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TUMOR-INFILTRATING LYMPHOCYTES AS EASILY ACCESSIBLE PROGNOSTIC TOOL IN ADENOCARCINOMA OF THE COLON

L. Zakhartseva[1, 2], *B. Shkurupii*[2, *]
[1]*Kyiv City Oncology Hospital, Kyiv 03115, Ukraine*
[2]*Bogomolets National Medical University, Kyiv 01601, Ukraine*

***Aim*: To determine the prognostic value of tumor-infiltrating lymphocytes (TILs) in colon adenocarcinomas. *Materials and Methods*: The study was performed on 180 paraffin blocks of operation material from patients diagnosed with adenocarcinoma of the colon, treated at the Kyiv City Oncology Center in 2013–2018. TILs were counted on histological slides stained with hematoxylin-eosin. By TILs count percentage in tumor slides, the samples were divided into three groups: 0–9% TILs (n = 65); 10–39% TILs (n = 79); and > 40% TILs (n = 36). *Results*: Kaplan — Meyer estimate showed that the difference in overall survival between groups was significant ($p = 0.001$). Multivariate Cox's proportional hazard regression model analysis evidenced on significantly better overall survival rates in groups with moderate TILs percentage (hazard ratio 0.54, 95% CI 0.30–0.97, $p = 0.042$) and high TILs percentage (hazard ratio 0.36, 95% CI 0.13–0.99, $p = 0.049$), respectively, as compared with low TILs percentage group. *Conclusion*: TILs content can be considered as an independent prognostic factor for colon adenocarcinoma and used as an additional tool in routine practice of pathologists.**

***Key Words*: colon cancer, adenocarcinoma, tumor infiltrating lymphocytes, prognosis, overall survival.**

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The incidence of colorectal cancer (CRC) is growing steadily every year. According to the latest statistics published by the World Health Organization,CRC ranks third in the incidence of malignant neoplasms and accounts for 10% of all malignant neoplasms; and ranks second in the structure of cancer mortality [1, 2]. Despite the improvement of diagnostics and existing treatment strategies, the overall 5-year survival is about 56.4% [3].

Instead, for most patients the administration of chemotherapy remains debatable. It is necessary to consider rather frequent cases of toxicity related to chemotherapy. Some studies indicate quite frequent cases of serious adverse reactions. [4–6]. The comparison of the effectiveness of adjuvant chemotherapy for 3 months and 6 months showed that only 0.9% of patients had improved survival rates but at the same time toxicity increased significantly [7].

Therefore, a clearer understanding of the prognosis of colon adenocarcinoma will improve overall survival (OS) by more accurately selecting high-risk patients who require chemotherapy. Other tools in assessing the prognosis of CRC include the determination of microsatellite instability [8, 9] and genetic mutations *KRAS, BRAF*, the value of which stays controversial [10, 11].

Tumor microenvironments, in particular tumor-infiltrating lymphocytes (TILs), are attracting the attention of numerous researchers. However, most studies focus on determining the composition of lymphocytic infiltrate [12, 13]. Immunohistochemical profiling requires additional costs. However, it is possible to assess the intensity of lymphocytic infiltrate during routine morphological examination of the tumor on hematoxylin-eosin (H&E) slides. The simplicity of the method and the absence of additional costs will allow implementing it into routine practice.

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*Correspondence: E-mail: bogdana.sulimenko@gmail.com
Abbreviations used: CI – confidence interval; CRC – colorectal cancer; H&E – hematoxylin-eosin; HR – hazard ratio; OS – overall survival; TILs – tumor-infiltrating lymphocytes.

MATERIALS AND METHODS

The study was performed on 180 paraffin blocks of operation material from patients diagnosed with adenocarcinoma of the colon and treated at the Kyiv City Oncology Center in 2013–2018. The stage of the disease was determined according to the fifth edition of the WHO classification of tumors of the digestive system, 2019 [14]. The study included patients with stages I–IV. Histological examination was performed on resection material of patients who did not receive neoadjuvant chemotherapy. The study was approved by the Commission on Bioethical Expertise (expert conclusion № 118 of 18.01.2019).

TILs were counted on histological slides stained with H&E, according to the recommendations proposed by the International Working Group on TILs evaluation in breast cancer [15]. Only lymphocytes in tumor stoma were considered in the evaluation. The granulocytes were excluded from the infiltrate count. To prevent bias, the assessment of TILs was blinded and reviewed by two independent pathologists, without access to patient's clinical data. Both pathologists were provided with the guidelines on TILs evaluation methodology that is summarized in Table 1. TILs count was presented as the percentage of tumor stromal area that was occupied by TILs. By TILs counts in tumor slides, the samples were divided into three groups: A, 0–9% TILs (n = 65); B, 10–39% TILs (n = 79); and C, > 40% TILs (n = 36). The representative microphotos of tumor sections of these three groups are shown

Table 1. Summary of TILs scoring recommendations (Based on recommendations by an International TILs Working Group 2014 [15])

1. TILs should be estimated as the percentage of tumor stromal area that was occupied by TILs
2. Granulocytes must be excluded from the infiltrate count
3. The evaluation of TILS count must be done on several zones without concentration on "hot spots"
4. TILs outside of the tumor must be excluded
5. Areas with artifacts, necrosis and hemorrhages must be excluded

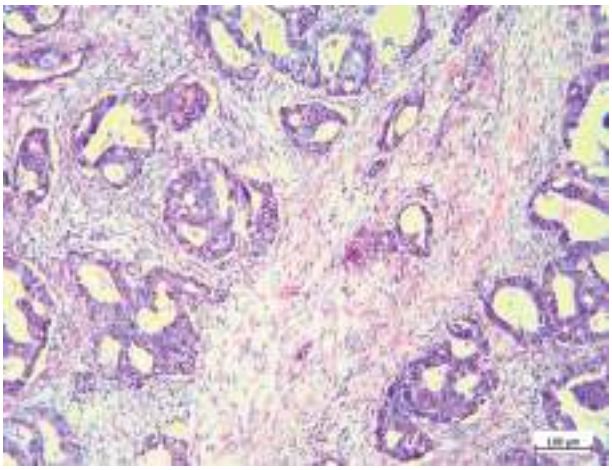

Fig. 1. Adenocarcinoma of the colon, group A — low TILs percentage (0–10%), ×10

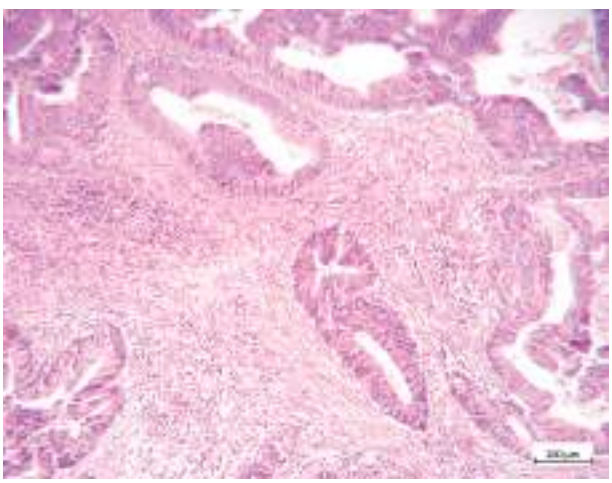

Fig. 2. Adenocarcinoma of the colon, group B — moderate TILs percentage (10–40%), ×10

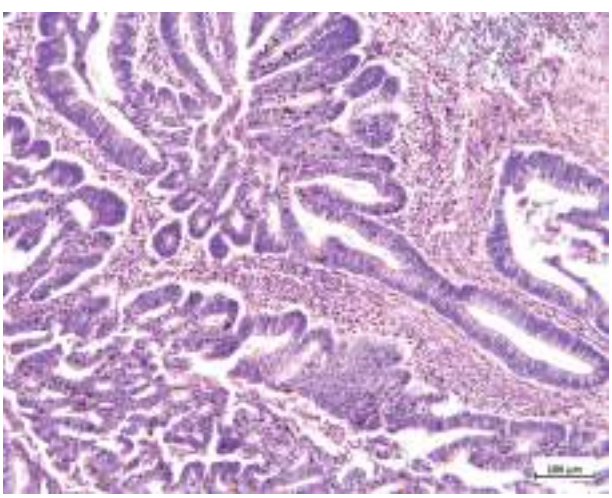

Fig. 3. Adenocarcinoma of the colon, group C — high TILs percentage (> 40%), ×10

in Fig. 1–3. The overall number of cases in each group was defined by 2 pathologists and represented in Table 2.

Statistical analysis was performed using EZR 1.35 software package (R statistical software version 3.4.3, R Foundation for Statistical Computing, Vienna, Austria) [16]. The Kappa Cohen coefficient (k) was used to determine consistency between pathologists. $k < 0.20$ was considered as poor level of agreement; $k = 0.21–0.41$ — fair; $k = 0.41–0.61$ — moderate; $k = 0.61–0.81$ — high; and $k > 0.81$ — almost perfect accordingly. Survival analysis was performed by the Kaplan — Meier method with a log-rank test. Monovariate and multivariate Cox's proportional hazard regression models were used to analyze general survival data. *P*-values less than 0.05 were considered statistically significant.

RESULTS

The study included 180 patients. The mean follow-up period was 3.1 years (range 0.12–7.3 years) for OS (Table 3).

Table 2. The overall number of CRC cases in TILs groups defined by 2 pathologists

Pathologist	TILs group A	TILs group B	TILs group C
1	65	79	36
2	74	71	35

Table 3. General characteristics of CRC cases

Index	Number	
	N = 180 patients	%
Age		
⩽ 40	2	1.1
> 40 <60	45	25
⩾ 60	133	73.9
Stage		
I	9	5
II	76	42.2
III	51	28.3
IV	44	24.5
Histological type		
Adenocarcinoma	159	88.3
Adenocarcinoma mucinous	10	5.5
Adenocarcinoma mucous producing	8	4.5
Signet ring cell carcinoma of colon	3	1.7
pT (Tumor)		
pT2	11	6.1
pT3	127	70.6
pT4	42	23.3
pN (Lymph nodes)		
pN0	91	50.6
pN1	64	35.5
pN2	25	13.9
M (Distant metastasis)		
M0	138	76.7
M1	42	23.3
Differentiation grade		
G1	8	4.5
G2	159	88.3
G3	13	7.2
Necrosis		
Yes	54	30
No	126	70
Neutrophils		
Yes	48	26.7
No	132	73.3
TILs		
A (0–10%)	65	36.1
B (10–40%)	79	43.9
C (> 40%)	36	20

The one-year OS in patients with colon adenocarcinoma is 87.8% ± 2.4%; two-year OS is 78.1% ± 3.0%; three-year OS is 72.2% ± 3.4%. In group A, one-year OS was 78.1% ± 5.1%; two-year OS — 65.6 ± 5.9%; three-year OS — 56.8% ± 6.3%. In group B, one-year OS was 91.1% ± 3.2%; two-year OS — 84.7 ± 4.0%; three-year OS — 77.9% ± 4.8%. In group C, one-year OS of 91.7% ± 4.6%; two-year OS — 85.9 ± 5.8%. Kaplan — Meyer curves showed that the difference in OS between groups A–C was significant ($p = 0.001$) (Fig. 4).

According to monovariate Cox's proportional hazard regression model, survival rates in groups B and C were significantly higher compared with group A (p = 0.05 and 0.003, respectively). In addition, the presence of metastases in lymph nodes pN ($p < 0.001$) and the presence of distant metastases M ($p < 0.001$) showed a statistically significant effect on OS (Table 4). Multivariate Cox's proportional hazard regression model analysis revealed that TILs and the presence of distant metastases have the greatest impact on OS. (Table 5).

Thus, TILs could be considered as an independent prognostic factor for colon adenocarcinoma.

153 of 180 cases had the same TILs scoring between both pathologists and the overall agreement was 85%. Expected frequency of agreements that would have been expected by chance was calculated by Pearson's Chi-squared test: it was 26.72 for group A; 31.16 for group B; and 7 for a group C. The Kappa was 0.76 that reflects a high level of consistency between pathologists assessing TILs.

DISCUSSION

Nowadays, the understanding of tumor microenvironment importance on cancer progression and treatment success becomes clearer [17, 18]. Numerous studies have shown prognostic value of TILs in colon cancer [19]. Moreover, some of the authors are concentrating on detailed profiling of TILs, and the following measuring of immune cell subset proportions. They assume that deeper study of immune response signature will be highly demanded [20]. Also, there has been observed a correlation between density of $CD8^+$ TILs and positive response to treatment, OS [21, 22]. Jakubowska *et al*. [23] have found an association between TILs localized at invasive tumor site and around tumor deposits with the liver metastases.

Numerous studies of TILs in breast cancer have shown their prognostic value [24]. The high density of TILs in breast carcinomas is associated with a better prognosis for OS and disease-free survival rates [25, 26]. Methodology of TILs assessment in breast cancer is described in recommendations by an International TILs Working Group 2014 [15]. Skriver *et al*. [27] showed the influence of high TILs on a poor treatment response in breast cancer patients. Additionally, due to numerous studies confirming TILs prognostic value, in WHO Classification of Tumors of the Breast,

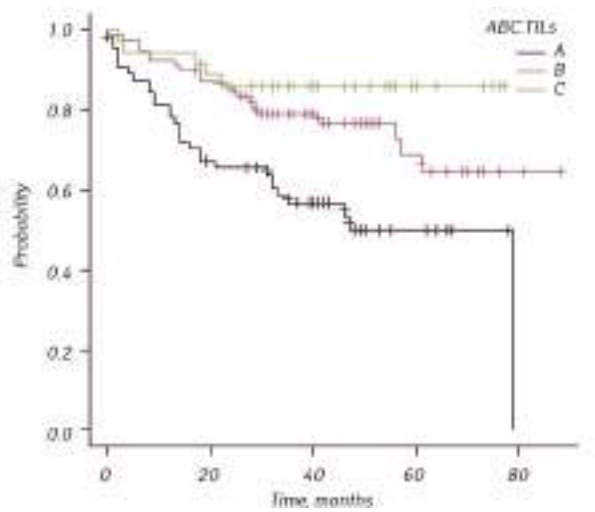

Fig. 4. Kaplan — Meier survival curve (OS), stratified by TILs groups

Table 4. Monovariate Cox's proportional hazard regression model of TILs prognostic value for the OS of CRC patients

Index	OS		
	Hazard ratio (HR)	Relative risk with 95% CI	*p*-value
Age			0.455
⩽40	Referent		
>40<60	0.42	0.05–3.26	0.414
⩾60	0.34	0.04–2.51	0.291
pT (Tumor)			0.143
pT2	Referent		
pT3	3.26	0.44–23.87	0.242
pT4	5.01	0.06–37.63	0.116
pN (Lymph nodes)			< 0.001
pN0	Referent		
pN1	3.92	1.99–7.72	< 0.001
pN2	5.72	2.63–12.43	< 0.001
M (Distant metastasis)			
M0	Referent		
M1	7.18	4.07–12.68	<0.001
Histological type			0.712
Adenocarcinoma	Referent		
Adenocarcinoma mucinous	0.31	0.04–2.26	0.249
Adenocarcinoma mucous producing	0.98	0.23–4.07	0.986
Signet ring cell carcinoma of colon	1.21	0.16–8.82	0.845
Differentiation grade			0.260
G1	Referent		
G2	2.43	0.33–17.69	0.378
G3	3.30	0.38–28.34	0.275
Necrosis			
Yes	Referent		
No	0.90	0.49–1.67	0.753
Neutrophils			
Yes	Referent		
No	1.09	0.60–1.98	0.770
TILs			0.002
A (0–10%)	Referent		
B (10–40%)	0.45	0.25–0.79	0.005
C (> 40%)	0.24	0.09–0.63	0.003

Table 5. Multivariate Cox's proportional hazard regression model of TILs prognostic value for the OS of CRC patients

Index	OS		
	HR	Relative risk with 95% CI	*p*-value
M (Distant metastasis)			
M0	Referent		
M1	5.37	2.79–10.31	< 0.001
TILs			0.041
A (0–10%)	Referent		
B (10–40%)	0.54	0.30–0.97	0.042
C (> 40%)	0.36	0.13–0.99	0.049

2019, it was proposed to consider TILs for clinical purposes [28].

Currently there is no standardized method of TILs assessment in colon cancer. Matsutani *et al*. [29] compared two methods of TILs evaluation: concentrating on "hot spots" and randomly selected fields. Both have shown statistical significance. Some of the study groups are working on software for TILs detecting and correct count [30, 31]. However, despite the fact we determined the number of TILs on H&E slides during routine light microscopy based on recommendations by an International TILs Working Group [15], and we received statistically significant results.

However, deeper study of TILs characteristics may contribute to understanding of key mechanisms of anticancer immunity and further development of anticancer therapy. Activated cytotoxic cells (T-cells and NK-cells) show direct activity against cancer cells by release of perforins and granzymes [32, 33]. This is a major pathway that makes cytotoxic cells kill tumor cells [34]. Wouters *et al.* [35] have shown an importance of B-cell and plasma cells presence in infiltrate as theoretically influencing the activity of T-cells and tumor microenvironment reactions. Nevertheless, these influences stay debatable [36].

Our study has some limitations. For patients in group C, OS data were available only for 2 years. Additionally, the number of chemotherapy cycles vary among the patients.

To sum up, OS is significantly higher in patients with moderate and high number of TILs. TILs count on H&E slides is an easy assessible method that can be done during routine morphological examination by light microscopy and do not require additional costs, thus may be implemented in everyday pathologist's practice. There was a high level of consistency between pathologists assessing this prognostic factor. Further study of TILs may help in precise selecting of high-risk patients and individualization of treatment.

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ВМІСТ ЛІМФОЦИТІВ, ЩО ІНФІЛЬТРУЮТЬ ПУХЛИНУ, ЯК ДОСТУПНИЙ ПРОГНОСТИЧНИЙ ТЕСТ ПРИ АДЕНОКАРЦИНОМІ ТОВСТОЇ КИШКИ

*Л. Захарцева[1, 2], Б. Шкурупій[2, *]*

[1]Київська міська онкологічна лікарня, Київ 03115, Україна

[2]Національний медичний університет ім. О. Богомольця, Київ 01601, Україна

Мета дослідження*:** Визначити прогностичну значимість пухлино-інфільтруючих лімфоцитів в аденокарциномі товстої кишки. Враховуючи велику кількість випадків розвитку токсичності, пов'язаної з хіміотерапією, існує потреба в пошуку додаткових інструментів для більш точного відбору пацієнтів, що потребують хіміотерапії, для покращення загальної виживаності. ***Матеріали та методи*:** Дослідження включає 180 зразків від пацієнтів з діагнозом аденокарциноми товстої кишки. Кількість пухлино-інфільтруючих лімфоцитів підраховували на гістологічних скельцях, забарвлених гематоксилін-еозином. ***Результати: На основі кривої виживаності Каплана — Майєра було показано, що співвідношення між кількістю пухлино-інфільтруючих лімфоцитів (ПІЛ) та загальною виживаністю є статистично значущим ($p = 0,001$). Аналіз моделі пропорційних ризиків Кокса показав, що ПІЛ мають статистично значущий вплив на загальну виживаність. У групах з ПІЛ 10–39% та > 40% відмічають достовірно кращі показники загальної виживаності (відносний ризик 0,54, 95% довірчий ризик 0,30–0,97, p = 0,042 та відносний ризик 0,36, 95% довірчий інтервал 0,13–0,99, $p = 0,049$ відповідно) у порівнянні з групою з низьким вмістом ПІЛ. ***Висновки*:** Кількість ПІЛ статистично достовірно пов'язана з вищими показниками загальної виживаності та її можна розглядати як самостійний прогностичний фактор щодо аденокарциноми товстої кишки. Завдяки простоті та економічності методу його можна рекомендувати як додатковий інструмент в рутинній практиці патологів.

***Ключові слова*:** рак товстої кишки, аденокарцинома, пухлинно-інфільтруючі лімфоцити, прогноз, загальна виживаність.