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The impact of palliative primary tumor resection on overall survival in minimally symptomatic (asymptomatic) colorectal cancer and synchronous unresectable metastases vs chemotherapy only: a comparative study of outcomes

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ABSTRACT *AIM: to evaluate the impact of primary tumor resection (PTR) on treatment outcomes in patients with asymptomatic or minimally symptomatic colorectal cancer (CRC) and synchronous unresectable metastases.*
PATIENTS AND METHODS: treatment outcomes of patients with minimally symptomatic CRC and synchronous unresectable metastases were retrospectively assessed (2016–2022). Patients with PTR followed by chemotherapy were compared to patients receiving chemotherapy only.
Survival was determined by the Kaplan-Meier method and differences were evaluated using the log-rank test and Cox proportional-hazards regression model. To reduce potential selection bias between two groups a propensity score matching (PSM) was performed.
RESULTS: no significant differences in 30-day mortality rate (p = 1,00) and the rate of surgical intervention due to complications of first treatment (p = 1,00) between the two groups. Before matching the median survivals were 27,8 and 24 months in the PTR and chemotherapy groups, respectively (p = 0,2). After PSM the overall survival rate at 3 years was 42,1% for the PTR group and 34% for the chemotherapy group (p = 0,47). The median survivals were 27,9 and 24,4 months, respectively. Three-year overall survival rate for patients with stage IVB was significantly higher in the PTR group than in the chemotherapy group (37,8% versus 4,8%; p = 0,02). The median survivals were 36,1 and 17,2 months, respectively. In multivariate analysis radical resection (R0) if unresectable metastases converted into resectable after initial treatment was the only significant prognostic factor for survival (p < 0,001).
CONCLUSIONS: PTR in patients with asymptomatic or minimally symptomatic CRC and synchronous unresectable metastases is associated with acceptable postoperative morbidity and mortality rates and may improve overall survival for patients with stage IVB comparing to chemotherapy as a treatment of first line. However, randomized controlled trials are needed.

KEYWORDS: *colorectal cancer; palliative resection; asymptomatic primary tumor; unresectable metastases; chemotherapy; overall survival*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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INTRODUCTION

Approximately 20% of patients with colorectal cancer (CRC) are diagnosed with stage IV and substantial number of them has unresectable synchronous metastases [1–3]. Currently, palliative primary tumor resection (PTR) for unresectable metastatic CRC is recommended only in cases of complications such as bowel obstruction, perforation or severe bleeding. According to Russian clinical [4,5], NCCN [6,7] and ESMO [8,9] guidelines the initial treatment for uncomplicated CRC is systemic chemotherapy with periodic assessment of respectability of metastases. However, the necessity of palliative PTR for patients with CRC with minimally symptomatic (asymptomatic) primary tumor and synchronous unresectable metastases is controversial, as only results of non-randomized comparative studies are available.

Some of these studies demonstrated statistically significant survival benefit of PTR [10–15], while others found no benefits of PTR [16–26]. In addition, some researchers reported that PTR is associated with unacceptable postoperative complications [16,27,28], which potentially can delay the initiation of systemic chemotherapy and decrease survival.

The aim of this retrospective study was to evaluate the impact of PTR followed by chemotherapy on overall survival versus chemotherapy alone in patients with minimally symptomatic CRC and synchronous unresectable metastases.

PATIENTS AND METHODS

The databases of three clinical centers (Ryzhikh National Medical Research Center of Coloproctology, Moscow Multidisciplinary Clinical Center “Kommunarka” of Moscow City Health Department, A.S. Loginov Moscow Clinical Scientific Center, Department of Health of Moscow) were analyzed retrospectively. The inclusion criteria were as follows: patients with histologically confirmed CRC; minimally symptomatic (asymptomatic) primary tumor with unresectable synchronous metastasis. The exclusion criteria were as follows: synchronous cancers; prior surgery, chemotherapy, radiation therapy for the primary tumor or distant metastases; carcinomatosis. The asymptomatic or minimally symptomatic nature of the tumor was defined as the absence of signs of perforation, severe bleeding or bowel obstruction. The absence of bowel obstruction was determined using radiologic examination methods. All patients underwent colonoscopy with biopsy, chest CT, abdominal CT/MRI with intravenous contrast, pelvic CT with intravenous contrast, pelvic MRI with/without intravenous contrast in case of rectal cancer. A multidisciplinary team consisting of an oncologist, radiation therapist, surgeon, radiologist, and chemotherapist made the final determination regarding treatment method. Between January 2016 and May 2022, 180 patients were selected according to eligibility criteria. The patients were divided into 2 groups: palliative primary tumor resection followed by chemotherapy and systemic chemotherapy. The included variables were gender, age, ECOG performance status, site of primary tumor, site of metastases, clinical tumor, nodal, metastasis stage, use targeted therapy in the first-line chemotherapy, radical resection (R0) if unresectable metastases converted into resectable after chemotherapy. The primary end point was overall survival. Secondary end points were 30-day mortality and rate of surgical intervention due to complications of first treatment. The detailed study protocol was published and registered (ClinicalTrials.gov Identifier: NCT05322486).

Pseudo-randomization (propensity score matching)

To reduce potential selection bias between two groups a propensity score matching (PSM) was performed.

Propensity scores were estimated by using logistic regression. A PSM analysis using IBM SPSS Statistics 27 for MacOS (SPSS. Inc, Chicago, IL, USA) was performed with the ratio of patients of each group being 1:1. The match tolerance was set

at 0.02, without replacement. Gender, age, ECOG performance status, site of primary tumor, site of metastases, clinical tumor, nodal, metastasis stage were selected as covariates in the regression model.

Statistical analyses

The Shapiro Wilk test was used to determine whether a data set is normally distributed for quantitative (continuous) variables. Continuous data were presented as median and range, categorical data — as absolute and relative frequencies. Continuous variables were compared using Mann-Whitney U test. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test. Survival rate was determined by using Kaplan-Meier analysis with a log-rank test. The OS was defined as the time from the date of start treatment until the death from any cause or last follow-up. Univariate and multivariate analyses for survival were conducted using Cox proportional hazard model. Categorical variables were included in Cox regression analysis using a repeated coding. In the univariable Cox regression analyses, variables with p value ⩽ 0.1 were included in the multivariable Cox regression analyses. All tests were 2-sided, and a P-value of < 0.05 was considered significant. Statistical analyses were performed using IBM SPSS Statistics 27 (SPSS. Inc, Chicago, IL, USA) software program. Survival curves were depicted using SAS JMP Pro 17.

RESULTS

The baseline characteristics of patients before and after PSM

We selected 180 patients who met the eligibility criteria. The median follow-up period was 23.2 (0.4–77.3) months. Before matching, there were considerable differences between the 2 groups, possibly due to selection bias. The most significant differences were seen in the categories of the site of primary tumor, site of metastases and clinical T, N, M stage. After PSM, 50 pairs of patients were selected. The groups were comparable for all 8 selected covariates: gender, age, ECOG performance status, site of primary tumor, site of metastases, clinical T, N, M stage. The mean age for the 100 patients (51 males and 49 females) was 60 years (29–83). The median follow-up period was 25.5 (0.4–77.3) months.

Chemotherapy

All 90 patients in the chemotherapy group received the following first-line chemotherapy regimens: 1) 5-fluorouracil and oxaliplatin-based chemotherapy with or without targeted agents (*n* = 63); 2) 5-fluorouracil, oxaliplatin and irinotecan-based chemotherapy with or without targeted agents (*n* = 22); 3) 5-fluorouracil and irinotecan-based chemotherapy with or without targeted agents (*n* = 5); 4) Use of targeted agents in the main chemotherapy regimen (*n* = 43).

Eighty-nine of 90 patients under went palliative chemotherapy after initial surgical resection (1 patient died within 30 days after surgery) with the following first-line chemotherapy regimens: 1) 5-fluorouracil and oxaliplatin-based chemotherapy with or without targeted agents (*n* = 76); 2) 5-fluorouracil, oxaliplatin and irinotecan-based chemotherapy with or without targeted agents (*n* = 4); 3) 5-fluorouracil and irinotecan-based chemotherapy with or without targeted agents (*n* = 9); 4) Use of targeted agents in the main chemotherapy regimen (*n* = 35). Bevacizumab, cetuximab or panitumumab were used as targeted agents in both groups. Thus, despite the use of different chemotherapy regimens, fluoropyrimidines were the baseline drugs in all regimens. The baseline characteristics of patients before and after PSM are reported in Table 1.

Complications of initial treatment

Five patients in the PTR group underwent reoperation due to complications of first treatment: colostomy necrosis (*n* = 1), colostomy fistula (*n* = 1), anastomotic leakage (*n* = 1), bowel obstruction (*n* = 2). In the chemotherapy group, 10 patients underwent surgery and in most cases were related to complications from the primary tumor: large

Table 1. *The baseline characteristics of patients before and after propensity score matching*

Variables	Overall cohort			Cohort after PSM		
	PTR (N = 90)	CT (N = 90)	P-value	PTR (N = 50)	CN (N = 50)	P-value
Age, median (range)	61.5 (29–88)	59 (33–82)	0.10	60.5 (29–83)	58 (33–80)	0.55
Gender (%)			0.77			1.00
Male	45 (50)	48 (53.3)		25 (50)	26 (52)	
Female	45 (50)	42 (46.7)		25 (50)	24 (48)	
ECOG performance status(%)			1.00			1.00
0-1	88 (97.8)	89 (98.9)		50 (100)	50 (100)	
2	2 (2.2)	1 (1.1)		0 (0)	0 (0)	
Site of primary tumor (%)			0.02			0.84
Colon	61 (67.8)	45 (50)		28 (56)	26 (52)	
Rectum	29 (32.3)	45 (50)		22 (44)	24 (48)	
Clinical T stage (%)			< 0.0001			0.50
T2	0 (0)	9 (10)		0	0	
T3	43 (47.8)	61 (67.8)		38 (76)	36 (72)	
T4a	31 (34.4)	15 (16.7)		10 (20)	9 (18)	
T4b	16 (17.8)	5 (5.6)		2 (4)	5 (10)	
Clinical N stage (%)			0.002			0.77
N0-1	80 (88.9)	62 (68.9)		44 (88)	42 (84)	
N2	10 (11.1)	28 (31.1)		6 (12)	8 (16)	
Clinical M stage (%)			0.01			0.60
M1a	78 (86.7)	63 (70)		40 (80)	43 (86)	
M1b	12 (13.3)	27 (30)		10 (20)	7 (14)	
Site of metastases (%)			0.03			0.68
Liver	70 (77.8)	62 (68.9)		37 (74)	42 (84)	
Lung	7 (7.8)	1 (1.1)		3 (6)	1 (2)	
Liver + lung	8 (8.9)	17 (18.9)		6 (12)	3 (6)	
Liver + retroperitoneal lymph nodes	2 (2.2)	7 (7.8)		2 (4)	2 (4)	
Multiple metastases, including liver	3 (3.3)	3 (3.3)		2 (4)	2 (4)	
Targeted therapy (first-line chemotherapy regimens) (%)*			0.29			1.00
No	54 (60.7)**	47 (52.2)		26 (53.1)	26 (52)	
Yes	35 (39.3)	43 (47.8)		23 (46.9)	24 (48)	
Radical surgery if unresectable metastases converted into resectable after chemotherapy (%)***			0.25			1.00
No	60 (66.7)	68 (75.6)		33 (66)	32 (64)	
Yes	30 (33.3)	22 (24.4)		17 (34)	18 (36)	

*Note: PTR –primary tumor resection, CT — chemotherapy, PSM — propensity score matching; * in the PTR group- after surgical intervention; ** one patient in the PTR group did not undergo palliative chemotherapy after initial surgical resection due to death within 30 days after surgery; *** in the PTR group the operation was considered radical (R0) if the metastases were completely removed; in the CT group R0 resection was defined as simultaneous or sequential removal of all metastases and primary tumor.*

bowel resection due to colon obstruction (n = 3), endoscopic stent placement due to colon obstruction (n = 3), diverting stoma due to colon obstruction (n = 2), large bowel resection due to colon necrosis (n = 1), per cutaneous transhepaticchol angiostomy (n = 1). In the PTR group, 1 patient died within 30 days after surgery of multiorgan failure caused by acute inferior mesenteric artery thrombosis and colon necrosis; there was no 30-day mortality in the chemotherapy group. There were no significant differences between the two groups in 30-day mortality rate (p = 1.00) and the rate of surgical intervention due to complications of first treatment (p = 0.28).

After performing propensity score matching, 4 patients in the PTR group underwent reoperation due to complications of first treatment: colostomy fistula (n = 1), anastomotic leakage (n = 1),

Table 2. *Surgical intervention due to complication of first treatment, 30-day mortality before and after PSM*

Variables	Overall cohort			Cohort after PSM		
	PTR (N = 90)	CT (N = 90)	P-value	PTR (N = 50)	CT (N = 50)	P-value
Surgical intervention due to complication of first treatment (%)	5 (5.6)	10 (11.1)	0.28	4 (8)	5 (10)	1.00
30-day mortality (%)	1 (1.1)	0 (0)	1,00	1 (2)	0 (0)	1.00

Note: PTR — primary tumor resection, CT — chemotherapy, PSM –propensityscore matching

Table 3. *Univariate and multivariate Cox regression analysis of factors correlated with overall survival before PSM*

Variables	Univariate Cox regression analysis		Multivariate Cox regression analysis	
	HR(95% CI)	P-value	HR(95% CI)	P-value
Age		0.90		–
< 60	1.00		–	
⩾ 60	0.98 (0.70–1.38)		–	
Gender		0.47		–
Female	1.00		–	
Male	1.14 (0.81–1.60)		–	
ECOG performance status		0.87		–
0–1	1.00		–	
2	0.89 (0.22–3.59)		–	
Site of primary tumor		0.48		–
Colon	1.00		–	
Rectum	1.13 (0.80–1.60)		–	
Clinical T stage		0.82		–
T2	1.00	0.82	–	
T3	0.68 (0.27–1.69)	0.40	–	
T4a	0.66 (0.26–1.70)	0.39	–	
T4b	0.76 (0.28–2.07)	0.59	–	
Clinical Nstage		0.09	–	0.23
N0-1	1.00		1.00	
N2	1.43 (0.95–2.17)		1.29 (0.85–1.95)	
Clinical Mstage		0.23		–
M1a	1.00		–	
M1b	1.29 (0.85–1.95)		–	
Site of metastases		0.68		–
Liver	1.00	0.68	–	–
Lung	0.98 (0.43–2.24)	0.97	–	–
Liver + lung	1.20 (0.72–2.01)	0.49	–	–
Liver + retroperitoneal lymph nodes	1.60 (0.74–3.46)	0.23	–	–
Multiple metastases, including liver	1.42 (0.62–3.25)	0.41	–	–
Palliative primary tumor resection		0.20		–
No	1.00		–	
Yes	0.80 (0.57–1.13)		–	
Targeted therapy (first-line chemotherapy regimens)*		0.89		–
No	1.00		–	
Yes	0.98 (0.69–1.38)		–	
Radical surgery if unresectable metastases converted into resectable after chemotherapy**		< 0.001		< 0.001
No	1.00		1.00	
Yes	0.38 (0.25–0.57)		0.39 (0.25–0.59)	

*Note: PTR — primary tumor resection, CT — chemotherapy, PSM — propensity score matching, HR — hazard ratio; * in the PTR group — after surgical intervention; ** in the PTR group the operation was considered radical (R0) if the metastases were completely removed; in the CT group R0 resection was defined as simultaneous or sequential removal of all metastases and primary tumor*

bowel obstruction (n = 2). In the chemotherapy group, 5 patients underwent surgery and in all cases were related to complications from the primary tumor: large bowel resection due to colon obstruction (n = 2), endoscopic stent placement due to colon obstruction (n = 2), diverting stoma due to colon obstruction (n = 1). In the PTR group, 1 patient died within 30 days after surgery of multiorgan failure caused by acute inferior mesenteric artery thrombosis and colon necrosis; there was no 30-day mortality in the chemotherapy group. Comparative analysis showed no significant differences between the two groups in 30-day mortality rate (p = 1.00) and the rate of surgical intervention due to complications of first treatment (p = 1.00). The results of treatment are reported in Table 2.

Univariate and multivariate Cox regression analysis of factors correlated with overall survival before and after PSM

Before performing propensity score matching within the overall cohort (n = 180) the 1-, 2-, and 3-year overall survival rates were 77.9%, 51.6%, and 35% and median survival was 26.8 months (23.3–30.3). In the univariable Cox regression analyses, variables with p value ⩽ 0.1 were included in the multivariable Cox regression analyses. In univariate analysis, clinical N2 stage was associated with decreased overall survival (HR1.43; 95% CI 0.95–2.17; p = 0.09). Radical resection (R0) if unresectable metastases converted into resectable after initial treatment was associated with significantly improved survival rates (HR0.38; 95% CI 0.25–0.57; p < 0.001). In the PTR group if unresectable metastases converted into resectable after initial treatment, the operation was considered radical (R0) if the metastases were completely removed; in the chemotherapy group R0 resection was defined as simultaneous or sequential removal of all metastases and primary tumor. In multivariate analysis radical resection if unresectable metastases converted into resectable after initial treatment was the only significant prognostic factor associated with improved survival (HR) 0.39; 95% CI 0.25–0.59; p < 0.001) (Table 3). Fifty-two patients underwent radical surgery after conversion from unresectable to resectable metastases after chemotherapy, 128 patients did not undergo radical surgery, the median survival was 40 months and 22.6 months, respectively.

After performing propensity score matching the 1-, 2-, and 3-year overall survival rates were 77.9%, 53.6% и 38%. Median survival was 26.9 months (22.7–31). In the univariable Cox regression analyses, variables with p value ⩽ 0.1 were included in the multivariable Cox regression analyses. In univariate analysis, IVB clinical stage (M1b) was associated with decreased overall survival (HR 1.57; 95% CI 0.91–2.70; p = 0.1); radical resection if unresectable metastases converted into resectable after initial treatment was associated with

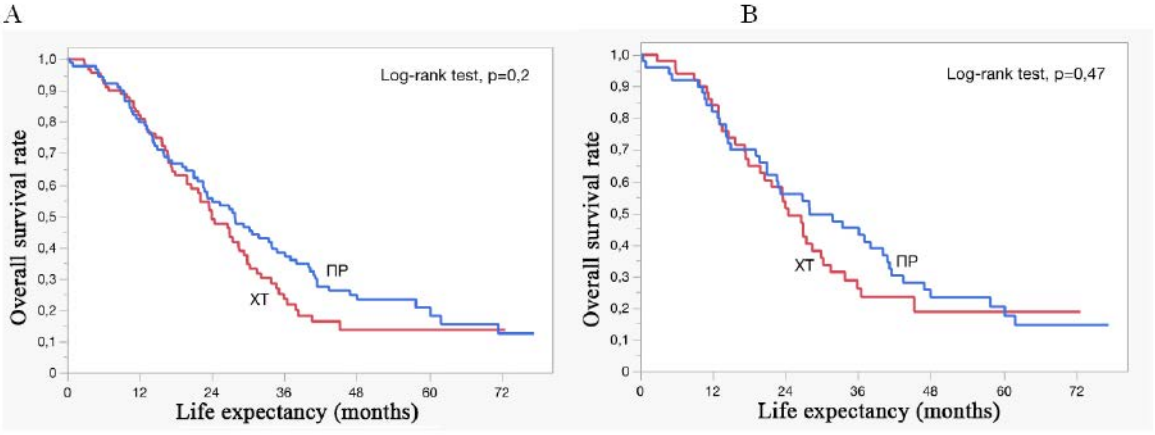

Figure 1. *Overall survival between groups (palliative primary tumor resection and chemotherapy) before (A) and after PSM (B)*

Table 4. *Univariate and multivariate Cox regression analysis of factors correlated with overall survival after PSM*

Variables	Univariate Cox regression analysis		Multivariate Cox regression analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age		0.22		–
< 60	1.00		–	
⩾ 60	1.33 (0.84–2.10)		–	
Gender		0.38		–
Female	1.00		–	
Male	1.22 (0.78–1.92)		–	
Site of primary tumor		0.72		–
Colon	1.00		–	
Rectum	1.09 (0.69–1.71)		–	
Clinical T stage		0.45		
T3	1.00	0.46	–	
T4a	1.11 (0.64–1.95)	0.71	–	–
T4b	1.71 (0.73–3.99)	0.22	–	–
Clinical N stage		0.72		–
N0-1	1.00		–	
N2	1.13 (0.58–2.21)		–	
Clinical M stage		0.10		0.98
M1a	1.00		1.00	
M1b	1.57 (0.91–2.70)		1.01 (0.58–1.76)	
Site of metastases		0.46		–
Liver	1.00	0.48	–	
Lung	0.96 (0.30–3.06)	0.94	–	–
Liver + lung	1.39 (0.69–2.81)	0.36	–	–
Liver + retroperitoneal lymph nodes	2.25 (0.81–6.23)	0.12	–	–
Multiple metastases, including liver	1.55 (0.56–4.31)	0.40	–	–
Palliative primary tumor resection No	1.00	0.47	–	–
Yes	0.85 (0.54–1.34)		–	
Targeted therapy (first-line chemotherapy regimens)*		0.91		–
No	1.00		–	
Yes	1.03 (0.65–1.62)		–	
Radical surgery if unresectable metastases converted into resectable after chemotherapy**		< 0.001		< 0.001
No	1.00		1.00	
Yes	0.28 (0.16–0.48)		0.28 (0.16–0.49)	

*Note: PTR — primary tumor resection, CT — chemotherapy, PSM — propensity score matching, HR — hazard ratio; * in the PTR group — after surgical intervention; ** in the PTR group the operation was considered radical (R0) if the metastases were completely removed; in the CT group R0 resection was defined as simultaneous or sequential removal of all metastases and primary tumor.*

improved overall survival (HR0.28; 95% CI 0.16–0.48; $p < 0.001$).

In multivariate analysis radical resection if unresectable metastases converted into resectable after initial treatment was the only significant prognostic factor associated with improved survival (HR 0.28; 95% CI 0.16–0.49; $p < 0.001$) (Table 4). Thirty-five patients underwent radical surgery after conversion from unresectable to resectable metastases after chemotherapy, 65 patients did not undergo radical surgery, the median survival was 46.9 months and 21.7 months, respectively.

Survival analysis and follow-up period

Before matching, overall survival in the PTR and the chemotherapy groups was comparable ($p = 0.2$). The follow-up period was significantly different between two groups (27.1 months vs. 19 months, $p = 0.02$). The overall survival rates at 1, 2 and 3 years were 80.1%, 58.1% and 39.9% in

the PTR group and 80%, 52.4% and 29.9% in the chemotherapy group. The median survivals were 27.8 (21.2–34.4) and 24 months (19.4–28.5) in the PTR and chemotherapy groups, respectively. After matching, there was also no significant differences in overall survival between the two groups ($p = 0.47$). The follow-up periods were comparable between the groups (27.3 months vs. 23.5 months, $p = 0.17$). The median survivals were 27.9 (13.9–41.9) and 24.4 months (20–28.8) in the PTR and chemotherapy groups, respectively. The overall survival rates at 1, 2 and 3 years were 79.8%, 59% and 42.1% in the PTR group and 81.5%, 55.8% and 34% in the chemotherapy group. The overall survival before and after PSM is demonstrated in Figure 1 A,B.

Patients from both the overall and the propensity score-matched cohorts were analyzed according to the clinical M stage by using Kaplan-Meier analysis. In the overall cohort, there was no overall survival benefit of palliative resection according to the clinical M stage (Figure 2). The overall survival rates at 1, 2 and 3 years for patients with clinical stage IVA (M1a) were 78.7%, 57.8% and 41% in the PTR group and 83.3%, 56% and 32% in the chemotherapy group ($p = 0.39$). The median survivals were 27.4 (21.2–33.6) and 26.6 months (21.9–31.3) in the PTR and chemotherapy groups, respectively ($p = 0.39$). The overall survival rates at 1, 2 and 3 years for patients with clinical stage IVB (M1b) were 91.8%, 66.2% and 35.5% in the PTR group and 72.2%, 44.6% and 25.3% in the chemotherapy group ($p = 0.25$). The median survivals were 36.1 (12.6–59.6) and 22.1 months (13.8–30.4) in the PTR and chemotherapy groups, respectively.

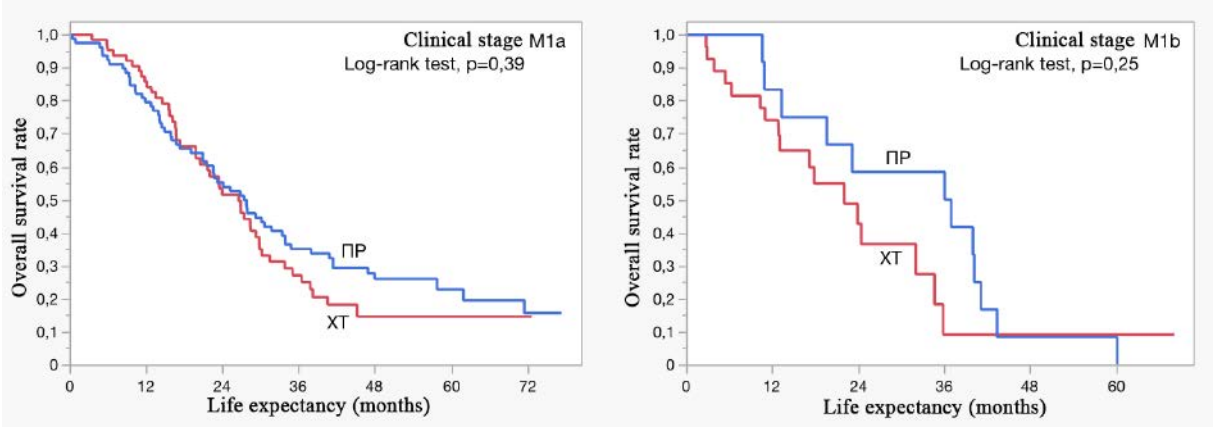

Figure 2. *Overall survival between groups (palliative primary tumor resection and chemotherapy) depending on clinical stage (M1a and M1b) before PSM*

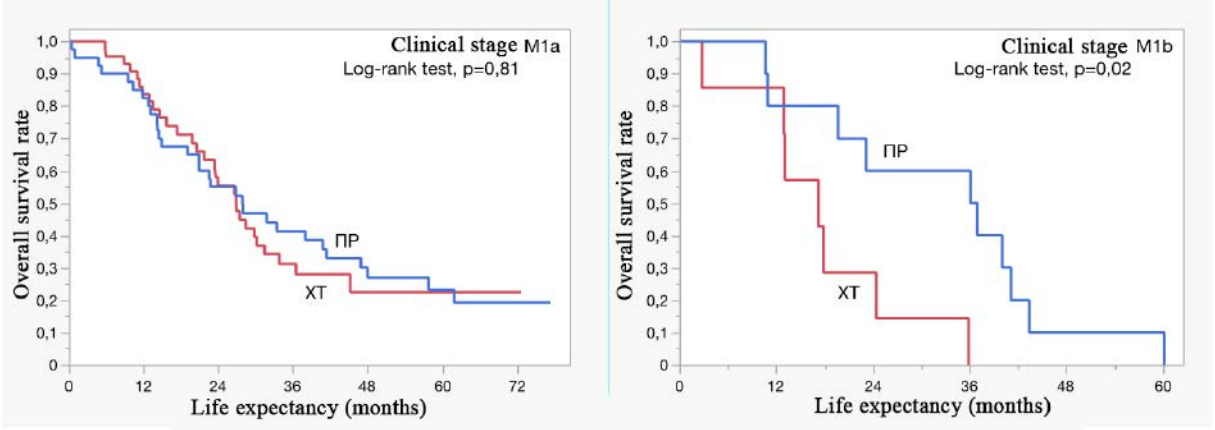

Figure 3. *Overall survival between groups (palliative primary tumor resection and chemotherapy) depending on clinical stage (M1a and M1b) after PSM*

Table 5. *Randomized controlled trials (RCTs)*

RCT name	Country	RCT №	Primary outcome	Simple size	Study start year/ estimated study completion year	Status
SYNCHRONOUS [29]	Germany	ISRCTN30964555	3 years OS	800 ⟶ 392	2011–2019	Ongoing/ no longer recruiting
CAIRO4 [30]	Netherlands	NCT01606098	5 years OS	360	2012–2020	Recruiting
CCRe-IV [31]	Spain	NCT02015923	2 years OS	336	2013–2018	Ongoing/ no longer recruiting
CLIMAT [32]	France	NCT02363049	2 years OS	278	2014–2018	Recruiting
PTR Trial [33]	Korea	NCT01978249	2 years OS	480	2013–2016	Early terminated*
China multicenter [34]	China	NCT02149784	3years OS	480	2015–2019	Recruiting
JCOG1007 [35]	Japan	UMIN000008147	3years OS	770 ⟶ 280	2012–2020	Early terminated*

** — trial was early terminated because of the difficulties of participant enrolment. OS — overall survival*

In the patients with clinical stage IVB (M1b) from the propensity score-matched cohort, palliative resection was associated with a significantly better survival rate (p = 0.02) (Figure 3). The overall survival rates at 1, 2 and 3 years for patients with clinical stage IVA (M1a) were 77.5%, 58.5% and 43.7% in the PTR group and 84%, 60.3% и 38.9% in the chemotherapy group (p = 0.81). The median survivals were 27.9 (15.1–40.7) and 26.9 months (21.7–32.1) in the PTR and chemotherapy groups, respectively. The overall survival rates at 1, 2 and 3 years for patients with clinical stage IVB (M1b) were 92.7%, 68.4% and 37.8% in the PTR group and 68%, 24.2% and 4.8% in the chemotherapy group (p = 0.02). The median survivals were 36.1 (14.7–57.5) and 17.2 months (6.6–27.9) in the PTR and chemotherapy groups, respectively.

The survival rates also were analyzed from both the overall and the propensity score-matched cohorts according to whether or not patients underwent radical surgery if unresectable metastases converted into resectable after initial treatment. In the overall cohort, 52 patients underwent radical surgery. Among them, 29 (55.8%) patients died, the median survival was 40 months (26.5–53.6). One hundred twenty-eight patients did not undergo radical surgery. Among them, 105 (82%) patients died, the median survival was 22.6 months (19.8–25.4). After matching, the median survival for patients who underwent radical surgery was 46.9 months (24.4–69.4; without radical surgery — 21.7 months (17.7–25.8). Radical surgery if unresectable metastases converted into resectable after initial treatment significantly increased rates of survival (p < 0.0001) (Figure 4).

DISCUSSION

The necessity of palliative PTR for asymptomatic or minimally symptomatic patients with CRC and

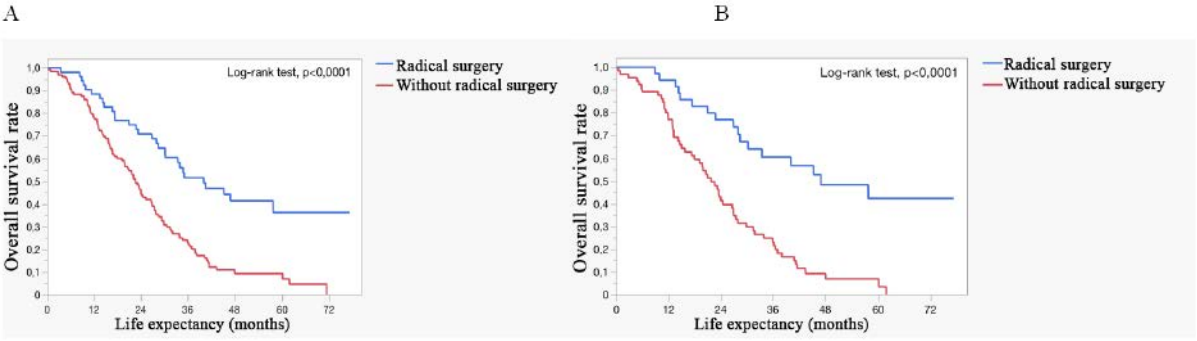

Figure 4. *Overall survival depending on the performance of radical resection (R0) if unresectable metastases converted into resectable after initial treatment before (A) and after PSM (B)*

synchronous unresectable metastases is controversial. Currently, only results of non-randomized studies are available on this issue. Several RCTs were initiated comparing PTR followed by chemotherapy with chemotherapy alone, but not completed yet (Table 5).

Two RCTs [33,35] were terminated early because of the complicated enrolment of patients, two interim analyses were published. The results of the first interim analysis [28], which included 165 patients of planned sample size of 280 patients, reported that PTR had no benefits in terms of survival, but resulted in higher postoperative mortality rate. The 3-year survival rates were comparable between the groups and were 32.9% and 33%, in the PTR and chemotherapy groups, respectively. Thirty-day mortality in the PTR group was 4%. However, the planned 70% statistical power of the study was not achieved.

The results of a second interim analysis [27], which included 44 patients of planned sample size of 480 patients, demonstrated a benefit for 2-year cancer-specific survival (72.3% vs. 47.1%; $p = 0.049$).

Although 2-year OS was higher by 25% in the PTR group (69.5% vs. 44.8%), the difference did not reach statistical significance ($p = 0.058$), which indicates that the study was obviously underpowered.

The results of the interim analyses from the SYNCHRONOUS (ISRCTN30964555) and CCRe-IV (NCT02015923) were presented during the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting [31]. Data were pooled with the Spanish CCRe-IV trial (NCT02015923) with similar eligibility criteria, interventions and endpoints. Because of similarity in eligibility criteria, interventions and endpoints, data from the two studies were pooled (295 patients from the SYNCHRONOUS trial and 98 patients from the CCRe-IV trial). Both studies compared PTR followed by chemotherapy with chemotherapy alone in patients with asymptomatic primary tumor and unresectable metastases CRC. There were no statistically significant differences between two groups in overall survival. Median overall survival was 16.7 months and 18.6 months in the PTR and chemotherapy groups, respectively (OR 0.95; 95% CI 0.74–1.22; $p = 0.69$) [36].

Full publication of results is expected.

Most previous meta-analyses on this issue included data from patients with both symptomatic and asymptomatic primary tumors [37–40]. The first meta-analysis including only asymptomatic patients was published by Cirocchi et al. in 2012 [41]. The authors included seven non-randomized trials (1086 patients), overall survival was analyzed in only 4 studies (443 patients). Researchers reported that PTR did not improve OS comparing to chemotherapy alone and did not prevent surgical interventions due to complications related to primary tumor. However, new studies published since 2012 which may change the outcomes and conclusions of this meta-analysis. A meta-analysis published in 2022 by Shu Y. et al. [42], which included 2805 patients with asymptomatic primary tumor and unresectable metastases CRC, showed a benefit of PTR in overall survival (OR: difference in mean (MD) 6.76 [3.39, 10.12]; I2 = 77%; P < 0.0001). The overall survival rates at 2, 3 and 5 years were significantly higher in the PTR group than in the chemotherapy group (OR 2.35 [1.74, 3.18]; I2 = 0%; P < 0.00001; OR 3.61 [2.35, 5.54]; I2 = 0%; P < 0.00001; OR 3.02 [1.72, 5.33]; I2 = 48%; P = 0.0001, respectively). A recent published meta-analysis based on the results of 16 non-randomized comparative studies and data from early terminated randomized controlled trials, which included 2999 patients, showed, that PTR significantly improves overall survival, allows to prevent surgical intervention due to complications related to primary tumor and is not associated with increased postoperative mortality rate [43]. Gender, age, site of primary tumor and distant metastasis of patients were comparable between groups in all analyzed studies. Two-year (38.2% vs. 21.1%; OR 0.42; 95% CI 0.28–0.64; $p < 0.0001$) and 5-year (12.7% vs. 5.3%; OR 0.45; 95% CI 0.21–0.97; $p = 0.04$) overall survival rates were significantly higher in the PTR group than in

the chemotherapy group. No significant differences in 30-day mortality rate between the two groups (1.7% vs. 1%; OR 1.92; 95% CI 0.79–4.68; $p = 0.15$). However, the rate of surgical intervention due to complications of first treatment was significantly lower in the PTR group comparing to the chemo/RT group (2.3% vs. 14.53%; OR 0.18; 95% CI 0.08–0.40; $p < 0.0001$). At the same time, 114 patients (13.8%; OR 0.19; 95% CI 0.09–0.40; $p < 0.0001$) in the chemotherapy group required surgery for symptoms associated with a primary tumor (13.8%; OR 0.19; 95% CI 0.09–0.40; $p < 0.0001$).

This study demonstrates that palliative resection of asymptomatic primary tumors in patients within resectable stage IV CRC was not associated with an improvement in overall survival. However, in a subgroup analysis performed according to the clinical M stage, palliative resection to provide significant benefit in terms of overall survival for patients with stage IVB in comparison with initial chemotherapy. It should be noted that the results were obtained on a small sample of 17 patients (10 patients underwent PTR followed by chemotherapy, 7 patients were treated with systemic chemotherapy).

An unexpected finding in univariate analysis, was that clinical T3, T4a, and T4b stages were associated with increased overall survival compared with clinical T2 stage. Also paradoxically, ECOG 2 performance status was associated with increased overall survival of patients compared to ECOG 0–1 performance status. The results could be explained by the fact that there were only 9 of the 180 patients with T2 stage and these patients were identified in the chemotherapy group only. ECOG 2 performance status had only 3 patients. After performing propensity score matching, patients with clinical T2 stage and ECOG 2 performance status were not included in the new cohort. In this way, the potential selection bias was reduced. After that, in univariate analysis clinical T4a, and T4b stages were associated with decreased overall survival compared with clinical T3 stage.

In addition, the results of our study demonstrated that PTR is a safe procedure and is not associated with increased postoperative mortality rate and postoperative complications requiring reoperation. Also, radical surgery if unresectable metastases converted into resectable after initial treatment is an independent prognostic factor for survival.

This study has several limitations. The small sample size did not allow statistical significance in some subgroups. Although the PSM process can reduce potential biases in retrospective studies, unlike randomized controlled trials, the biases caused by unobserved covariates cannot be eliminated. SYNCHRONOUS (ISRCTN30964555), CAIRO4 (NCT01606098), CCRe-IV (NCT02015923), CLIMAT (NCT02363049) and China multicenter (NCT02149784) are still in progress, and acquisition of data allows to elucidate the role of PTR in treatment of disseminated CRC in patients with minimally symptomatic (asymptomatic) primary tumor.

CONCLUSION

The results of the presented study with propensity score matching demonstrate, that PTR in patients with asymptomatic or minimally symptomatic CRC and synchronous unresectable metastases is associated with acceptable postoperative morbidity and mortality rates and may improve overall survival for patients with stage IVB (M1b) comparing to chemotherapy as a treatment of first line. However, randomized controlled trials are mandatory.

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