Survival Outcomes in Unresectable Metastatic Rectal Cancer Patients after both Primary Site Resection and Chemoradiotherapy: A Population-based Study

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Research article

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Abstract

Background: The liver is the most common site for rectal cancer metastases and metastases to the liver is the major cause of death. A significant proportion of liver metastases cannot surgically remove. However, very limited data are available in the literature regarding the survival outcomes of these patients. This study aims to investigate the survival pattern of unresectable metastatic rectal cancer patients after both chemoradiotherapy and primary tumor resection.

Methods: A total of 51178 rectal cancer patients were identified from Surveillance, Epidemiology, and End Results (SEER) database, of whom 448 patients were with synchronous liver metastasis and underwent both chemoradiotherapy and primary site resection. Kaplan-Meier analysis was used to compare the survival differences between the two groups. Cox proportional hazard regression model was used to analyses independent prognostic factors and exact 95% confidence intervals (CIs).

Results: Among the 448 metastatic rectal cancer patients with both chemoradiotherapy and primary site resection, 270 (60.3%) patients were undergone hepatic resection. The mean survival, 2-year overall survival, 5-year overall survival were 37.0 months, 68.5%, 32.9% among patients who did not undergo hepatic resection compared with 56.0 months, 87.4%, 48.0% among patients who underwent hepatic resection (P<0.001). The multivariate Cox regression analysis suggested that male, poor histological type and lack of hepatic resection were independently associated with poor overall survival (all p<0.05).

Conclusions: Primary site resection and chemoradiotherapy might be able to accomplish a satisfying survival outcome in unresectable metastatic rectal cancer patients. Non-hepatic resection is the strongest risk factor associated with poor prognosis.

Background

Colorectal cancer (CRC) is a common malignancy of the digestive tract, according to Global Cancer Statistics, it ranks third in terms of incidence and second in terms of mortality [1]. The development of the distant metastatic disease is the main cause of death, and the liver is the most common site, followed by the lungs, peritoneal cavity, bone and brain[2, 3]. Approximately 15%-25% of all colorectal cancer patients are presented with liver metastasis at the time of diagnosis and almost 45-50% of patients will develop liver metastases during their course of the disease[4, 5]. Currently, radical resection is one of the most effective therapies for metastatic colorectal cancer patients. Unfortunately, liver metastases are unresectable in up to 85% of patients initially[6]. The median survival in patients with untreated liver metastasis is reported to be around eight months, and for patients with unresectable liver metastasis, the 5-year overall survival rate is less than 5%[7, 8]. While, primary resection of liver metastases from colorectal cancer is potentially curative, with a 5-year survival rate of 40-50% and 10-year survival of 20% [9, 10].

Systemic chemotherapy represents the standard of care for unresectable metastatic patients, and it may result in downstaging of the metastases and converting unresectable liver metastases to resectable

one[9]. The results of Bismuth et al reported that neoadjuvant chemotherapy allows 15% unresectable colorectal liver metastases patients to be rescued by liver surgery[11]. However, the liver metastases in a significant number of patients who underwent neoadjuvant chemotherapy still cannot radically resected. According to the National Comprehensive Cancer Network (NCCN) guidelines, for synchronous unresectable metastases, the continuation of intensive chemotherapy is recommended and now the main therapeutic option, other therapies include radiofrequency ablation therapy, molecular targeted therapy[12]. And there is little objective data regarding the survival outcomes in the unresectable metastatic rectal cancer patients.

Several studies indicate that rectal cancer is different from colon cancer. From an anatomical point of view, the rectum and colon have a different embryological origin as the colon originates in the midgut, while the rectum originates from the hindgut[13]. From a clinical point of view, colonic and rectal cancer are two distinct entities, they differ in their biological behavior, metastatic pattern, clinical treatment methods, relapse survival rate[14-16]. Metastatic rectal and colon cancer treated differently according to the NCCN guidelines. The noted difference is that radiotherapy is applied in metastatic rectal cancer for better local control of disease prior to surgery[12, 17]. And several studies indicate that there may be some benefits in both overall survival (OS) and progression-free survival (PFS) from resection of the primary in the setting of unresectable colorectal metastases[18-20].

Many well-conducted studies have confirmed the potential curability of simultaneous or staged resection of liver metastases with colorectal carcinoma. However, there is limited published data to date concern about unresectable patients who received intensive systemic chemoradiotherapy[9, 10]. To better define this issue, we conducted this study with Surveillance, Epidemiology, and End Results Program database registered during 2010-2015 to analyze the survival patterns in metastatic rectal cancer patients who underwent both chemoradiotherapy and primary site tumor resection at a population level, including determine rates of hepatic resection in metastatic rectal cancer patients, evaluation of long-term and identify risk factors that affect the prognosis of these patients.

Methods

Data resources

We extracted newly diagnosed rectal cancer cases from the SEER database. The SEER database contains demographics, incidence, and survival data from 18 population-based registries that represent approximately 28% of the US population. And it is an open public database; all patient's data are de-identified; therefore, written informed consent is not needed for this study. This study was conducted following the ethical standards of the Declaration of Helsinki and with national and international guidelines. The Institutional Review Board of our hospital approved this study.

Study population

Initially, 51178 rectal cancer patients from January 1st, 2010 to December 31st, 2015 were identified using the SEER database. The tumor staging was conducted according to the American Joint Committee on Cancer (AJCC TNM) (7th edition) staging system. Besides, we included only patients with liver metastases, patients who received chemotherapy, radiotherapy and the primary site of the tumor was surgically resected. The surgical procedure of the primary site includes two modalities: 1) partial proctectomy, such as low anterior resection, Hartmann's operation, total mesorectal excision; 2) total proctectomy (abdominoperineal resection). Patients who underwent local tumor excision, local tumor destruction were excluded. We restricted the radiation code to beam radiation (radiation sequence may before, after surgery or both) and patients with other radiation codes (refused, none / unknown, radioactive implants, radioisotopes) were excluded. Moreover, we included only patients with tumor sequence numbers labeled "one primary only" and patients with Collaborative Stage (CS) Mets at Diagnosis labeled "metastasis limited to a single distant organ" or "staged as M1a". After excluding 50730 cases who were not eligible, 448 patients were included in the study. Patients were stratified into the following two groups based on the treatment strategy of the liver metastases: 1. Patients who received hepatic resection; 2. No hepatic surgery was performed (Fig.1). Other clinical characteristics include gender, age, race, marital status, tumor grade, tumor size, AJCC T-stage and AJCC N-stage were also collected.

Statistical analysis

Categorical data were presented as proportions and analyzed using the Chi-square test. OS was defined as the survival time after surgery and cancer-specific survival (CSS) was defined as the time from the date of surgery to the date of cancer death. The survival probability was estimated by the Kaplan-Meier methods, and the differences in the survival of the two groups of patients were compared by using Log-rank tests. To build a model for the prediction of overall survival, univariate and multivariate Cox proportional hazards regression models were performed, clinical variables with $p<0.10$ in univariate analysis were included in multivariate analysis. Statistical analysis was performed using SPSS version 21.0 (IBM Corp, Armonk, NY, USA).

Results

Patient characteristics

Demographic data for metastatic rectal cancer patients are shown in Table 1. The mean age at diagnosis is 60.39 ± 11.59 years. The majority of patients were male (65.6%), white (82.8%) and married (60.7%). Most of the patients (74.4%) had well and moderately differentiated tumors. Tumor size <5cm was more frequent in patients (67.4%). Among the 448 included patients, 401 (89.5%) and 47 (10.5%) were categorized as T3/T4 and T1/T2; 342 (76.3%) and 106 (23.7%) patients were categorized as N1/N2 and N0, respectively. Regarding the treatment, hepatic resection was performed in 178 (39.7%) patients. Baseline characteristics were presented according to treatment modality in Table 2. There was no significant difference in sex, race, tumor grade, AJCC T stage, AJCC N stage and marital status between

the hepatic resection group and no hepatic resection group. Liver resection was detected more often in patients with age <60 years (66.3% vs 54.8%, p=0.016) and with primary tumor size >5cm (39.3% vs 28.1%, p=0.014).

Patient survival

Kaplan-Meier curves for the overall survival and cancer-specific survival of metastatic rectal cancer patients are shown in Fig. 2. The mean, 2-, and 5-year overall survival of metastatic rectal cancer patients with both chemoradiotherapy and primary site resection are shown in Table 3. The mean overall survivals in the hepatic resection group and non-hepatic resection group are 56.0 months and 37.0 months, and the 5-year OS are 48.0% and 32.9%, respectively.

Univariate and multivariate regression analyses were used to explore the risk factors for OS of the metastatic rectal cancer patients. Variables with p<0.10 in the univariate analysis, including sex (p=0.012), tumor grade (p=0.003), T-stage (p=0.099), treatment modality (p<0.001), were taken forward to multivariate analysis. Consequently, male sex (HR,1.434; 95% CI,1.063-1.935; P=0.018), poor or undifferentiated tumor grade (HR,1.680; 95% CI,1.190-2.373; P=0.003), no liver resection (HR,1.783; 95% CI,1.326-2.397; P<0.001) were confirmed to be independent risk factors for poor prognosis Table 4.

Discussion

Colorectal cancer liver metastatic disease is a significant clinical problem. 15% to 25% of patients with colorectal cancer present with synchronous liver metastases and up to 85% of these patients have unresectable metastatic liver disease[4, 6]. Hepatic resection combined with chemotherapy is the standard treatment for metastatic rectal cancer patients and can lead to 5-year OS to 40-50%[9]. In our study, the 2-year and 5-year OS in patients with hepatic resection were 87.4% and 48.0%, similar to the findings by other researchers.

Although the only potentially curative treatment for metastatic CRC patients is surgical resection, the majority of the metastatic patients are too advanced to undergo curative surgery. For these patients, whether resection of the primary tumor affords a survival advantage remains a matter of debate. According to the NCCN guidelines, if the primary tumor is not acutely obstructed, palliative resection of the primary is rarely recommended, because incomplete resection (R1/R2 resection) has not been shown to be beneficial[21]. However, two registry studies in the United States suggested that nearly 70% of metastatic CRC patients have undergone resection of the primary site, and both studies observed a significant survival advantage[22, 23]. Matthieu et al reported the outcomes of 810 CRC patients with unresectable synchronous metastases, 59% (n=478) underwent resection of their primary tumor, compared with patients in the non-resection group, the hepatic resection group were more likely to have a lower baseline carcinoembryonic antigen (CEA) and alkaline phosphatase levels, primary tumor resection was independently associated with better OS and progression-free survival (PFS). The median survival of the hepatic resection group and non-hepatic group were 19.2 months and 13.3 months (p<0.001), respectively[18]. Our study suggests a better survival outcome in the unresectable metastases patients

who underwent primary site resection. In the metastatic CRC patients, 1387 (24.2%) patients underwent surgery to the primary site (Fig.1).

In the final cohort, 270 (60.3%) metastatic rectal cancer patients did not receive hepatic resection and the median survival in this group was 37.0 months with 2-year, 5-year OS 68.5% and 32.9%. Compare with other studies[24, 25], the overall survival results of the unresectable metastatic rectal cancer patients in this study were satisfactory. After comparing the inclusion criteria of our study to the others, we think the main difference is that we added radiotherapy to our inclusion criteria, and also the constantly updated chemotherapy and radiotherapy play a significant role in the improvement of survival outcomes, especially the application of the total neoadjuvant therapy (TNT) approach in the recent years. The TNT approach, which means induction or consolidation chemotherapy with chemoradiotherapy prior to surgery, was first in the use of the local advanced rectal cancer patients (T3/4, N0, or node-positive). According to a large study conducted by Memorial Sloan Kettering Cancer Center, the complete response (CR) rates in the advanced rectal cancer patients was 36% in the TNT group and 21% in the chemoradiotherapy with planned adjuvant chemotherapy group. They also noted that patients receiving TNT were more likely to complete planned chemotherapy with fewer dose reduction. This was consistent with the idea of intensive systemic therapy for the treatment of unresectable synchronous metastases[26]. Several advantages have also been pointed out by some other relevant studies: improved delivery of planned therapy, increased downstaging, and in-vivo assessment of chemosensitivity[27, 28]. With these advantages, the TNT approach was more likely to convert patients with unresectable synchronous liver metastases into the resectable status.

In our study, we performed univariate and multivariate cox proportional hazard regression analysis for the survival of metastatic rectal cancer patients. Here, we found that non-hepatic resection was the strongest risk factor associated with poor prognosis; this was inconsistent with previous reports[2, 25]. The Cox regression analysis also indicates that male sex was associated with worse prognosis in stage IV patients. Several studies have shown that women are less likely to develop colorectal cancer than men, and women with colorectal cancer have a longer survival time than men[29, 30]. One explanation of the sex differences lies in circulating androgens which will decrease the effectiveness of chemotherapy through the TUBB3 pathway in males[31]. In our study, poorly or undifferentiated tumors account for 14.7% of all malignant neoplasms, but it also shows a significant correlation with poor survival. This might be because poorly or undifferentiated cancer cells display reduced cohesiveness and have a stronger ability to invade surrounding tissues.

One of the greatest strengths of the present study is the large sample size provided by the SEER database, however, as a retrospective database, it has several limitations. First, the seer database lacks some key clinical information that might be important for prognosis, such as tumor markers, margin of resection, comorbidities and complications. Second, the SEER database does not provide detailed information about chemoradiotherapy regimens, biological targeted therapy, which could also influence the prognosis. Third, it is not possible to distinguish patients between those with isolated hepatic

metastases or multiple hepatic metastases, and there is little information about the treatment strategies for the liver metastasis, this may affect patients' prognosis.

Conclusions

Data are limited on the long-term survival outcomes in unresectable metastatic rectal cancer patients after both chemoradiotherapy and primary tumor resection. Our results show that after chemoradiotherapy and primary tumor resection, the 2-year and 5-year overall survival in these patients were 68.5% and 32.9%, respectively. Non-hepatic resection is the strongest risk factor associated with poor survival outcomes.

Abbreviations

CRC: Colorectal cancer; SEER: Surveillance, Epidemiology, and End Results; CIs: confidence intervals; NCCN: National Comprehensive Cancer Network; OS: overall survival; PFS progression-free survival; AJCC: the American Joint Committee on Cancer; CS: Collaborative Stage; CSS: cancer-specific survival; HR: Hazard ratio; TNT: the total neoadjuvant therapy; CR: complete response; CEA: Carcinoembryonic antigen; N: Number.

Declarations

Ethics approval and consent to participate

Since the data collected from the SEER database were anonymized and de-identifed prior to release, they do not require informed patient consent in our study. This study was approved by the Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College institutional review board. All methods were performed in accordance with relevant guidelines of the SEER database.

Consent for publication

Not applicable.

Availability of data and materials

The database used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' Contributions

JC, ZL designed the study. MY and CM collected the data. WP and ZW analyzed the data. JC, ZL organized the manuscript. QL and JY reviewed the paper and revised the manuscript. All authors (JC, ZL, MY, CM, WP, ZW, QL and JY) have read and approved the final manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians* 2018, 68(6):394-424.
2. Engstrand J, Nilsson H, Strömberg C, Jonas E, Freedman J: Colorectal cancer liver metastases - a population-based study on incidence, management and survival. *BMC Cancer* 2018, 18(1):78.
3. Guan X, Ma C-X, Quan J-C, Li S, Zhao Z-X, Chen H-P, Yang M, Liu Z, Jiang Z, Wang X-S: A clinical model to predict the risk of synchronous bone metastasis in newly diagnosed colorectal cancer: a population-based study. *BMC Cancer* 2019, 19(1):704.
4. Van Cutsem E, Nordlinger B, Cervantes A: Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. *Ann Oncol* 2010, 21 Suppl 5:v93-v97.
5. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier A-M: Epidemiology and management of liver metastases from colorectal cancer. *Annals of surgery* 2006, 244(2):254-259.
6. Zervoudakis A, Boucher T, Kemeny NE: Treatment Options in Colorectal Liver Metastases: Hepatic Arterial Infusion. *Visc Med* 2017, 33(1):47-53.
7. Petrelli NJ, Abbruzzese J, Mansfield P, Minsky B: Hepatic resection: the last surgical frontier for colorectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2005, 23(20):4475-4477.
8. House MG, Ito H, Gönen M, Fong Y, Allen PJ, DeMatteo RP, Brennan MF, Blumgart LH, Jarnagin WR, D'Angelica MI: Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1,600 patients during two decades at a single institution. *Journal of the American College of Surgeons* 2010, 210(5).

9. Kemeny NE, Melendez FDH, Capanu M, Paty PB, Fong Y, Schwartz LH, Jarnagin WR, Patel D, D'Angelica M: Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2009, 27(21):3465-3471.
10. Park M-S, Yi N-J, Son S-Y, You T, Suh S-W, Choi YR, Kim H, Hong G, Lee KB, Lee K-W *et al*: Histopathologic factors affecting tumor recurrence after hepatic resection in colorectal liver metastases. *Ann Surg Treat Res* 2014, 87(1):14-21.
11. Bismuth H, Adam R, Lévi F, Farabos C, Waechter F, Castaing D, Majno P, Engerran L: Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Annals of surgery* 1996, 224(4).
12. Benson AB, Venook AP, Al-Hawary MM, Cederquist L, Chen Y-J, Ciombor KK, Cohen S, Cooper HS, Deming D, Engstrom PF *et al*: Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2018, 16(7):874-901.
13. Li F-y, Lai M-d: Colorectal cancer, one entity or three. *J Zhejiang Univ Sci B* 2009, 10(3):219-229.
14. Slattery ML, Wolff E, Hoffman MD, Pellatt DF, Milash B, Wolff RK: MicroRNAs and colon and rectal cancer: differential expression by tumor location and subtype. *Genes Chromosomes Cancer* 2011, 50(3):196-206.
15. Comprehensive molecular characterization of human colon and rectal cancer. *Nature* 2012, 487(7407):330-337.
16. Tamas K, Walenkamp AME, de Vries EGE, van Vugt MATM, Beets-Tan RG, van Etten B, de Groot DJA, Hospers GAP: Rectal and colon cancer: Not just a different anatomic site. *Cancer Treat Rev* 2015, 41(8):671-679.
17. Benson AB, Venook AP, Al-Hawary MM, Cederquist L, Chen Y-J, Ciombor KK, Cohen S, Cooper HS, Deming D, Engstrom PF *et al*: NCCN Guidelines Insights: Colon Cancer, Version 2.2018. *J Natl Compr Canc Netw* 2018, 16(4):359-369.
18. Faron M, Pignon J-P, Malka D, Bourredjem A, Douillard J-Y, Adenis A, Elias D, Bouché O, Ducreux M: Is primary tumour resection associated with survival improvement in patients with colorectal cancer and unresectable synchronous metastases? A pooled analysis of individual data from four randomised trials. *European journal of cancer (Oxford, England : 1990)* 2015, 51(2):166-176.
19. Karoui M, Roudot-Thoraval F, Mesli F, Mitry E, Aparicio T, Des Guetz G, DesGuetz G, Louvet C, Landi B, Tiret E *et al*: Primary colectomy in patients with stage IV colon cancer and unresectable distant metastases improves overall survival: results of a multicentric study. *Diseases of the colon and rectum* 2011, 54(8):930-938.
20. Venderbosch S, de Wilt JH, Teerenstra S, Loosveld OJ, van Bochove A, Sinnige HA, Creemers G-JM, Tesselaar ME, Mol L, Punt CJA *et al*: Prognostic value of resection of primary tumor in patients with stage IV colorectal cancer: retrospective analysis of two randomized studies and a review of the literature. *Annals of surgical oncology* 2011, 18(12):3252-3260.

21. Altendorf-Hofmann A, Scheele J: A critical review of the major indicators of prognosis after resection of hepatic metastases from colorectal carcinoma. *Surg Oncol Clin N Am* 2003, 12(1).
22. Cook AD, Single R, McCahill LE: Surgical resection of primary tumors in patients who present with stage IV colorectal cancer: an analysis of surveillance, epidemiology, and end results data, 1988 to 2000. *Annals of surgical oncology* 2005, 12(8):637-645.
23. Temple LKF, Hsieh L, Wong WD, Saltz L, Schrag D: Use of surgery among elderly patients with stage IV colorectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2004, 22(17):3475-3484.
24. Chen H-H, Lin J-K, Chen J-B, Chuang C-H, Liu M-C, Wang J-Y, Changchien C-R: Neoadjuvant therapy of bevacizumab in combination with oxaliplatin and capecitabine (XELOX) for patients with metastatic colorectal cancer with unresectable liver metastases: a phase II, open-label, single-arm, noncomparative trial. *Asia Pac J Clin Oncol* 2018, 14(1):61-68.
25. Nozawa H, Ishihara S, Kawai K, Hata K, Kiyomatsu T, Tanaka T, Nishikawa T, Otani K, Yasuda K, Sasaki K *et al*: Conversion to Resection in Patients Receiving Systemic Chemotherapy for Unresectable and/or Metastatic Colorectal Cancer-Predictive Factors and Prognosis. *Clin Colorectal Cancer* 2018, 17(1):e91-e97.
26. Cercek A, Roxburgh CSD, Strombom P, Smith JJ, Temple LKF, Nash GM, Guillem JG, Paty PB, Yaeger R, Stadler ZK *et al*: Adoption of Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer. *JAMA Oncol* 2018, 4(6):e180071.
27. Chau I, Brown G, Cunningham D, Tait D, Wotherspoon A, Norman AR, Tebbutt N, Hill M, Ross PJ, Massey A *et al*: Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2006, 24(4):668-674.
28. Cercek A, Goodman KA, Hajj C, Weisberger E, Segal NH, Reidy-Lagunes DL, Stadler ZK, Wu AJ, Weiser MR, Paty PB *et al*: Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. *J Natl Compr Canc Netw* 2014, 12(4):513-519.
29. Lydrup ML, Höglund P: Gender aspects of survival after surgical treatment for rectal cancer. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2015, 17(5):390-396.
30. Anderin C, Martling A, Hellborg H, Holm T: A population-based study on outcome in relation to the type of resection in low rectal cancer. *Diseases of the colon and rectum* 2010, 53(5):753-760.
31. Mariani M, Zannoni GF, Sioletic S, Sieber S, Martino C, Martinelli E, Coco C, Scambia G, Shahabi S, Ferlini C: Gender influences the class III and V β-tubulin ability to predict poor outcome in colorectal cancer. *Clin Cancer Res* 2012, 18(10):2964-2975.

Tables

Table 1. Patients demographics and clinical characteristics (n=448)

Characteristics	Number of Patients	(%)
Age at diagnosis, years		
Mean ± SD	60.39±11.59	
<60	266	59.4%
≥60	182	40.6%
Sex		
Male	294	65.6%
Female	154	34.4%
Race		
White	371	82.8%
Black	32	7.1%
Others	45	10.0%
Marital Status		
Married	272	60.7%
Unmarried	154	34.4%
Unknown	22	4.9%
Tumor Grade		
Poor + Undifferentiated	66	14.7%
Well + Moderate	333	74.3%
Unknown	49	10.9%
Tumor Size		
0-5cm	302	67.4%
>5cm	146	32.6%
AJCC T Stage		
T1/T2	47	10.5%
T3/T4	401	89.5%
AJCC N Stage		
N0	106	23.7%

N1/N2	342	76.3%
Treatment Modality		
Liver resection	178	39.7%
No liver resection	270	60.3%

SD: Standard deviation; AJCC: American Joint Committee on Cancer

Table 2. Baseline characteristics of Group A (Liver resection) and B (No liver resection)

Variables	Group A (n=178)	Group B (n=270)	p-value
Sex			0.713
Male	115(64.6%)	179(66.3%)	
Female	63(35.4%)	91(33.7%)	
Age			0.016
<60	118(66.3%)	148(54.8%)	
≥60	60(33.7%)	122(45.2%)	
Race			0.652
Black	13(7.3%)	19(7.0%)	
White	150(84.3%)	221(81.9%)	
Other	15(8.4%)	30(11.1%)	
Tumor Grade			0.651
Poor +Undifferentiated	24(13.5%)	42(15.6%)	
Well Moderate	132(74.2%)	201(74.4%)	
Unknown	22(12.4%)	27(10.0%)	
AJCC T Stage			0.399
T1/T2	16(9.0%)	31(11.5%)	
T3/T4	162(91.0%)	239(88.5%)	
AJCC N Stage			0.165
N0	36(20.2%)	70(25.9%)	
N1/N2	142(79.8%)	200(74.1%)	
Tumor Size			0.014
0-5cm	108(60.7%)	194(71.9%)	
>5cm	70(39.3%)	76(28.1%)	
Marital Status			0.811
Married	111(62.4%)	161(59.6%)	
Unmarried	58(32.6%)	96(35.6%)	
Unknown	9(5.1%)	13(4.8%)	

AJCC: American Joint Committee on Cancer

Table 3. Mean survival and 2-, 5-year OS of metastatic rectal cancer patients (n=448)

Variables	Mean survival (mon)	2-year OS	5-year OS
Liver surgery group	56.0	0.874	0.480
Non-liver surgery group	37.0	0.685	0.329

OS: overall survival

Table 4. Univariate and multivariate analysis for OS of all patients (n=448)

Variables		Univariate analysis		Multivariate analysis	P-value
		HR [95%CI]	P-value	HR [95%CI]	
Age	<60	1		1	
	≥60	0.681-1.195	0.471		
Sex	Female	1		1	
	Male	1.086-1.974	0.012	1.063-1.935	0.018
Race	White	1		1	
	Black	0.698-1.850	0.608		
	Others	0.904-2.203	0.130		
Marital status	Married	1		1	
	Unmarried	0.850-1.515	0.392		
	Unknown	0.520-2.017	0.944		
Tumor Grade	Moderate +Well	1		1	
	Poor +Undifferentiated	1.187-2.364	0.003	1.190-2.373	0.003
	Unknown	0.622-1.527	0.911		
T-stage	T1/T2	1		1	
	T3/T4	0.924-2.502	0.099	0.947-2.572	0.081
N-stage	N0	1		1	
	N1/N2	0.899-1.785	0.176		
Tumor Size	<5	1		1	
	≥5	0.699-1.257	0.665		

Treatment modality	Liver resection	1		1	
	No liver resection	1.326-2.395	<0.001	1.326-2.397	<0.001

OS: overall survival; CI: confidence intervals

Figures

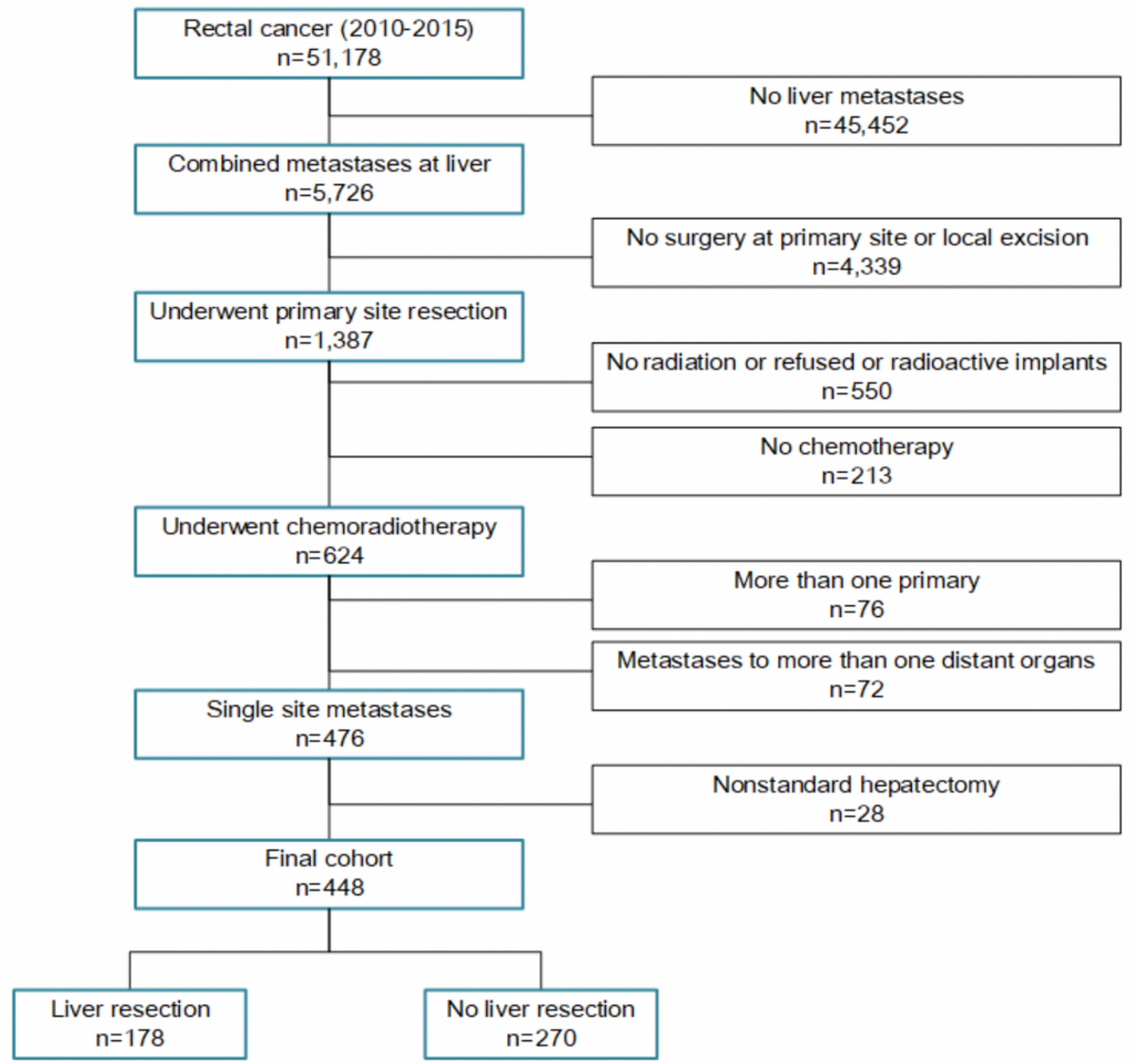

Figure 1

Flow chart for the creation of the patient cohort data set.

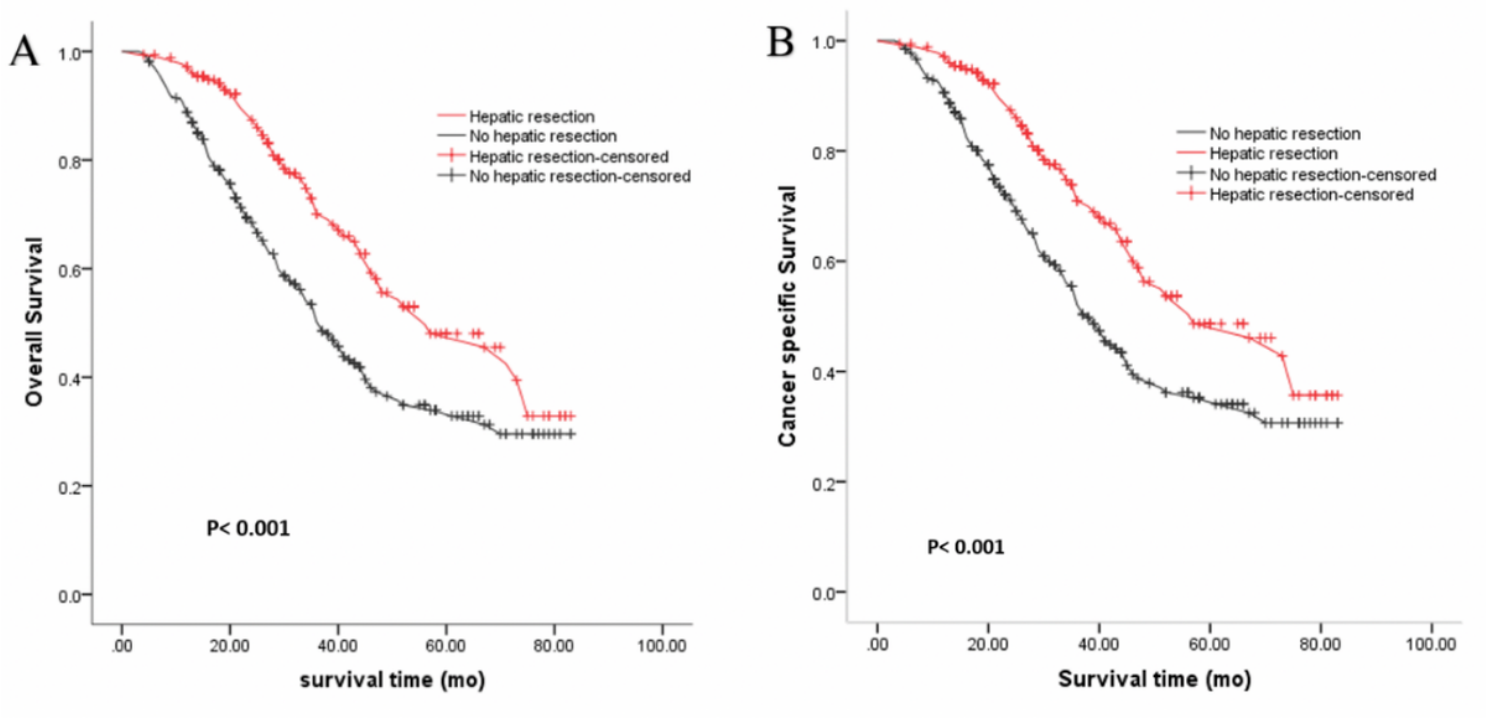

Figure 2

Overall survival (OS) (A) and cancer specific survival (CSS) (B) estimated with the Kaplan-Meier method for metastatic rectal cancer patients.