Survival outcomes in unresectable metastatic rectal cancer patients after both primary site resection and chemoradiotherapy: a SEER-based observational study

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Background: The liver is the most common site for rectal cancer metastasis, and liver resection combined with chemotherapy is the only treatment offering the possibility of long-term survival in patients with metastatic rectal cancer. However, a significant proportion of liver metastases cannot be surgically removed, and very limited data are available regarding the survival outcomes of these patients. This study aimed to investigate the survival pattern of rectal cancer patients with unresectable liver metastases after both chemoradiotherapy and primary tumor resection.

Methods: A total of 51,178 rectal cancer patients were identified from the Surveillance, Epidemiology, and End Results (SEER) database, of whom 448 had synchronous liver metastases and underwent both chemoradiotherapy and primary tumor resection. According to different treatment modalities, patients were divided into a hepatic resectable group and an unresectable group. The Kaplan-Meier method was used to estimate patient survival, and differences between the hepatic resectable and unresectable groups were compared using the log-rank test. Univariate and multivariate Cox regression models were used to analyze independent prognostic factors for unresectable tumors.

Results: Among the 448 metastatic rectal cancer patients, 60.3% (270) had unresectable liver metastasis. The median survival period, 2-year overall survival (OS) rate, and 5-year OS rate of the unresectable group were 37.0 months, 68.5%, and 32.9%, respectively, compared with 56.0 months, 87.4%, and 48.0%, respectively, in the hepatic resectable group (P<0.001). Multivariate Cox regression analysis suggested that a poor or undifferentiated histological type was independently associated with poor CSS in patients with unresectable liver metastases (P=0.001).

Conclusions: Primary tumor resection combined with chemoradiotherapy might be able to yield a satisfactory survival outcome in unresectable metastatic rectal cancer patients. Resection of liver metastases remains the primary treatment for prolonging the OS and CSS time in stage IV patients.

Keywords: Rectal cancer; liver metastasis; primary tumor resection; prognosis; the surveillance, Epidemiology, and End results database (SEER)

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Introduction

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 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 CRC patients present with liver metastases at the time of diagnosis, and almost 45–50% of patients develop liver metastases during the disease course (4,5). Currently, radical resection is the standard treatment for metastatic CRC patients. Unfortunately, liver metastases are unresectable in up to 85% of patients initially (6). The median survival period in patients with untreated liver metastases is reported to be approximately eight months, and the 5-year overall survival (OS) rate is less than 5% (7,8). Primary resection of liver metastases from CRC is potentially curative, with a 5-year survival rate of 40–50% and a 10-year survival rate of 20% (9,10).

Systemic chemotherapy represents the standard of care for metastatic patients, and it may result in the downstaging of metastases and the conversion of unresectable liver metastases to resectable metastases (9). Bismuth *et al.* (11) reported that neoadjuvant chemotherapy allows 15% of unresectable liver metastases to become resectable. However, liver metastases remain unresectable even after systemic therapy in most patients. According to the National Comprehensive Cancer Network (NCCN) guidelines, for synchronous unresectable metastases, the continuation of intensive chemotherapy (12) is recommended as the main therapeutic option, and other therapies include radiofrequency ablation therapy and molecular targeted therapy (13,14).

Many studies have confirmed the potential curability of simultaneous or staged resection of liver metastases. However, the majority of rectal cancer metastases are unresectable, and there are limited published data to date on the survival outcomes of unresectable patients who have received intensive systemic chemoradiotherapy (9,10). The primary aim of this study was to explore the survival outcomes of unresectable metastatic rectal cancer patients who had undergone systemic therapy and to identify risk factors that may affect prognosis. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1399/rc).

Methods

Data resources

We extracted rectal cancer data 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. It is an open public database; all patient data are deidentified; therefore, written informed consent was not needed for this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional ethical approval and informed consent were waived.

Study population

Initially, 51,178 rectal cancer patients diagnosed between January 1st, 2010, and December 31st, 2015, were identified using the SEER database. Tumor staging was performed according to the American Joint Committee on Cancer (AJCC) TNM staging system (7th edition). We included only patients with liver metastases and patients who received chemotherapy, radiotherapy, and primary tumor resection. The surgical procedure of the primary tumor included two modalities: (I) partial proctectomy, such as low anterior resection, Hartmann's operation, and total mesorectal excision, and (II) total proctectomy (abdominoperineal resection). Patients who underwent local tumor excision or local tumor destruction were excluded. We restricted the radiation code to beam radiation (radiation sequence y before surgery, after surgery, or both) and excluded other radiation codes (refused, none/unknown, radioactive implants, radioisotopes). In addition, 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 50,730 patients who were not eligible, 448 were included in
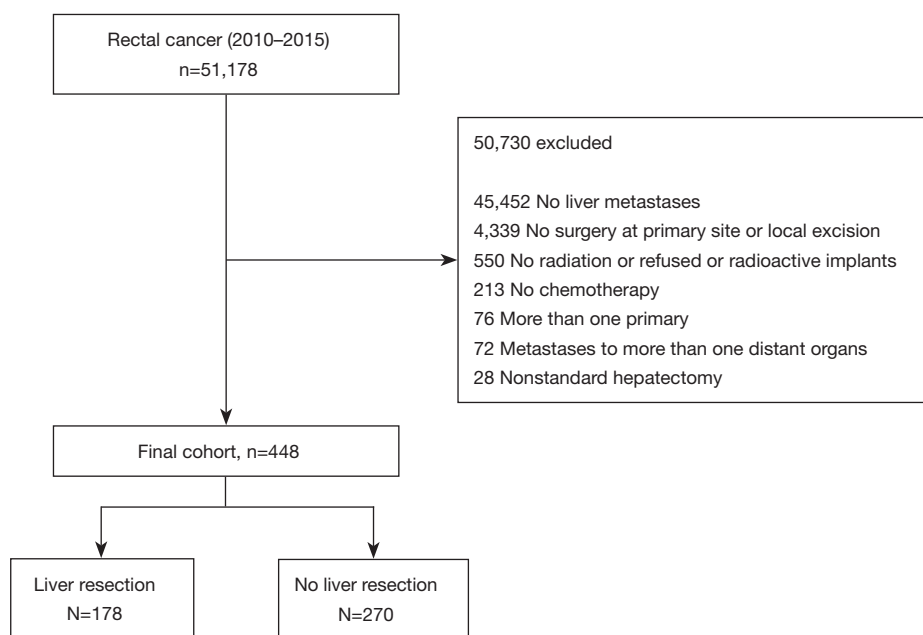
Figure 1 Flowchart of the inclusion and exclusion criteria.

this study. Patients were then stratified into two subgroups based on the treatment strategy of the liver metastases: (I) patients who received hepatic resection and (II) patients in whom hepatic resection was not performed (*Figure 1*). Other clinical characteristics, including sex, age, race, marital status, tumor grade, tumor size, AJCC T stage, and AJCC N stage, were also collected.

Statistical analysis

Baseline characteristics of the metastatic rectal cancer patients who had or had not undergone hepatic resection were compared using the chi-square test. Our primary outcomes were OS and cancer-specific survival (CSS). OS was defined as the time in months from diagnosis to either death or the last follow-up date, and CSS was defined as the time from the date of surgery to cancer-related death. The survival probability was estimated by the Kaplan-Meier method, and differences in survival between the two groups of patients were compared by using log-rank tests. Univariate and multivariate Cox regression models were used to identify prognostic factors in unresectable metastatic patients. The statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism (version 8, GraphPad Prism Software Inc.).

Results

Patient characteristics

The demographic data of metastatic rectal cancer patients are shown in *Table 1*. The mean age at diagnosis was 60.39±11.59 years. The majority of patients were male (65.6%), white (82.8%), and married (60.7%). Most of the patients (74.3%) had well or moderately differentiated tumors. Tumor size ≤5 cm 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, respectively; 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 are presented according to treatment modality in *Table 2*. There was no significant difference in sex, race, tumor grade, AJCC T stage, AJCC N stage, or marital status between the liver resectable group and the unresectable group. Liver resection was performed more often in patients aged <60 years (66.3% *vs.* 54.8%, P=0.016) and with a primary tumor size >5 cm (39.3% *vs.* 28.1%, P=0.014).

Patient survival

Kaplan-Meier curves for the OS and CSS of metastatic

Table 1 Baseline characteristics of unresectable metastatic rectal cancer patients (n=448)

Characteristics	Number of patients, n (%)
Age at diagnosis, years, no. (%)	
Mean ± SD	60.39±11.59
<60	266 (59.4)
≥60	182 (40.6)
Sex, no. (%)	
Male	294 (65.6)
Female	154 (34.4)
Race, no. (%)	
White	371 (82.8)
Black	32 (7.1)
Others	45 (10.0)
Marital status, no. (%)	
Married	272 (60.7)
Unmarried	154 (34.4)
Unknown	22 (4.9)
Tumor grade, no. (%)	
Poor + undifferentiated	66 (14.7)
Well + moderately	333 (74.3)
Unknown	49 (10.9)
Tumor size, cm, no. (%)	
0–5 cm	302 (67.4)
>5 cm	146 (32.6)
AJCC T stage, no. (%)	
T1/T2	47 (10.5)
T3/T4	401 (89.5)
AJCC N stage, no. (%)	
N0	106 (23.7)
N1/N2	342 (76.3)
Treatment modality, no. (%)	
Hepatic resection	178 (39.7)
Non-resection	270 (60.3)

SD, standard deviation; AJCC, American Joint Committee on Cancer.

rectal cancer patients are shown in *Figure 2*. The mean survival periods and 2- and 5-year OS rates of metastatic rectal cancer patients after both chemoradiotherapy and primary tumor resection are shown in *Table 3*. The median OS periods of the liver resectable patients and liver unresectable patients were 56.0 and 37.0 months, and the 5-year OS rates were 48.0% and 32.9%, respectively.

Subgroup univariate and multivariate Cox regression analyses were used to explore the risk factors for survival in unresectable metastatic rectal cancer patients. Univariate Cox regression analysis showed that male sex and poor or undifferentiated tumors were independent predictors of OS (HR, 1.332, 95% CI: 1.104–1.560, P=0.003; HR, 2.045; 95% CI: 1.370–3.055; P<0.001). Furthermore, in the multivariable Cox regression analysis, male sex (HR, 1.781; 95% CI: 1.190–2.373; P=0.003), an unmarried status (HR, 1.521; 95% CI: 1.055–2.193; P=0.025), and poor or undifferentiated tumors (HR, 2.059; 95% CI: 1.346–3.149; P=0.001) were confirmed to be independent risk factors for a poor prognosis (*Table 4*). The results of univariate and multivariate Cox regression analysis for cancer-specific survival of liver unresectable patients are described in *Table 5*. The Multivatiate Cox regression analysis suggested that a poor or undifferentiated histological type were independently associated with poor CSS in patients with unresectable liver metastases.

Discussion

CRC with liver metastases is a significant clinical problem. Fifteen percent to 25% of CRC patients present with synchronous liver metastases at the time of diagnosis, and in up to 85% of these patients, metastatic lesions cannot be surgically resected (5,6). Hepatic resection combined with chemotherapy is the standard treatment for metastatic rectal cancer patients and can lead to a 5-year OS rate of 40–50% (9). In our study, the 2- and 5-year OS rates in patients who underwent hepatic resection were 73.0% and 48.0%.

For unresectable metastatic patients, whether resection of the primary tumor affords a survival advantage remains controversial. According to the NCCN guidelines, if the primary tumor is not acutely obstructed, palliative resection of the primary tumor is rarely recommended

Table 2 Baseline characteristics of Group A (liver resectable) and B (liver unresectable)

Variables	Group A (n=178)	Group B (n=270)	P-value
Sex, no. (%)			0.713
Male	115 (64.6)	179 (66.3)	
Female	63 (35.4)	91 (33.7)	
Age, no. (%)			0.016
<60	118 (66.3)	148 (54.8)	
≥60	60 (33.7)	122 (45.2)	
Race, no. (%)			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, no. (%)			0.651
Poor + undifferentiated	24 (13.5)	42 (15.6)	
Well + moderately	132 (74.2)	201 (74.4)	
Unknown	22 (12.4)	27 (10.0)	
AJCC T stage, no. (%)			0.399
T1/T2	16 (9.0)	31 (11.5)	
T3/T4	162 (91.0)	239 (88.5)	
AJCC N stage, no. (%)			0.165
N0	36 (20.2)	70 (25.9)	
N1/N2	142 (79.8)	200 (74.1)	
Tumor size, no. (%)			0.014
0–5 cm	108 (60.7)	194 (71.9)	
>5 cm	70 (39.3)	76 (28.1)	
Marital status, no. (%)			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.

because incomplete resection of the tumor (R1/R2 resection) has not shown a survival benefit (15). However, two registry studies in the United States suggested that nearly 70% of metastatic CRC patients have undergone resection of the primary tumor, and both studies reported a significant survival advantage (16,17). Faron *et al.* (18) also reported the outcomes of 810 CRC patients with unresectable synchronous metastases; 59% (n=478) underwent resection of the primary tumor. Compared with patients in the nonprimary tumor resection group, those in the resection group were more likely to have lower baseline carcinoembryonic antigen (CEA) and alkaline phosphatase levels, and primary tumor resection was independently associated with better OS and PFS. The median survival periods of the primary tumor resection group and nonprimary tumor resection group were 19.2 months and 13.3 months (P<0.001), respectively (18). In clinical research, there are limited data
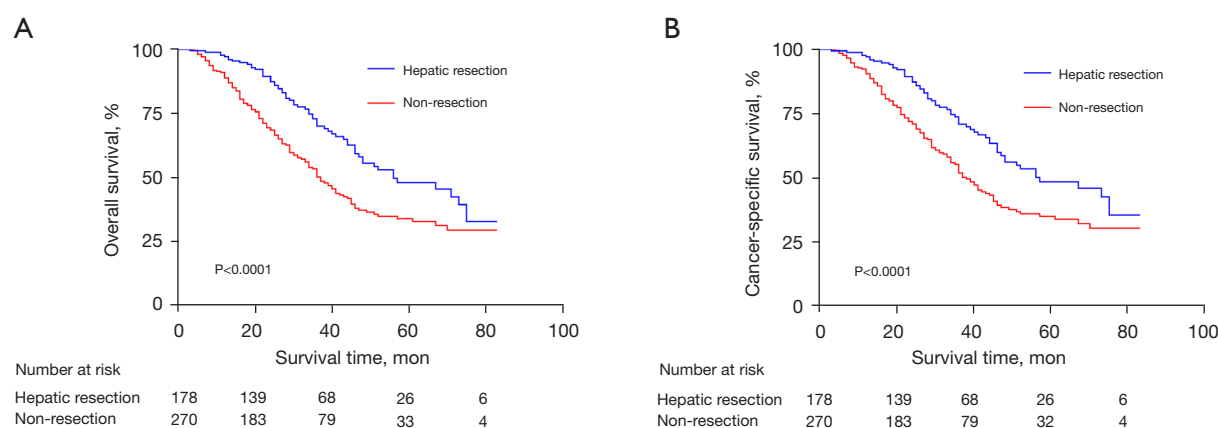
Figure 2 OS (A) and CSS (B) estimated with the Kaplan-Meier methods for metastatic rectal cancer patients. OS, overall survival; CSS, cancer-specific survival.

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

Variables	Mean survival (mons)	2-year OS	5-year OS
Liver resectable	56.0	0.874	0.480
Liver unresectable	37.0	0.685	0.329

OS, overall survival.

regarding the survival pattern of unresectable metastatic patients who have undergone both primary tumor resection and systemic therapy. Our study suggests a satisfactory survival outcome in these patients, with a median survival period of 37.0 months and a 5-year OS rate of 32.9%. Compared to the reported primary tumor resection rate of 70% in metastatic CRC patients, in our study, 24.2% of metastatic rectal cancer patients underwent surgery at the primary site (*Figure 1*). The main reasons for this difference may be that rectal surgery frequently requires a diverting stoma, and abdominoperineal resection has to be performed for patients with low rectal cancer, making neither surgeons nor patients willing to accept surgery as a preferred treatment method.

Compared with other studies (19,20), the OS rates of the unresectable metastatic rectal cancer patients in our study were satisfactory. After comparing the inclusion criteria of our study to those of others, we believe that the main difference is that we added radiotherapy to our inclusion criteria, and constantly updated chemotherapy and radiotherapy have played significant roles in the improvement of survival outcomes. Recently, total neoadjuvant therapy (TNT) approach is increasingly being utilized in clinical practice. The TNT approach,

which means induction or consolidation chemotherapy with chemoradiotherapy prior to surgery, was first used in patients with locally advanced rectal cancer p (T3/4, N0, or node positive). According to a large study conducted at the Memorial Sloan Kettering Cancer Center, the complete response (CR) rate in 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 who received TNT were more likely to complete the planned chemotherapy regiment with less dose reductions. Several advantages of the TNT approach have also been pointed out by some other relevant studies: the improved delivery of planned therapy, increased downstaging, and the *in vivo* assessment of chemosensitivity (21,22).

In our study, we also used univariate and multivariate Cox regression models to analyze the survival of unresectable metastatic rectal cancer patients. We found that poor or undifferentiated tumors, which accounted for 14.7% of all malignant neoplasms, were the strongest risk factor associated with a poor prognosis, consistent with previous reports (23,24); this might be because poor or undifferentiated cancer cells display reduced cohesiveness and have a stronger ability to invade surrounding tissues

Table 4 Subgroup univariate and multivariate Cox regression analyses for OS of liver unresectable patients (n=270)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, year				
<60	1		1	
≥60	0.770 (0.550–1.078)	0.127	0.731 (0.516–1.036)	0.078
Sex				
Female	1		1	
Male	1.332 (1.104–1.560)	0.003	1.781 (1.190–2.373)	0.003
Race				
White	1		1	
Black	1.058 (0.568–1.969)	0.859	1.144 (0.603–2.169)	0.68
Others	1.457 (0.895–2.371)	0.13	1.328 (0.800–2.205)	0.273
Marital status				
Married	1		1	
Unmarried	1.239 (0.877–1.751)	0.224	1.521 (1.055–2.193)	0.025
Unknown	0.775 (0.314–1.912)	0.58	0.750 (0.301–1.866)	0.536
Tumor grade				
Well + moderately	1		1	
Poor + undifferentiated	2.045 (1.370–3.055)	<0.001	2.059 (1.346–3.149)	0.001
Unknown	0.967 (0.552–1.695)	0.908	0.964 (0.541–1.716)	0.9
T-stage				
T1/T2	1		1	
T3/T4	1.534 (0.829–2.841)	0.173	1.700 (0.898–3.220)	0.103
N-stage				
N0	1		1	
N1/N2	1.204 (0.811–1.787)	0.358	0.864 (0.574–1.299)	0.482
Tumor size, cm				
0–5	1		1	
≥5	0.938 (0.654–1.345)	0.728	0.936 (0.641–1.366)	0.732

OS, overall survival.

and are more likely to metastasize to distant organs. Cox regression analysis also indicated that male sex was associated with a poor prognosis in stage IV patients. Several studies have shown that women are less likely to develop CRC than men, and women with CRC have a longer survival time than men (25,26). One explanation for the sex differences lies in circulating androgens, which will decrease the effectiveness of chemotherapy through the TUBB3 pathway in males (27). We also found that married patients had a better prognosis than unmarried patients, and some studies have indicated that psychosocial support is the reason for better survival (28).

One of the greatest strengths of the present study is the large sample size provided by the SEER database; however,

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Table 5 Subgroup univariate and multivariate Cox regression analyses for CSS of liver unresectable patients (n=270)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, year				
<60	1		1	
≥60	0.824 (0.655–1.126)	0.110	0.646 (0.365–1.024)	0.058
Sex				
Female	1		1	
Male	1.483 (1.116–1.705)	0.016	0.763 (0.390–1.254)	0.083
Race				
White	1		1	
Black	1.128 (0.798–1.583)	0.721	1.216 (0.613–2.235)	0.55
Others	1.283 (0.763–2.338)	0.21	1.422 (0.701–2.635)	0.339
Marital status				
Married	1		1	
Unmarried	1.325 (0.863–1.639)	0.252	1.471 (1.173–2.218)	0.066
Unknown	0.733 (0.332–1.875)	0.472	0.679 (0.366–1.975)	0.373
Tumor grade				
Well + moderately	1		1	
Poor + undifferentiated	2.292 (1.284–3.519)	<0.001	2.402 (1.304–3.295)	0.001
Unknown	0.870 (0.492–1.339)	0.908	0.997 (0.285–1.916)	0.840
T-stage				
T1/T2	1		1	
T3/T4	1.529 (0.811–2.53)	0.173	1.620 (0.838–3.442)	0.119
N-stage				
N0	1		1	
N1/N2	1.228 (0.821–1.942)	0.362	0.404 (0.274–1.199)	0.325
Tumor size, cm				
0–5	1		1	
≥5	0.946 (0.534–1.435)	0.629	0.749 (0.441–1.429)	0.647

CSS, cancer-specific survival.

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, the margin of resection, and postoperative complications and due to its retrospective nature, there may be selection bias in our study, a multicenter prospective research is needed to confirm these results. Second, the SEER database does not provide detailed information about chemoradiotherapy regimens, biological targeted therapy, CEA level, Kras, which could also influence prognosis. Third, it is not possible to distinguish between patients with isolated hepatic metastasis or multiple hepatic metastases, and there is little information about the treatment strategies for liver metastasis, which may also affect patient prognosis.

In conclusion, our results show that after chemoradiotherapy and primary tumor resection, the median survival period and 2-, and 5-year OS rates in unresectable metastatic rectal cancer patients were 37.0 months, 68.5%, and 32.9%, respectively. A poor or undifferentiated tumor is the strongest risk factor associated with poor survival outcomes.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1399/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1399/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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