The Primary Tumor Surgery Prolongs the Medium Cancer Specific Survival in Metastatic Colorectal Cancer Patients with Initial Isolated Unresectable Lung Metastasis: A SEER-based Retrospective Study

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Research article

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Abstract

Background: The efficiency of primary tumor surgery (PTS) to patients who are diagnosed as colorectal cancer (CRC) with initial isolated unresectable lung metastasis (URLM) is still on debates.

Methods: 1580 patients are involved in this study eventually, data from the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2015. Chi-square (X2) test examines the categorical variables. Hazard ratio (HR) and 95% confidence interval (95% CI) are used as the estimation of risk for mortality in univariate and multivariate Cox regression. Propensity score match (PSM) simulates the random progress. Kaplan-Meier method outputs the medium cancer specific survival (mCSS) and delineates the survival curve.

Results: After PSM, PTS prolongs the mCSS time in surgery group compared to no-surgery group (40 months *vs.* 14 months, HR=0.396, P<0.001), and raises the 3-year CSS rate (37% *vs.* 12%, P<0.001). Radiotherapy has further survival benefits in surgery group (49 months *vs.* 32 months, HR=0.434, P=0.001). Chemotherapy, radiotherapy, and no peritoneum metastasis have better mCSS (31 months, 33 months, 30months respectively). Multivariate Cox regression turns out that patients older than 75 (HR=1.869, P<0.001), with poor differentiation or undifferentiation pathological grade (HR=1.796, P<0.001), with peritoneum metastasis (HR=1.650, P<0.001) have higher risks of death, and PTS (HR=0.396, P<0.001), chemotherapy (HR=0.330, P<0.001) are favor prognostic factors in mCRC with URLM.

Conclusion: This study affirms the effectiveness of primary tumor surgery in the colorectal cancer patients with initial isolated unresectable lung metastasis. More random clinical trials or real-world researches need to be implemented.

Instruction

Colorectal cancer (CRC), the third most common and forth death-related cancer in the United States, and the fifth in China, has relatively high risk to metastasize.[1, 2] Among all metastatic sites, as the second popular one, following liver, lung has 24.5% probability to be the initial distant metastasis .[3] 37.7–44.5% CRC patients with initial lung metastasis (LM) have only isolated lung metastasis, of which 67.5–78.9% have no chance to undergo a radical surgical intervention of primary tumor.[3, 4] Some studies observe that primary tumor resection (PTR) without metastasectomy has no superiority to palliative stoma surgery.[5, 6] Another SEER-based study shows a trend toward fewer PTS from 1988 to 2010 with better survival.[7] However, there are still other studies affirming the effectiveness of PTR, especially which present with related symptoms.[8–11]

For mCRC patients, the choice of surgical intervention to primary tumor is still controversial, considering the delay in systemic therapy.[6] The decision is up to the symptoms, localization and size of the primary site, the number and status of metastases and patient's general state, all of which are evaluated by multidisciplinary team (MDT),[8] considering that the aim of these late-stage patients is to prolong

lifetime and prevent progression with minimal treatment burden instead of resection of primary and metastatic sites.[12] Accordingly, though lung metastasis usually means relatively slower growth and better survival,[13] for those individuals, there are still much debate about the strategy of primary tumor operation.[14]

In this research, we emphatically investigated the effectiveness of primary tumor surgery (PTS) in mCRC patients with initial isolated unresectable lung metastasis (URLM).

Material And Methods

Data collection

We collected the patients who were diagnosed as colorectal cancer with pulmonary metastases and had no surgeries to distant metastatic sites from 2010 to 2015 recorded in the surveillance, epidemiology, and end results (SEER) database (primary site code: C18.0 and C18.2-C18.4 as right colon cancer, C18.5-C18.9 as left colon cancer, C19.9 and C20.9 as rectal cancer according to the Third Edition of International Classification of Diseases for Oncology (ICD-O-3)).[15] Individuals who had only one type of primary cancer filed and isolated lung metastasis were involved in the study and those who underwent the surgery of distant sites were excluded. Then they were divided into two groups according to PTS or not. The radiotherapy and chemotherapy data was obtained by sending an application to the SEER*Stat Team and getting their permission.[16] Data about metastasis is limited to record at the time of diagnosis and data about cancer-specific survival months (CSS) is certain.[16] CSS is delimited as the time from the day of diagnosis to the day of death attributed to CRC.[17] A total of 1580 patients were included in the study eventually.

Variable definitions

The following variables were exported: gender, race (white, black and other), age (< 75 and > = 75) at diagnosis, primary tumor anatomic site, pathological grade, peritoneum status, T stage, N stage, radiation and chemotherapy. Because the peritoneum metastasis information in SEER database is independent on the description of metastasis at distant, we investigate this group specifically. The surgical treatment of primary site including endoscopic resection, local tumor destruction, partial colectomy and total colectomy. The interpretations of all variables can be found in the filed description of SEER Text Data downloaded from the SEER website.

Statistical analysis

Given that all variables are categorical variables, we adopt the chi-square (X^2) test to evaluate the differences between no-surgery group (NSR) and surgery group (SR). After univariate Cox regression, the variables with P value < 0.1 combining with clinical meanings enter the multivariate Cox regression, exporting the hazard ratio (HR) and 95% confidence interval (95% CI) used as the estimation of risk for mortality. To reduce the selection bias, we use Propensity Score Match (PSM) adjusting the potentially confounding variables (including age, primary site, pathological grade, peritoneum status, T stage, N

stage, radiation and chemotherapy) between NSR and SR, after excluding missing data. The method is “nearest”, with ratio = 2 and caliper = 0.2. At last, 389 adjusted patients (NSR = 164, SR = 225) are matched imitating random group. Then we make out the survival curve by Kaplan-Meier method and the P value is performed by the log-rank test. The condition of statistically significant difference is equal to two-sided P value < 0.05 and confidence intervals (CI) are set as 95%. We extract the data using SEER*Stat software and analyze them by SPSS 25.0. PSM progress is achieved by R.

Study outcomes

Cancer specific survival (CSS) is defined as the main survival outcome which is calculated from the date of diagnosis as cancer to the date of death attributed to the cancer instead of any other reason, and mCSS was the symbol of medium CSS. The 3-year CSS rate means the ratio that survivals (overall number eliminating the patients who died because of cancer) accounted for the total quantity after 3 years.

Results

Patient characteristics

A total of 1580 patients before PSM identified as colorectal cancer with initial isolated lung metastasis that did not undergo surgery from 2010 to 2015 in the SEER database were involved in the study eventually. (Figure.1) The medium age is 66 years old. According to the baseline characteristics analysis, race, gender, and perioperative radiotherapy are balanced between NSR and SR and most of them received the radiation therapy (80.9%&79.9%). After the Propensity Score Match (PSM) matching the rest factors, there are no discrepancy except the T stage and N stage (P = 0.031&0.043), majority of the SR group with later T and N stage. The patients who operate surgery are mostly younger than 75-year-old, higher differentiated and without peritoneum metastases. Whether there is surgical intervention, chemotherapy accounts for more than half of the population. (Table.1)

Cox regression analysis

In the entirety before PSM, Univariate Cox regression analysis for cancer-specific survival (CSS) demonstrates that older than 75 (HR = 2.655, P < 0.001), poor or undifferentiated (HR = 1.877, P < 0.001), with peritoneum metastasis (HR = 1.848, P < 0.001) are risk factors, and rectum (HR = 0.684, P < 0.001), primary tumor surgery (PTS) (HR = 0.487, P < 0.001), chemotherapy (HR = 0.272, P < 0.001), radiotherapy (HR = 0.568,P < 0.001) are protective factors. Though later T (HR = 0.815, P = 0.055) and N positive (HR = 0.807, P = 0.005) show opposite hazard ratio first, then they are corrected after Multivariate Cox analysis (HR = 1.372, P = 0.074/HR = 1.107, P = 0.439). Involving all variables with P value < 0.1 into the next Multivariate Cox regression analysis shows that older than 75 (HR = 1.869, P < 0.001), poor or undifferentiated (HR = 1.796, P < 0.001), with peritoneum metastasis (HR = 1.650, P < 0.001) still have higher risks, and PTS (HR = 0.396, P < 0.001), chemotherapy (HR = 0.330, P < 0.001) are still protective

factors, but the benefits of primary site (P = 0.677) and radiotherapy (HR = 0.830, P = 0.250) are adjusted in the analysis. (Table.2)

Match the confounding factors between NSR and SR group, according to above results, including age, primary site, pathological grade, peritoneum status, T stage, N stage, radiation and chemotherapy using PSM. Then the multivariate Cox analysis concludes the effects of age > 75 (HR = 1.507, P = 0.032), pathological grade (HR = 1.566, P = 0.015), peritoneum status (HR = 1.904, P = 0.002), PTS (HR = 0.355, P < 0.001) and chemotherapy (HR = 0.383, P < 0.001) finally. (Table.3) It seems that though after PSM, the imbalance of T and N stage between NSR and SR group have no influence on the Multivariate COX analysis result.

Survival outcomes

The 3-year CSS rate in NSR and SR group after PSM is 12% *vs.* 37%, and medium CSS (mCSS) raises from 14 months to 40 months (P < 0.001). (Table.3, Figure.2A) In whole group, patients received chemotherapy or radiotherapy have better mCSS respectively (31 *vs.* 9 months, 33 *vs.* 26 months, both P < 0.05). (Table.3, Fig. 2B-C) In the NSR group, radiotherapy subgroup shows more 5 months mCSS in the basis of 12 months, but has no statistically significant (P = 0.163). (Figure.2E) While in the SR group, radiation has further survival benefits from 32 to 49 months (P = 0.001). (Figure.2E) As for the peritoneum metastasis which is independent on the description of distant metastasis, mCSS in no peritoneum metastasis group is twice longer than that in the other group (30 *vs.* 15 months, P < 0.001), and it is consistent with previous studies. (Figure.2D)

Discussion

According to the sequence of metastatic sites, CRC lung metastases (LM) can be classified to non-initial LM and initial LM, and part of them have only LM without extrapulmonary metastases which can be defined as isolated LM, this study focuses on these initial isolated CRC LM.[14] To those metastases which are initially unsuitable for resection because of the number or size or position with lung or blood vessels etc., part of them can transform from unresectable to resectable or achieve to no evidence of disease (NED) through intensive conversion therapy, but with only 5.7–7.1% conversion rate.[14, 18, 19] As for the remainder that have no opportunity to be resected or NED, in this article whom we defined as initial isolated unresectable lung metastasis(URLM), they rely on dominantly systemic therapy, combining chemotherapy, targeted therapies and palliative local treatment which is based on the consideration of patients' general condition and organ function, and the emergency complication of local disease site that have to be operated.[14] Actually in the past, prophylactic resection of primary lesion was used to prevent related complications such as bleeding, perforation even obstruction especially in the patients who were chemorefractory, though tiny of them suffered from primary tumor-related symptoms actually.[20, 21] Systematic reviews and original researches show that non-curative resection of asymptomatic colorectal primary lesions brings benefits to survival.[11, 22–25]

As the abundance of systemic therapy increasing in recent decade, including chemotherapy, targeted therapy and immunotherapy, metastatic colorectal cancer (mCRC) has already gotten survival benefits observably. There is clinical trial already showing that FOLFIRI with cetuximab as first-line treatment in mCRC has median overall survival (mOS) about 20-23.5 months.[26] Similarly in another study of CRC LM, pharmacotherapy alone also have mOS about 23.8 months.[3] In view of the chemosensitivity of primary site, the potential delay of systemic therapy and possible risk of severe complications caused by surgery, the chemotherapy-first approach and surgery-rescue option for symptoms has been accepted widely.[27–29] Involving the effect of systemic therapy, there are still some studies support that PTS makes overall survival improvement, but they ignore the difference between metastatic sites especially the lung and liver considering the probable better outcome of the former.[8, 11, 30] In the situation of these contradictions between different system review about PTS in mCRC, we think that may be related with the great heterogeneity between the primary evidence, the large time span between studies and the different use of extra pharmacotherapy. Furthermore, retrospective study usually has selection bias, which means that better survival may be influenced by the other meaningful good characteristics including better performance status, earlier T or N stage, lesser tumor burden, which are apt to choose operation, not only disposal itself.

To clarify the specific situation in mCRC with pulmonary metastasis, in this study, we affirm the effectiveness of primary tumor surgery in the colorectal cancer patients with initial isolated unresectable lung metastasis based on a large sample from SEER database. We use PSM to avoid confounding factors being involved into survival time and operation of surgery as far as possible. After PSM, PTS prolongs the mCSS time in surgery group compared to no-surgery group from 14 months to 40 months. Though TN stage are still imbalanced after PSM, multivariate Cox regression proves that they have no influence on the last CSS outcome. The censored data and progress of match reduces the available patients, and the last number involved in the survival analysis is less than 400 which is not prior to other retrospective studies. And we focus on the specific population who are initial isolated CRC URLM which is another reason. Limited by the weakness of PSM, the strength of evidence still weaker than random clinical trial (RCT). What's more, the quality of life (QOL) after surgery which has been proved meaningful in the evaluation of survival benefit is missed in this study due to data unavailable.[8, 11, 30]

In addition, we only involve part of the meaningful factors, and other researches have already investigated that right colon, late TN stage, carcinoembryonic antigen (CEA) and lactate dehydrogenase (LDH) etc. are also prognostic predictor.[31–35] Meanwhile, limited to the lack of specific regimens and using-time or sequence of agents in the SEER database, we have no idea about the exact effect of varieties of monotherapy or combinations and multi-line systemic therapy.

Besides the PTS, the other local site treatment-radiotherapy (RT) also improves the mCSS from 26 months to 33 months compared to no-radiotherapy for CRC URLM patients without PTS. When PTS combined RT, it gets the more survival benefit than PTS alone (49 months *vs.* 32 months). Although that the RT procedure which is not clear enough may produce bias, the role of RT adding to PTS is worth discussing further. There are another two multicentric, prospective, random, controlled trials,

SYNCHRONOUS and CAIRO4, concerning on primary site resection, under study with expectation on get positive conclusions.[36, 37] The abstract of iPACS published on ASCO in 2020 announces a negative outcome of PTS, we look forward to more details about this study.[38]

Overall, we focus on the survival benefit of PTS in the CRC with initial isolated unresectable LM (URLM) and confirm that it has effectiveness to these IV stage patients. Though we analysis the Cox regression, we still need to work on the selection criteria of surgical intervention, and how to evaluate the requirement of local resection accurately is next-stage task. What's more, the questions that whether aggressively both primary and distant tumor resection can benefit CRC LM patients and the sequence are still need clarity. These problems need more RCT and real-world researches to investigate.

Abbreviation

primary tumor surgery (PTS), primary tumor resection (PTR), colorectal cancer (CRC), lung metastasis (LM), unresectable lung metastasis (URLM), Surveillance, Epidemiology, and End Results (SEER), hazard ratio (HR), confidence interval (95% CI), propensity score match (PSM), medium cancer specific survival (mCSS), cancer specific survival (CSS), multidisciplinary team (MDT), no-surgery (NSR), surgery (SR),no-chemotherapy (NCT), chemotherapy (CT), no-radiotherapy (NRT), radiotherapy (RT), no- peritoneum metastasis (NPM), peritoneum metastasis (PM)

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the Surveillance, Epidemiology, and End Results Program Database repository, https://seer.cancer.gov/ or https://seer.cancer.gov/seerstat/.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors have contributed significantly to the study and preparation of the manuscript and have approved the final version. Fuxiang Zhou and Chen Liang contributed equally as co-senior authors.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All authors have declared that no competing interests exist. Surveillance, Epidemiology, and End Results Program is a public database containing information on cancer statistics among the U.S. population. The author has application to the SEER*Stat Team and permission to getting data containing chemoradiotherapy. For more information about SEER, please refer to https://seer.cancer.gov/ or https://seer.cancer.gov/seerstat/.

CODE AVAILABILITY

The process of propensity score match (PSM) needs R. The code can be accessed in the attachment.

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Tables

Due to technical limitations, table PDF is only available as a download in the Supplemental Files section.

Figures

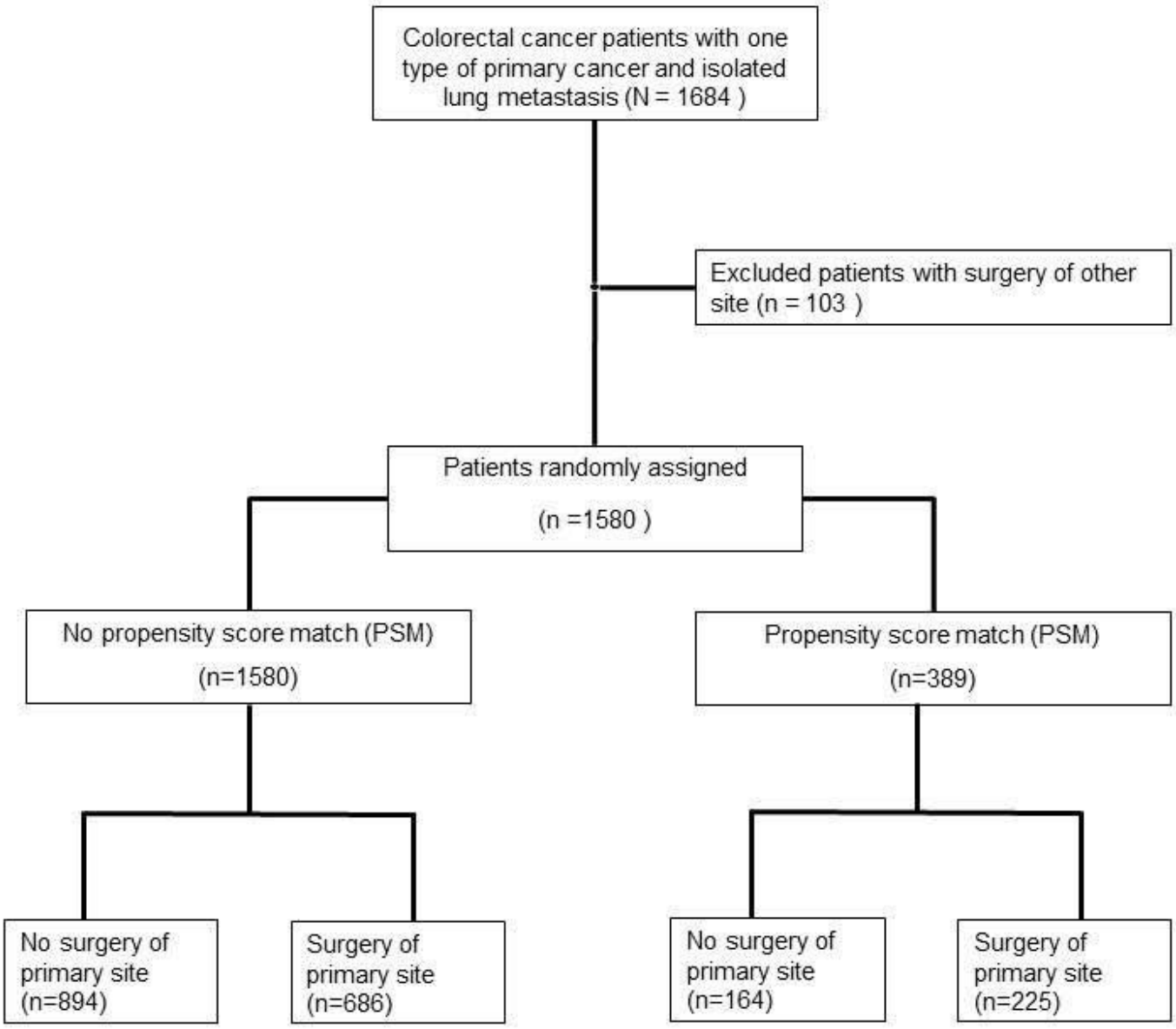

Figure 1

Data collection

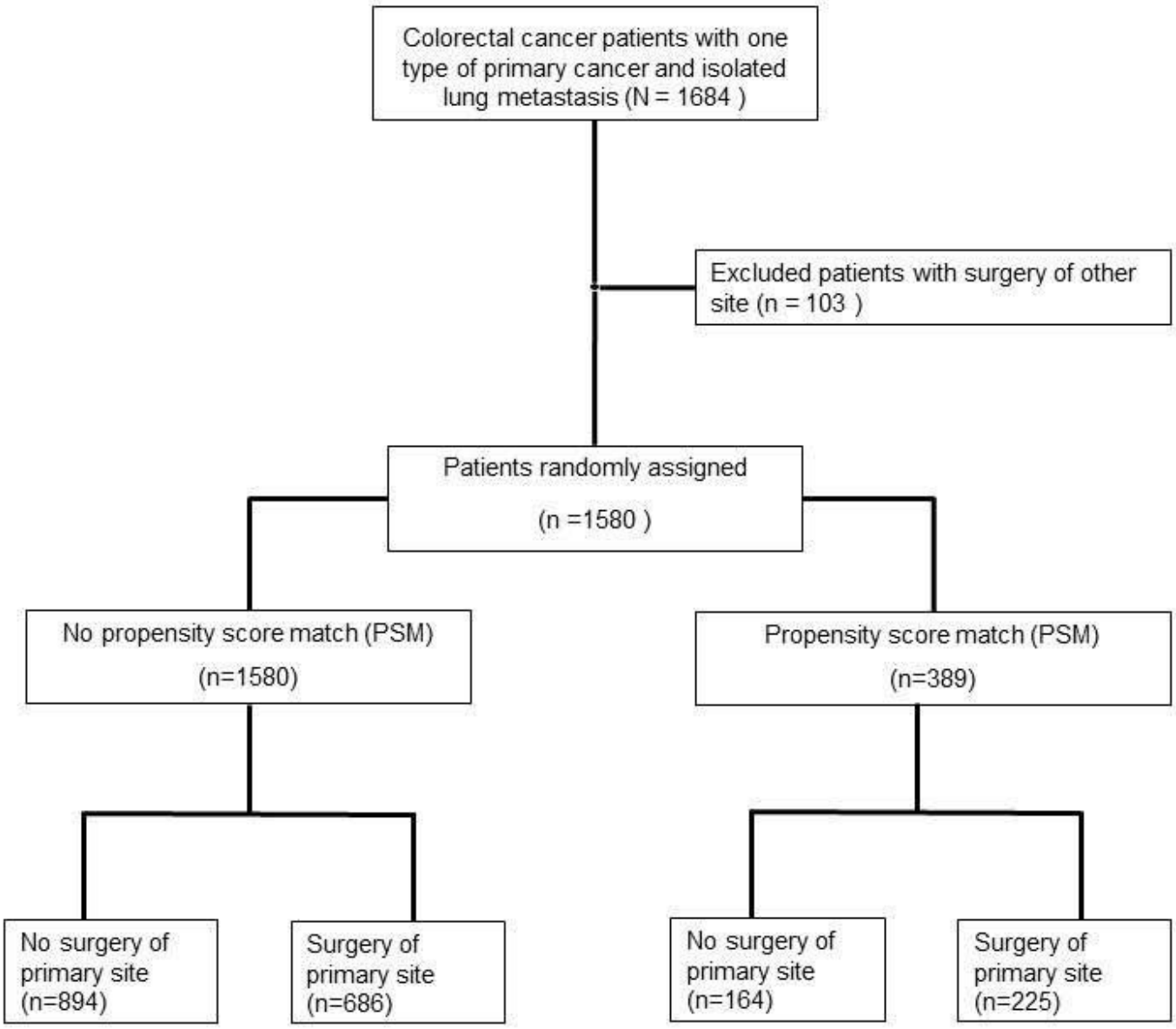

Figure 1

Data collection

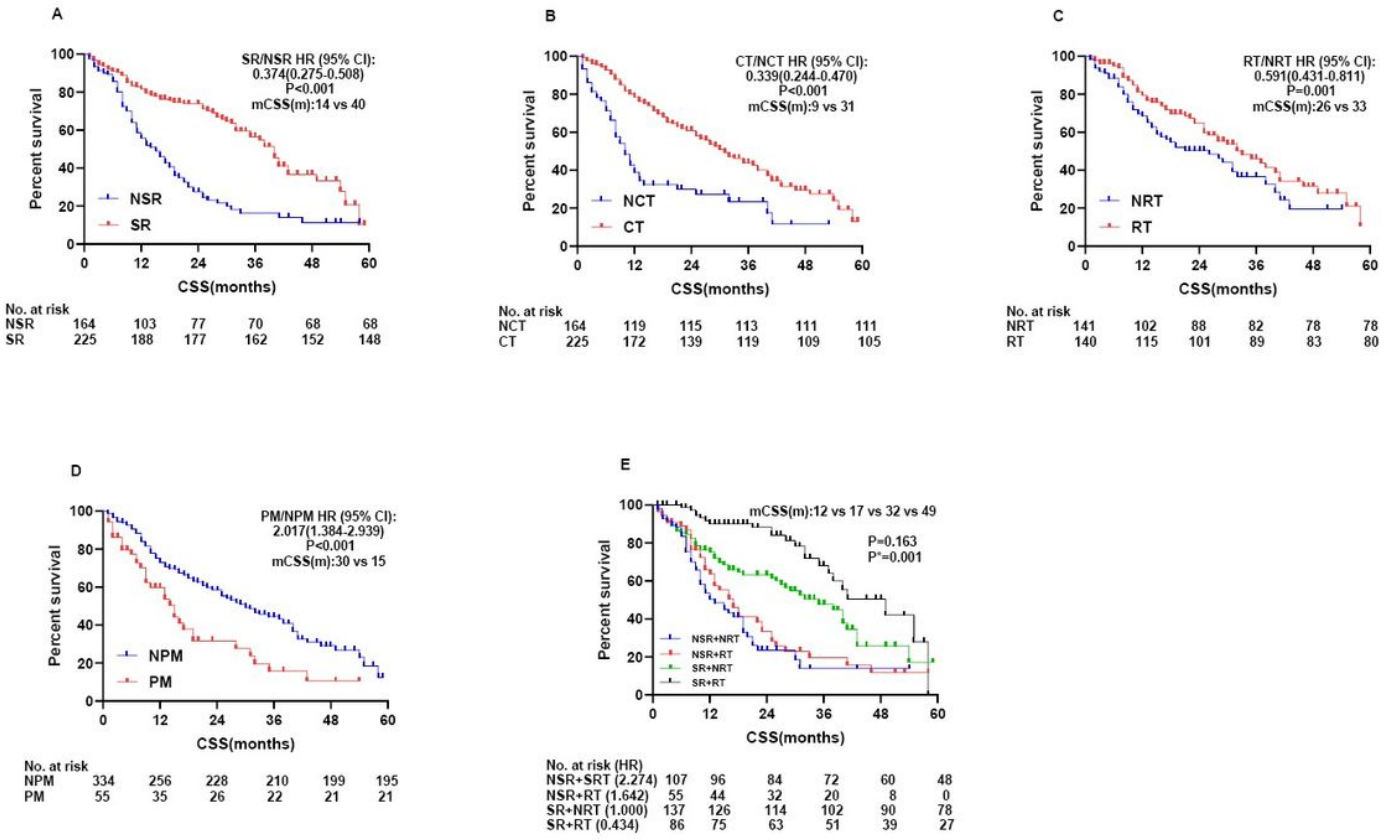

Figure 2

KM curves of CSS after PSM The cancer-specific survival of stage IV colorectal cancer patients after PSM. Primary tumor surgery (PTS). Hazard ratio (HR) is calculated by Univariate COX Analysis. (A) NSR= no surgery, SR= surgery. (B) NCT= no-chemotherapy, CT= chemotherapy. (C) NRT= no-radiotherapy, RT= radiotherapy. (D) NPM= no- peritoneum metastasis, PM= peritoneum metastasis. (E) Combination of surgery and radiotherapy; P: the p value between NSR+NRT and NSR+RT; P*: the p value between SRN+RT and SR+RT.

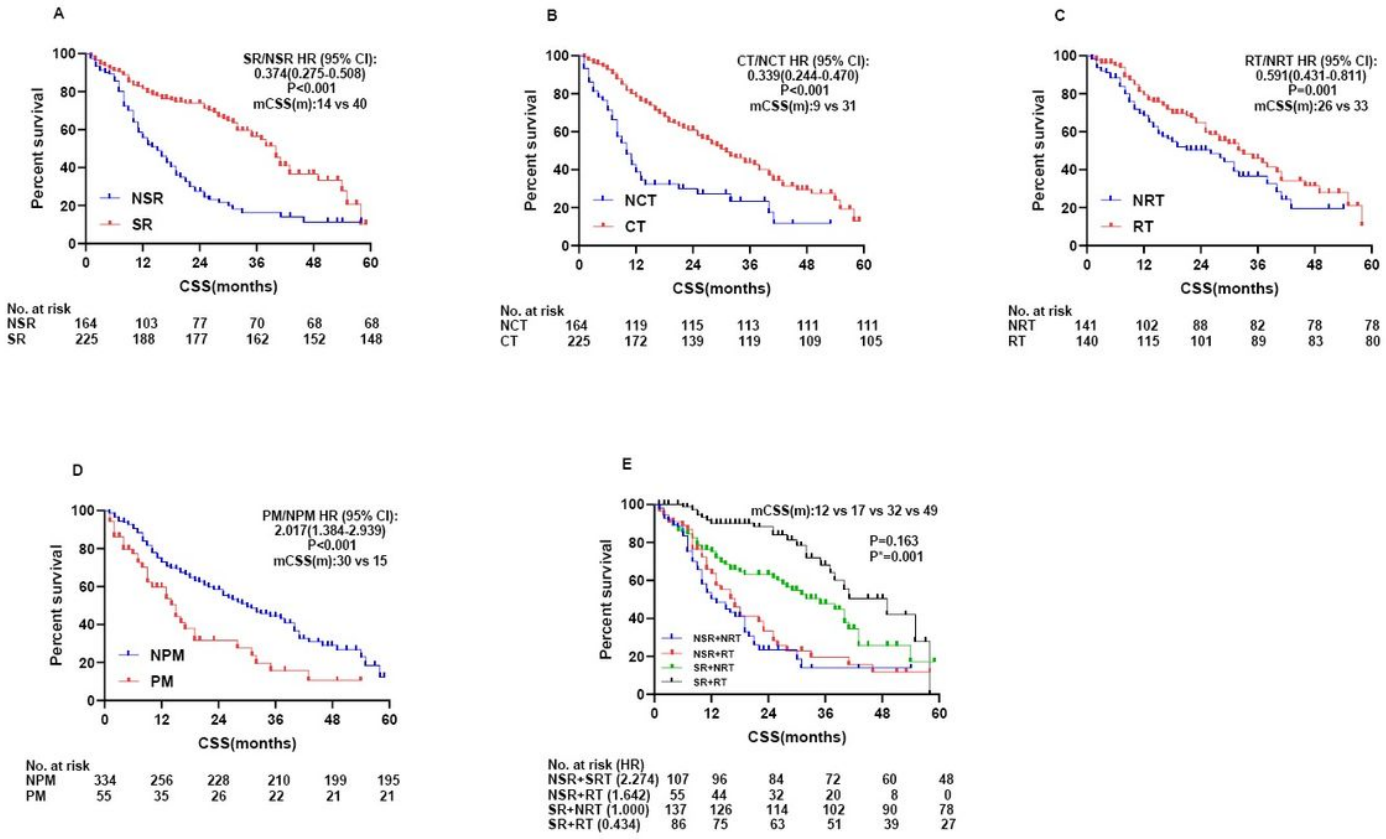

Figure 2

KM curves of CSS after PSM The cancer-specific survival of stage IV colorectal cancer patients after PSM. Primary tumor surgery (PTS). Hazard ratio (HR) is calculated by Univariate COX Analysis. (A) NSR= no surgery, SR= surgery. (B) NCT= no-chemotherapy, CT= chemotherapy. (C) NRT= no-radiotherapy, RT= radiotherapy. (D) NPM= no- peritoneum metastasis, PM= peritoneum metastasis. (E) Combination of surgery and radiotherapy; P: the p value between NSR+NRT and NSR+RT; P*: the p value between SRN+RT and SR+RT.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table13.pdf
- Table13.pdf
- PSMRcode.doc
- PSMRcode.doc