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The prognostic role of $\gamma\delta$ T cells in colorectal cancer based on nomogram



Rulan Ma^{1,2}, Meijun Gong¹, Tuanhe Sun¹, Lin Su² and Kang Li^{1*}

Abstract

Objective The aim of the present study was to explore the prognostic role of $\gamma\delta$ T cells in colorectal cancer, and establish a nomogram for predicting the survival of the patients.

Methods Immunohistochemistry was performed to analyze the infiltration degree of $\gamma\delta$ T cells in tumor and normal tissues of colorectal cancer. The relationship between $\gamma\delta$ T cells infiltration in tumor tissues and the prognosis of patients with colorectal cancer were determined by Cox regression analysis and survival analysis. R software was used to establish and verify a nomogram for predicting the prognosis of patients with colorectal cancer.

Results The degree of $\gamma\delta$ T cell infiltration in tumor tissues and normal tissues of CRC was not different (t=0.35, P=0.73). However, the infiltration of $\gamma\delta$ T cell was related to the survival status of the patients (x^2 =4.88, P=0.03). Besides, the infiltrating degree of $\gamma\delta$ T cells in tumor tissue was obviously related to the prognostic improvement of the patients with colorectal cancer (log-rank P=0.02) and could reflect the benefit of adjuvant chemotherapy. The nomogram based on tumor diameter, tumor location, AJCC stage, chemotherapy, serum CEA level and $\gamma\delta$ T cell infiltration was established and could provide a reference for predicting the survival of colorectal cancer patients.

Conclusion $\gamma \delta T$ cell infiltration degree in tumor tissue was an important factor to improve the outcome of patients with colorectal cancer, and can predict the benefit of adjuvant chemotherapy.

Keywords Colorectal cancer, $\gamma\delta$ T cell, Prognosis, Adjuvant chemotherapy, Nomogram

Introduction

Colorectal cancer (CRC) is one of the most malignant tumors. Globally, the incidence of CRC ranks 3rd, and CRC is the 2nd leading cause of tumor death [1]. According to the latest research, about 1.8 million patients worldwide were diagnosed with CRC, and about 0.86 million patients died of CRC in 2018 [2]. Although the mortality rate of CRC has shown an overall descending trend in the last several decades, the incidence of CRC has increased year by year among patients under the age of 50 [3, 4]. At present, surgery-based treatment is mainly aimed at CRC patients in the early stages. However, for patients with advanced CRC, especially those with distant metastasis, radical surgery cannot be performed, and the progress of CRC can only be controlled by radiotherapy, chemotherapy, endocrine therapy or immunotherapy. Hence, it is crucial to search for a novel prognostic factor and treatment target for CRC.

 $\gamma\delta$ T cells are a unique subset of T lymphocytes and an important component of the innate immune system in the human body, participating in the formation of the first line of defense against pathogens [5]. They can recognize and kill tumor cells in a manner that does not depend on MHC-I molecules. Researches have shown that $\gamma\delta$ T cells can directly kill tumor cells by secreting cytokines such as IFN- γ , TNF- α , perforin, granzyme B,



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and they can also exert anti-tumoral effect through the death receptor-ligand pathway, antibody-mediated cell cytotoxicity, or direct contact [6-9]. However, some studies have also shown that $\gamma\delta$ T cells can exert a protumoral effect by recruiting myeloid-derived suppressor cells, inflammatory monocytes, and neutrophils through secreting IL-17 and other pro-inflammatory cytokines [10–14]. Previous studies on the prognosis of $\gamma\delta$ T cells in tumors have shown that in gastric cancer, the degree of infiltration of $\gamma\delta$ T cells is related to improved patient prognosis and benefits from postoperative adjuvant chemotherapy [15]. However, in other tumors such as breast cancer, gallbladder cancer, and ovarian cancer, the increased infiltration of $\gamma\delta$ T cells in tumor tissue is closely related to poor prognosis [16-18]. These suggest that $\gamma\delta$ T cells play different roles in different types of tumors.

In CRC, Meraviglia S and Gentles AJ et al. reported that increase of $\gamma\delta$ T cells could obviously improve the prognosis of patients [7, 19]. However, these two studies are bioinformatics analysis and lack experimental verification. A later study suggested that the sorting algorithm used by Gentles AJ et al. could not accurately distinguish CD8⁺ T cells, $\gamma\delta$ T cells and NK cells because of the overlap of transcriptome [20]. Therefore, the elevated infiltration of $\gamma\delta$ T cells was not always related to the better prognosis of CRC patients [20]. Besides, Pin Wu et al. confirmed the positive correlation between the degree of infiltration of $\gamma\delta T17$ cells in tumor tissues and the clinical and pathological characteristics of CRC patients, as well as its promoting effect on human CRC and its mechanism [14]. These studies indicate that the role played by $\gamma\delta$ T cells in the prognosis of CRC is still controversial. Therefore, it is necessary to further validate the relationship between $\gamma\delta T$ cell infiltration and the prognosis and clinical pathological characteristics of CRC cancer patients.

Thus, in this study, we aimed to confirm the relationship of $\gamma\delta$ T cell infiltration with the prognosis of CRC patients and establish a prediction model for forecasting survival rate of CRC patients based on $\gamma\delta$ T cell infiltration degree, thereby providing a new prognostic indicator for CRC patients.

Methods

Patients

Fifty-eight paraffin-embedded tumor tissue samples and 20 matched adjacent normal tissue samples were collected. All CRC patients received operations from January 2010 to December 2013 in the First Affiliated Hospital of Xi'an Jiaotong University. The inclusion criteria were as follows: (1) age: 18–75 years old; (2) postoperative pathology: CRC; (3) the clinicopathological data and follow-up data were completed. This study was carried out under the approval and supervision of the Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University (No. XJTU1AF2022LSK-250).

Immunohistochemistry

Tissue specimens were embedded in paraffin, sliced into serial 4-mm sections. The slides were deparaffinized, rehydrated and incubated with the primary antibody (anti-TCR gamma/delta antibody, VA288448, 1:100 dilution, Invitrogen, USA) overnight at 4 °C. Then, the slides were incubated with the secondary antibody (Goat antirabbit IgG, 1:200 dilution, Thermo Fisher Scientific, USA) for 60 min at 24 °C. The slides were stained with hematoxylin, dehydrated and slip-covered. Images of stained slides were obtained using an optical microscope.

The sections were observed under a microscope at low magnification. Yellow or brown cell were recognized as the positive cells. The Leica Microsystems was used to scan the slice at 200×magnification. Qualitative and quantitative analysis was performed by using IHC Profiler plug-in of Image J software. The bar value was set to 100 µm. Five visual fields were randomly selected for each slice to determine the positive rate, and the average value was recognized as the positive expression rate of $\gamma\delta$ T cells in this slide. The average positive rate of $\gamma\delta$ T cells in per three consecutive sections was taken as the degree of infiltration of $\gamma\delta$ T cells in the tumor or adjacent normal tissues of the patient. Our study showed that the cut-off value of $\gamma\delta$ T cell infiltration in tumor tissue was 57.32%, thus defining \geq 57.32% as high $\gamma\delta$ T cell infiltration and < 57.32% as low $\gamma\delta$ T cell infiltration.

Statistical analysis

The statistical analysis was performed by SPSS 26.0 and Graphpad Prism 8.0. The data are expressed as $x \pm S$ or ratio. The differences between the two groups are analyzed by t-test, Chi-squared test or Fisher's exact probability method. Univariable and multivariable analysis was conducted by using Cox regression analysis. The factors with P-value < 0.05 in univariable analysis into further multivariable analysis. Kaplan-Meier method was used to analyze the cumulative survival rate, and the log-rank test was used to analyze the survival difference. According to the result of multivariable Cox regression analysis, a nomogram was established by using R 3.6.2. 1000 Bootstrap resampling internal verification and calibration curve were performed to validate the nomogram. The accuracy of the nomogram was evaluated by concordance index (C-index). The closer the C-index is to 1, the more accurate the prediction ability of the nomogram.

Results

The clinicopathological features of the patients

In our study, the tumor tissues of 58 CRC patients and 20 matched adjacent normal tissues were included. Among these patients, 33 cases are males and 25 cases are females, with an average age of 60.45 ± 2.18 years old. The basic clinical and pathological features of the patients are shown in Table 1.

Table 1 Clinicopathological features of 58 patients withcolorectal cancer

Variables	ltems	Ν	%
Gender	Male	33	56.90
	Female	25	43.10
Age (Y)	≥50	50	86.21
(60.45±12.18)	< 50	8	13.79
Tumor location	Rectum	40	68.97
	Right semi-colon	10	17.24
	Left semi-colon	5	8.62
	Whole colon	3	5.17
Tumor diameter (cm)	≥5	25	43.10
(4.25±1.47)	<5	33	56.90
Grade	1	3	8.57
	II	29	82.86
	111	3	8.57
Т	Tis	1	1.72
	1	2	3.45
	2	11	18.97
	3	31	53.45
	4	13	22.41
Ν	0	38	65.52
	1	14	24.14
	2	6	10.34
Μ	0	51	87.93
	1	7	12.07
AJCC stage	0	1	1.72
	1	12	20.69
	2	23	39.66
	3	15	25.86
	4	7	12.07
Intravascular infiltration	Yes	1	1.72
	No	57	98.28
Chemotherapy	Yes	26	44.83
	No	32	55.17
Radiotherapy	Yes	54	93.10
	No	4	6.90
CEA (ng/mL)	≥5	18	31.03
(28.38±88.40)	<5	40	68.97

Infiltrating degree of $\gamma\delta\,T$ cells in tumor tissues and adjacent normal tissues of CRC patients

The result of immunohistochemistry showed that the positive rate of $\gamma\delta$ T cell expression in tumor tissues was 56.72% ± 11.72%, while that in adjacent normal tissues was 55.66% ± 12.39% (Fig. 1A, B). Student's t-test showed that the relative abundance of $\gamma\delta$ T cells in CRC tumor tissues was not different from the infiltrating degree of $\gamma\delta$ T cells in adjacent normal tissues (t=0.35, *P*>0.05) (Fig. 1B).

The relationship between the tumor-infiltrating degree of $\gamma\delta\,T$ cells and the clinicopathological features of patients with CRC

The relationship between clinicopathological characteristics and the degree of $\gamma\delta$ T cell infiltration in tumor tissue was analyzed by x^2 test. The results suggested that the infiltrating degree of $\gamma\delta$ T cells in tumor tissue was not related to age, gender, tumor size, TNM stage and so on, but it was relevant to the survival status of the patients (x^2 =4.884, P=0.027) (Table 2).

The relationship of $\gamma\delta$ T cell infiltration degree in tumor tissues with the prognosis of patients with CRC

In order to determine whether the tumor-infiltrating degree of $\gamma\delta$ T cells was related to the prognosis of the patients with CRC, we utilized the Kaplan-Meier method to calculate the cumulative survival rate of patients with low or high $\gamma\delta$ T cell infiltration. The difference in the survival rates between the two groups was evaluated by the log-rank test. The results showed that the lower tumor-infiltrating degree of $\gamma\delta$ T cells was related to the poorer prognosis of CRC patients, while the higher the infiltrating degree of $\gamma\delta$ T cells in tumor tissues, the better the prognosis (log-rank *P*=0.016) (Fig. 2).



Fig. 1 Expression of $\gamma\delta$ T cells in tumor tissues and adjacent normal tissues in colorectal cancer. **A** Results of immunohistochemistry. **B** Quantitative analysis. *T* tumor tissues, *N* adjacent normal tissues

Variables	ltems	γδ T infiltration		P-value
		High	Low	
Gender	Male	13	12	0.79
	Female	16	17	
Age (Y)	≥50	4	4	1.00 ^a
	< 50	25	25	
Tumor location	Rectum	19	21	0.57
	Colon	10	8	
Tumor diameter (cm)	≥5	12	13	0.79
	< 5	17	16	
Grade	I	2	1	0.60 ^a
	/	15	17	
Т	Tis/0/1/2	6	8	0.54
	3/4	23	21	
Ν	0	17	21	0.27
	1/2	12	8	
Μ	0	23	28	0.10 ^a
	1	6	1	
AJCC stage (Version 8.0)	0/1/11	16	20	0.28
	III/IV	13	9	
Adjuvant chemotherapy	Yes	17	15	0.60
	No	12	14	
Adjuvant radiotherapy	Yes	3	1	0.61 ^a
	No	26	28	
CEA (ng/mL)	≥5	11	7	0.26
	< 5	18	22	
Survival status	Survive	23	15	0.03
	Death	6	14	

Table 2 The relationship between $\gamma\delta$ T cell infiltration and the clinicopathological features of patients with colorectal cancer

^a Using Fisher's exact probability method to analyze the difference between two groups



Fig. 2 The relationship of the infiltration of $\gamma\delta$ T cells in tumor tissues with the prognosis of patients with colorectal cancer

Factors associated with the prognosis of CRC patients by Cox regression analysis

We used Cox regression analysis to explore the factors

that might impact the overall survival of the patients with CRC. The result of the univariable analysis suggested that AJCC stage (HR:3.322, 95%CI 1.353–8.152, P=0.009), serum CEA level (HR:3.922, 95%CI 1.615–9.521, P=0.003) and the abundance of tumor-infiltrating $\gamma\delta$ T cells (HR:0.327, 95%CI 0.125–0.854, P=0.022) were the factors related to the prognosis of CRC patients (Fig. 3). Further multivariable analysis indicated that AJCC stage (HR 3.139, 95%CI 1.248–7.894, P=0.015), serum CEA level (HR:3.665, 95%CI 1.476–9.102, P=0.005) and $\gamma\delta$ T cell infiltration degree in tumor tissue (HR:1.379, 95%CI:0.144,0.994, P=0.049) were the independent prognostic factors correlated with the prognosis of patients with CRC (Fig. 4).

Infiltrating degree of $\gamma\delta\,T$ cells was related to the survival benefit of adjuvant chemotherapy for CRC patients

Given that $\gamma\delta$ T cell infiltration in tumor tissue is a critical factor related to the prognosis of CRC patients, we further analyzed the relationship between the infiltrating degree of $\gamma\delta$ T cells and the prognosis of patients who received adjuvant chemotherapy. We found that in patients who received postoperative adjuvant chemotherapy, high $\gamma\delta$ T cell infiltration was associated with the improved prognosis of CRC patients (log-rank *P*=0.003) (Fig. 5A, B). Besides, in patients with high infiltration of $\gamma\delta$ T cells, adjuvant chemotherapy could obviously improve the prognosis of CRC patients (log-rank *P*=0.444) (Fig. 5C, D). Taken together, the degree of $\gamma\delta$ T cell infiltration in CRC tumor tissues can predict whether patients can benefit from postoperative adjuvant chemotherapy.

Establishment and validation of the nomogram for predicting the prognosis of CRC patients

According to the multivariate Cox regression analysis, we included AJCC stage, serum CEA level and yo T cell infiltration degree into the establishment of the nomogram. Given that tumor diameter [21], tumor location [22] and chemotherapy [23] could impact the prognosis of the patients, we also included these three factors into the development of the nomogram. The nomogram aimed to predict the prognosis of CRC patients was developed as shown in Fig. 6. The predicted rate of 1-, 2-, 5-year survival can be obtained by summing the scores of the six factors. The C-index was 0.788 (95% confidence interval: 0.695-0.881), indicating the discrimination of the nomogram is relatively good. The calibration curves for 1-, 2-, 5-year survival also showed the relative accuracy of nomogram in predicting the prognosis of patients (Fig. 7A–C).











Fig. 5 The relationship between $\gamma\delta$ T cell infiltration and the survival benefit of postoperative adjuvant chemotherapy. **A** Patients with adjuvant chemotherapy. **C** Patients with high $\gamma\delta$ T cells infiltration. **D** Patients with low $\gamma\delta$ T cells infiltration



with colorectal cancer

Discussion

As the first line for the anti-infection and anti-tumor immune response, it was proved that $\gamma\delta$ T cells could infiltrate into tumor tissue and exert an essential role. Previous studies have shown that $\gamma \delta T$ cells play different roles in different types of tumors. For example, increased infiltration of $\gamma\delta$ T cells in tumor tissues is an independent protective factor for the prognosis of gastric cancer patients [15]. However, in tumors such as breast cancer, pancreatic cancer, ovarian cancer, and gallbladder cancer, the degree of $\gamma\delta$ T cell infiltration is positively correlated with poor prognosis in patients [11, 16–18, 24]. However, in CRC, the relationship between $\gamma\delta$ T cell infiltration and patient prognosis is still controversial [7, 14, 19, 20]. Therefore, in this study, we further clarified the relationship between the degree of $\gamma\delta$ T cell infiltration and the prognosis of CRC patients through immunohistochemical staining and prognosis analysis.

Through immunohistochemical analysis, we found that although there was no significant difference in the relative abundance of $\gamma\delta$ T cells between tumor tissue and adjacent normal tissue, the abundance of $\gamma\delta$ T cells in tumor tissue was significantly correlated with the survival status of patients with CRC. The results of survival analysis also indicated that the increased $\gamma\delta$ T cell infiltration could improve the survival rate. Patients with a high level of $\gamma\delta$ T cell infiltration acquired a better prognosis after receiving postoperative chemotherapy. Meanwhile, among patients who received adjuvant chemotherapy, the cumulative survival of patients with the increased $\gamma\delta$ T cell infiltration was better than that of patients with lower $\gamma\delta$ T cell infiltration. These results suggested that the tumor-infiltrating $\gamma\delta$ T cells, regardless of subtypes, was positively correlated with the improvement of the prognosis of CRC patients.

A previous study showed the expression of $\gamma\delta$ T cells in tumor and adjacent tissues was not different in rectal cancer [25], which was consistent with the result of our study. Similarly, S. Meraviglia et al. found that the abundance of $\gamma\delta$ T cells in tumor tissues was not significantly different from that in non-tumor colon tissues by analyzing the abundance and composition of $\gamma\delta$ T cell subtypes (V\delta1 T cells and V\delta2 T cells) in CRC [7]. However, their study showed that most of the $\gamma\delta$ T cells in tumor tissues and adjacent normal tissues are V δ 1 T cell subtypes and showed effector phenotypes. Moreover, their ability to produce IL-17 was insufficient, which was contrary to the conclusion that $\gamma\delta$ T cells were the main producers of IL-17 in CRC studied by Pin Wu et al. [14]. Their further analysis found that this might be caused by some inhibitory molecules produced by tumor stem cells in the tumor microenvironment [7]. Of note, S. Meraviglia et al. also found that there was no significant difference in the abundance of $\gamma\delta$ T cells in tumor tissues and normal tissues [7]. But their bioinformatic analysis of transcriptome data indicated that CRC patients with enrichment of $\gamma\delta$ T cells in tumor tissues had a longer 5-year disease-free survival [7], which was consistent with our results. In addition, our study suggested that the abundance of $\gamma\delta$ T cells was related to whether patients could benefit from postoperative adjuvant chemotherapy, which was consistent with previous studies in gastric cancer [15]. The reason why our results were not consistent with those of other researchers might be mainly related to the difference in the effects of $\gamma\delta$ T cells and other factors in the different tumor microenvironments. How the tumorinfiltrating $\gamma\delta$ T cells play an inhibitory role in CRC is still a problem that we need to further explore and prove.

The nomogram is a prediction model based on multivariate regression analysis [26]. It can predict the probability of a specific event and present the relationship of the prediction model with the predicted factors. According to the result of the Cox regression analysis, we established a nomogram based on tumor diameter, tumor location, AJCC stage, chemotherapy, serum CEA level and $\gamma\delta$ T cell infiltration. The C-index and the calibration curve suggested that the nomogram had a relatively good ability for predicting survival of patients with CRC. This nomogram could provide a reference for predicting the 1-, 2-, 5-year survival rate of CRC patients in clinical practice.

However, the limitations in this study cannot be ignored. First, the sample size in this study is small. Although we obtained some positive results, the verification based on large sample is still necessary. Second, only immunohistochemistry analysis is used for detecting the infiltration of $\gamma\delta$ T cells in CRC. And the relationship between subtype of $\gamma\delta$ T cells and the prognosis of the patients is not evaluated. Next, we need to verify these by qPCR, flow cytometry and so on.



Fig. 7 The calibration curves for 1-, 2-, 5-year survival. A The calibration curve for 1-year survival. B The calibration curve for 2-year survival. C The calibration curve for 5-year survival

Nonetheless, we can conclude that the infiltration of $\gamma\delta$ T cells in tumor tissue is an important protective factor for the prognosis of patients with CRC, and the abundance of tumor-infiltrating $\gamma\delta$ T cells can predict the benefit of patients from postoperative adjuvant chemotherapy.

Acknowledgements

None.

Author contributions

KL and RM participated in the design of this study. RM, MG, TS and LS performed the experiment, collected data and performed the statistical analysis. RM drafted the manuscript. KL reviewed the manuscript. All authors read and approved the final manuscript.

Funding

None.

Availability of data and materials

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

Declarations

Ethics approval and consent to participate

This study was carried out under the approval and supervision of the Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University (No. XJTU1AF2022LSK-250).

Consent for publication

All authors agreed to publish this manuscript.

Competing interests

All authors declare that they have no competing interests.

Received: 25 September 2022 Accepted: 17 October 2023 Published online: 27 October 2023

References

- Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol. 2019;16(12):713–32.
- 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 Cancer J Clin. 2018;68(6):394–424.
- Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020. https://doi.org/10.3322/caac.21601.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7–30.
- 5. Ma R, Yuan D, Guo Y, Yan R, Li K. Immune effects of $\gamma\delta$ T Cells in colorectal cancer: a review. Front Immunol. 2020;11:1600.
- Wakita D, Sumida K, Iwakura Y, Nishikawa H, Ohkuri T, Chamoto K, Kitamura H, Nishimura T. Tumor-infiltrating IL-17-producing gammadelta T cells support the progression of tumor by promoting angiogenesis. Eur J Immunol. 2010;40(7):1927–37.
- Meraviglia S, Lo Presti E, Tosolini M, La Mendola C, Orlando V, Todaro M, Catalano V, Stassi G, Cicero G, Vieni S, et al. Distinctive features of tumorinfiltrating gammadelta T lymphocytes in human colorectal cancer. Oncoimmunology. 2017;6(10): e1347742.
- Corvaisier M, Moreau-Aubry A, Diez E, Bennouna J, Mosnier JF, Scotet E, Bonneville M, Jotereau F. V gamma 9V delta 2 T cell response to colon carcinoma cells. J Immunol. 2005;175(8):5481–8.
- Bruni E, Cimino MM, Donadon M, Carriero R, Terzoli S, Piazza R, Ravens S, Prinz I, Cazzetta V, Marzano P, et al. Intrahepatic CD69(+)V&1 T cells recirculate in the blood of patients with metastatic colorectal cancer and limit

- Ma S, Cheng Q, Cai Y, Gong H, Wu Y, Yu X, Shi L, Wu D, Dong C, Liu H. IL-17A produced by γδ T cells promotes tumor growth in hepatocellular carcinoma. Cancer Res. 2014;74(7):1969–82.
- 11. Coffelt SB, Kersten K, Doornebal CW, Weiden J, Vrijland K, Hau CS, Verstegen NJM, Ciampricotti M, Hawinkels L, Jonkers J, et al. IL-17-producing $\gamma\delta$ T cells and neutrophils conspire to promote breast cancer metastasis. Nature. 2015;522(7556):345–8.
- Jin C, Lagoudas GK, Zhao C, Bullman S, Bhutkar A, Hu B, Ameh S, Sandel D, Liang XS, Mazzilli S, et al. Commensal microbiota promote lung cancer development via γδT Cells. Cell. 2019;176(5):998-1013.e1016.
- McAllister F, Bailey JM, Alsina J, Nirschl CJ, Sharma R, Fan H, Rattigan Y, Roeser JC, Lankapalli RH, Zhang H, et al. Oncogenic Kras activates a hematopoieticto-epithelial IL-17 signaling axis in preinvasive pancreatic neoplasia. Cancer Cell. 2014;25(5):621–37.
- Wu P, Wu D, Ni C, Ye J, Chen W, Hu G, Wang Z, Wang C, Zhang Z, Xia W, et al. gammadeltaT17 cells promote the accumulation and expansion of myeloid-derived suppressor cells in human colorectal cancer. Immunity. 2014;40(5):785–800.
- Wang J, Lin C, Li H, Li R, Wu Y, Liu H, Zhang H, He H, Zhang W, Xu J. Tumorinfiltrating gammadeltaT cells predict prognosis and adjuvant chemotherapeutic benefit in patients with gastric cancer. Oncoimmunology. 2017;6(11): e1353858.
- 16. Ma C, Zhang Q, Ye J, Wang F, Zhang Y, Wevers E, Schwartz T, Hunborg P, Varvares MA, Hoft DF, et al. Tumor-infiltrating $\gamma\delta$ T lymphocytes predict clinical outcome in human breast cancer. J Immunol. 2012;189(10):5029–36.
- Patil RS, Shah SU, Shrikhande SV, Goel M, Dikshit RP, Chiplunkar SV. IL17 producing γδT cells induce angiogenesis and are associated with poor survival in gallbladder cancer patients. Int J Cancer. 2016;139(4):869–81.
- Chen X, Shang W, Xu P, Wu M, Zhang X, Huang P, Wang F, Pan S. Distribution and functions of γδ T cells infiltrated in the ovarian cancer microenvironment. J Transl Med. 2019;17(1):144.
- Gentles AJ, Newman AM, Liu CL, Bratman SV, Feng W, Kim D, Nair VS, Xu Y, Khuong A, Hoang CD, et al. The prognostic landscape of genes and infiltrating immune cells across human cancers. Nat Med. 2015;21(8):938–45.
- Tosolini M, Pont F, Poupot M, Vergez F, Nicolau-Travers ML, Vermijlen D, Sarry JE, Dieli F, Fournie JJ. Assessment of tumor-infiltrating TCRVgamma9Vdelta2 gammadelta lymphocyte abundance by deconvolution of human cancers microarrays. Oncoimmunology. 2017;6(3): e1284723.
- Maeda C, Hidaka E, Mori Y, Mukai S, Miyachi H, Sawada N, Ishida F, Kudo SE. tumor diameter is an easy and useful predictor of recurrence in stage II colorectal cancer. Dig Surg. 2015;32(5):338–43.
- Zheng C, Jiang F, Lin H, Li S. Clinical characteristics and prognosis of different primary tumor location in colorectal cancer: a population-based cohort study. Clin Transl Oncol. 2019;21(11):1524–31.
- Franke AJ, Skelton WP, Starr JS, Parekh H, Lee JJ, Overman MJ, Allegra C, George TJ. Immunotherapy for colorectal cancer: a review of current and novel therapeutic approaches. J Natl Cancer Inst. 2019;111(11):1131–41.
- Daley D, Zambirinis CP, Seifert L, Akkad N, Mohan N, Werba G, Barilla R, Torres-Hernandez A, Hundeyin M, Mani VRK, et al. gammadelta T cells support pancreatic oncogenesis by restraining alphabeta T cell activation. Cell. 2016;166(6):1485–99.
- Rong L, Li K, Li R, Liu HM, Sun R, Liu XY. Analysis of tumor-infiltrating gamma delta T cells in rectal cancer. World J Gastroenterol. 2016;22(13):3573–80.
- Mo S, Zhou Z, Li Y, Hu X, Ma X, Zhang L, Cai S, Peng J. Establishment and validation of a novel nomogram incorporating clinicopathological parameters into the TNM staging system to predict prognosis for stage II colorectal cancer. Cancer Cell Int. 2020;20:285.

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