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Survival outcome of palliative primary tumor resection for colorectal cancer patients with synchronous liver and/or lung metastases: A retrospective cohort study in the SEER database

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Abstract

Background: There is a great matter of controversies whether some of these synchronous metastatic colorectal cancer patients can benefit from palliative primary tumor resection (pPTR) and there is still no reported randomized control trial to address this issue.

Methods: Patients with microscopically proven metastatic colorectal cancer were identified within the SEER database (2010 to 2016). Patients were propensity matched 1:1 into pPTR and non-surgery groups and among the matched cohort, the univariable and multivariable Cox proportional hazards regression models were performed to identify predictors of survival. Median survival was calculated by using the Kaplan-Meier method.

Results: Of 21405 colorectal cancer patients diagnosed with synchronous liver and/or lung metastases, 7386 were identified in the matched cohort. The median overall survival was 12.0 months, 22.0 months in the non-surgery, surgery groups, respectively ($p < 0.001$) and the corresponding median cancer-specific survival was 13.0 months, 22.0 months, respectively ($p < 0.001$). Multivariable Cox regression analysis demonstrated that surgery was independently associated with improved overall survival (hazard ratio, 0.531) as well as cancer-specific survival (hazard ratio, 0.516). In stratified analyses by primary site and patterns of distant metastases, those patients with pPTR had better prognosis. In addition, stratified analysis revealed that trimodality therapy was linked with the greatest therapeutic effect followed by addition of chemotherapy to pPTR.

Conclusions: pPTR may offer some therapeutic benefits among carefully selected patients, and surgery-based multimodality therapy was associated with better survival.

Keywords: palliative primary tumor resection, colorectal cancer, synchronous liver and/or lung metastases, propensity score matching analysis, SEER database.

1. Introduction

Colorectal cancer (CRC), one of the most common malignancies in the world, ranks third in terms of incidence but second in terms of mortality [1]. At the time of diagnosis, approximately 20–25% of patients with CRC presented with synchronous metastases, which were unresectable in 75–90% of these cases [2, 3].

According to the current guidelines, such as the NCCN [4, 5], and ESMO guidelines [6, 7], systemic therapy is the first-line treatment for these cases. Palliative primary tumor resection (pPTR) may only be required for primary tumor–related adverse events, such as obstruction, perforation, or intractable hemorrhage. Furthermore, at the setting of current great advances in systemic treatment of

metastatic colorectal cancer (mCRC), the risk of primary tumor-related emergency situations and the need of urgent surgical interventions are lower than before [8, 9]. However, some researches demonstrated that not all these patients could benefit from systemic chemotherapy and they unavoidably suffered from the adverse events linked to the primary tumor in the end [10, 11]. A previous meta-analysis reported that when unresectable stage IV patients were initially received chemotherapy, approximately 22% of these patients presented with primary tumor-related complications, with 87% of them requiring emergency surgery [12]. It is supported by data showing that patients who suffer from complications due to the primary tumor during chemotherapy are more likely to have a poor prognosis [12, 13]. These results suggest that pPTR is inevitable in a substantial percentage of some CRC patients. Moreover, there are high operative morbidity and mortality for emergency situation compared with lower complication rates in the elective colorectal surgery [14, 15].

Thus, there is no particularly effective and suitable therapy for these patients due to their high heterogeneities [11]. Previous attempts to conduct randomized controlled trials for mCRC patients have prematurely shut down due to poor recruiting [16, 17]. Nonetheless, there is no reported randomised control trial comparing treatment with pPTR versus systemic chemotherapy, and a number of ongoing trials such as the Dutch CAIRO4 trial (NCT02149784) [18], the Chinese trials (NCT02149784 and NCT02291744) [19], the French GRECCAR 8 trial (NCT02314182) [20] are also investigating this issue. This study explored the SEER database and conducted 1:1 propensity score matching (PSM) analysis to compare survival outcomes of pPTR for CRC patients with synchronous liver and/or lung metastases.

2. Materials and Methods

2.1. Patients selection

This study analyzed the SEER database [Incidence-SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975–2016 varying)], released in August 8, 2019 as data source. We obtained access to the SEER database using the ID number 10898-Nov2018. We used the SEER*Stat software (version 8.3.6) to extract clinicopathologic and survival information. CRC based on the value of the primary site variables ({Site and Morphology. Site recode ICD-O-3/WHO 2008} ='Colon and Rectum') was identified from the SEER database. CRC patients with synchronous liver and/or lung metastases diagnosed between 2010 and 2016 were selected from the SEER database, since we were able to get the detailed information of synchronous liver and/or lung metastases from these cases. All procedures performed in this study were in line with the STROCSS criteria [21]. Patients were enrolled according to the following criteria: (1) being diagnosed with CRC only; (2) confirmed synchronous liver and/or lung metastases; (3) they did not receive metastasectomy; (4) whether they underwent pPTR was known; (5) their cause of death was known; (6) their survival time were known and greater than 0 month; (7) they were diagnosed with histologic confirmation. A flow chart of the study population selection was displayed

in Figure 1.

In place of the possibility of randomization, a logistic regression model capable of predicting the likelihood of receiving pPTR was constructed and used as the propensity score. Patients were then propensity matched 1:1 into pPTR and non-surgery groups through the nearest neighbor method with a caliper of 0.1 times the standard deviation of the propensity score. No replacement was allowed, and patients were matched only once. Variables used for matching were as follows: insurance, marital status, age, race, gender, year of diagnosis, primary site, grade, adenocarcinoma, tumor size, preoperative CEA levels, synchronous metastases patterns. Standardized mean differences with mirror histograms before and after matching are illustrated in Figure 2 and Figure 3.

2.2. Statistical analysis

All analyses were performed with the IBM SPSS Statistics 22.0 software (IBM, Armonk, NY, USA), R version 3.6.2 (www.r-project.org) and two-tailed p-values < 0.05 were assessed as statistically significant.

In this study, a 1:1 PSM analysis (without replacement) was conducted via the nearest neighbor method with a caliper of 0.1 times the standard deviation of the propensity score. Standardized differences were used to examine the balance across baseline covariates before and after matching, and a standardized difference below 10% was reliable enough to provide well-balanced covariates after matching. Next, $\chi 2$ statistics were utilized to compare patient and tumor characteristics in both matched and unmatched cohorts. The primary endpoint of this study was OS and CSS. OS is defined as the time interval between the diagnosis of CRC and death from any cause, whereas CSS is defined as the time interval between the diagnosis of CRC and death caused by CRC. Survival among the pPTR and non-surgery cohorts in the matched population were compared by using the Kaplan-Meier analysis by the log-rank test and stratified by synchronous metastases patterns and primary site. In the matched population, univariable and multivariable Cox proportional hazards regression models were performed to identify the independent prognostic factors for mCRC patients.

3. Results

3.1. Baseline characteristics

In this investigation, 21405 of 262285 patients diagnosed with CRC between 2010 and 2016 met our selection criteria for additional analysis. Of those, 9049 (42.3%) patients underwent pPTR, whereas 12356 (57.7%) did not (Table 1). A PSM analysis was then conducted and 7386 patients were 1:1 matched, comprising a surgery and non-surgery cohort. Distribution of the baseline characteristics was well-balanced in the matched cohort (Table 2).

3.2. Impact of pPTR on overall survival

The OS of the matched cohort was calculated by the Kaplan-Meier method. The results revealed a significant difference in survival between patients who underwent pPTR and those who did not (log-rank $p < 0.001$) (Figure 4A). The median OS for those who received pPTR was 22.0 months (95% CI, 21.1 months to 22.9 months) and 12.0 months (95% CI, 11.3 months to 12.7 months) for those who did not. When performing a univariable Cox proportional hazards regression analysis in the matched population, all the baseline characteristics including marital status, age, race, gender, primary site, grade, adenocarcinoma, tumor size, preoperative CEA levels, synchronous metastases patterns, surgery, radiation and chemotherapy significantly correlated with these patients' OS and these variables were all included in the following multivariate Cox analysis. After multivariable risk adjusting in the Cox proportional hazard regression analysis, pPTR was a statistically significant protective factor for OS (HR, 0.531; 95% CI, 0.501 to 0.563, $P < 0.001$) (Table 3). Besides, marital status, age, race, primary site, grade, tumor size, preoperative CEA levels, synchronous metastases patterns, radiation and chemotherapy were validated as independent risk or protective factors as well.

3.3. Impact of pPTR on cancer-specific survival

Median CSS for those who received pPTR was 22.0 months (95% CI, 21.1 months to 22.9 months) and 13.0 months (95% CI, 12.3 months to 13.7 months) for those who did not (Figure 4B). In the univariable Cox proportional hazards regression analysis, marital status, age, race, gender, primary site, grade, adenocarcinoma, tumor size, preoperative CEA levels, distant synchronous metastases, surgery, radiation and chemotherapy were also correlated with CSS and they were further adjusted in the multivariate Cox regression. After multivariable analysis, pPTR was a statistically significant protective factor for CSS (HR, 0.516; 95% CI, 0.487 to 0.547, $P < 0.001$) (Table 4). Besides, other covariates including marital status, age, race, primary site, grade, tumor size, preoperative CEA levels, synchronous metastases patterns and chemotherapy also proved to be independent prognostic factors for CSS.

3.4. Survival outcomes stratified by primary site, synchronous metastatic patterns and treatment

Patients who underwent pPTR exhibited a considerable survival benefit (log-rank $p < 0.001$) (Figure 5), an effect that was observed across primary site subgroups but that was most prominent among the rectum tumor subgroup, followed by the left-sided and then the right-sided tumor subgroups. (Figure 8A) In the cohort of patients who did not go through pPTR, the rectum group led to better OS than the right-sided colon subgroup 0.55 (95% CI, 0.50 to 0.60), followed by the left-sided colon subgroup 0.69 (95% CI, 0.63 to 0.76). The rectum subgroup presented the highest improvement in OS following pPTR with the HR decreasing to 0.31 (95% CI, 0.28 to 0.34), followed

by the left-sided colon subgroup 0.41 (95% CI, 0.37 to 0.45) and finally the right-sided colon subgroup 0.57 (95% CI, 0.52 to 0.63). (Figure 8B) A similar improvement was also observed that in the cohort of patients who did not undergo pPTR, in which the rectum subgroup led to better CSS than the right-sided colon group 0.55 (95% CI, 0.50 to 0.60), followed by the left-sided colon group 0.70 (95% CI, 0.63-0.77). The rectum subgroup also led to the greatest CSS after pPTR with the HR decreasing to 0.31 (95% CI, 0.28 to 0.34), followed by the left-sided colon subgroup 0.41 (95% CI, 0.36 to 0.45) and then the right-sided colon subgroup 0.57 (95% CI, 0.52 to 0.63).

Patients who underwent pPTR displayed a significant survival improvement (log-rank P < 0.001) (Figure 6), a finding that was observed across different synchronous metastases patterns but that was most prominent among patients with only lung metastases, followed by those with only liver metastases and eventually those with only liver and lung metastases. (Figure 8A) In the matched cohort where pPTR was not undergone, patients with only lung metastases led to more favorable OS than only liver metastases 0.84 (95% CI, 0.74 to 0.96), followed by only liver and lung metastases 1.14 (95% CI, 1.04 to 1.25). Patients with only lung metastases presented the greatest improvement in OS after pPTR with the HR dropping to 0.41 (95% CI, 0.35 to 0.48), followed by those with only liver metastases 0.54 (95% CI, 0.50 to 0.58) and then those with only liver and lung metastases 0.86 (95% CI, 0.78 to 0.94). (Figure 8B) A similar improvement was also noticed in the matched cohort without undergoing pPTR, as patients with only lung metastases were also associated with better CSS than those with only liver metastases 0.82 (95% CI, 0.71 to 0.94), followed by those with only liver and lung metastases 1.16 (95% CI, 1.02 to 1.27). Moreover, patients with only lung metastases demonstrated the greatest improvement in CSS after pPTR with the HR declining to 0.40 (95% CI, 0.34 to 0.47), followed by those with only liver metastases 0.53 (95% CI, 0.50 to 0.58) and then those with only liver and lung metastases 0.84 (95% CI, 0.76 to 0.93). Compared to patients with liver-only metastases who did not receive pPTR, there was an increased risk or no significance in OS as well as CSS in the remaining subgroups but after pPTR, there was no significance in OS as well as CSS in all these remaining subgroups.

Subsequently, patients were then stratified based on the receipt of each therapy, which revealed that the surgery-based trimodality therapy was associated with the best OS and CSS followed by addition of chemotherapy to pPTR, meanwhile the worst survival was observed in the no therapy cohort (log-rank P < 0.001) (Figure 7). In addition, a subgroup analysis was conducted to explore whether the survival benefit of pPTR, chemotherapy, and/or radiation therapy interacted with one another (Figure 9). The greatest therapeutic effect on OS was observed in trimodality therapy (HR, 0.15; 95% CI, 0.13 to 0.18), followed by the addition of chemotherapy to pPTR (HR, 0.23; 95% CI, 0.21 to 0.25), and then the addition of radiation to pPTR (HR, 0.41; 95% CI, 0.27 to 0.61). Exclusively undergoing chemotherapy (HR, 0.37; 95% CI, 0.34 to 0.41) led to a greater impact on OS compared to just receiving pPTR (HR, 0.55; 95% CI, 0.50 to 0.60). Correspondingly, the greatest CSS benefit was also observed in trimodality therapy (HR, 0.15; 95% CI, 0.13 to 0.18), followed by

addition of chemotherapy to pPTR (HR, 0.23; 95% CI, 0.21 to 0.25), then addition of radiation to pPTR (HR, 0.41; 95% CI, 0.27 to 0.62). Receiving chemotherapy alone (HR, 0.37; 95% CI, 0.34 to 0.41) led to a better effect on CSS than pPTR alone (HR, 0.53; 95% CI, 0.48 to 0.59). However, there were no statistically significant differences in OS as well as CSS between the addition of radiation to pPTR and chemotherapy or exclusively performing pPTR. There were also nonsignificant survival benefits for radiation therapy alone, and chemoradiation therapy due to a lower sample size within these subgroups.

4. Discussion

At the time of diagnosis, a substantial percentage of CRC patients present with unresectable distant synchronous metastases, but the optimal management for these patients still remains debated due to their high heterogeneities and the fact that urgent surgical interventions are only recommended to primary tumor–related complications according to the aforementioned current treatment guidelines [9, 22]. This study analyzed the survival outcomes of administration of pPTR to CRC patients with synchronous liver and/or lung metastases using the SEER database. It was discovered that remarkable improvements were observed in survival in patients undergoing pPTR. After adjusting these variables in the multivariable analysis, our research proved that surgery and chemotherapy were independently associated with improved survival while primary tumor location and metastatic patterns also correlated with the prognosis. In addition, stratified analysis revealed that surgery-based multimodality therapy was associated with better survival.

Our results indicated that the median OS and median CSS have been prolonged to nearly 2 years in patients who underwent pPTR. However, currently, there is still no reported randomized control trial comparing treatment with pPTR versus systemic chemotherapy due to poor recruiting, and hence clinical trial evidence for this recommendation is limited. Several retrospective analyses of clinical trials and literature reviews have shown that pPTR in synchronous mCRC patients may lead to survival benefits [23-25]. Similar survival benefits have been reported in randomized control trials by removing primary renal [26, 27] and ovarian tumors [28] in the presence of metastatic disease, but it is unclear whether these results can be applied directly to CRC patients. Recently, the mechanism through which survival time might be prolonged in mCRC patients undergoing pPTR remains uncertain. Recent researches conclude that the presence of the primary tumor is associated with higher levels of circulating tumor cells (CTCs) leading to micrometastases which finally progress to become macrometastases, such as liver metastasis, lung metastasis and so on [29, 30]. Consequently, reducing CTCs by pPTR may possibly prolong the survival time [19]. Based on current epidemiological findings, some researchers suggested that all distant metastases were initiated before excision of the primary tumor and that metastases themselves did not metastasize again [31, 32]. Also, some previous researches discovered that primary tumor resection was associated with recovery of the immune system, leading to survival improvement [19, 33]. Patients

with mCRC were often observed with elevated neutrophil-lymphocyte ratio, as one of the markers of systemic inflammation [34-36]. Compared to local tumor inflammation, systemic inflammation is associated with enhanced tumor growth and survival, possibly caused by T cell anergy and loss of cytotoxicity [37, 38]. It is supposed that pPTR could probably reverse systemic inflammation and restore the immune function [33, 39]. Furthermore, some studies equally found that the addition of chemotherapy to pPTR was associated with better survival, which may be attributed to a better response to chemotherapy after reduction of systemic tumor burden [40].

Previous research projects discovered that mCRC patients with a left-sided primary tumor carry a better prognosis than patients with tumors originating on the right side, but afterwards this phenomenon was found to be linked to treatment response [11, 41]. In agreement with the previous studies, in this study, subgroup analysis pointed out that regardless of whether therapy was initiated or not, compared to patients with right-sided primary colon tumors, those with rectum tumors led to greatest survival, followed by those with left-sided colon tumors. Many other studies also concluded that in the RAS wild-type mCRC populations, first-line therapies clearly benefited patients with left-sided tumors, whereas patients with right-sided tumors derived limited benefits from standard treatments [42, 43]. Some studies supposed that due to these differences in embryological origin, left-sided and right-sided tumors possess unique gene expression profiles [44]. Therefore, we supposed that in terms of mCRC patients without response to systematic therapies, such as these patients with right-sided tumors, may relatively benefit from pPTR.

Some studies demonstrated that some variability of mCRC patients in survival existed dependent on the site of metastases and the number of sites involved [45, 46]. In this study, subgroup analysis indicated that regardless of undergoing treatments or not, mCRC patients with lung-only metastases were associated with the greatest survival, followed by those with liver-only metastases and then liver and lung-only metastases. Previous epidemiologic research also suggested that compared to colon cancer patients, patients with rectal primaries were more likely to present with lung metastases and less likely to present with liver metastases at the time of diagnosis [47]. This observation is consistent with what we reported that mCRC patients with rectum tumors benefited greatest survival.

The best survival outcomes in the treatment of mCRC patients have been achieved with surgery-based trimodality therapy. Being consistent with previous studies, our study found that the median survival of patients undergoing trimodality therapy nearly approached to 36 months. In subgroup analyses, surgery-based trimodality therapy exhibited the best long-term survival, followed by pPTR in combination with chemotherapy. Adan Z. Becerra et al. noticed that addition of chemotherapy to pPTR was superior to administering exclusively pPTR or chemotherapy at 1, 3, and 5 years [48]. Some previous studies also demonstrated that among mCRC patients, pPTR in conjunction with postoperative chemotherapy may grant better survival improvement over pPTR alone or chemotherapy alone [48, 49].

There are several limitations to this study. First, given its retrospective nature, despite the conduction of PSM analysis in this study, there may be unobserved

confounders not addressed in the propensity matching. Foremost of these unobserved covariates may be that patients who are suitable to undergo pPTR or surgery-based trimodality therapy may be inherently different from those who are not. Nevertheless, only an intention-to-treat analysis in the setting of a randomized control trial can adequately address selection bias. Secondly, in the SEER database, there is lack of information on chemotherapeutic drugs or radiation dose used and likewise, information about comorbidities, performance status, as well as site and number of metastases are not disclosed. The types of surgery were simplified, and classifications including local excision, partial removal, total resection, radical surgery and not otherwise specified could not fully reflect the details of these surgical procedures. Thirdly, it is not certain whether the primary tumor was truly asymptomatic from the SEER database. To which extent these factors might have affected the selection of patients undergoing pPTR remains unclear. Therefore, further studies especially for randomized control trials are needed to verify our findings.

5. Conclusions

Among these carefully selected patients, surgery-based multimodality therapy was associated with better survival compared to administering exclusively chemotherapy or pPTR.

Conflict of interest

No conflicts of interest.

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Tables

Table 1. Patient characteristics in the unmatched cohort

Variable	Non-surgery	Surgery	p
All participants	12356(100.0%)	9049(100.0%)	
Insurance			0.145
Insured	11490(93.0%)	8475(93.7%)	
Uninsured	651(5.3%)	437(4.8%)	
Unknown	215(1.7%)	137(1.5%)	
Marital status			<0.001
Married	5875(47.5%)	4816(53.2%)	
Single	2790(22.6%)	1721(19.0%)	
Divorced/Widowed/ Separated	3041(24.6%)	2107(23.3%)	
Unknown	650(5.3%)	405(4.5%)	
Age			0.014
<60	4905(39.7%)	3743(41.4%)	
>=60	7451(60.3%)	5306(58.6%)	
Race			0.006
White	9109(73.7%)	6773(74.8%)	
Black	2039(16.5%)	1368(15.1%)	
Asian or Pacific Islander	1044(8.4%)	818(9.0%)	
American Indian/Alaska Native	128(1.0%)	67(0.7%)	
Unknown	36(0.3%)	23(0.3%)	
Gender			0.052
Male	7029(56.9%)	5027(55.6%)	
Female	5327(43.1%)	4022(44.4%)	
Year of diagnosis			<0.001
2010	1416(11.5%)	1426(15.8%)	
2011	1598(12.9%)	1384(15.3%)	
2012	1646(13.3%)	1330(14.7%)	
2013	1746(14.1%)	1336(14.8%)	
2014	1937(15.7%)	1246(13.8%)	
2015	2053(16.6%)	1196(13.2%)	
2016	1960(15.9%)	1131(12.5%)	
Primary site			<0.001
Right-sided	3321(26.9%)	3992(44.1%)	
Left-sided	2844(23.0%)	3017(33.3%)	
Rectum	4988(40.4%)	1795(19.8%)	
Unknown	1203(9.7%)	245(2.7%)	

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Variable	Non-surgery	Surgery	P
Grade			<0.001
I/II	5562(45.0%)	6188(68.4%)	
III/IV	1654(13.4%)	2445(27.0%)	
Unknown	5140(41.6%)	416(4.6%)	
Adenocarcinoma			<0.001
YES	11555(93.5%)	8756(96.8%)	
NO	523(4.2%)	244(2.7%)	
Unknown	278(2.2%)	49(0.5%)	
Tumor size			<0.001
<5cm	2021(16.4%)	3597(39.8%)	
>=5cm	3299(26.7%)	4850(53.6%)	
Unknown	7036(56.9%)	602(6.7%)	
Preoperative CEA			<0.001
Positive	8067(65.3%)	4978(55.0%)	
Negative	888(7.2%)	1200(13.3%)	
Unknown	3401(27.5%)	2871(31.7%)	
Synchronous metastases patterns			<0.001
Only liver metastases	6798(55.0%)	6638(73.4%)	
Only lung metastases	979(7.9%)	779(8.6%)	
Only liver and lung metastases	3151(25.5%)	1223(13.5%)	
Liver metastases combined with other metastases outside the lung	493(4.0%)	155(1.7%)	
Lung metastases combined with other metastases outside the liver	145(1.2%)	41(0.5%)	
Liver and lung metastases combined with other metastases	543(4.4%)	109(1.2%)	
Liver metastases combined with unknown metastases outside the lung	98(0.8%)	52(0.6%)	
Lung metastases combined with unknown metastases outside the liver	12(0.1%)	11(0.1%)	
Liver and lung metastases combined with unknown other metastases	137(1.1%)	41(0.5%)	

Note: $\chi 2$ statistics were used to compare patient and tumor characteristics in the unmatched cohort. Two-tailed P-values < 0.05 were assessed as statistically significant.

Table 2. Patient characteristics in the propensity score matched cohort

Variable	Non-surgery	Surgery	P
All participants	3693(100.0%)	3693(100.0%)	
Insurance			0.994
Insured	3452(93.5%)	3452(93.5%)	
Uninsured	180(4.9%)	181(4.9%)	
Unknown	61(1.7%)	60(1.6%)	
Marital status			0.800
Married	1884(51.0%)	1862(50.4%)	
Single	753(20.4%)	765(20.7%)	
Divorced/Widowed/ Separated	873(23.6%)	866(23.4%)	
Unknown	183(5.0%)	200(5.4%)	
Age			0.173
<60	1610(43.6%)	1552(42.0%)	
>=60	2083(56.4%)	2141(58.0%)	
Race			0.930
White	2763(74.8%)	2768(75.0%)	
Black	559(15.1%)	541(14.6%)	
Asian or Pacific Islander	337(9.1%)	344(9.3%)	
American Indian/Alaska Native	27(0.7%)	32(0.9%)	
Unknown	7(0.2%)	8(0.2%)	
Gender			0.211
Male	2182(59.1%)	2129(57.6%)	
Female	1511(40.9%)	1564(42.4%)	
Year of diagnosis			0.791
2010	454(12.3%)	451(12.2%)	
2011	501(13.6%)	493(13.3%)	
2012	519(14.1%)	509(13.8%)	
2013	535(14.5%)	533(14.4%)	
2014	546(14.8%)	595(16.1%)	
2015	593(16.1%)	597(16.2%)	
2016	545(14.8%)	515(13.9%)	
Primary site			0.533
Right-sided	1149(31.1%)	1203(32.6%)	
Left-sided	966(26.2%)	951(25.8%)	
Rectum	1431(38.7%)	1405(38.0%)	
Unknown	147(4.0%)	134(3.6%)	

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Variable	Non-surgery	Surgery	P
Grade			0.378
I/II	2481(67.2%)	2476(67.0%)	
III/IV	765(20.7%)	801(21.7%)	
Unknown	447(12.1%)	416(11.3%)	
Adenocarcinoma			0.373
YES	3504(94.9%)	3515(95.2%)	
NO	139(3.8%)	141(3.8%)	
Unknown	50(1.4%)	37(1.0%)	
Tumor size			0.735
<5cm	1208(32.7%)	1215(32.9%)	
>=5cm	1858(50.3%)	1876(50.8%)	
Unknown	627(17.0%)	602(16.3%)	
Preoperative CEA			0.812
Positive	2324(62.9%)	2335(63.2%)	
Negative	396(10.7%)	379 (10.3%)	
Unknown	973(26.3%)	979(26.5%)	
Synchronous metastases patterns			0.994
Only liver metastases	2320(62.8%)	2300(62.3%)	
Only lung metastases	346(9.4%)	340(9.2%)	
Only liver and lung metastases	751(20.3%)	763(20.7%)	
Liver metastases combined with metastases outside the lung	105(2.8%)	112(3.0%)	
Lung metastases combined with metastases outside the liver	24(0.6%)	27(0.7%)	
Liver and lung metastases combined with other metastases	91(2.5%)	96(2.6%)	
Liver metastases combined with unknown metastases outside the lung	22(0.6%)	19(0.5%)	
Lung metastases combined with unknown metastases outside the liver	4(0.1%)	6(0.2%)	
Liver and lung metastases combined with unknown other metastases	30(0.8%)	30(0.8%)	

Note: $\chi 2$ statistics were used to compare patient and tumor characteristics in the matched cohort. Two-tailed P-values < 0.05 were assessed as statistically significant.

Table 3. Prognostic factors for overall survival

Variable	Univariable			Multivariable		
	Crude HR	95% CI	P	Adjusted HR	95% CI	P
Insurance						
Insured	[reference]					
Uninsured	1.018	0.897 to 1.156	0.778			
Unknown	1.097	0.895 to 1.344	0.372			
Marital status						
Married	[reference]			[reference]		
Single	1.168	1.087 to 1.256	<0.001	1.143	1.062 to 1.230	<0.001
Divorced/Widowed/ Separated	1.345	1.258 to 1.438	<0.001	1.173	1.096 to 1.256	<0.001
Unknown	0.950	0.835 to 1.081	0.440	0.960	0.843 to 1.093	0.535
Age						
<60	[reference]			[reference]		
>=60	1.469	1.389 to 1.555	<0.001	1.303	1.228 to 1.383	<0.001
Race						
White	[reference]			[reference]		
Black	1.185	1.099 to 1.278	<0.001	1.098	1.017 to 1.187	0.017
Asian or Pacific Islander	0.963	0.872 to 1.062	0.447	0.887	0.803 to 0.980	0.018
American Indian/Alaska Native	0.947	0.682 to 1.315	0.744	0.896	0.645 to 1.246	0.515
Unknown	0.408	0.153 to 1.087	0.073	0.529	0.198 to 1.411	0.203
Gender						
Male	[reference]					
Female	1.111	1.051 to 1.174	<0.001			
Primary site						
Right-sided	[reference]			[reference]		
Left-sided	0.718	0.668 to 0.771	<0.001	0.772	0.718 to 0.831	<0.001
Rectum	0.566	0.530 to 0.605	<0.001	0.671	0.625 to 0.720	<0.001
Unknown	1.009	0.875 to 1.163	0.905	1.048	0.905 to 1.215	0.529
Grade						
I/II	[reference]			[reference]		
III/IV	1.765	1.653 to 1.885	<0.001	1.770	1.655 to 1.893	<0.001
Unknown	1.122	1.029 to 1.223	0.009	1.067	0.972 to 1.170	0.174
Adenocarcinoma						
No	[reference]			[reference]		
Yes	0.758	0.660 to 0.871	<0.001	1.050	0.906 to 1.216	0.521
Unknown	1.382	1.053 to 1.815	0.020	1.576	1.191 to 2.087	0.001

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Variable	Univariable			Multivariable		
	Crude HR	95% CI	P	Adjusted HR	95% CI	P
Tumor size						
<5cm	[reference]			[reference]		
>=5cm	1.183	1.112 to 1.259	<0.001	1.218	1.144 to 1.296	<0.001
Unknown	1.076	0.990 to 1.169	0.086	1.069	0.981 to 1.166	0.128
Preoperative CEA						
Positive	[reference]					
Negative	0.756	0.686 to 0.833	<0.001	0.746	0.676 to 0.823	<0.001
Unknown	1.034	0.971 to 1.101	0.298	0.915	0.856 to 0.978	0.009
Synchronous metastases patterns						
Only liver metastases	[reference]			[reference]		
Only lung metastases	0.817	0.737 to 0.906	<0.001	0.814	0.733 to 0.905	<0.001
Only liver and lung metastases	1.344	1.256 to 1.439	<0.001	1.346	1.257 to 1.442	<0.001
Liver metastases combined with other metastases outside the lung	1.775	1.526 to 2.065	<0.001	1.844	1.583 to 2.147	<0.001
Lung metastases combined with other metastases outside the liver	1.732	1.273 to 2.358	<0.001	1.697	1.245 to 2.313	0.001
Liver and lung metastases combined with other metastases	1.977	1.686 to 2.318	<0.001	1.992	1.696 to 2.339	<0.001
Liver metastases combined with unknown metastases outside the lung	1.246	0.880 to 1.766	0.216	0.926	0.653 to 1.313	0.666
Lung metastases combined with unknown metastases outside the liver	1.332	0.554 to 3.204	0.522	1.412	0.585 to 3.406	0.443
Liver and lung metastases combined with unknown other metastases	1.819	1.386 to 2.387	<0.001	1.556	1.185 to 2.043	0.001
Surgery						
No	[reference]			[reference]		
Yes	0.588	0.556 to 0.621	<0.001	0.531	0.501 to 0.563	<0.001
Radiation						
No	[reference]			[reference]		
Yes	0.451	0.399 to 0.510	<0.001	0.871	0.762 to 0.995	0.043
Chemotherapy						
No	[reference]			[reference]		
Yes	0.399	0.376 to 0.424	<0.001	0.407	0.382 to 0.434	<0.001

Note: In the matched population, univariable and multivariable Cox proportional hazards regression models were performed to identify the independent prognostic factors for colorectal cancer patients with synchronous liver and/or lung metastases. Values are expressed as HR with 95% CI unless otherwise indicated. Two-sided P-values < 0.05 were assessed as statistically significant.

Abbreviation: HR, hazard ratio.

Table 4. Prognostic factors for cancer-specific survival

Variable	Univariable			Multivariable		
	Crude HR	95% CI	P	Adjusted HR	95% CI	P
Insurance						
Insured	[reference]					
Uninsured	1.043	0.917 to 1.186	0.522			
Unknown	1.070	0.867 to 1.322	0.528			
Marital status						
Married	[reference]			[reference]		
Single	1.161	1.078 to 1.250	<0.001	1.136	1.053 to 1.225	0.001
Divorced/Widowed/ Separated	1.325	1.237 to 1.420	<0.001	1.159	1.081 to 1.243	<0.001
Unknown	0.936	0.819 to 1.069	0.328	0.947	0.829 to 1.083	0.429
Age						
<60	[reference]			[reference]		
>=60	1.439	1.358 to 1.524	<0.001	1.281	1.205 to 1.361	<0.001
Race						
White	[reference]			[reference]		
Black	1.188	1.100 to 1.284	<0.001	1.104	1.020 to 1.195	0.014
Asian or Pacific Islander	0.959	0.867 to 1.061	0.413	0.885	0.799 to 0.980	0.019
American Indian/Alaska Native	0.996	0.717 to 1.384	0.983	0.947	0.681 to 1.316	0.745
Unknown	0.430	0.161 to 1.146	0.092	0.561	0.210 to 1.496	0.248
Gender						
Male	[reference]					
Female	1.122	1.060 to 1.188	<0.001			
Primary site						
Right-sided	[reference]			[reference]		
Left-sided	0.724	0.673 to 0.779	<0.001	0.774	0.718 to 0.835	<0.001
Rectum	0.566	0.529 to 0.606	<0.001	0.660	0.615 to 0.709	<0.001
Unknown	1.030	0.891 to 1.191	0.686	1.069	0.920 to 1.243	0.381
Grade						
I/II	[reference]			[reference]		
III/IV	1.799	1.682 to 1.924	<0.001	1.808	1.689 to 1.937	<0.001
Unknown	1.142	1.045 to 1.247	0.003	1.078	0.980 to 1.185	0.121
Adenocarcinoma						
No	[reference]			[reference]		
Yes	0.763	0.661 to 0.880	<0.001	1.060	0.911 to 1.234	0.450
Unknown	1.403	1.062 to 1.885	0.017	1.601	1.201 to 2.134	0.001

(continued on following page)

Variable	Univariable			Multivariable		
	Crude HR	95% CI	P	Adjusted HR	95% CI	P
Tumor size						
<5cm	[reference]			[reference]		
>=5cm	1.179	1.107 to 1.257	<0.001	1.217	1.142 to 1.298	<0.001
Unknown	1.085	0.997 to 1.182	0.060	1.073	0.983 to 1.172	0.115
Preoperative CEA						
Positive	[reference]					
Negative	0.749	0.679 to 0.828	<0.001	0.739	0.668 to 0.817	<0.001
Unknown	1.027	0.963 to 1.095	0.418	0.912	0.851 to 0.976	0.008
Synchronous metastases patterns						
Only liver metastases	[reference]			[reference]		
Only lung metastases	0.801	0.719 to 0.891	<0.001	0.797	0.715 to 0.889	<0.001
Only liver and lung metastases	1.347	1.257 to 1.444	<0.001	1.353	1.261 to 1.451	<0.001
Liver metastases combined with metastases outside the lung	1.786	1.530 to 2.085	<0.001	1.841	1.576 to 2.152	<0.001
Lung metastases combined with metastases outside the liver	1.737	1.266 to 2.383	0.001	1.675	1.220 to 2.300	0.001
Liver and lung metastases combined with other metastases	2.017	1.716 to 2.372	<0.001	2.001	1.700 to 2.355	<0.001
Liver metastases combined with unknown metastases outside the lung	1.269	0.891 to 1.808	0.187	0.943	0.661 to 1.344	0.745
Lung metastases combined with unknown metastases outside the liver	1.123	0.421 to 2.995	0.817	1.209	0.452 to 3.235	0.705
Liver and lung metastases combined with unknown other metastases	1.806	1.366 to 2.389	<0.001	1.551	1.172 to 2.053	0.002
Surgery						
No	[reference]			[reference]		
Yes	0.582	0.550 to 0.616	<0.001	0.516	0.487 to 0.547	<0.001
Radiation						
No	[reference]					
Yes	0.457	0.403 to 0.518	<0.001			
Chemotherapy						
No	[reference]			[reference]		
Yes	0.401	0.377 to 0.427	<0.001	0.403	0.378 to 0.430	<.0001

Note: In the matched population, univariable and multivariable Cox proportional hazards regression models were performed to identify the independent prognostic factors for colorectal cancer patients with synchronous liver and/or lung metastases. Values are expressed as HR with 95% CI unless otherwise indicated. Two-sided P-values < 0.05 were assessed as statistically significant.

Abbreviation: HR, hazard ratio.

Figure legends

Figure 1. Flow chart illustrating patients selection.

Figure 2. Standardized differences before and after the match.

Figure 3. Propensity-matched analysis of synchronous liver and/or lung metastatic colorectal cancer. Mirror histograms. (A) Before match. (B) After match.

Figure 4. Kaplan-Meier-curves for overall and cancer-specific survival in patients with and without primary cancer resection. Life tables for patients at risk are given below each plot. (A) Overall survival. (B) Cancer-specific survival.

Figure 5. Kaplan-Meier-curves for overall and cancer-specific survival in patients with and without primary cancer resection stratified based on primary site. Life tables for patients at risk are given below each plot. (A) Right-sided, Overall survival. (B) Right-sided, Cancer-specific survival. (C) Left-sided, Overall survival. (D) Left-sided, Cancer-specific survival. (E), Rectum, Overall survival. (F) Rectum, Cancer-specific survival.

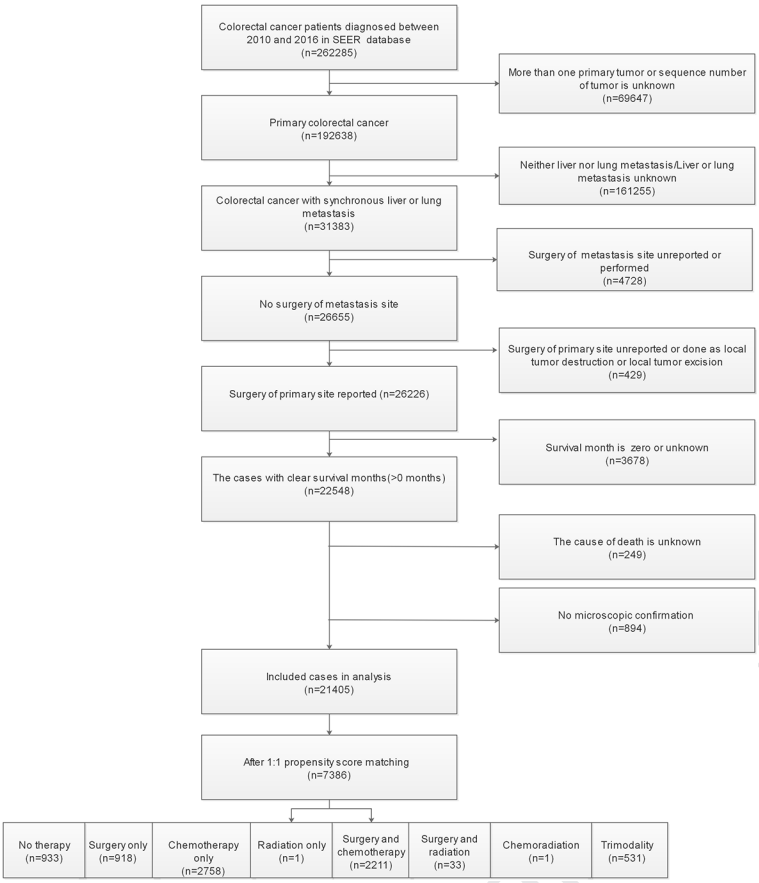
Figure 6. Kaplan-Meier-curves for overall and cancer-specific survival in patients with and without primary cancer resection stratified by synchronous metastases patterns. Life tables for patients at risk are given below each plot. (A) Only liver metastases, Overall survival. (B) Only liver metastases, Cancer-specific survival. (C) Only lung metastases, Overall survival. (D) Only lung metastases, Cancer-specific survival. (E) Only liver and lung metastases, Overall survival. (F) Only liver and lung metastases, Cancer-specific survival. (G) Liver metastases combined with other metastases outside the lung, Overall survival. (H) Liver metastases combined with other metastases outside the lung, Cancer-specific survival. (I) Lung metastases combined with other metastases outside the liver, Overall survival. (J) Lung metastases combined with other metastases outside the liver, Cancer-specific survival. (K) Liver and lung metastases combined with other metastases, Overall survival. (L) Liver and lung metastases combined with other metastases, Cancer-specific survival. (M) Liver metastases combined with unknown metastases outside the lung, Overall survival. (N) Liver metastases combined with unknown metastases outside the lung, Cancer-specific survival. (O) Lung metastases combined with unknown metastases outside the liver, Overall survival. (P) Lung metastases combined with unknown metastases outside the liver, Cancer-specific survival. (Q) Liver and lung metastases combined with unknown other metastases, Overall survival. (R) Liver and lung metastases combined with other unknown metastases, Cancer-specific survival.

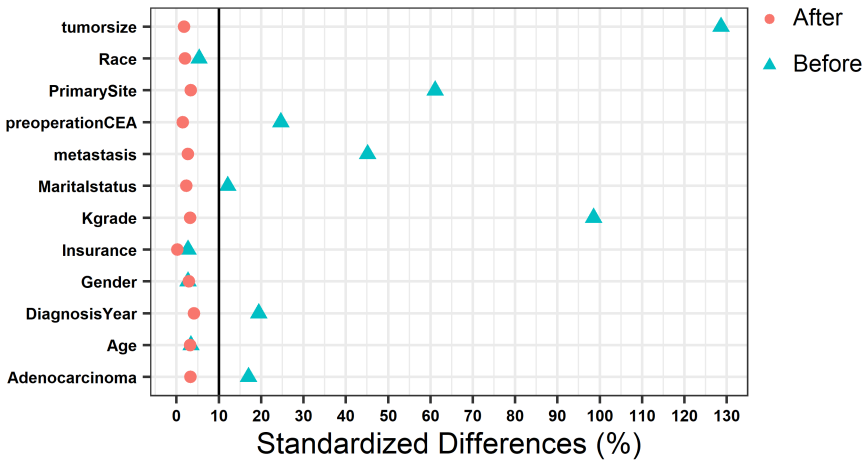
Figure 7. Kaplan-Meier-curves for overall and cancer-specific survival in patients

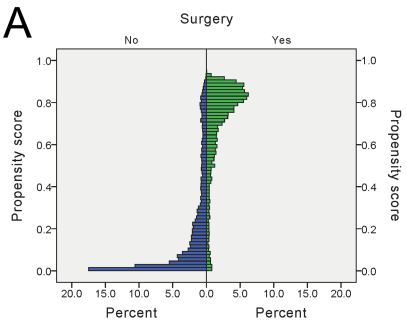
with and without primary cancer resection stratified by treatment. Life tables for patients at risk are given below each plot. (A) Overall survival. (B) Cancer-specific survival.

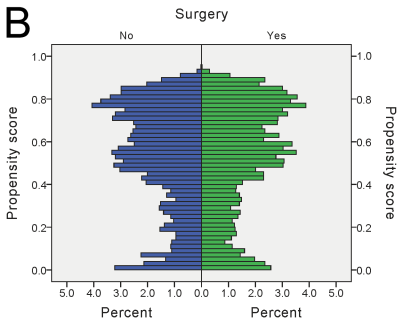
Figure 8. Subgroup analysis of primary site and synchronous metastatic patterns. (A) Based on overall survival. (B) Based on cancer-specific survival.

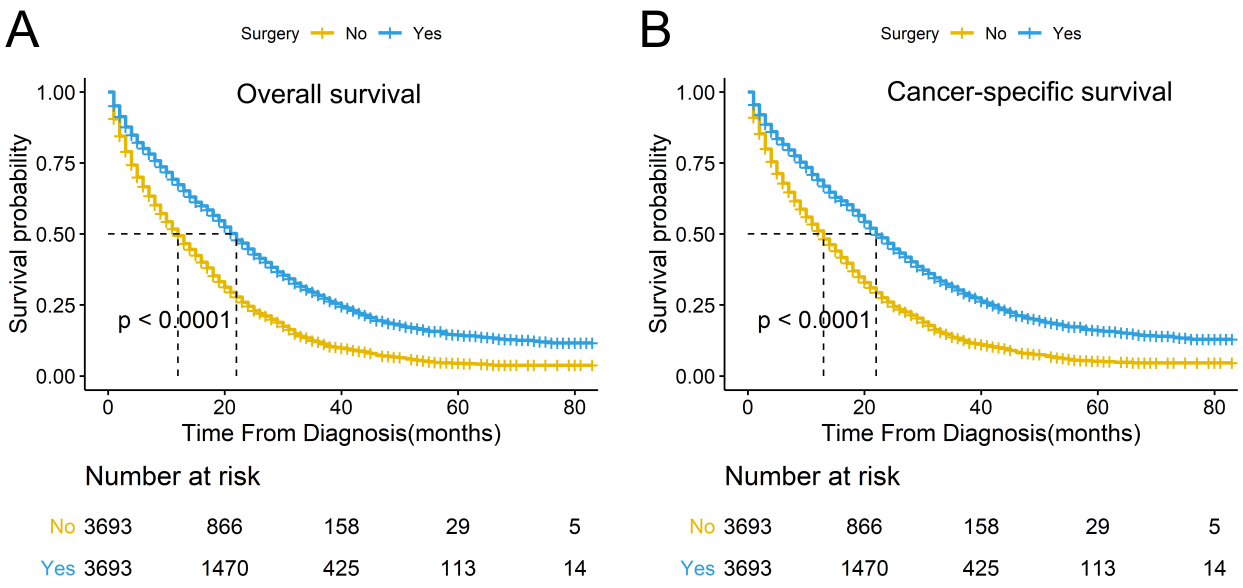
Figure 9. Subgroup analysis of treatment modalities. (A) Based on overall survival. (B) Based on cancer-specific survival.

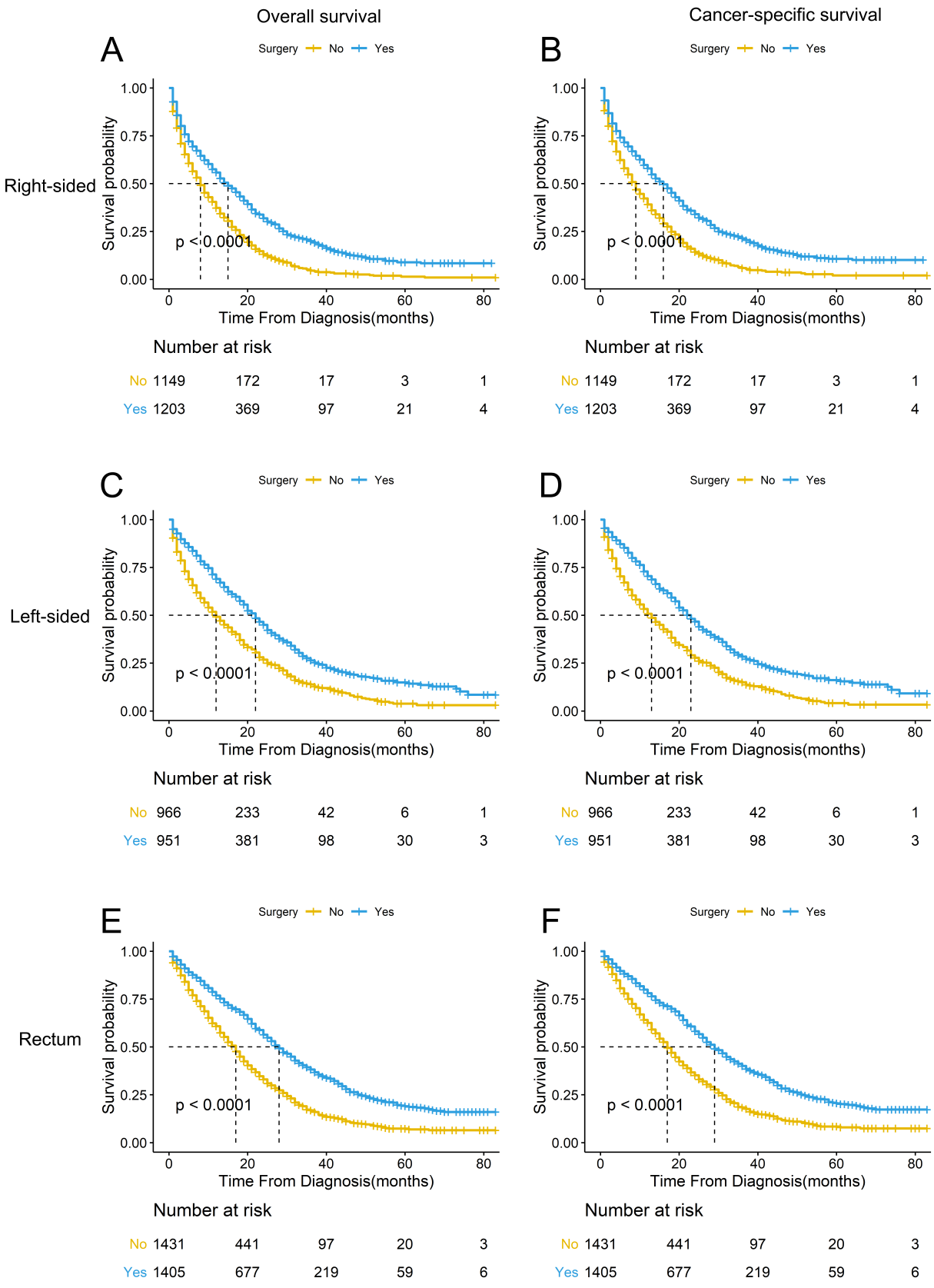




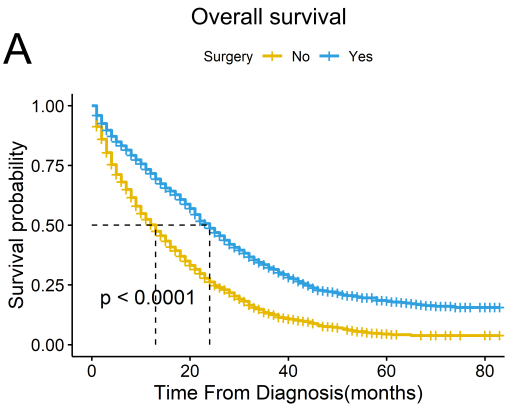






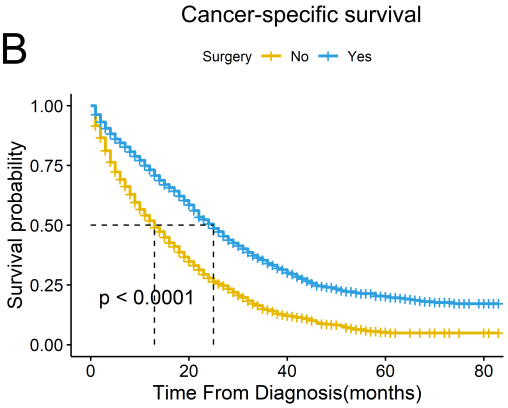

Overall survival
Cancer-specific survival
A
B
C
D
E
F
Right-sided
Left-sided
Rectum
Surgery No Yes
Survival probability
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0 20 40 60 80
Time From Diagnosis(months)
Number at risk
No 1149 172 17 3 1
Yes 1203 369 97 21 4
No 966 233 42 6 1
Yes 951 381 98 30 3
No 1431 441 97 20 3
Yes 1405 677 219 59 6

Only liver metastases



Number at risk

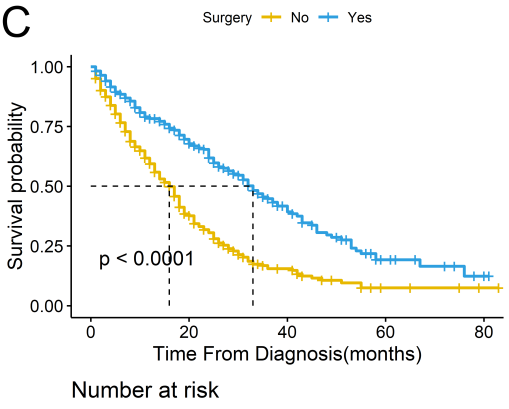
No	2320	566	103	16	4
Yes	2300	994	318	93	12



Number at risk

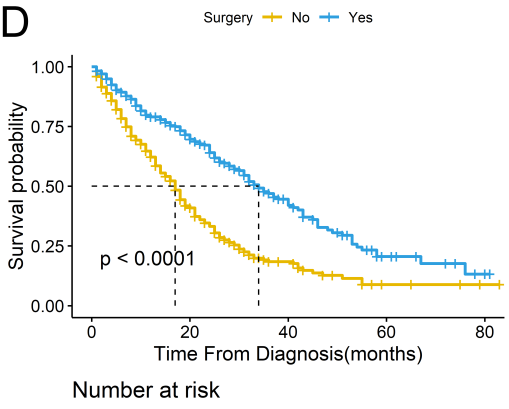
No	2320	566	103	16	4
Yes	2300	994	318	93	12

Only lung metastases



Number at risk

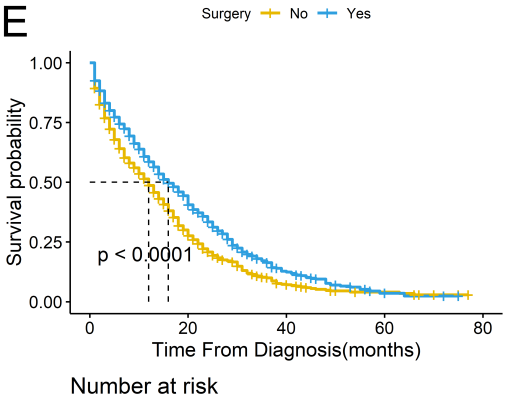
No	346	96	23	4	1
Yes	340	154	51	12	2



Number at risk

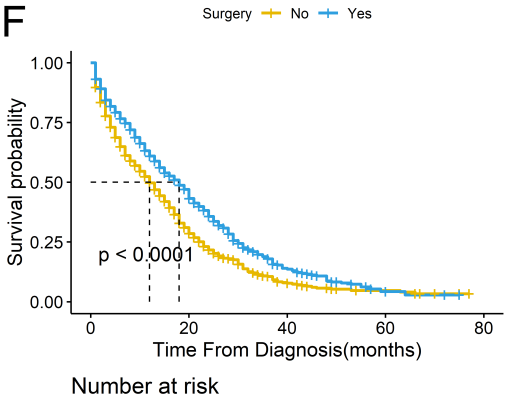
No	346	96	23	4	1
Yes	340	154	51	12	2

Only liver and lung metastases



Number at risk

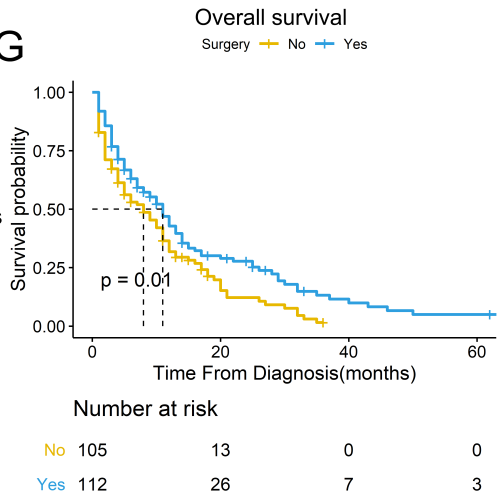
No	751	163	27	7	0
Yes	763	245	41	4	0

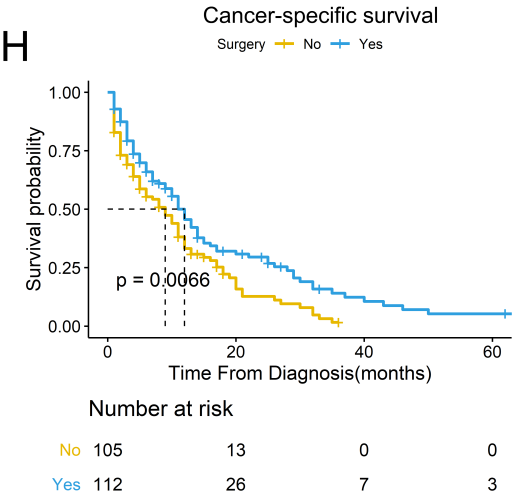


Number at risk

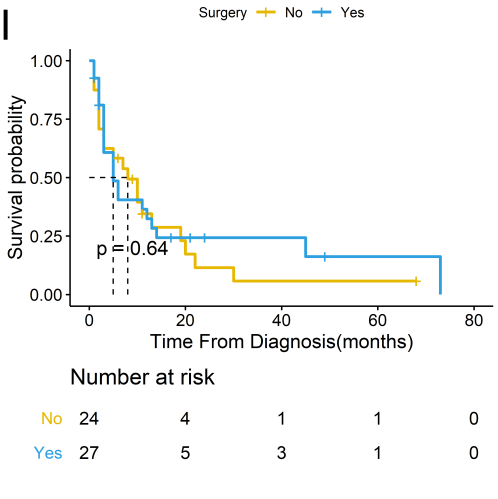
No	751	163	27	7	0
Yes	763	245	41	4	0

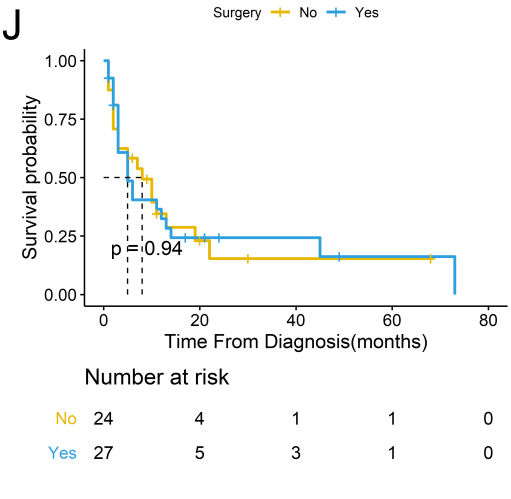
Liver metastases combined with other metastases outside the lung



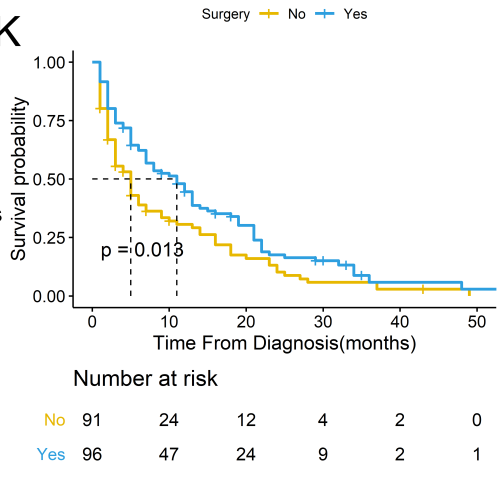


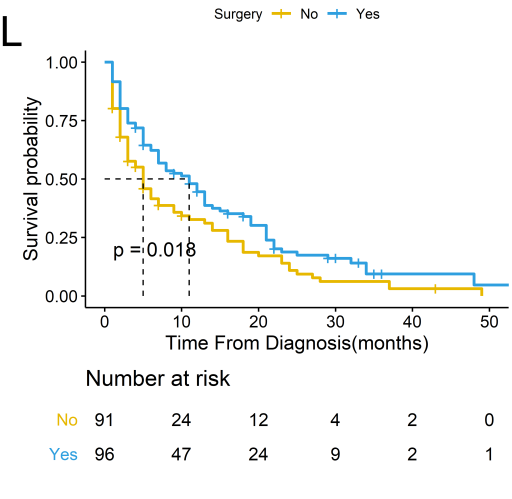
Lung metastases combined with other metastases outside the liver



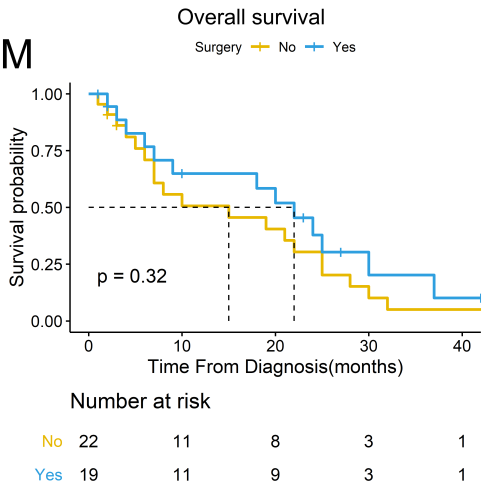


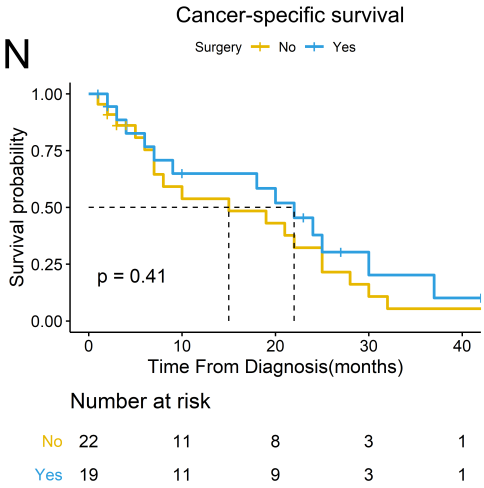
Liver and lung metastases combined with other metastases



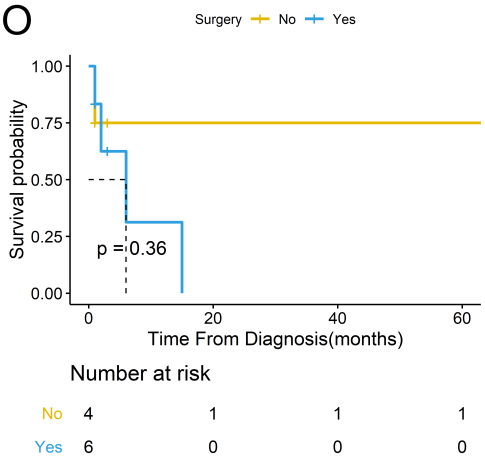


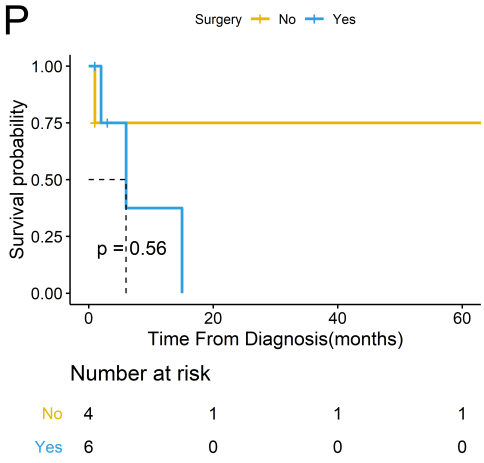
Liver metastases combined with unknown metastases outside the lung



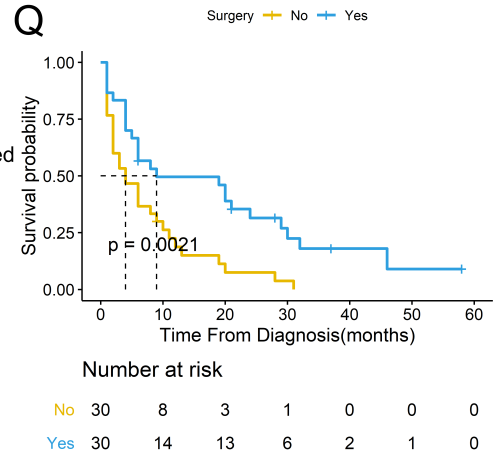


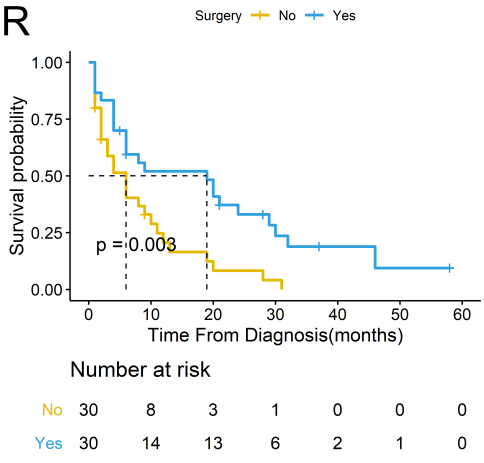
Lung metastases combined with unknown metastases outside the liver



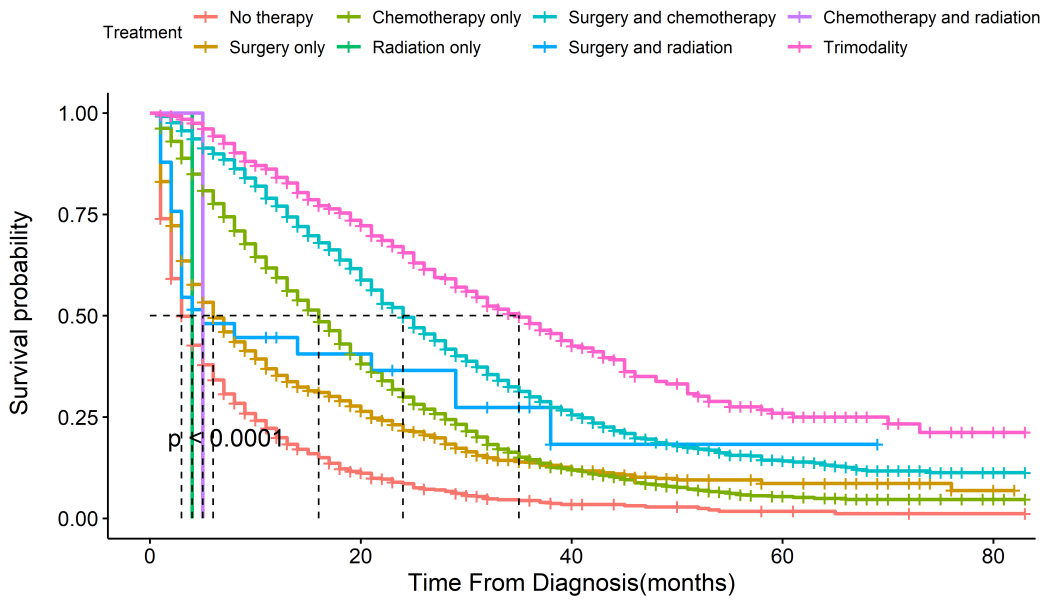


Liver and lung metastases combined with unknown other metastases





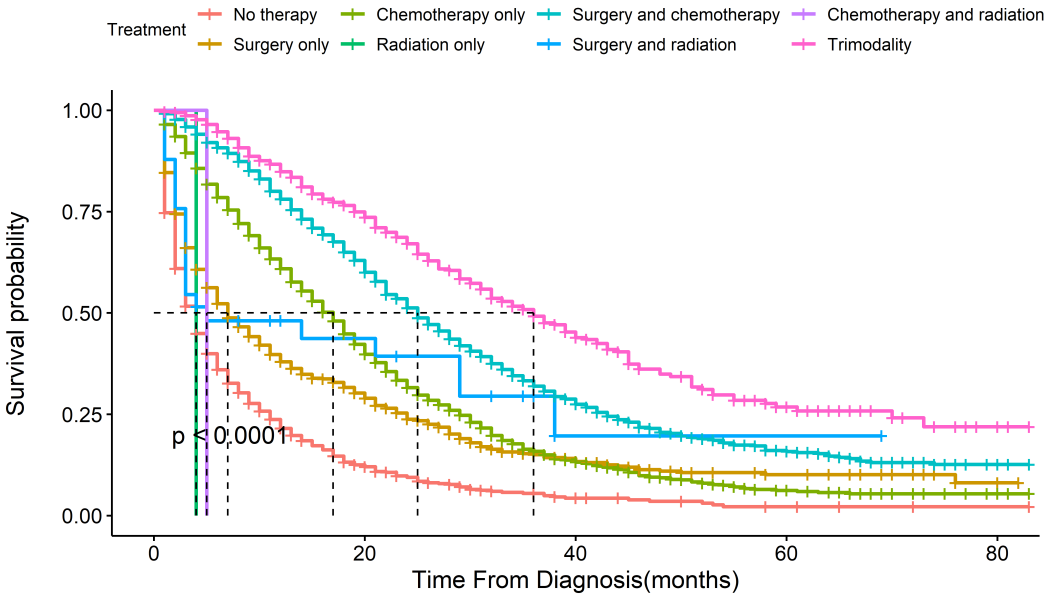
A



Number at risk

No therapy	933	76	14	4	1
Surgery only	917	189	56	16	2
Chemotherapy only	2758	790	144	25	4
Radiation only	1	0	0	0	0
Surgery and chemotherapy	2211	994	270	67	9
Surgery and radiation	33	10	1	1	0
Chemotherapy and radiation	1	0	0	0	0
Trimodality	531	277	98	29	3

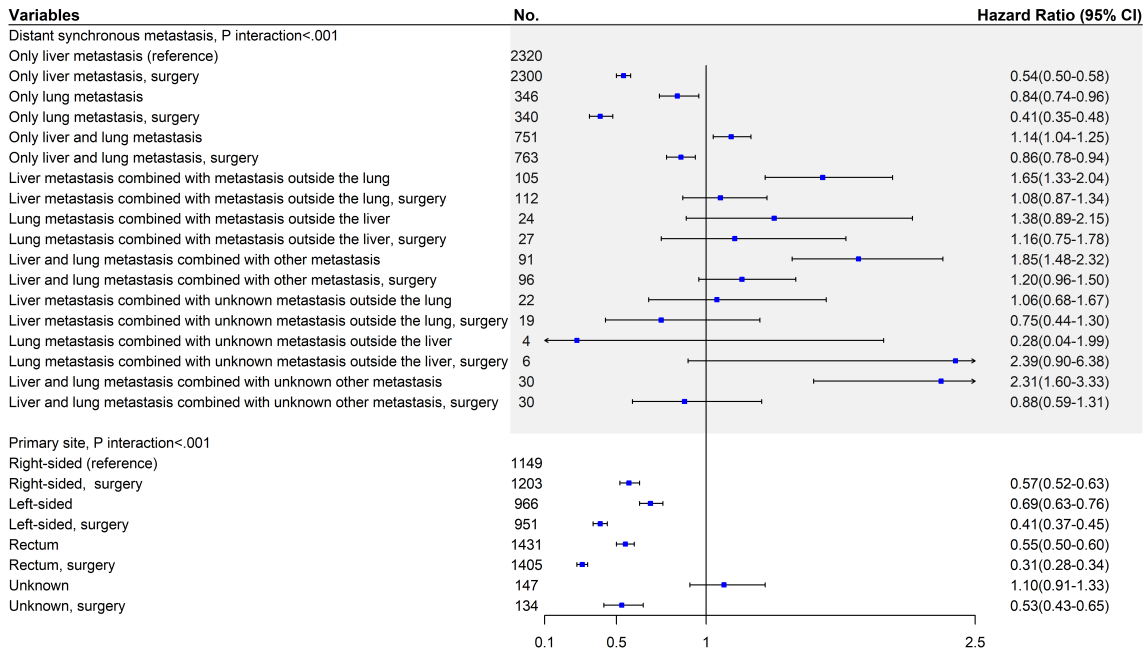
B



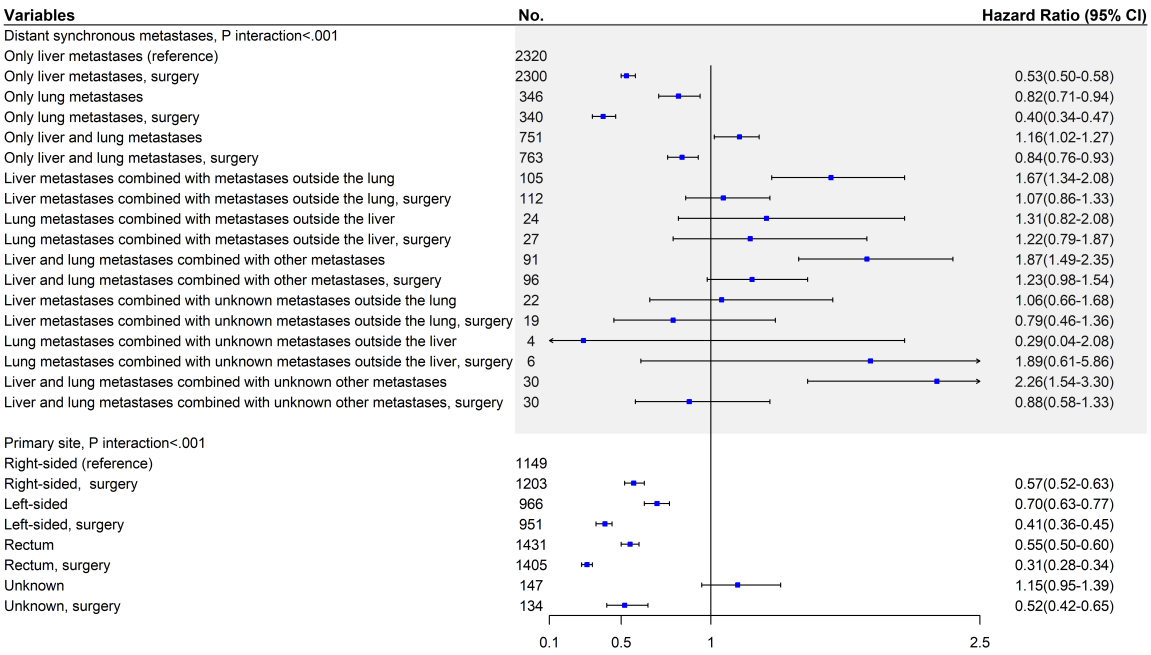
Number at risk

No therapy	933	76	14	4	1
Surgery only	917	189	56	16	2
Chemotherapy only	2758	790	144	25	4
Radiation only	1	0	0	0	0
Surgery and chemotherapy	2211	994	270	67	9
Surgery and radiation	33	10	1	1	0
Chemotherapy and radiation	1	0	0	0	0
Trimodality	531	277	98	29	3

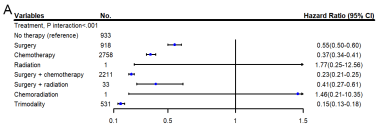
A


Variables
No.
Hazard Ratio (95% CI)
Distant synchronous metastasis, P interaction<.001
Only liver metastasis (reference) 2320
Only liver metastasis, surgery 2300 0.54(0.50-0.58)
Only lung metastasis 346 0.84(0.74-0.96)
Only lung metastasis, surgery 340 0.41(0.35-0.48)
Only liver and lung metastasis 751 1.14(1.04-1.25)
Only liver and lung metastasis, surgery 763 0.86(0.78-0.94)
Liver metastasis combined with metastasis outside the lung 105 1.65(1.33-2.04)
Liver metastasis combined with metastasis outside the lung, surgery 112 1.08(0.87-1.34)
Lung metastasis combined with metastasis outside the liver 24 1.38(0.89-2.15)
Lung metastasis combined with metastasis outside the liver, surgery 27 1.16(0.75-1.78)
Liver and lung metastasis combined with other metastasis 91 1.85(1.48-2.32)
Liver and lung metastasis combined with other metastasis, surgery 96 1.20(0.96-1.50)
Liver metastasis combined with unknown metastasis outside the lung 22 1.06(0.68-1.67)
Liver metastasis combined with unknown metastasis outside the lung, surgery 19 0.75(0.44-1.30)
Lung metastasis combined with unknown metastasis outside the liver 4 0.28(0.04-1.99)
Lung metastasis combined with unknown metastasis outside the liver, surgery 6 2.39(0.90-6.38)
Liver and lung metastasis combined with unknown other metastasis 30 2.31(1.60-3.33)
Liver and lung metastasis combined with unknown other metastasis, surgery 30 0.88(0.59-1.31)
Primary site, P interaction<.001
Right-sided (reference) 1149
Right-sided, surgery 1203 0.57(0.52-0.63)
Left-sided 966 0.69(0.63-0.76)
Left-sided, surgery 951 0.41(0.37-0.45)
Rectum 1431 0.55(0.50-0.60)
Rectum, surgery 1405 0.31(0.28-0.34)
Unknown 147 1.10(0.91-1.33)
Unknown, surgery 134 0.53(0.43-0.65)
0.1
0.5
1
2.5

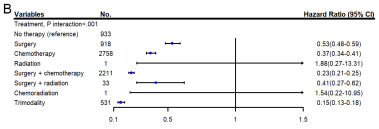
B


Variables
No.
Hazard Ratio (95% CI)
Distant synchronous metastases, P interaction<.001
Only liver metastases (reference) 2320
Only liver metastases, surgery 2300 0.53(0.50-0.58)
Only lung metastases 346 0.82(0.71-0.94)
Only lung metastases, surgery 340 0.40(0.34-0.47)
Only liver and lung metastases 751 1.16(1.02-1.27)
Only liver and lung metastases, surgery 763 0.84(0.76-0.93)
Liver metastases combined with metastases outside the lung 105 1.67(1.34-2.08)
Liver metastases combined with metastases outside the lung, surgery 112 1.07(0.86-1.33)
Lung metastases combined with metastases outside the liver 24 1.31(0.82-2.08)
Lung metastases combined with metastases outside the liver, surgery 27 1.22(0.79-1.87)
Liver and lung metastases combined with other metastases 91 1.87(1.49-2.35)
Liver and lung metastases combined with other metastases, surgery 96 1.23(0.98-1.54)
Liver metastases combined with unknown metastases outside the lung 22 1.06(0.66-1.68)
Liver metastases combined with unknown metastases outside the lung, surgery 19 0.79(0.46-1.36)
Lung metastases combined with unknown metastases outside the liver 4 0.29(0.04-2.08)
Lung metastases combined with unknown metastases outside the liver, surgery 6 1.89(0.61-5.86)
Liver and lung metastases combined with unknown other metastases 30 2.26(1.54-3.30)
Liver and lung metastases combined with unknown other metastases, surgery 30 0.88(0.58-1.33)
Primary site, P interaction<.001
Right-sided (reference) 1149
Right-sided, surgery 1203 0.57(0.52-0.63)
Left-sided 966 0.70(0.63-0.77)
Left-sided, surgery 951 0.41(0.36-0.45)
Rectum 1431 0.55(0.50-0.60)
Rectum, surgery 1405 0.31(0.28-0.34)
Unknown 147 1.15(0.95-1.39)
Unknown, surgery 134 0.52(0.42-0.65)
0.1
0.5
1
2.5

A



B



Highlights

1. Whether palliative primary tumor resection is beneficial to metastatic colorectal cancer is unknown
2. Propensity score matching analysis of Surveillance, Epidemiology, and End Results Database
3. Explore the effect surgery interaction with other therapies on survival
4. Focus on common metastatic sites of colorectal cancer patients

International Journal of Surgery Author Disclosure Form

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories, then this should be stated.

Please state any conflicts of interest

None.

Please state any sources of funding for your research

1. Science and Technology Planning Project of Guangdong Province, China (No. 2017A0300223006);
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5. Medical Science and Technology Research Fund of Guangdong Province, China (No. 2016111010432541);
6. Medical Science and Technology Research Fund of Guangdong Province, China (No. 2016111182715305).

Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number

This study is a retrospective cohort study in SEER database. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The SEER Program collects data from population-based cancer registries with anonymous information. The SEER is a publicly available database, thus no ethical approval is required.

Research Registration Unique Identifying Number (UIN)

Please enter the name of the registry, the hyperlink to the registration and the unique identifying number of the study. You can register your research at http://www.researchregistry.com to obtain your UIN if you have not already registered your study. This is mandatory for human studies only.

1. Name of the registry: Chinese Clinical Trial Registry

2. Unique Identifying number or registration ID: ChiCTR2000030297

3. Hyperlink to your specific registration (must be publicly accessible and will be checked): http://www.chictr.org.cn/showproj.aspx?proj=50177

Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

1. **Xianzhe Chen:** Conceptualization, Data curation, Writing-Original draft preparation, Writing- Reviewing and Editing.
2. **Chengzhi Huang:** Methodology, Data curation.
3. **Weijun Liang:** Investigation, Data curation.
4. **Jie Zhang:** Software, Data curation.
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12. **Junjiang Wang:** Visualization
13. **Xueqing Yao:** Supervision, Writing- Reviewing and Editing.

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. Please note that providing a guarantor is compulsory.

Xueqing Yao is the guarantor of this study.

Data statement

The raw data of this study are derived from the SEER database, which is a publicly available database. All detailed data included in the study are available upon request by contact with the corresponding author.