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Grading of lymphocyte infiltrating tumor can be used as a prognosis factor compared to T Pathology and N Pathology on recurrency of colon cancer

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ABSTRACT

Background: 30-50% of colon cancer patients will experience recurrence and then die. Several factors that can be used as a prognosis for recurrence are tumor staging, number of lymph nodes resected, high pT, and grading of TILs as an immune response that is useful for suppressing tumor growth. This study aimed to determine whether the TILs grading can be used as a prognostic factor for recurrence than pT and pN.

Methods: This study used a descriptive retrospective study with all colon cancer patients who had hemicolectomy R0 right and left and patients who had received chemotherapy folfox who experienced recurrence at Dr. Soetomo Surabaya. Data were analyzed using SPSS version 25.0 for Windows.

Results: It was found that 33 people (32.4%) experienced a recurrence of less than 2 years and 69 people (67.9%) experienced a recurrence of 2-5 years. Low-grade TILs were 37 people (32.4%), and high TILs were 65 (63.7%). Patients with low-grade TILs at most 21 people (56.7%) will experience a recurrence of less than 2 years, while patients with high-grade TILs at most 53 people (81.5%) will experience a recurrence in years 2 - 5. pT4 has a recurrence of less than 2 years as many as 6 people (46.2%), less than pT4 with a recurrence of 2-5 years, namely 7 people (58.3%) while pT3 who experienced a recurrence of less than 2 years, the number was higher than pT4, namely 22 people (32.8%). pN0 will experience the highest recurrence in years 2-5 as many as 37 people (80.4%), while pN2 will experience the highest recurrence in less than 2 years as many as 14 people (66.6%). Grading TILs were significant ($p = 0.018$) in determining the prognosis than pT ($p = 0.204$) and pN ($p = 0.083$) in the first 2 years.

Conclusion: Grading of TILs can be a prognostic factor for colon cancer recurrence in only the first 2 years.

Keywords: Grading TILs, pT, pN, Colon Cancer
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INTRODUCTION

Surgical resection is the best treatment option in patients with colon cancer, but cancer recurrence after resection is associated with a higher risk of death. Two-thirds of colon cancer patients who undergo resection at the time after diagnosis, 30-50% will experience a recurrence and then die.[1] Some of the factors that can be used as a prognosis for recurrence are the staging of the tumor, the number of lymph nodes resected, the high pT, haematologic markers, and the immune system of colon cancer patients themselves.[2-6] The use of pT itself as a prognostic factor has drawbacks, where pT becomes less precise as a prognostic factor in the third year or above 5 years. This is because, after 3 years of surgery, the hazard ratio time pT will decrease to half.[7] The number of lymph nodes still influences the pT factor as a prognosis for recurrence. With these considerations, pT cannot be used as the leading benchmark in assessing recurrence. It is necessary to have other tests besides pT as a prognostic factor for recurrence.

For the risk factors for the number of lymph nodes experiencing metastasis, research shows pN0 has a greater life expectancy of 86% than pN2, which is only 69%.[8] However, research by Ong W et al states that recurrence can still occur in 20-30% even without lymph node metastasis, so that it can affect the prognosis and overall survival of patients.[9] The pN examination was also influenced by anatomic pathology expertise in calculating the number of N, T size, and length of the specimen.[10] Based on these factors, the lymph nodes themselves cannot be the primary benchmark in assessing the recurrence prognosis.

Tumor cells themselves have a way to survive T lymphocyte attack by hiding their antigens so that activated T lymphocytes cannot recognize tumor

cells.[11] Lymphocytes that can be found in the tumor area are called Tumour-Infiltrating lymphocytes (TILs). TILs consisting of activated lymphocytes can recognize MHC I on tumor cells' surface to later undergo apoptosis through perforin protein and granzyme B produced by T lymphocytes.[12] So that TILs can be considered as an immune response that is useful in suppressing tumor growth. Based on the previous studies, getting high-grade TILs had better disease-free survival and better overall patient survival than low ones.[2,4] This TILs examination can be done through the hematoxylin-eosin (H&E) examination according to the International TILs Working Group (ITWG) system. The H&E examination is an examination that is quite fast, routine, low price but can still provide information as a predictor and prognosis factor.[13]

Because of this background, we want to research by taking medical record data of patients treated at Dr. Soetomo Hospital for 5 years from 2015 - 2019, evaluating whether the TILs grading can be linked as a marker of recurrence of colon cancer patients and whether the TILs grading is more significant in determining the prognosis of recurrence than pT or pN

METHOD

This study uses a descriptive retrospective study method. This study is expected to prove the grading of TILs as a prognostic factor for colon cancer recurrence compared to pT and pN to be a determinant of subsequent therapy. In this study, the subjects included were all colon cancer patients who had hemicolectomy R0 right and left and patients who had received folfox chemotherapy who experienced recurrence either through clinical, laboratory, or radiological examinations at RSUD Dr. Soetomo Surabaya from 2015–2019, where patients were excluded from incomplete medical records. The sampling technique was taken by patients who met the inclusion and exclusion criteria of the study. The general data of the subjects were recorded.

The variables examined in this study were the grading of TILs from the slides of specimen preparations with hematoxylin & eosin (H&E) staining, pT measurement, and pN calculation from specimens of colon cancer patients in the Department of Pathology, Anatomy, RSUD Dr. Soetomo Surabaya. Patients were then grouped into the recurrence group <2 and 2-5 years. Data were recorded and recapitulated for analysis. Data management was carried out using the SPSS version 25.0 for Windows program. The data is presented in the form of a frequency distribution table and cross-tabulation.

Table 1. Baseline characteristics of respondents

Characteristics	N (%)
Gender	
Man	52 (50.9%)
Woman	50 (49.0%)
Age (Years)	
<50	59 (57.8%)
>50	43 (42.1%)
Stadium	
Stadium I	6 (5.8%)
Stadium II	40 (39.2%)
Stadium III	55 (53.9%)
pT	
pT2	22 (21.5%)
pT3	67 (65.6%)
pT4	13 (12.7%)
pN	
pN0	46 (45%)
pN1	35 (34.3%)
pN2	21 (20.5%)
Grading TILs	
Low	37 (32.4%)
High	65 (63.7%)
Recurency (Years)	
< 2	33 (32.4%)
2-5	69 (67.6%)

Table 2. Grading distribution of TILs, pT, and pN based on recurrence

Variables	Recurrence (N=102)		Total	P
	< 2 years (n=33)	2 – 5 Years (n=69)		
Grading TILs, n (%)				
Low	21 (56.7)	16 (43.2)	37 (100.0)	0.018*
High	12 (18.4)	53 (81.5)	65 (100.0)	
pT, n (%)				
pT2	5 (22.7)	17 (77.2)	22 (100.0)	0.204
pT3	22 (32.8)	45 (67.2)	67 (100.0)	
pT4	6 (46.2)	7 (58.3)	13 (100.0)	
pN, n (%)				
pN0	9 (19.5)	37 (80.4)	46 (100.0)	0.083
pN1	10 (28.5)	25 (71.4)	35 (100.0)	
pN2	14 (66.6)	7 (33.3)	21 (100.0)	

*Statistically significant if p-value less than 0.05

RESULT

In this study, there were 102 research subjects with the following descriptions: 52 male (50.9%) and 50 female (49.0%), 59 people aged less than 50 years (57.8%), and over 50 years of age 43 people (42.1%). The description of the next research subject can be seen in Table 1.

In this study, it was found that a total of 33 people experienced a relapse of less than 2 years, where 21 people (56.7%) had

low grading TILs and 12 people (18.4%) had high-grade TILs. For recurrence in 2-5 years, 69 people were obtained, where 16 people (43.2%) had low grading TILs, and 53 people (81.5%) had a high-grade description of the results can be seen in Table 2.

DISCUSSION

Infiltration of lymphocytes is a characteristic part of a tumor and is considered a prognostic factor in colorectal cancer. Infiltration of these lymphocytes can be checked with hematoxylin & eosin (H&E). The H&E examination is an examination that is routinely carried out.[13] The price is cheap but can still provide information as a predictor and prognosis factor.[13]

In our study, anatomical pathologists who performed TILs were examined using the criteria of Jakubowska K et al., which indicates the presence of lymphocyte infiltration in the tumor-stromal by percentage, this system was chosen because it is easier to interpret immune cell infiltration to the tumor.[14] Jakubowska K et al divides TILs into 3, namely low (0-10% TILs), medium (20-40% TILs) and high (50-90% TILs) grading.[14] In this study, some grading was between 10-20%, or between 40-50% it was decided to go into closer grading, so to facilitate the sample analysis, we divided the grading TILs into two, namely low and high TILs grading.

In this study, we obtained data grading TILs played a role in showing recurrence of less than 2 years, this can be seen from the number of patients who experienced recurrence as many as 21 people (56.7%) had low TILs and 12 people (18.4%) had high TILs, whereas 16 people (43.2%) had low TILs and 53 (81.5%) had high TILs recurrence at years 2–5. High–grade TILs still experience recurrences that occur in years 2–5. This is explained in several theories, stating that cancer cells can avoid body immunity by hiding their antigens or hiding physically.[15] To support this hypothesis, a previous study showed many cancer cells removed up to 90% of normal MHC I expression.[16] Cancer cells can also defend against T cells by utilizing the FasL/Fas (PDL-1/PD1) pathway.[17] The hypothesis states that FasL (PDL-1) expression that is too high on the surface of cancer cells allows cancer cells to inhibit the tumor lymphocyte infiltration (TIL).

FasL expression is also believed to be associated with in vivo tumor-infiltrating cell apoptosis.[17] Immune therapy targets immune checkpoints, such as the CD28/CTLA4 and PD-1/PD-L1 pathways that have been shown to have significant clinical efficacy in many types of cancer.[18-20] Immune checkpoint inhibitors such as anti-PD1 / PD-L1, anti-CTLA-4 have emerged as the most effective immunotherapy.

This study also linked pT and pN based on recurrence. From the data obtained at pT4, 7 people (58.3%) experienced recurrence in 2–5 years, while only 6 people (46.2%) had a relapse of less than 2 years. Meanwhile, pT3 experienced a recurrence of less than 2 years, and the number was higher than pT4, namely 22 people (32.8%). This result is not in accordance with the research by Maeda H et al. which stated that high pT makes the prognosis of colon cancer patients worse.[21] This discrepancy can be caused by other factors that influence recurrence, including the body's immune system, such as lymphocytes, and the number of lymph nodes that experience metastasis.[21] In pT4, 7 people (71.4%) experienced recurrence in 2–5 years, and of these 7 people, 5 (71.4%) turned out to have a high grade of TILs. This makes the pT variable unable to become the primary benchmark in assessing the prognosis of recurrence.

The data we get from pN, we get pN0 will experience the highest recurrence in years 2-5 as many as 37 people (80.4%), while pN2 will experience the highest recurrence in less than 2 years as many as 14 people (66.6%) and will decrease in next. This is not in accordance with the research by He WZ et al which states that negative lymph nodes indicate a strong immune reaction against cancer cells.[22] This discrepancy can be caused by the presence of other factors that influence relapse. These factors include, first, physically the cancer cells are able to separate themselves from the introduction of immune cells and avoid destruction. These second cancer cells fail to migrate through the lymph glands. Although the antigen is at risk of being recognized by the adaptive immune cells, they still manage to escape immune cells' introduction. A previous study by Ong W at al also states that recurrence still occurs in 20-30% even without lymph node metastasis.[9] It can be concluded that pN cannot be used as a prognostic factor for recurrence.

Grading TILs can be used to determine recurrence, although the results are consistent only in the first 2 years, whereas those between 2-5 years are not. We hypothesize that cancer cells need time to produce PDL to fight the immune system played by T lymphocytes. Data from low and high-grade TILs will continue to recur in 2–5 years. Grading TILs may be used as a determinant of when cancer cells will produce PDL. Likewise, our hypothesis on dendritic cells' reaction to limit T-lymphocyte activity is expected to occur over 2 years.

CONCLUSION

Grading TILs can be a prognostic factor for colon cancer recurrence in only the first 2 years. Grading TILs were more significant in determining prognosis than pT and pN in the first 2 years.

ETHICAL CLEARANCE

This research has received ethical clearance approval from the ethics committee of Dr. Soetomo Hospital.

CONFLICT OF INTEREST

This research has no conflict of interest or affiliation with any company.

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AUTHOR CONTRIBUTIONS

Budipramana, S. Vicky as main author, Saraswati, Ayu Putu and Rahniayu, Alphania as co-author.

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