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ORIGINAL RESEARCH

Hematologic Markers of Lung Metastasis in Stage IV Colorectal Cancer

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Abstract

Background Many studies showed an association between absolute neutrophil count (ANC), absolute monocyte count (AMC), neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR) with poor overall survival (OS) in patients with cancer. However, only a few studies were conducted to further investigate this association in colorectal cancer (CRC).

Methods Clinical data from 299 stage IV CRC patients treated at King Hussein Cancer Center from 2004 to 2012 have been retrospectively reviewed. We examined the association between ANC, AMC, MLR, PLR, and NLR with lung metastasis in stage IV CRC. Receiver Operating Characteristic (ROC) curve analysis was operated to determine the optimal NLR cutoff value. Univariate and multivariate analysis were performed.

Results The ROC value of 3.4 was determined as the cutoff value of NLR to study the association. Univariate and multivariate analysis showed that patients with high baseline NLR (≥ 3.4) had more baseline lung metastasis than patients with low NLR (< 3.4) ($p = 0.0001$, $p = 0.0151$, respectively). Also, baseline NLR correlated significantly with the presence of lymphovascular invasion ($p = 0.001$). In patients with no baseline lung metastasis, high post-treatment NLR was associated with consequent development of lung metastasis ($p = 0.0227$). Other markers including ANC, AMC, MLR, and PLR were significantly associated with lung metastasis at time of diagnosis ($p = 0.0006$, $p = 0.0006$, $p = 0.0187$, and $p = 0.001$, respectively).

Conclusion Results are suggesting that different hematologic markers obtained from a cheap test (CBC) could potentially be used to predict the likelihood of lung metastasis in stage IV CRC. Prospective studies are needed to further assess the immune cells' role in tumor metastasis promotion.

Keywords Colorectal cancer · Neutrophil-lymphocyte ratio · Lung metastasis · Stage IV

Introduction

Colorectal cancer (CRC) is one of the most common gastrointestinal tumors and the fourth most common cause of cancer-related death universally. [1, 2] Recently, the linkage between inflammation and the carcinogenesis has been better outlined. Different studies have revealed that cancer-related inflammation influences various stages of carcinogenesis. [3, 4]

Many studies have shown that several blood markers including absolute neutrophil count (ANC), absolute monocyte count (AMC), neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR) are associated significantly with worse prognosis of different types of solid tumors including CRC. [5–7] A high NLR is detected when the absolute neutrophil count is high and the absolute lymphocyte count is low. Though it remains poorly understood why a high NLR is associated with dismal prognosis in different types of solid tumors [6–15], it may be explained by the promotion of seeding of distant sites via certain growth factors such as VEGF and specific proteases secreted by abundant neutrophils. [9] Also, a low lymphocyte count may influence their essential role in fighting tumor cells by

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inducing cytotoxic cell death and impeding tumor cell proliferation and migration, thus diminishing the immune response to malignancy. [4] Interestingly, a recent article suggested that a high NLR is an independent predictive factor for the baseline presence and subsequent development of brain metastases in advanced non-small cell lung cancer (NSCLC). [16] The value of NLR as a predictive factor for the identification of metastasis may apply also to other solid tumors like CRC.

Metastasis is considered the leading cause of the majority of cancer-related deaths among patients with various types of malignancy. Nearly half of patients diagnosed with CRC die due to malignancy-related etiologies [17] Around 20% of patients with CRC already have distant metastases at the time of diagnosis, and this proportion has been constant over the last several years. [18] However, the overall survival (OS) of all patients with metastatic CRC regardless of their histologic subtypes is grim and the main aim of treatment is to lengthen survival while maintaining an appropriate quality of life. [2, 19] Actually, early detection of metastasis is important to identify patients with limited disease who potentially could benefit from a more aggressive approach aiming to stop micro-metastasis lesions from progressing into an uncontrollable macro-metastasis. Therefore, looking for new biomarkers for detecting the commencement of metastatic process can decrease mortality among CRC patients by encouraging a more intensive imaging surveillance and other prophylactic strategies.

Although the biologic behavior of the different hematologic parameters was tremendously researched, no study has been conducted to explore the association between these markers and the distant metastases of CRC. This retrospective study focuses on the potential predictive value of ANC, ALC, AMC, NLR, MLR, and PLR by examining their association with the baseline presence and subsequent development of lung metastases in patients with stage IV CRC.

Materials and Methods

This is a retrospective chart review study that was approved by the Institutional Review Board at King Hussein Cancer Center (KHCC). Two hundred ninety-nine patients diagnosed with stage IV colorectal adenocarcinoma, as confirmed by histopathology and/or radiology reports, received their treatment for CRC at KHCC (Amman, Jordan) between 2004 and 2012 were included. Patients using glucocorticoids before starting definitive CRC treatment were excluded. Chest computed tomography (CT) scans have been used to detect CRC lung metastasis. Clinical data, age and gender, location of the tumor, and TNM stage were assessed for possible correlation with the baseline presence and subsequent development of lung metastasis.

The results of the routinely obtained complete blood count (CBC) at the time of diagnosis before initiation of any treatment were reviewed. Total white blood cells (WBC) count and the individual count of each component including neutrophil, lymphocyte, and monocyte were also obtained. The pre-treatment baseline NLR, MLR, and PLR have been calculated using these formulas; NLR = ANC/ALC, MLR = AMC/ALC, and PLR = Platelet Count/ALC, respectively.

The time period to the development of CRC lung metastases in patients with no baseline CRC lung metastasis was calculated from the day of confirming the diagnosis of CRC to the day of confirming the presence of lung metastasis. The mean was determined as 15 months. So, all patients who died within the first 12 months after the date of stage IV CRC diagnosis were excluded to diminish the competing effect. Post-treatment NLR was obtained from the CBC results at the date of, or the last CBC results before, the confirmed lung metastases. In patients without lung metastases, post-treatment NLR has been obtained at a cutoff point of 15 months after the date of stage IV CRC diagnosis. For patients who died between 12 and 15 months, the last available CBC result was used to calculate the post-treatment NLR.

The Receiver Operating Characteristic (ROC) curve was used to determine the optimal cut-off value of NLR, matching the most extreme joint sensitivity and specificity. The association between NLR and the clinical factors including the age, gender, location, and TNM staging with the presence of CRC lung metastasis was examined. Univariate and multivariate logistic regression analysis were used to test this association. A P value of ≤ 0.05 was determined as the cut off for significant association.

Our analysis proceeded stepwise. In phase-1, we examined the association between baseline NLR with the presence of CRC lung metastasis and lymphovascular invasion. In the second phase, we examined the association between other hematologic parameters like ANC, ALC, AMC, MLR, and PLR and the baseline presence of CRC lung metastasis. In the third phase, we examined the association between baseline ANC, ALC, AMC, NLR, MLR, and PLR with the subsequent development of CRC lung metastasis in patients with no baseline CRC lung metastasis. In the last phase, we examined the association between post-treatment NLR with subsequent development of CRC lung metastasis in patients with no baseline CRC lung metastasis.

Results

The clinical features of 299 stage IV CRC patients were summarized in Table 1. The age ranged from 14 to 83 years (median 56 years), 161 (53.8%) were male and 138 (46.2%) were female. One hundred and one patients (33.8%) had lung metastases at the time of diagnosis, 68 (22.7%) developed lung metastasis during the treatment period, and 130 (43.5%) did not develop

Table 1 Characteristics of stage IV CRC patients

Patients features	No. of patients (%)
Age, median (range)	56 (14–83%)
Gender:	
Male	161 (53.8%)
Female	138 (46.2%)
cT stage:	
T1–2	6 (3.3%)
T3–4	177 (96.7%)
cN stage:	
N0–1	101 (34%)
N2	81 (27%)
NX	117 (39%)
Location	
Colon	227 (77%)
Rectum	68 (23%)
Sites of metastasis at time of diagnosis	
Lung	101 (34%)
Liver	235 (78%)
Peritoneum	70 (23%)
Bone	15 (5%)
Brain	7 (2%)

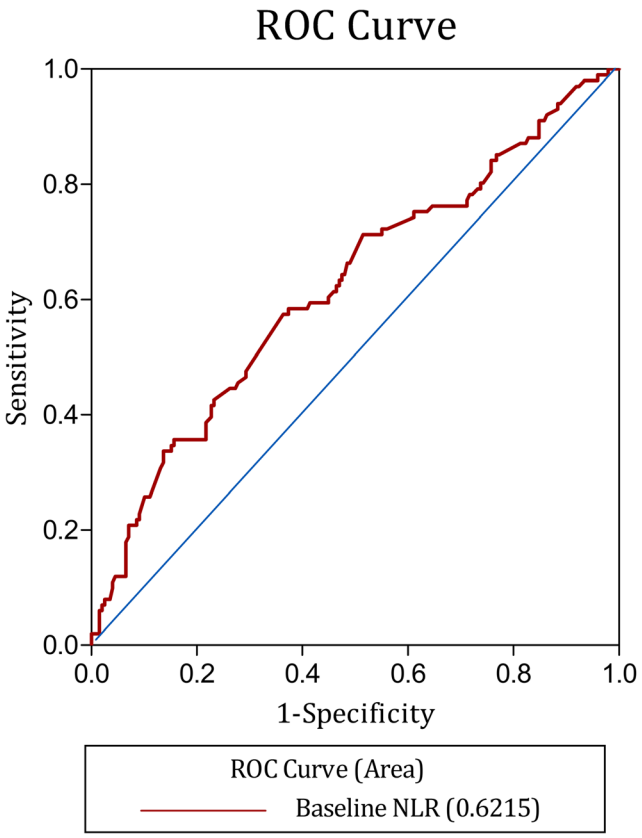

Fig. 1 Receiver-operating-characteristic (ROC) and area under the curve (AUC) for the baseline NLR

lung metastasis. The mean of baseline NLR was 4 (median 3 and range 1–45), while the mean of post-treatment NLR was 5 (median 3 and range 1–99). The optimal NLR cutoff value was determined as 3.4, an area under the curve AUC recorded as 0.6215 (95% confidence interval (CI) 0.552–0.700) (Fig. 1).

In univariate analysis, tumor location (colon versus rectal), cN stage as well as high baseline NLR were significantly associated with baseline lung metastasis. Patients with high baseline NLR (≥ 3.4) had more lung metastasis in comparison to patients with low baseline NLR, (Table 2). In multivariate analysis, it remained an independent prognostic factor of baseline lung metastasis (OR 1.24, 95% CI 1.042–1.47, $p = 0.015$) (Table 2).

When we performed univariate and multivariate analysis, using NLR as a continuous variable, NLR remained a significant predictor of lung metastasis at diagnosis ($P = 0.001$ and $P = 0.015$, respectively).

Additionally, baseline ANC, AMC, MLR, and PLR were significantly associated with baseline presence of lung metastasis ($P = 0.0006$, $P = 0.0007$, $P = 0.0187$, and $P = 0.0001$, respectively) (Table 3).

We then examined the association between baseline NLR, ANC, AMC, MLR, and PLR with consequent development of lung metastases in patients with no lung metastasis at diagnosis. The results showed that these baseline parameters, NLR, ANC, AMC, MLR, and PLR, were not associated with post-treatment development of lung metastasis in patients with no baseline lung metastasis.

We then assessed the association between post-treatment NLR with subsequent development of lung metastases in patients with no baseline lung metastasis. The incidence of subsequent development of lung metastasis was much higher among patients with post-treatment NLR (≥ 3.4) than patients with post-treatment NLR (< 3.4) ($P = 0.0227$) (Table 4).

Discussion

In this study, we assessed new hematological indices for predicting the baseline presence and the subsequent development of lung metastases in patients with stage IV CRC. An elevated baseline NLR (≥ 3.4) was an independent factor of the baseline presence of CRC lung metastases. Patients with elevated baseline ANC, AMC, MLR, and PLR had more lung metastasis in comparison to patients with low baseline indices.

Furthermore, an elevation of NLR during therapy was associated with a high rate of subsequent CRC lung metastasis among patients with no baseline lung metastasis. These findings suggest that post-treatment elevation of NLR might be used as an indicator of lung metastasis development in stage IV CRC.

To the best of our knowledge, this is the first description of the potential predictive value of these hematologic parameters for detecting lung metastasis. These markers are easily

Table 2 Univariate and multivariate analysis for the association of different variables with the presence of baseline lung metastasis

Variables	Baseline lung metastasis		Univariate		Multivariate	
	Present	Absent	*P* value	OR (95% CI)	*P* value	OR (95% CI)
Age			0.414		0.0210	
Age > 56	53 (52.5%)	94 (47.5%)		0.819 (0.507–1.323)		0.406 (0.189–0.873)
Age ≤ 56	48 (47.5%)	104 (52.5%)				
Gender			0.962		0.705	
Male	56 (34.8%)	105 (65.2%)		0.907 (0.561–1.468)		0.705 (0.334–1.489)
Female	45 (32.6%)	93 (67.4%)				
cT stage			0.98		0.9811	
T1–2	0	6 (100%)		NA		NA
T3–4	44 (25.3%)	130 (74.7%)				
cN stage			0.0458		0.0268	
N0–1	33 (33%)	67 (67%)		2.041 (1.013–4.109)		2.305 (1.101–4.826)
N2	15 (19%)	66 (81%)				
Location			0.002		0.054	
Colon	65 (29%)	162 (71%)		NA		0.421 (0.175–1.015)
Rectum	33 (49%)	35 (51%)				
Baseline NLR			0.001		0.015	
NLR > 3.4	58 (44%)	74 (56%)		0.442 (0.27–0.72)		0.448 (0.219–0.916)
NLR ≤ 3.4	43 (26%)	124 (74%)				

obtained from an affordable test, the CBC, which is done routinely during the management and follow-up of all patients with malignancy.

The association between systemic inflammatory response and carcinogenesis is well documented in literature. [20–22] Though it remains poorly understood which mechanisms are responsible for this relationship, several theories offer some acceptable explanations. [23] Previous studies suggested that malignant tumors might be responsible for significant increments of cytokines, precipitation of angiogenesis process, and manipulation of the molecular components of apoptosis. [20, 22] Neoplastic cells may also stimulate the release of granulocyte colony-stimulating factor (GCSF) that can precipitate neutrophilia. Neutrophils may play a vital role in angiogenesis process by releasing pro-angiogenic factors like matrix-metalloproteinase, IL-8, VEGF, and elastase enzymes. (13, 24] All of these different inflammatory mediators may promote neoplastic cells proliferation and metastasis. Several studies reported that monocyte cell lineage stimulates neoplastic cells migration, enhance tumor microenvironment angiogenesis process, and inhibit antitumor immunity. [25–27) In contrast, lymphocytes have a key role in supplying antitumor immunity. [23, 28) Elevated lymphocyte count has also been reported as a good prognostic marker in patients with different types of solid tumors such as breast, colorectal, and skin cancer. [29–31]

Several retrospective studies delineated the significance of NLR changes as prognostic tools. [32, 33] One reported that post-treatment NLR changes can be used to predict the recurrence in patients with renal tumors. [33] Another study reported that early drop of NLR correlated with an excellent outcome in patients with metastatic stage IV renal cell carcinoma [32].

The lung is the second most common site of metastasis from CRC after liver, with 34–44% of patients developing

Table 3 The association of baseline ANC, AMC, MLR, and PLR with the baseline presence of lung metastasis

	Baseline lung metastasis		*P* value
	Present	Absent	
Mean of baseline ANC	7300	6000	0.0006
Mean of baseline ALC	1900	1950	0.3741
Mean of baseline MLR	0.46	0.37	0.0187
Mean of baseline PLR	25.5	18.4	0.0001

Table 4 Post-treatment NLR associated with the subsequent development of lung metastasis

Post-treatment NLR	Subsequent lung metastasis		*P* value
	Present	Absent	
NLR > 3.4	32 (45%)	39 (55%)	0.0227
NLR < 3.4	33 (26%)	91 (74%)	

lung metastasis throughout the disease course. [34] Thoracic radiation therapy, adjuvant chemotherapy, and surgical resection of lung metastasis (metastectomy) are the prevailing treatment options for CRC lung metastases.

The NLR may assist identifying CRC patients more prone to develop lung metastases. Frequent thoracic imaging investigation and prophylactic treatment approaches in this special group could improve the final outcome and quality of life.

Limitations of this study include the retrospective nature with all cases collected from a single center. Further prospective studies are needed to confirm the predictive role of NLR and its association with CRC lung metastases. Though there have been several previous studies assessing the prognostic aspect of NLR in CRC patients, a well-established NLR cutoff value was not recognized due to various study populations and diverse selection methods. Our identified NLR cutoff value needs to be confirmed by other studies. Large lung metastases (greater than 1–2 cm in size) could be detected by the optimum quality chest CT techniques with a high level of accuracy. Microscopic metastases (smaller than 1–2 mm in size) are rarely detected by anatomic imaging methods; therefore, patients who developed metastasis after treatment might have had small, tiny, and non-measurable metastases not being detected by the initial CT scan.

Using glucocorticoids prior to the date of measuring baseline NLR may be a confounding factor. Actually, extreme and persistent leukocytosis can be induced by administration small doses of glucocorticoids. [35] Glucocorticoids can cause neutrophilia by pushing neutrophil cells from the marginated pool into the main blood stream pool. [36] Therefore, we excluded all patients taking glucocorticoids to avoid the confounding effect. However, there are other factors that may affect and alter the CBC results, like systemic inflammatory conditions and infection, which could not have been controlled in this retrospective study.

In conclusion, our results suggest that an elevated baseline NLR is an independent predictive factor for the presence of baseline CRC lung metastasis. Also, other hematologic indices including ANC, AMC, MLR, and PLR can be used to recognize the presence of lung metastasis in stage IV CRC patients at the time of diagnosis. Our study results also showed that subsequent CRC lung metastasis occur more frequently in patients with elevated post-treatment NLR (≥ 3.4) than patients with low post-treatment NLR (< 3.4). Therefore, post-treatment elevation of NLR can be used to recognize patients prone to develop lung metastasis shortly, who may benefit from a more aggressive management plan. However, multicenter studies are needed to confirm the predictive value of these blood markers in predicting the presence of lung metastases in stage IV CRC.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Haggar FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clin Colon Rectal Surg. 2009;22(4):191–7. https://doi.org/10.1055/s-0029-1242458. PubMed PMID: 21037809; PubMed Central PMCID: PMCPMC2796096.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66(1):7–30. Epub 2016/01/07. https://doi.org/10.3322/caac.21332. PubMed.
3. Moore MM, Chua W, Charles KA, Clarke SJ. Inflammation and cancer: causes and consequences. Clin Pharmacol Ther 2010;87(4):504–508. Epub 2010/02/10. https://doi.org/10.1038/clpt.2009.254. PubMed.
4. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140(6):883–99. https://doi.org/10.1016/j.cell.2010.01.025. PubMed PMID: 20303878; PubMed Central PMCID: PMCPMC2866629.
5. Tan D, Fu Y, Su Q, Wang H. Prognostic role of platelet-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. Medicine (Baltimore). 2016;95(24):e3837. https://doi.org/10.1097/MD.0000000000003837 . PubMed PMID: 27310960; PubMed Central PMCID: PMCPMC4998446.
6. Nagasaki T, Akiyoshi T, Fujimoto Y, Konishi T, Nagayama S, Fukunaga Y, Ueno M Prognostic impact of neutrophil-to-lymphocyte ratio in patients with advanced low rectal cancer treated with preoperative chemoradiotherapy. Dig Surg 2015;32(6):496–503. Epub 2015/11/07. https://doi.org/10.1159/000441396. PubMed.
7. Li MX, Liu XM, Zhang XF, Zhang JF, Wang WL, Zhu Y, Dong J, Cheng JW, Liu ZW, Ma L, Lv Y Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. Int J Cancer 2014;134(10):2403–2413. Epub 2014/01/29. https://doi.org/10.1002/ijc.28536. PubMed.
8. An X, Ding PR, Wang FH, Jiang WQ, Li YH. Elevated neutrophil to lymphocyte ratio predicts poor prognosis in nasopharyngeal carcinoma. Tumour Biol 2011;32(2):317–324. Epub 2010/10/30. https://doi.org/10.1007/s13277-010-0124-7. PubMed.
9. An X, Ding PR, Li YH, Wang FH, Shi YX, Wang ZQ, He YJ, Xu RH, Jiang WQ Elevated neutrophil to lymphocyte ratio predicts survival in advanced pancreatic cancer. Biomarkers 2010;15(6):516–522. https://doi.org/10.3109/1354750X.2010.491557. PubMed.
10. Liu H, Liu G, Bao Q, Sun W, Bao H, Bi L, Wen W, Liu Y, Wang Z, Yin X, Bai Y, Hu X The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in rectal carcinoma. J Gastrointest Cancer 2010;41(2):116–120. https://doi.org/10.1007/s12029-009-9125-4. PubMed.
11. Gondo T, Nakashima J, Ohno Y, Choichiro O, Horiguchi Y, Namiki K, Yoshioka K, Ohori M, Hatano T, Tachibana M Prognostic value of neutrophil-to-lymphocyte ratio and establishment of novel preoperative risk stratification model in bladder cancer patients treated with radical cystectomy.

Urology 2012;79(5):1085–1091. Epub 2012/03/23. https://doi.org/10.1016/j.urology.2011.11.070. PubMed.
12. Stotz M, Gerger A, Eisner F, Szkandera J, Loibner H, Ress AL, et al. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. Br J Cancer. 2013;109(2):416–21. Epub 2013/06/25. https://doi.org/10.1038/bjc.2013.332. PubMed PMID: 23799847; PubMed Central PMCID: PMCPMC3721392.
13. Paramanathan A, Saxena A, Morris DL. A systematic review and meta-analysis on the impact of pre-operative neutrophil lymphocyte ratio on long term outcomes after curative intent resection of solid tumours. Surg Oncol 2014;23(1):31–39. Epub 2013/12/20. https://doi.org/10.1016/j.suronc.2013.12.001. PubMed.
14. Szkandera J, Absenger G, Liegl-Atzwanger B, Pichler M, Stotz M, Samonigg H, et al. Elevated preoperative neutrophil/lymphocyte ratio is associated with poor prognosis in soft-tissue sarcoma patients. Br J Cancer. 2013;108(8):1677–83. Epub 2013/04/04. https://doi.org/10.1038/bjc.2013.135. PubMed PMID: 23558897; PubMed Central PMCID: PMCPMC3668478.
15. Ying HQ, Deng QW, He BS, Pan YQ, Wang F, Sun HL, Chen J, Liu X, Wang SK The prognostic value of preoperative NLR, d-NLR, PLR and LMR for predicting clinical outcome in surgical colorectal cancer patients. Med Oncol 2014;31(12):305. Epub 2014/10/30. https://doi.org/10.1007/s12032-014-0305-0. PubMed.
16. Koh YW, Choi JH, Ahn MS, Choi YW, Lee HW. Baseline neutrophil-lymphocyte ratio is associated with baseline and subsequent presence of brain metastases in advanced non-small-cell lung cancer. Sci Rep. 2016;6:38585. Epub 2016/12/07. https://doi.org/10.1038/srep38585. PubMed PMID: 27924837; PubMed Central PMCID: PMCPMC5141478.
17. Riihimäki M, Thomsen H, Sundquist K, Hemminki K. Colorectal cancer patients: what do they die of? Frontline Gastroenterol. 2012;3(3):143–9. Epub 2012/04/27. https://doi.org/10.1136/flgastro-2012-100141. PubMed PMID: 28839655; PubMed Central PMCID: PMCPMC5517285.
18. van der Geest LG, Lam-Boer J, Koopman M, Verhoef C, Elferink MA, de Wilt JH. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. Clin Exp Metastasis 2015;32(5):457–465. Epub 2015/04/22. https://doi.org/10.1007/s10585-015-9719-0. PubMed.
19. Noone AM, Cronin KA, Altekruse SF, Howlader N, Lewis DR, Petkov VI, et al. Cancer incidence and survival trends by subtype using data from the Surveillance Epidemiology and End Results Program, 1992–2013. Cancer Epidemiol Biomarkers Prev. 2017;26(4):632–41. Epub 2016/12/12. https://doi.org/10.1158/1055-9965.EPI-16-0520. PubMed PMID: 27956436; PubMed Central PMCID: PMCPMC5380602.
20. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357(9255):539–545. https://doi.org/10.1016/S0140-6736(00)04046-0. PubMed.
21. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454(7203):436–444. https://doi.org/10.1038/nature07205. PubMed.
22. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860–7. https://doi.org/10.1038/nature01322. PubMed PMID: 12490959; PubMed Central PMCID: PMCPMC2803035.
23. Kitamura T, Qian BZ, Pollard JW. Immune cell promotion of metastasis. Nat Rev Immunol. 2015;15(2):73–86. https://doi.org/10.1038/nri3789. PubMed PMID: 25614318; PubMed Central PMCID: PMCPMC4470277.
24. Kusumanto YH, Dam WA, Hospers GA, Meijer C, Mulder NH. Platelets and granulocytes, in particular the neutrophils, form important compartments for circulating vascular endothelial growth factor. Angiogenesis 2003;6(4):283–287. https://doi.org/10.1023/B:AGEN.0000029415.62384.ba. PubMed.
25. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. Cell. 2010;141(1):39–51. https://doi.org/10.1016/j.cell.2010.03.014. PubMed PMID: 20371344; PubMed Central PMCID: PMCPMC4994190.
26. Dirkx AE, Oude Egbrink MG, Wagstaff J, Griffioen AW. Monocyte/macrophage infiltration in tumors: modulators of angiogenesis. J Leukoc Biol 2006;80(6):1183–1196. Epub 2006/09/22. https://doi.org/10.1189/jlb.0905495. PubMed.
27. Yuan A, Chen JJ, Yang PC. Pathophysiology of tumor-associated macrophages. Adv Clin Chem 2008;45:199–223. PubMed.
28. Kitayama J, Yasuda K, Kawai K, Sunami E, Nagawa H. Circulating lymphocyte is an important determinant of the effectiveness of preoperative radiotherapy in advanced rectal cancer. BMC Cancer. 2011;11:64. Epub 2011/02/10. https://doi.org/10.1186/1471-2407-11-64. PubMed PMID: 21306650; PubMed Central PMCID: PMCPMC3041780.
29. Mahmoud SM, Paish EC, Powe DG, Macmillan RD, Grainge MJ, Lee AH, et al. Tumor-infiltrating CD8+ lymphocytes predict clinical outcome in breast cancer. J Clin Oncol 2011;29(15):1949–1955. Epub 2011/04/11. https://doi.org/10.1200/JCO.2010.30.5037. PubMed.
30. Clemente CG, Mihm MC, Bufalino R, Zurrida S, Collini P, Cascinelli N. Prognostic value of tumor infiltrating lymphocytes in the vertical growth phase of primary cutaneous melanoma. Cancer 1996;77(7):1303–1310. https://doi.org/10.1002/(SICI)1097-0142(19960401)77:7<1303::AID-CNCR12>3.0.CO;2-5. PubMed.
31. Ogino S, Nosho K, Irahara N, Meyerhardt JA, Baba Y, Shima K, et al. Lymphocytic reaction to colorectal cancer is associated with longer survival, independent of lymph node count, microsatellite instability, and CpG island methylator phenotype. Clin Cancer Res. 2009;15(20):6412–20. Epub 2009/10/13. https://doi.org/10.1158/1078-0432.CCR-09-1438. PubMed PMID: 19825961; PubMed Central PMCID: PMCPMC2771425.
32. Templeton AJ, Knox JJ, Lin X, Simantov R, Xie W, Lawrence N, Broom R, Fay AP, Rini B, Donskov F, Bjarnason GA, Smoragiewicz M, Kollmannsberger C, Kanesvaran R, Alimohamed N, Hermanns T, Wells JC, Amir E, Choueiri TK, Heng DYC Change in neutrophil-to-lymphocyte ratio in response to targeted therapy for metastatic renal cell carcinoma as a prognosticator and biomarker of efficacy. Eur Urol 2016;70(2):358–364. Epub 2016/02/28. https://doi.org/10.1016/j.eururo.2016.02.033. PubMed.
33. Ohno Y, Nakashima J, Ohori M, Gondo T, Hatano T, Tachibana M. Followup of neutrophil-to-lymphocyte ratio and recurrence of clear cell renal cell carcinoma. J Urol 2012;187(2):411–417. Epub 2011/12/15. doi: https://doi.org/10.1016/j.juro.2011.10.026. PubMed.
34. Riihimäki M, Hemminki A, Sundquist J, Hemminki K. Patterns of metastasis in colon and rectal cancer. Sci Rep. 2016;6:29765. Epub 2016/07/15. doi: https://doi.org/10.1038/srep29765. PubMed PMID: 27416752; PubMed Central PMCID: PMCPMC4945942.
35. Shoenfeld Y, Gurewich Y, Gallant LA, Pinkhas J. Prednisone-induced leukocytosis. Influence of dosage, method and duration of administration on the degree of leukocytosis. Am J Med 1981;71(5):773–778. PubMed.
36. Nakagawa M, Terashima T, D'yachkova Y, Bondy GP, Hogg JC, van Eeden SF. Glucocorticoid-induced granulocytosis: contribution of marrow release and demargination of intravascular granulocytes. Circulation 1998;98(21):2307–2313. PubMed.