IDO1/COX2 Expression Is Associated With Poor Prognosis In Colorectal Cancer Liver Oligo-metastases

Wenjuan Ma
Sun Yat-sen University Cancer Center
Xing Wang
Huazhong University of Science and Technology Tongji Medical College
Lulu Wang
Huazhong University of Science and Technology Tongji Medical College
Tinglan Chen
Sun Yat-sen University Cancer Center
Shanshan Hu
Rutgers University New Brunswick
Haineng Xu
University of Pennsylvania
Zhizhong Pan
Sun Yat-sen University Cancer Center
Gong Chen
Sun Yat-sen University Cancer Center
Zhongguo Zhou
Sun Yat-sen University Cancer Center
Rong-xin Zhang (zhangrx@sysucc.org.cn)
Sun Yat-sen University Cancer Center

Research

Keywords: Colorectal cancer, oligometastases, IDO1, COX2, prognosis.

Posted Date: July 8th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-40422/v1

Abstract

Background: IDO1 and COX2 have emerged as promising immunotherapy targets, and their inhibitors could enhance T cell responses to tumor cells. Whether IDO1 and COX2 expression in colorectal cancer (CRC) patients with liver oligometastases could be an independent predictor for overall survival (OS) and progression-free survival (PFS) is unclear. The purpose of this study was to investigate the correlation of IDO1 and COX2 expression with OS and PFS in CRC patients with liver oligometastases.

Methods: The expression levels of IDO1 and COX2 were assessed by immunohistochemistry in 107 specimens from patients with liver oligometastases. The correlation between the expression of IDO1 and COX2 and the clinicopathological parameters and OS/PFS in patients was examined.

Results: The expression level of IDO1/COX2 was significantly correlated with age and was not associated with gender, BMI, T stage, N stage, primary tumor size, liver metastasis size, CEA, CA19-9, CD3 TILs or CD8 TILs. In univariate analysis, we found that IDO1/COX2 expression, CEA and N stage all yielded significantly poor OS and PFS outcomes. In our multivariate Cox model, IDO1/COX2 coexpression, CEA and N stage were found to be significantly correlated with OS; IDO1/COX2 coexpression and CEA were significantly correlated with PFS.

Conclusions: IDO1/COX2 coexpression has a pivotal role and may act as a potential prognostic biomarker for survival in CRC patients with liver oligometastases.

Background

Colorectal cancer (CRC) is a leading cause of cancer-related death worldwide. The liver is recognized as the most common site of CRC metastasis, and approximately 14 to 18% of CRC patients are diagnosed at the first medical consultation, and more than 50% of patients with colorectal cancer will develop metastasis in the liver[1–4].

Accumulating evidence suggests that immunotherapy has become one of the most common treatments for CRC. A recent study showed that radiofrequency ablation (RFA) increased PD-L1 expression and infiltrating T cells in the tumor microenvironment in patients with synchronous colorectal cancer liver metastases, and then, through mouse tumor models, the results showed that the combined therapy of RFA and PD-1 blockade synergistically improved T cell-mediated immune responses and tumor rejection[5–7]. Several other inhibitory factors suppress T cell-mediated immune responses in the tumor microenvironment. The catabolism of tryptophan is an important pathway to establish innate and adaptive immune tolerance, which is driven by the rate-limiting enzymes indoleamine-2,3-dioxygenase 1 (IDO1) and tryptophan-2,3-dioxygenase 2 (TDO), resulting in a local decrease in tryptophan and accumulation of kynurenine and its derivatives[8]. T cells in the tumor microenvironment sense low tryptophan and high kynurenine via the mTORC and GCN signaling pathways to initiate an amino acid starvation response, resulting in T cell cycle arrest and favoring the differentiation of regulatory T cells, finally forming a profoundly immunosuppressive tumor microenvironment[9].

Cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) expression drive constitutive expression of IDO1 in many human tumor cells through the PKC and PI3K pathways [10]. The MAPK signaling pathway controls COX2 expression, which indirectly induces IDO1 expression. IFN-r is expressed by activated T cells and can induce IDO1 expression in most tissues and cell types, resulting in inhibiting T cell responses to tumor cells. Because most tumors carry oncogenic mutations in the MAPK signaling pathway, they may favor constitutive IDO1 expression without IFN-r[10]. Above all, IDO1 and COX2 have attracted attention in cancer research and may be promising prognostic and therapeutic biomarkers of tumor tissues.

IDO1 expression levels are correlated with the overall survival (OS) of several cancer types, such as endometrial carcinoma and liver and ovarian cancers [11–14]. One recent study showed that cytoplasmic IDO1/COX2 coexpression, but not nuclear IDO1/COX2 coexpression, could be identified as a poor independent predictor for OS in CRC patients[15]. However, whether IDO1/COX2 coexpression is correlated with OS and PFS in patients with liver metastases of colorectal cancer remains unknown.

In this study, we conducted a retrospective analysis for the potential prognostic importance of the correlation of IDO1/COX2 expression in OS and PFS in CRC patients with liver oligometastases of colorectal cancer.

Methods

Patients and specimens

This study was approved by the Institutional Review Board and Human Ethics Committee of Sun Yat-Sen University Cancer Center. Written consent for using the samples for research purposes was obtained from all patients before surgery. All tissues were collected from 107 patients who had undergone surgical resection from June 1, 1999 to December 1, 2016 at the Department of Colorectal Surgery of Sun Yat-sen University (Guangzhou, China). Patients from all the groups received colorectal tumor and hepatic oligometastatic resection at different time points. The eligibility criteria were as follows: (1) CRC with hepatic oligometastasis; (2) all tumor tissue pathological diagnoses confirmed to be CRC and liver metastases by a pathologist; and (3) none of the patients received anticancer therapies before the operation.

Immunohistochemical staining

A total of 107 CRC tumor tissues were used in the immunohistochemistry (IHC) analysis. All formalin-fixed, paraffin-embedded tumor specimens were cut into four-μm sections as previously described [15]. After baking for at 60 °C for 2 h, the samples were deparaffinized in xylene and rehydrated in a series of graded ethanol. Then, 3% hydrogen peroxide was used to block endogenous peroxidase activity for 10–15 min. The samples were microwaved for antigen retrieval for 30 min in 0.01 mol/L sodium citrate buffer (pH 6.0) and then preincubated for 30 min in 10% normal goat serum to block nonspecific staining; the sections were incubated with the primary rabbit anti-human COX2 monoclonal antibody (working

dilution, 1:200; Beijing Golden Bridge Biotechnology, China), rabbit anti-human IDO1 monoclonal antibody (working dilution, 1:100; Cell Signaling Technology, Danvers, MA, United States), mouse anti-human CD8 monoclonal antibody (working dilution, 1:100; Beijing Golden Bridge Biotechnology), and rabbit anti-human IDO1 monoclonal antibody (working dilution: 1:50; Beijing Golden Bridge Biotechnology) overnight at 4 °C. The next day, the samples were incubated at room temperature for 30 min with the secondary antibody (Dako, Glostrup, Denmark).

Assessments of the staining were scored by two experienced independent pathologists blinded to the patients' identity. H-scores of the percentage of positive tumor cells (0–100%) and dominant staining intensity (0 to 3) of immunostaining were used for the expression data analysis. The final quantitation of each specimen was obtained by multiplying the two scores. COX2 expression was considered high if the score was higher than the median score of 0.6. IDO1 expression was classified as high if the H-score was higher than 0.1. T cell infiltration of tumors was assessed by semiquantitative estimation of the density of CD8-positive/CD3-positive (CD8+/CD3+) cells. An H-score of 3+/4 + for CD8+/CD3 + expression was considered high[16].

Follow-up

The last follow-up date was April 1, 2018. All patients (65 males and 42 females) were followed up every three months in the first two years and every six months after that for a total of 5 years. Carbohydrate antigen 199 (CA199), carcinoembryonic antigen (CEA) and abdominal and pelvic ultrasound tests were recommended at baseline and every 3 to 6 months for two years, then every six months for a total of 5 years. Colonoscopy is recommended at approximately one year after resection.

During the follow-up, 74 patients (69.2%) were still alive. However, 33 patients (30.8%) died of cancer-related causes at the time of the last follow-up report. Overall survival (OS) was defined as the date of liver resection to the date of death or last follow-up. Progression-free survival (PFS) was measured from the date of surgery until the date of relapse or last follow-up.

Statistical analysis

The GraphPad Prism (version 7.0; GraphPad Software Inc, La Jolla, CA, United States) and SPSS software packages (version 23.0; IBM Corp, Armonk, NY, United States) were used for statistical analysis. The chi-square test was used to assess the correlation between clinicopathologic characteristics and IDO1 status. Survival curves were assessed by the Kaplan-Meier method, and the log-rank test generated differences between curves. P-values less than 0.05 were considered statistically significant.

Results

IDO1/COX2 expression in patients

To illuminate the biological significance of IDO1/COX2 in patients with liver oligometastases of colorectal cancer, we used immunohistochemical staining to test the expression of IDO1 and COX2 in 107

specimens. We detected high expression of IDO1 and COX2 in 72/107 (67.3%) and 69/107 (64.5%) primary CRC specimens, respectively (Fig. 1).

Correlation of IDO1/COX2 expression with clinicopathological variables

To gain insight into the role of the IDO1/COX2 expression level in CRC, we correlated IDO1/COX2 expression level in 107 patients with liver oligometastases of colorectal cancer with 11 widely recognized clinicopathological features (Table 1). IDO1/COX2 expression level was significantly correlated with age ($P = 0.004$); in contrast, we observed no correlation between IDO1/COX2 expression level and other clinical factors, such as gender, BMI, T stage, N stage, primary tumor size, liver metastases size, CEA, CA19-9, CD3 TILs and CD8 TILs (all $P > 0.05$).

Table 1
Correlation of IDO-1/COX2 expression with clinicopathological parameters in patients with liver metastases of colorectal cancer

Characteristics	No. of patients	IDO-1/COX2 expression (%)		*P*-value
		One or both low	Both high	
Gender				
Male	65	33 (50.8%)	32 (49.2%)	0.424
Female	42	18 (42.9%)	24 (57.1%)	
Age (years)				
≥ 60	51	17 (33.3%)	35 (66.7%)	0.004
< 60	56	34 (60.7%)	22 (39.3%)	
BMI				
≥ 25	25	13 (52.0%)	12 (48.0%)	0.620
< 25	82	38 (46.3%)	44 (53.7%)	
T stage				
4	32	12 (37.5%)	20 (62.5%)	0.415
2/3	75	39 (52.0%)	46 (48.0%)	
N stage				
1/2	63	28 (44.4%)	35 (55.6%)	0.425
0	44	23 (52.3%)	21 (47.7%)	
Primary tumor size (cm)				
> 5	20	9 (45.0%)	11 (55.0%)	0.791
≤ 5	87	42 (48.3%)	45 (51.7%)	
Liver metastases size (cm)				
> 2	44	21 (47.7%)	23 (52.3%)	0.991
≤ 2	63	30 (46.7%)	33 (53.3%)	
CEA in ng/mL				
> 5	62	28 (45.2%)	44 (54.8%)	0.195
≤ 5	45	23 (51.1%)	22 (48.9%)	
CA19-9 in U/mL				

Characteristics	No. of patients	IDO-1/COX2 expression (%)		*P*-value
		One or both low	Both high	
> 37	29	15 (51.7%)	14 (48.3%)	0.608
≤ 37	78	36 (46.2%)	42 (53.8%)	
CD3 TILs				
High	19	10 (52.3%)	9 (47.7%)	0.633
Low	88	41 (46.6%)	47 (53.4%)	
CD8 TILs				
High	18	10 (55.6%)	8 (44.4%)	0.462
Low	89	41 (46.1%)	48 (53.9%)	

Univariate analysis of the correlation of clinicopathological parameters with OS

To further confirm the effect of traditional clinicopathological parameters on OS in patients with liver oligometastases of colorectal cancer, we performed univariate analysis of traditional clinicopathological parameters for prognosis. The results revealed that N stage (1/2 vs. 0) ($P = 0.050$) and CEA level (ng/mL) (> 5 vs. ≤ 5) ($P = 0.024$) were significantly correlated with OS for patients with liver oligometastases of colorectal cancer (Fig. 2b-2c). We observed other clinicopathological parameters, such as gender, age, BMI, T stage, tumor size, liver metastasis size, CA19-9, CD3 TILs, and CD8 TILs, that were not significantly correlated with OS for patients with liver metastases of colorectal cancer (Fig. 2d-2n). We found that IDO1/COX2 coexpression (Group IV vs. Group I/II/III), not IDO1 or COX2 alone, was significantly correlated with OS ($P = 0.002$) (Fig. 2a).

Univariate analysis of the correlation of clinicopathological parameters with PFS

Kaplan-Meier analysis demonstrated that N stage (1/2 vs. 0) ($P = 0.026$) and CEA level (ng/mL) (> 5 vs. ≤ 5) ($P = 0.006$) were significantly correlated with PFS for patients with liver oligometastases of colorectal cancer (Fig. 3b-3c). Other traditional clinicopathological parameters, including gender, age, BMI, T stage, tumor size, liver metastasis size, CA19-9, CD3 TILs, and CD8 TILs, were not significantly correlated with PFS for patients with colorectal cancer liver oligometastases (Fig. 3d-3n). We also performed univariate analysis to assess whether IDO-1 and COX2 were associated with prognosis. We observed that IDO-1/COX2 coexpression, not IDO1 or COX2 alone, was significantly correlated with PFS ($P = 0.0024$) (Fig. 3a).

Multivariate analysis of the correlation of clinicopathological parameters with OS

We also performed multivariate Cox modeling to analyze whether traditional clinicopathological parameters and IDO-1/COX2 coexpression represent potential independent predictors for OS outcome in patients with liver oligometastases of colorectal cancer. We observed that CEA level (ng/mL) (> 5 vs. ≤ 5) (*P* = 0.050; HR = 2.137; 95% CI: 1.001–4.566) and IDO-1/COX2 (Group IV vs. Group I/II/III) (*P* = 0.037; HR = 2.315; 95% CI: 1.052–5.102) were significantly correlated with OS for patients with liver oligometastases of colorectal cancer (Table 2). However, IDO-1 or COX2 could not be an individual predictor for OS in multivariate Cox modeling. Other traditional clinicopathological parameters, including gender, age, BMI, T stage, N stage, primary tumor size, liver metastasis size, CA19-9, CD3 TILs, and CD8 TILs, were not significant with OS for patients with liver oligometastases of colorectal cancer (Table 2).

Table 2
Univariate and multivariate analysis of the correlation of clinicopathological parameters with prognosis in patients with liver metastases of colorectal cancer

Variables*	OS				PFS			
	Univariate	Multivariate			Univariate	Multivariate		
	P-value	*P*-value	HR	95% CI	*P*-value	*P*-value	HR	95% CI
Gender (Male vs. Female)	NS	NS			NS	NS		
Age, years (≥ 60 vs. < 60)	NS	NS			NS	NS		
BMI (≥ 25 vs. < 25)	NS	NS			NS	NS		
T stage (4 vs. 2/3)	NS	NS			NS	NS		
N stage (1/2 vs. 0)	0.050	NS			0.026	NS		
Primary tumor size (cm) (> 5 vs. ≤ 5)	NS	NS			NS	NS		
Liver metastases size (cm) (> 2 vs. ≤ 2)	NS	NS			NS	NS		
CEA (ng/mL) (> 5 vs. ≤ 5)	0.024	0.050	2.137	1.001–4.566	0.006	0.007	2.538	1.291-5.000
CA19-9 (U/mL) (> 37 vs. ≤ 37)	NS	NS			0.19	NS		
CD3 TILs (High vs. Low)	NS	NS			NS	NS		
CD8 TILs (High vs. Low)	NS	NS			NS	NS		
IDO-1 (High vs. Low)	NS	NS			NS	NS		
COX2 (High vs. Low)	NS	NS			NS	NS		
IDO-1/COX2 (Group IV vs. Groups I/II/III)	0.002	0.037	2.315	1.052–5.102	0.0024	0.013	2.347	1.197–4.608

Multivariate analysis of the correlation of clinicopathological parameters with PFS

We demonstrated that CEA level (ng/mL) (> 5 vs. ≤ 5) (P = 0.007; HR = 2.538; 95% CI: 1.291-5.000) and IDO-1/COX2 (Group IV vs. Group I/II/III) (P = 0.013; HR = 2.347; 95% CI: 1.197–4.608) were significantly correlated with PFS for patients with liver oligometastases of colorectal cancer (Table 2). However, IDO-1 or COX2 could not be an individual predictor for PFS in multivariate Cox modeling. Other traditional clinicopathological parameters, such as gender, age, BMI, T stage, N stage, tumor size, liver metastasis size, CA19-9, CD3 TILs, and CD8 TILs, were not significant with PFS for patients with liver oligometastases of colorectal cancer (Table 2).

Discussion

Although current immunotherapy has achieved promising results in many tumor types, such as melanoma and non-small cell lung cancer, more than 50% of cancer patients will progress with resistance to immunotherapy and will need more new therapies. Tumors that avoid immune destruction are dependent on various mechanisms. IDO1 expression is associated with T-cell infiltration and is induced by the IFN-r produced by infiltrating T cells. A recent study also showed that tumor cells that produce IDO1 are constitutively dependent on COX2 and PGE2 via the PKC and PI3K pathways and continuously prevent T-cell infiltration. Therefore, inhibiting IDO1 has become a new target for cancer therapy. One recent study validated that a COX2 inhibitor or an IDO1 inhibitor could reject tumors in NSG mice. In previous studies, high IDO1 expression in CRC was significantly correlated with a reduction in CD3-positive TILs and the presence of metastatic disease, revealing the important role of IDO1 in the therapeutic blockade for this disease. We recently evaluated treated and untreated CRC patients for celecoxib, an inhibitor of COX2, and found that cytoplasmic IDO1 and COX2, but not nuclear IDO1 and COX2, were correlated with OS in patients treated with or without celecoxib. However, clinical studies have not been shown to show IDO1 and COX2 coexpression in CRC patients with liver oligometastases of colorectal cancer.

In the present study, univariate analysis, but not multivariate analysis, revealed that N stage was correlated with OS and PFS in CRC patients with liver oligometastases of colorectal cancer. In both the univariate and multivariate analysis results, CEA and IDO-1/COX2 were significantly associated with OS and PFS in our patients. As CRC cells lose their polarity, CEA begins to accumulate on the surface of cells and is then released into the bloodstream. As such, the amount of CEA increases as the tumor size increases. Our results showed that CEA might be an independent prognostic factor for CRC patients with liver oligometastases. In our previous study, we found that the coexpression of cytoplasmic IDO-1/COX2 plays a key role in survival prognosis for CRC patients treated with or without celecoxib. Furthermore, in CRC patients with liver oligometastases, IDO-1/COX2 could be an independent prognostic factor for OS and PFS. In this study, individual IDO1 or COX2 had no significant relationship with OS and PFS, and

there may be other signaling pathways activating IDO1 expression in CRC patients with liver oligometastases.

There are limitations to our study. First, to minimize bias and immunohistochemistry methodological limitations, we adopted rigorous standardized assay methods, and two well-trained and blinded clinical pathologists independently affirmed immunohistochemistry scores. Second, the number of patients is modest. More specimens need to be collected to confirm our results, and more CRC liver oligometastases patients need to be considered. Lastly, this study was a retrospective study with its intrinsic associated limitation.

Conclusions

The results of our current study reveal that CEA and IDO-1/COX2 may serve as feasible biomarkers for prognostic prediction to predict CRC patients with liver oligometastases of colorectal cancer OS and PFS.

Declarations

Ethics approval and consent to participate

Sun Yat-sen University Cancer Center ethic committee approved this article.

Consent for publication

Not applicable.

Availability of data and material

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

Competing interests

All authors declare no competing interests.

Authors' contributions

Wen-juan Ma and Xing Wang carried out the data analysis and wrote the manuscript; Lulu Wang did the IHC staining; Tinglan Chen, Shanshan Hu and Haineng Xu did statistic analyze; Zhizhong Pan and Gong Chen supervised the research program and edited the manuscript, Zhongguo Zhou and Rongxin Zhang designed the research and reviewed the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We would like to give our thanks to Dr. Yang Zhao and Bin-yin Xiao for collecting clinical samples. The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (www.researchdata.org. cn).

Funding

The work was supported by grants from the National Natural Science Foundation of China (Grant Nos. 81502459 and 81602143), and research fund from CSCO (Chinese Society of Clinical Oncology).

References

1. Gogna S, Goyal P. Recent Strategies and Paradigm Shift in Management of Hepatic Metastasis from Colorectal Cancer. Indian J Surg Oncol. 2018;9:456–60.
2. Campos-da-Paz M, Dorea JG, Galdino AS, Lacava ZGM, Almeida Santos MFM. **Carcinoembryonic Antigen (CEA) and Hepatic Metastasis in Colorectal Cancer: Update on Biomarker for Clinical and Biotechnological Approaches**. *Recent Pat Biotechnol* 2018.
3. Valderrama-Trevino AI, Barrera-Mera B, Ceballos-Villalva JC, Montalvo-Jave EE. Hepatic Metastasis from Colorectal Cancer. Euroasian J Hepatogastroenterol. 2017;7:166–75.
4. Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, Kemeny N, Brennan MF, Blumgart LH, D'Angelica M. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol. 2007;25:4575–80.
5. Wissniowski TT, Hansler J, Neureiter D, Frieser M, Schaber S, Esslinger B, Voll R, Strobel D, Hahn EG, Schuppan D. Activation of tumor-specific T lymphocytes by radio-frequency ablation of the VX2 hepatoma in rabbits. Cancer Res. 2003;63:6496–500.
6. Dromi SA, Walsh MP, Herby S, Traughber B, Xie J, Sharma KV, Sekhar KP, Luk A, Liewehr DJ, Dreher MR, et al. Radiofrequency ablation induces antigen-presenting cell infiltration and amplification of weak tumor-induced immunity. Radiology. 2009;251:58–66.
7. Shi L, Chen L, Wu C, Zhu Y, Xu B, Zheng X, Sun M, Wen W, Dai X, Yang M, et al. PD-1 Blockade Boosts Radiofrequency Ablation-Elicited Adaptive Immune Responses against Tumor. Clin Cancer Res. 2016;22:1173–84.
8. Hennequart M, Pilotte L, Cane S, Hoffmann D, Stroobant V, Plaen E, Van den Eynde BJ. Constitutive IDO1 Expression in Human Tumors Is Driven by Cyclooxygenase-2 and Mediates Intrinsic Immune Resistance. Cancer Immunol Res. 2017;5:695–709.
9. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366:2455–65.
10. Brandacher G, Perathoner A, Ladurner R, Schneeberger S, Obrist P, Winkler C, Werner ER, Werner-Felmayer G, Weiss HG, Gobel G, et al. Prognostic value of indoleamine 2,3-dioxygenase expression in colorectal cancer: effect on tumor-infiltrating T cells. Clin Cancer Res. 2006;12:1144–51.

11. Gao YF, Peng RQ, Li J, Ding Y, Zhang X, Wu XJ, Pan ZZ, Wan DS, Zeng YX, Zhang XS. The paradoxical patterns of expression of indoleamine 2,3-dioxygenase in colon cancer. J Transl Med. 2009;7:71.
12. Ino K, Yoshida N, Kajiyama H, Shibata K, Yamamoto E, Kidokoro K, Takahashi N, Terauchi M, Nawa A, Nomura S, et al. Indoleamine 2,3-dioxygenase is a novel prognostic indicator for endometrial cancer. Br J Cancer. 2006;95:1555–61.
13. Takamatsu M, Hirata A, Ohtaki H, Hoshi M, Ando T, Ito H, Hatano Y, Tomita H, Kuno T, Saito K, et al. Inhibition of indoleamine 2,3-dioxygenase 1 expression alters immune response in colon tumor microenvironment in mice. Cancer Sci. 2015;106:1008–15.
14. Asghar K, Farooq A, Zulfiqar B, Rashid MU. Indoleamine 2,3-dioxygenase: As a potential prognostic marker and immunotherapeutic target for hepatocellular carcinoma. World J Gastroenterol. 2017;23:2286–93.
15. Ma WJ, Wang X, Yan WT, Zhou ZG, Pan ZZ, Chen G, Zhang RX. Indoleamine-2,3-dioxygenase 1/cyclooxygenase 2 expression prediction for adverse prognosis in colorectal cancer. World J Gastroenterol. 2018;24:2181–90.
16. Dahlin AM, Henriksson ML, Van Guelpen B, Stenling R, Oberg A, Rutegard J, Palmqvist R. Colorectal cancer prognosis depends on T-cell infiltration and molecular characteristics of the tumor. Mod Pathol. 2011;24:671–82.

Figures

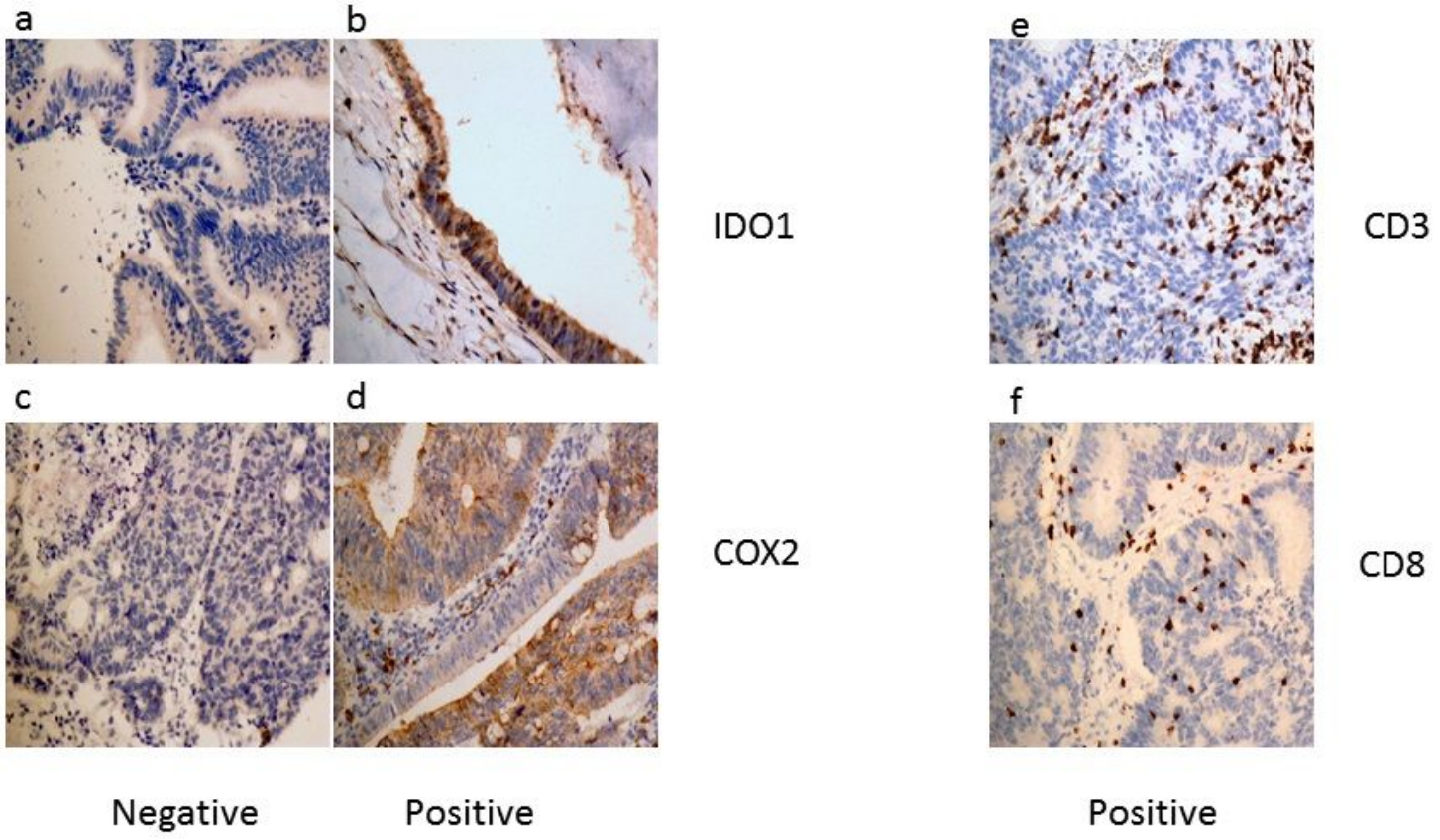

Figure 1

IDO1, COX2, CD3 and CD8 expression in CRC patients with liver oligometastases. (a) Immunohistochemistry (IHC) of negative IDO1 expression in CRC liver oligometastases; (b) immunohistochemistry (IHC) of positive IDO1 expression in CRC patients with liver oligometastases; (c) immunohistochemistry (IHC) of negative COX2 expression in CRC liver oligometastases; (d) immunohistochemistry (IHC) of positive COX2 expression in CRC liver oligometastases; (e) immunohistochemistry (IHC) of positive CD3 expression in CRC liver oligometastases; (f) immunohistochemistry (IHC) of positive CD8 expression in CRC liver oligometastases.

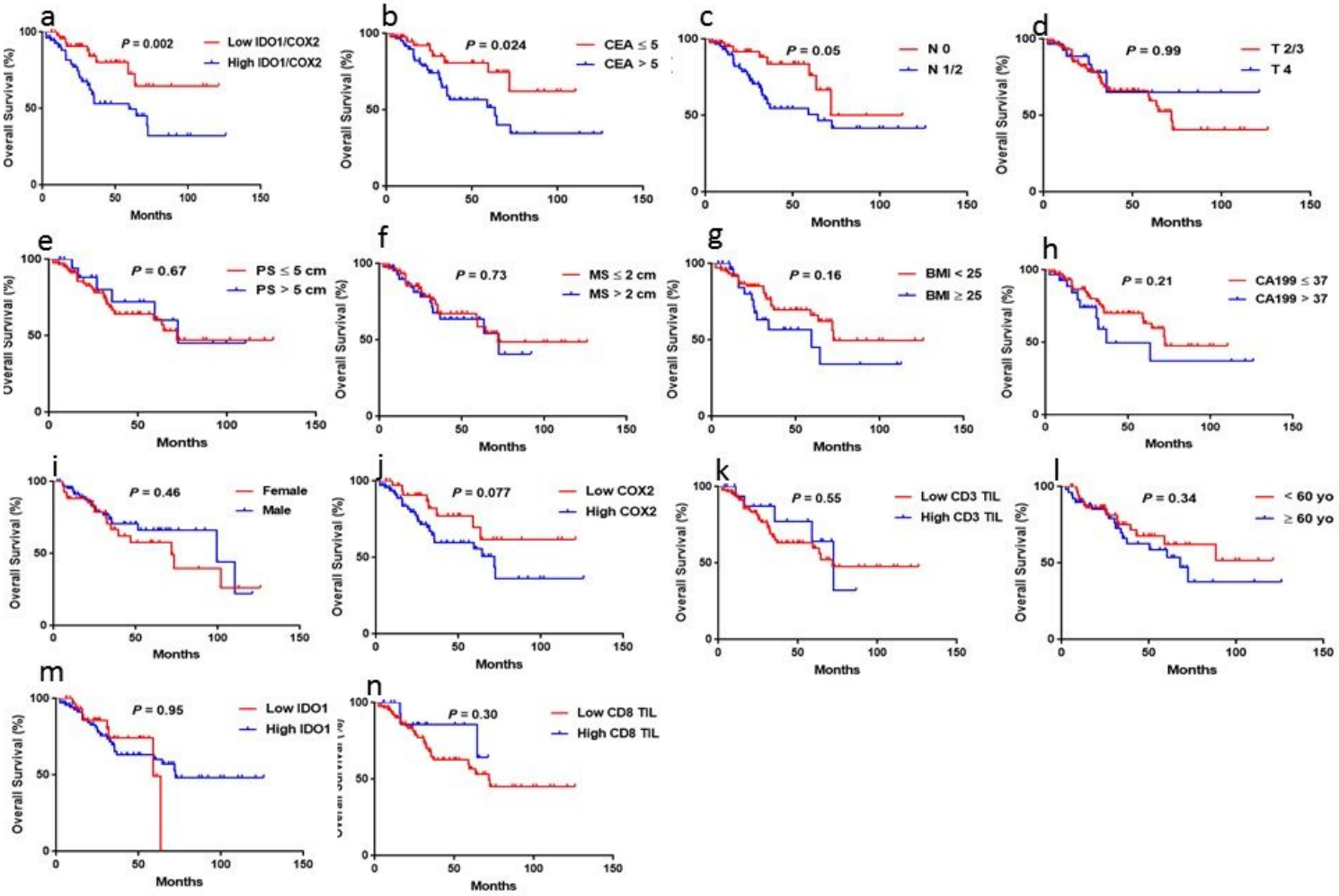

Figure 2

Correlation of the clinicopathological parameters with OS in CRC patients with liver oligometastases. Survival curves were generated using the Kaplan-Meier method, and differences between survival curves were estimated by the log-rank test. (a) We divided all patients into four groups based on the level of IDO1 and COX2 expression. Group I: IDO1LowCOXLow; Group II: IDO1HighCOXLow; Group III: IDO1LowCOXHigh; Group IV: IDO1HighCOXHigh. The association of the four groups (IV vs I / II /III) with OS was significant (P = 0.002); (b-c) correlation between CEA and N stage and OS in patients; b: CEA (P = 0.024); c: N stage (P = 0.05). (d-n): Correlation between other clinicopathological parameters and OS in patients. (P > 0.05).

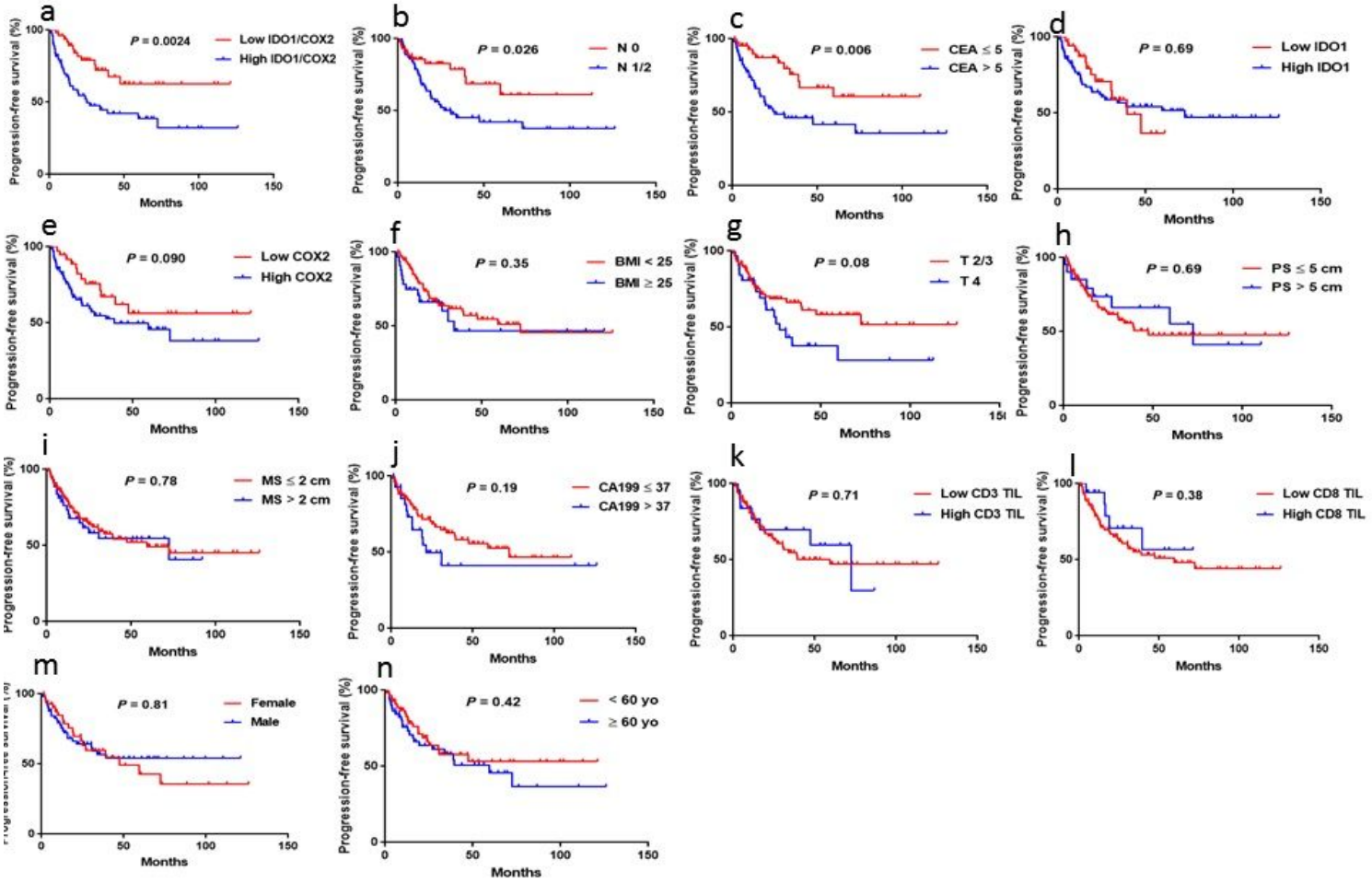

Figure 3

Correlation of the clinicopathological parameters with PFS in CRC patients with liver oligometastases. Survival curves were generated using the Kaplan-Meier method, and differences between survival curves were estimated by the log-rank test. (a) We divided all patients into four groups based on the level of IDO1 and COX2 expression. Group I: IDO1LowCOXLow; Group II: IDO1HighCOXLow; Group III: IDO1LowCOXHigh; Group IV: IDO1HighCOXHigh. The association of the four groups (IV vs I / II /III) with PFS was significant (P = 0.0024); (b-c) correlation between CEA and N stage and PFS in patients; c: N stage (P = 0.026); b: CEA (P = 0.006). (d - n): Correlation between other clinicopathological parameters and PFS in patients. (P > 0.05).