizumab in patients with resected pulmonary metastases from colorectal cancer

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Abstract

Introduction: We investigated the impact of modern chemotherapy regimens and bevacizumab following pulmonary metastasectomy (PM) from metastatic colorectal cancer (CRC).

Methods: A total of 122 consecutive patients who were curatively resected for pulmonary metastases of CRC in twelve oncology centers were retrospectively analysed between January 2000 and April 2012.

Results: Of 122 patients, 14 did not receive any treatment following PM. The remaining 108 patients received fluoropyrimidine-based ($n = 12$), irinotecan-based ($n = 56$) and oxaliplatin-based ($n = 40$) chemotherapy combinations. Among these, 52 patients received bevacizumab (BEV) while 56 did not (NoBEV). Median recurrence-free survival (RFS) was 17 months and median overall survival (OS) has not been reached at a median follow-up of 25 months after PM. Three and five-year OS rates were 66% and 53%, respectively. RFS and OS were similar, irrespective of the chemotherapy regimen or BEV use. Positive pulmonary margin, KRAS mutation status, and previous liver metastasectomy were negative independent prognostic factors for RFS, while pathologically confirmed thoracic lymph node involvement was the only negative independent prognostic for OS in multivariate analysis.

Conclusions: No significant RFS or OS difference was observed in respect to chemotherapy regimens with or without BEV in patients with pulmonary metastases of CRC following curative resection.

Introduction

Metastatic colorectal cancer (CRC) is a major cause of cancer related mortality.[1] The lung is the most common extra-abdominal metastasis site from CRC. After resection of the primary carcinoma, approximately 10% of patients develop pulmonary metastases.[2] Despite the lack of randomized trials, pulmonary metastasectomy (PM) has become the standard of care for patients with pulmonary-limited metastatic CRC.[3]

After curative resection of pulmonary metastasis from CRC, chemotherapy is frequently administered. There is no randomized trial evaluating the impact of chemotherapy following PM. Similar to the situation after liver metastasectomy from CRC,[4] a universally accepted administration of chemotherapy following PM is still lacking. Several small retrospective trials evaluating the impact of chemotherapy following PM showed conflicting results.[5–16] Therefore, we conducted this retrospective study to investigate whether there is any difference in recurrence-free survival (RFS) or overall survival (OS) among patients treated with different cytotoxic regimens combined with or without bevacizumab (BEV) after PM from CRC. We also reviewed prognostic factors affecting survival following PM.

Patients and Methods

Patients

Medical records of unselected consecutive patients with metastatic CRC who underwent PM were reviewed retrospectively in twelve oncology centers between January 2000 and April 2012. To be eligible, patients were required to have pulmonary resection with curative intent. The patients had to have histologically proven synchronous or metachronous pulmonary metastases from colorectal adenocarcinoma. For patients with synchronous metastases, the primary tumor had to be either already resected or judged to be resectable. Exclusion criteria were as follows: innumerable lung metastases, non-hepatic extra-thoracic metastases, radiofrequency ablation (RFA) alone without PM, and gross residual disease (R2) following resection. All patients had adequate hematological, hepatic, and renal functions, and Eastern Cooperative Oncology Group performance status of 0–2.

Chemotherapy regimens

Chemotherapy regimens were chosen at the discretion of the attending physician. The chemotherapy regimens were either fluoropyrimidine-based (5-fluorouracil + leucovorin [FU/LV][17] or capecitabine alone[18]); irinotecan-based (FOLFIRI,[19] XELIRI[20] and IFL[21]), or oxaliplatin-based (FOLFOX6,[19] FOLFOX4,[22] FLOX[23] and XELOX[24]). BEV was given at a dose of 5 mg/kg every two weeks or 7.5 mg/kg every three weeks.

Statistical analysis

RFS was defined as the time from the date of PM until disease recurrence or death from any cause. For patients who were lost to follow-up, data were censored on the date when the patients were last seen alive without recurrence. OS was defined as the time between the date of PM and the death of the patient or the date of last follow-up. Disease-free interval (DFI) was defined as the time from primary cancer surgery to the detection of metastasis in metachronous patients. The Kaplan-Meier method and the log-rank test were used to estimate and compare RFS and OS. For comparison of categorical variables, the Pearson chi-square test was used. Cox's proportional hazards model was used for multivariate analysis. Variables with less than 0.10 significance determined on univariate analysis were recruited into multivariate analysis. A P-value of <0.05 was considered significant.

Results

Patient characteristics

A total of 122 patients with metastatic CRC who underwent PM were identified. Fourteen patients were excluded for various reasons: delayed or no chemotherapy ($n = 8$), metastases outside the liver and lungs ($n = 3$), early disease recurrence within six weeks after metastasectomy ($n = 1$), gross residual disease following PM ($n = 1$), and second malignancy ($n = 1$). The clinical characteristics of the analyzed 108 patients are summarized in Table 1. The median age was 56 years (range, 23–78). Fifty-eight patients were males and 50 females. The primary site of the tumor was the rectum in 52 patients. Of 108 patients, 25 had synchronous disease and 83 metachronous disease. The surgical procedure was wedge resection in 88, lobectomy in 18, and pneumonectomy in two patients. The median number of pulmonary metastases removed per patient was one lesion (range, 1–6). The vast majority of patients (94.3%) had ≤3 pulmonary metastases. The median size of pulmonary metastases was 2 cm (range, 1–6), and 101 patients had pulmonary metastases <5 cm. Nineteen patients had a microscopically positive surgical margin of pulmonary resection. Finally, three patients underwent pulmonary RFA.

Chemotherapeutic regimens

Twelve patients received fluoropyrimidine-based, 56 irinotecan-based, and 40 oxaliplatin-based regimens (Table 1). There was no significant difference in baseline patient characteristics in terms of cytotoxic regimens, except

Table 1 Patient characteristics

	Chemotherapy regimen				Bevacizumab use		
	FLP-based *n* = 12 (%)	Irinotecan-based *n* = 56 (%)	Oxaliplatin-based *n* = 40 (%)	*P*-value	BEV *n* = 52 (%)	NoBEV *n* = 56 (%)	*P*-value
Age, >65 years	3 (27)	12 (21)	9 (22)	0.901	11 (20)	13 (24)	0.817
Gender, females	2 (18)	28 (49)	20 (50)	0.142	25 (46)	25 (46)	1.000
Primary tumor site, rectum	6 (54)	28 (49)	18 (45)	0.835	25 (46)	27 (50)	0.700
K-RAS status, mutant	4 (66)	13 (36)	8 (42)	0.368	13 (38)	12 (44)	0.820
Prethoracotomy CEA, ≥5	3 (30)	13 (29)	11 (42)	0.505	16 (39)	11 (28)	0.387
DFI ≤1 year	2 (20)	11 (23)	5 (16)	0.727	11 (25)	7 (15)	0.370
Metastatic pattern, synchronous	3 (27)	12 (21)	10 (25)	0.851	14 (26)	11 (20)	0.648
No. of lung metastases, ≥2	4 (36)	9 (16)	4 (10)	0.114	9 (17)	8 (15)	0.791
Size of lung metastases, ≥3 cm	1 (9)	10 (18)	7 (18)	0.769	9 (17)	9 (16)	0.965
Lung resection margins, R1	1 (9)	11 (20)	7 (18)	0.706	12 (22)	7 (13)	0.311
Thoracic LN involvement, yes	2 (40)	7 (26)	2 (12)	0.335	8 (28)	3 (14)	0.401
CT before lung resection, yes	2 (18)	15 (26)	5 (13)	0.269	15 (27)	7 (13)	0.062
Prior adjuvant CT, yes	9 (82)	40 (70)	27 (68)	0.654	16 (29)	16 (29)	1.000
Median CT duration, months	4.2 (2–6)	6 (2–6)	4.5 (2–8)	0.885	4 (2–6)	4.0 (2–8)	0.701
Median CT cycles, number	5 (2–8)	12 (3–12)	6 (3–12)	0.001	6 (2–12)	6 (2–12)	0.048
Distribution of BEV use, according to cytotoxics	2 (17)	46 (82)	6 (15)	<0.001			
Distribution of cytotoxics according to BEV use					FLP: 2 (4) IRI: 44 (85) OXA: 6 (11)	FLP: 10 (18) IRI: 12 (18) OXA:34 (63)	<0.001
Detailed distribution of CT regimens	FU/LV: 4 CAP: 6 CAP-BEV: 2	IFL: 2 XELIRI: 2 FOLFIRI: 8 IFL-BEV: 1 FOLFIRI-BEV: 43	FLOX: 2 XELOX: 12 FOLFOX: 20 FLOX-BEV: 1 XELOX-BEV: 2 FOLFOX-BEV: 3		CAP-BEV: 2 FLOX-BEV: 1 XELOX-BEV: 2 FOLFOX-BEV: 3 IFL-BEV: 1 FOLFIRI-BEV:43	FU/LV: 4 CAP: 6 IFL: 2 XELIRI:2 FOLFIRI:8 FLOX: 2 XELOX: 12 FOLFOX: 20	

Figures in parentheses are percentages or range. BEV, bevacizumab; CAP, capecitabine alone, every three weeks; CEA, carcinoembryonic antigen; CT, chemotherapy; DFI, disease-free interval (only for metachronous disease); FLOX, oxaliplatin and bolus 5-fluorouracil with leucovorin, weekly; FLP, fluoropyrimidine; FOLFIRI, irinotecan and infusional 5-fluorouracil with leucovorin, every two weeks; FOLFOX, oxaliplatin and infusional 5-fluorouracil with leucovorin, every two weeks; FU/LV, bolus 5-fluorouracil and leucovorin, every four weeks; IFL, irinotecan and bolus 5-fluorouracil with leucovorin, weekly; IRI, irinotecan; LN, lymph node; NoBEV, without bevacizumab; OXA, oxaliplatin; XELIRI, capecitabine and irinotecan every three weeks; XELOX, capecitabine and oxaliplatin, every three weeks.

for the significantly higher number of patients receiving BEV combined with the irinotecan-based regimens, compared to other regimens ($P < 0.001$). Fifty-six patients were treated with cytotoxics alone (NoBEV), whereas 52 were treated with cytotoxics plus BEV based regimens (BEV). BEV and NoBEV arms were also well balanced in terms of baseline characteristics. A total of 22 patients (20.3%) had received chemotherapy before PM. The details of these treatments were not available in terms of aims, cytotoxic agents or treatment response. The number of patients who had received chemotherapy before PM was slightly higher in the BEV arm when compared to NoBEV arm, but this difference was not statistically significant ($P = 0.062$). The median number of chemotherapy cycles administered was six (range, 2–12), and this was significantly different both among cytotoxics ($P = 0.001$) and between BEV and NoBEV arms ($P = 0.048$) because of varying intervals of chemotherapy regimens used. Therefore, we preferred to calculate "median chemotherapy duration," the time period during which the patients were exposed to chemotherapy (4.5 months; range, 2–8). When median chemotherapy duration was taken into consideration, the differences among cytotoxics and between BEV and NoBEV arms disappeared.

Survival

The median follow-up time after PM was 25 months (range, 3–107). At the time of analysis, 39 patients were alive with no evidence of recurrence, 42 were alive with evidence of disease recurrence, 25 died of disease, and two died of other causes. Of the 69 relapsed patients, 25 were curatively resected again.

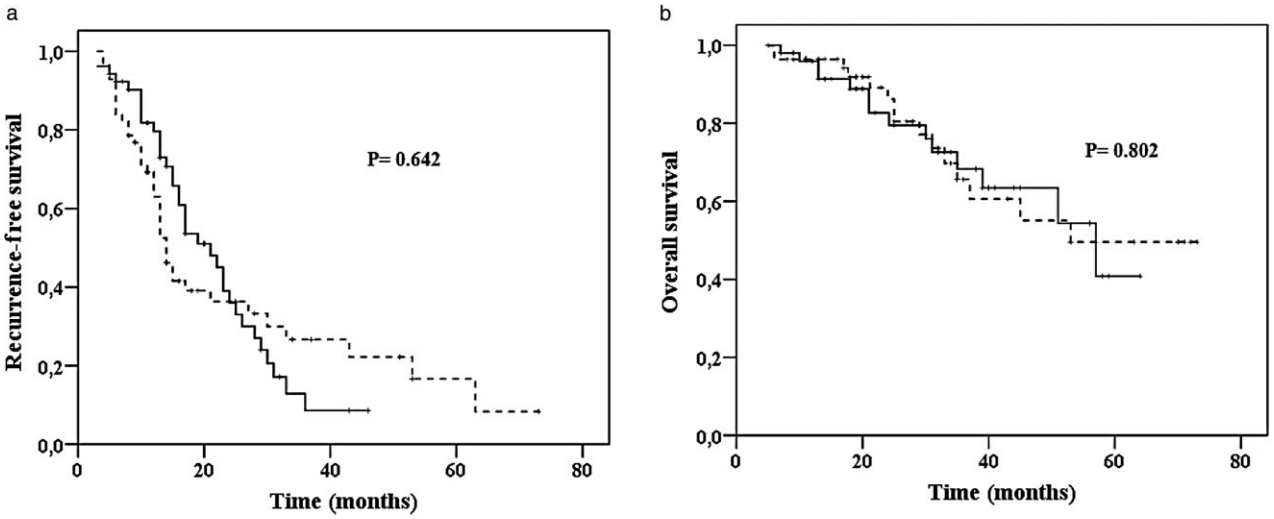

Figure 1 (**a**) Recurrence-free survival (RFS) and (**b**) overall survival (OS) according to bevacizumab (BEV) use in patients with resected pulmonary metastases from colorectal cancer. ——, BEV; - - -, NoBEV.

The median RFS was 17 months (95% confidence interval [CI]; 11.5–22.0), while median OS has not been reached. Three and five-year OS rates were 66% and 53%, respectively. There was no significant difference among cytotoxic regimens with respect to either RFS or OS ($P = 0.477$ and $P = 0.328$, respectively). Similarly, there was no significant difference between BEV and NoBEV arms with respect to RFS and OS ($P = 0.642$ and $P = 0.802$, respectively) (Fig 1a,b).

KRAS status was available in 66 patients (61%). There were 26 patients with mutant type KRAS (mt-KRAS) and 40 wild-type KRAS (wt-KRAS) tumors. When patients with mt-KRAS tumors were taken into consideration, there was a significant RFS advantage with the addition of BEV to cytotoxic regimens (16.3 months vs. 6.5 months, respectively, [$P = 0.005$]). Similarly, a positive trend favoring BEV use in wt-KRAS tumors in terms of RFS did not reach statistical significance ($P = 0.067$). However, a small number of patients and lack of details of subsequent therapy, especially with anti-EGFR agents, diminishes the significance of this finding.

In univariate analysis, previous liver metastasectomy ($P = 0.047$), positive pulmonary margin ($P = 0.023$), DFI <12 months ($P = 0.017$), and mt-KRAS tumor ($P = 0.020$) were significant poor prognostic factors predicting RFS. Pathologically confirmed thoracic lymph node involvement (pt-LNI) ($P = 0.003$) and a higher presurgery carcinoembryonic antigen (p-CEA) level ($P = 0.026$) were significant poor prognostic factors for OS (Table 2).

Cox multivariate analysis showed that positive pulmonary margin (hazard ratio [HR] 2.187; 95% CI 1.056–4.527; $P = 0.035$), mt-KRAS tumor (HR 2.083; 95%CI 1.113–3.898; $P = 0.022$), and previous liver metastasectomy (HR 2.184; 95% CI 1.121–4.256; $P = 0.022$) were independent poor prognostic factors for RFS. The only independent significant poor prognostic factor for OS was pt-LNI (HR 5.891; 95% CI 1.134–30.608; $P = 0.035$) (Table 3).

Discussion

Pulmonary metastasectomy is now accepted as the standard intervention for resectable pulmonary metastasis from CRC.[25] There is no doubt that PM can be performed safely.[26] Although most studies suggest a prolonged survival after PM,[27] the real benefit of surgery in this setting remains controversial. The benefit of chemotherapy in patients who underwent curative resection of pulmonary metastases remains undefined. Our retrospective analysis showed that all current chemotherapies are equally effective with no superiority of one regimen over another in this setting. Furthermore, the addition of BEV did not provide any advantage over NoBEV regimens.

In an attempt to identify patients who may benefit further from PM, most studies have specifically focused on identifing prognostic factors. More recently, systematic reviews have reported several prognostic factors.[8,10,26,28,29] The presence of multiple pulmonary metastases, elevated p-CEA, pt-LNI, positive pulmonary margin, short DFI, and larger tumor size were found to be significantly associated with poor prognosis. In our study, consistent with these trials, pt-LNI was the only independent poor prognostic factor for OS, whereas positive pulmonary margin, mt-KRAS tumor, and previous liver metastasectomy were independently associated with poor RFS. With respect to the prognostic effect of KRAS status, conflicting results have been reported in the literature.[30–35] It was not unexpected that prior liver resection was an adverse

Table 2 Factors associated with recurrence-free survival (RFS) and overall survival (OS) in univariate analysis

	Median RFS, Months, 95%CI	*P*-value	Median OS, Months, 95%CI	*P*-value
Size of lung metastases,		0.674		0.739
≥3 cm	13.3 (3.6–22.9)		59.9 (56.1–82.8)	
<3 cm	16.8 (11.4–22.2)		66.2 (38.3–94.1)	
Number of lung metastases,		0.257		0.210
Multiple	15.6 (10.2–21.0)		46.4 (29.7–63.1)	
Single	17.9 (10.8–25.0)		66.2 (52.8–79.6)	
CEA level,		0.260		0.026
Normal	20.5 (15.1–25.8)		59.9 (42.5–77.3)	
High	14.7 (9.6–19.7)		35.7 (27.0–44.4)	
Lung resection margins		0.023		0.746
R1 resection	11.6 (8.0–15.2)		39.9 (25.4–54.3)	
R0 resection	17.9 (13.3–22.5)		–	
Thoracic lymhatic involvement		0.845		0.003
Positive	15.6 (5.0–26.1)		30.1 (3.7–57.4)	
Negative	16.5 (12.9–20.1)		51.9 (43.7–71.3)	
K-RAS status		0.020		0.400
Wild type	16.8 (9.3–24.2)		–	
Mutant type	11.6 (7.3–15.9)		51.1 (35.0–67.1)	
History of liver resection		0.047		0.622
Yes	12.3 (9.8–14.9)		59.9 (39.7–79.8)	
No	17.9 (13.8–22.0)		66.2 (55.8–82.1)	
Disease-free interval		0.017		0.440
≤1 year	11.6 (5.0–18.2)		39.9 (33.3–46.4)	
>1 year	20.5 (15.7–25.2)		66.2 (45.9–86.5)	

CEA, car cinoembryonic antigen; OS, overall survival; RFS, recurrence-free survival.

prognostic factor because it indicates that patients already had disseminated disease outside of the lungs prior to PM, with increased risk of imminent relapse. Short DFI and multiple pulmonary metastases were not prognostic in our multivariate analysis. In brief, the majority of our results regarding prognostic factors were similar to published studies. The reasons for the discrepancies in prognostic factors among previous studies may be partly explained by the small sample size and variations in the definition of prognostic factors, as well as the retrospective nature of the studies.

Although an important aspect of the present study was the question to which extent patients with resected pulmonary metastases benefit from chemotherapy, definitive conclusions

Table 3 Negative prognostic factors associated with recurrence-free survival (RFS) and overall survival (OS) in multivariate analysis

	Recurrence-free survival			Overall survival		
Risk factor	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Thoracic lymphatic involvement						0.035
Negative				1		
Positive				5.891	1.134–30.608	
K-RAS status			0.022			
Wild type	1					
Mutant type	2.083	1.113–3.898				
Margins of lung resection			0.035			
R0	1					
R1	2.187	1.056–4.527				
Prior liver resection			0.022			
No	1					
Yes	2.184	1.121–4.256				

Factors associated with survival with a significance <0.1 in univariate analysis were recruited into the Cox regression model. CI, confidence interval; HR, hazard ratio.

regarding the role of chemotherapy in the post-PM period cannot be discerned with this study because we had no chemotherapy-free control arm (only eight patients were chemotherapy-free). Despite widespread use of post-PM chemotherapy, studies are limited and most of them are retrospective, evaluating the impact of chemotherapy on survival outcomes. Furthermore, none of the currently available trials evaluating this issue were designed to assess the impact of chemotherapy on outcomes as a primary outcome. Of these retrospective studies, seven[5–11] found no contribution of chemotherapy, one[12] had no detailed outcomes of chemotherapy, one[13] found an OS advantage of chemotherapy, two[14,16] found a non-significant trend towards higher five-year survival in patients receiving chemotherapy, and one[15] found a significant benefit in patients undergoing "adjuvant chemoradiotherapy" with a non-significant trend towards reduction in death at three years. In fact, there is no compelling evidence to advocate chemotherapy following PM, although it is widely practiced in clinical oncology. We observed no survival difference with respect to various chemotherapy regimens in the post-PM setting. Although we have failed to show any significant difference among cytotoxic regimens, it is reasonable to make a suggestion towards chemotherapy use, at least for patients with pt-LNI, as it was an independent poor prognostic factor in multivariate analysis.

Recent randomized trials have shown that the addition of BEV to oxaliplatin-based chemotherapy in patients with resected stage II/III colon cancer has no survival advantage in the adjuvant setting.[36,37] It is not known if the addition of BEV in stage IV advanced stage patients who underwent metastasectomy and had no evidence of disease (stage IV no evidence of disease) elsewhere will provide any benefit. However, our study did not demonstrate any positive additive activity of BEV to known cytotoxic agents in patients with resected PM from metastatic CRC.

Our study had some limitations. First, it was retrospective with an unavoidable selection bias, as in all non-randomized studies. However, all patients who underwent PM were included in the analysis, which minimizes the likelihood of selection bias. Second, not having a chemotherapy-free control arm limited our comments on the benefit of adding chemotherapy following PM. Third, KRAS data was not available in a significant proportion of the study population, which limited the power of the relationship between survival and KRAS mutation.

Conclusion

In conclusion, we could not demonstrate any difference in the efficacy of various chemotherapy regimens after PM from metastatic CRC. The addition of BEV did not confer further improvement on the efficacy of cytotoxic chemotherapy in this setting.

Disclosure

No authors report any conflict of interest.

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