The Relationship Between Expression of EpCAM Cancer Stem Cell Marker with Histopathological Grading, Lymphovascular Invasion, and Metastases in Colorectal Adenocarcinoma

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The Relationship Between Expression of EpCAM Cancer Stem Cell Marker with Histopathological Grading, Lymphovascular Invasion, and Metastases in Colorectal Adenocarcinoma

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Abstract

Objective: The aim of this study was to analyze the expression of EpCAM in the colorectal adenocarcinoma. **Material and methods:** This study used a cross-sectional design. One hundred and thirteen paraffin embedded block of Colorectal Adenocarcinoma were assessed using anti-EpCAM/Epithelial Specific Antigen (Ber-EP4) mouse monoclonal antibody and their expression were performed using Olympus CX-43 light microscope. The relationship between EpCAM expression with histopathological grade of colorectal adenocarcinoma, lymphovascular invasion and metastases ability were statistically analyzed by Chi-Square tests and presented in tables using SPSS 18. **Results:** From 113 samples, in samples with lymphovascular invasion there were 37 samples (32.7%) with strong expression, while those with weak expression were 19 samples (16.8%). There were 39 samples with metastases and strong expression of EpCAM (34.5%), while 21 samples with weak expression (18.6%). There was a significant relationship between the expression of cancer stem cell marker EpCAM with lymphovascular invasion and colorectal adenocarcinoma metastases ($p = 0.002$), but there was no significant relationship with histopathological grade ($p = 0.574$). **Conclusion:** The EpCAM expression can be used as a prognostic factor, and can be considered as a predictive or an option for target therapy in colorectal adenocarcinoma.

Keywords: Colorectal adenocarcinoma- Cancer Stem Cells- EpCAM- lymphovascular invasion- metastases

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Introduction

Colorectal cancer is the third most common cancer in men, the second in women, and it's the second for leading cause of cancer death worldwide, with more than 1.2 million new cancer cases and 608,700 deaths (Effendi-YS and Rey, 2018; Liao et al., 2015). In Indonesia, the incidence based on male and female sex respectively is 15.9 and 10.1 per 100,000 (Yusuf et al., 2021). The age category of colorectal adenocarcinoma sufferers aged > 40 years (Miskad et al., 2020). According to GLOBOCAN 2020, Indonesia had 33,427 new cases of colorectal cancer, or around 8.4% of all cancer cases worldwide (396,914) (World Health Organization, 2020). Based on the study by Kristina et al, the number of Mortality (NOM) and Alcohol-Attributable Morbidity (AAM) of eight types of cancer related to alcohol consumption in Indonesia 2016 for colorectal cancer reached 163 people (Kristina et al., 2018).

Although therapeutic methods have developed well, but the tumor cells being resistant to therapy in some patients (Li et al., 2014), and the possibility of recurrence and metastasis are the main causes of cancer-related morbidity and mortality (Kumar et al., 2021) Cancer stem cells (CSCs) are thought to be the cause of carcinogenesis and are intimately linked to tumor metastasis, drug resistance, and recurrence after primary treatment, according to recent studies. CSCs are a small subset of tumor cells that exhibit stem cell traits such the capacity for self-renewal, differentiation into several lineages, and infinite capacity for multiplication. CSCs are now known to exist in a wide variety of malignancies, including colorectal cancer (Li et al., 2014).

A cell with epithelial characteristics, known as EpCAM (Epithelial Cell Adhesion Molecule), may be extracted from colorectal cancer, and this cell exhibits stem cell-like behaviors such growth, invasion, and metastasis (Zhou et al., 2018). A wide range of human cancers, including

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colorectal and hepatocellular carcinoma, are thought to be caused by EpCAM positive cells, which are thought to function as cancer stem cells (Aiman et al., 2020). On the majority of primary and metastatic malignancies, EpCAM is also overexpressed. There are numerous treatments being explored that target EpCAM using antibody-based methods (Eslami-S et al., 2020; Huang et al., 2018).

Eighty five percent (85%) of colorectal carcinomas express EpCAM. Overexpression of EpCAM increases the capacity of tumors to proliferate and invasively (Liu et al., 2014) EpCAM overexpression correlates with aggressiveness and poor prognosis in colon cancer (Abdelaziz et al., 2017).

EpCAM overexpression may be attributed to a higher proportion of cancer stem cells (CSCs) that have the potential become metastatic initiator cells (MIC) (Eslami-S et al., 2020). Further investigation into cellular mechanisms proved that inhibiting EpCAM can suppress Wnt pathway expression and reduce the proliferative and invasive potential of tumor cells. The findings of this study suggest that EpCAM may represent a new therapeutic target in colon cancer adjuvant treatment (Zhou et al., 2015). According to research by Chai et al., (2015) patients with a strong positive expression had a much worse prognosis than those with a weak positive expression.

Therefore, this study assessed whether EpCAM expression correlates with histopathological grading, lymphovascular invasion status, and colorectal adenocarcinoma metastases, so that it can be one of the candidate prognostic biomarkers of colorectal adenocarcinoma.

Materials and Methods

From January 2016 to July 2021, we obtained 113 paraffin block samples from patients who had been diagnosed with colorectal adenocarcinoma at the Anatomical Pathology Laboratory Dr. Wahidin Sudirohusodo, Hasanuddin University Faculty of Medicine, and Makassar Pathology Diagnostic Center for this study.

EpCAM mouse monoclonal antibody immunohistochemical staining was carried out on slides that had not been stained. The paraffin blocks were used to create slides, which were subsequently cut using a 3 µm thick microtome. A poly-L-lysinie slide was used to take the cut in the water bath, and it was later deparaffinized. using mouse monoclonal EpCAM antibody for immunohistochemical staining.

Using a 400x light microscope, the expression of EpCAM was examined on the membrane and cytoplasm of tumor cells. Assessment performed by two pathologists who were blinded of clinical data and results.

The intensity and proportion of stained tumor cells were used to score EpCAM expression in a semi-quantitative manner, and the total immunostaining score (TIS) was used to determine the overall score. The EpCAM expression score is the total immunostaining score (0-12) obtained by multiplying the proportion score of the tumor area stained positively (0-4) with the EpCAM staining intensity score (0-3).

The proportion score 0: None; 1: Stained <10%; 2: Stained 10-50%; 3: Stained 51-80%; 4: Stained > 80%. The intensity of EpCAM: uncolored : 0/negative;, weak: +1; moderate: +2; strong: +3. Furthermore, EpCAM expression was declared strong if TIS >6 and weak if TIS <6 (Abdelaziz, Lobna et al., 2017; Spizzo et al., 2011).

Statistical Program for Social Science (SPSS) 18 for Windows was used to process the data for this investigation. To evaluate the correlation between categorical variables, the Chi-Square test was applied.

Results

Table 1 shows the distribution of the 113 samples of colorectal adenocarcinoma by age, gender, tumor site, histopathological grade, lymphovascular invasion, metastases, and EpCAM expression.

Based on Table 1, it can be seen that this study used a total of 113 samples, which the mean of age was 56.98 years old with a standard deviation of 11.06 years old. Samples with the age category <50 years were 27 samples (23.9%) and the age category > 50 years were 86 samples (76.1%). There were 65 samples of male (57.5%) and 48 samples of female (42.5%). Based on the location of the tumor, the location of tumor in the right colon were 35 samples (31.0%), in the left colon were 40 samples (35.4%), and in the rectum were 38 (33.6%) samples.

Table 1. Characteristics of the Sample

Characteristics	Total	
	n	%
Age		
Mean + SD	56,98 + 11,06	
<50 years old	27	23.9
>50 years old	86	76.1
Gender		
Male	65	57.5
Female	48	42.5
Tumor location		
Right colon	35	31
Left colon	40	35.4
Rectum	38	33.6
Histopathological grade		
Low grade	71	62.8
High grade	42	37.2
Lymphovascular invasion		
Positive	56	49.6
Negative	57	50.4
Metastases		
Positive	60	53.1
Negative	53	46.9
EpCAM expression		
Strong	58	51.3
Weak	55	48.7
Total	113	100

Table 2. Relationship of EpCAM Expression with Histopathological Grade, Lymphovascular Invasion and Metastases

EpCAM Expression	Strong n (%)	Weak n (%)	Total n (%)	p[a]
Histopathological grade				
High grade	23 (20,4)	19 (16,8)	42 (37,2)	0.574
Low grade	35 (32,0)	36 (31,9)	71 (62,8)	
Lymphovascular invasion				
Positive	37 (32.7)	19 (16,8)	56 (49,6)	0.002
Negative	21 (18,6)	36 (31.9)	57 (50,4)	
Metastases				
Positive	39 (34.5)	21 (18.6)	60 (53,1)	0.002
Negative	19 (16,8)	34 (30.1)	53 (46,9)	

[a], Chi-Square test

The low-grade colorectal adenocarcinoma group were consisted of 71 samples (62.8%) and 42 samples (37.2%) of the high-grade. Samples with positive lymphovascular invasion were 56 samples (49.6%) and 57 samples (50.4%) were negative. Samples with metastases were 60 samples (53.1%), while those without metastases were 53 samples (46.9%). EpCAM expression with strong expression were 58 samples (51.3%), while those with weak expression were 55 samples (48.7%).EpCAM immunohistochemical examination results were assessed using a semi-quantitative scoring system based on proportion and color intensity. Tumor cells membranes and cytoplasms both displayed varying amounts and intensities of EpCAM expression. An example of EpCAM expression assessment for each color intensity is shown in Figure 1 below.

Table 2 shows that from 113 samples of colorectal adenocarcinoma, in high grade group there were 23 samples (20.4%) with strong expression and 19 samples with weak expression (37.2%). Meanwhile, in low grade group there were 35 samples (32.0%) had a strong expression and 36 samples (31.9%) had a weak expression. In samples with lymphovascular invasion there were 37 samples (32.7%) with strong expression, while those with weak expression were 19 samples (16.8%). For

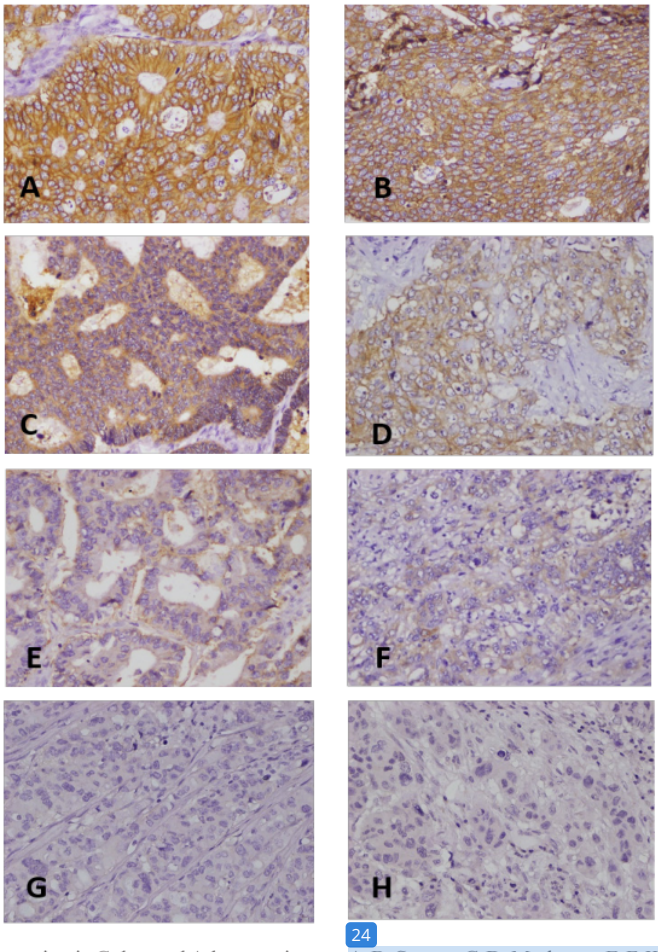

Figure 1. EpCAM Expression in Colorectal Adenocarcinoma. A-B, Strong; C-D, Moderate; E-F, Weak; G-H, Negative (400x Magnification).

samples without lymphovascular invasion, there were 21 samples (18.6%) with strong expression and 36 samples (31.9%) with weak expresion. Regarding to the metastases, there were 39 samples with metastases and strong expression of EpCAM (34.5%), while 21 samples with weak expression (18.6%). For samples without metastases, there were 19 samples (16.8%) with strong expression and 34 samples (30.1%) with weak expression. Based on statistical analysis using Chi-Square test, it shows that there were a significant relationship between EpCAM expression status and lymphovascular invasion and metastases (p=0.002), but there were no relationship between EpCAM expression status and histopathological grade (p=0.574).

Discussion

One of the antigens for cancer stem cells (CSCs) is epithelial cell adhesion molecule (EpCAM). EpCAM is a transmembrane glycoprotein with a single intracellular domain, a brief intramembranous domain, and an extracellular domain that is expressed on the surface of epithelial cells (EpICD) (Boesch et al., 2018). EpCAM is mostly found in the gastrointestinal tract (colon, rectum, and gallbladder) and is expressed in the cytoplasm and membranes of glandular epithelial cells (Gao et al., 2021). In malignant tumor cells, EpICD entry into the nucleus activates β-catenin/c-Myc pathway thereby promotes the growth of tumor cells (Liu et al., 2014). In some tumor types, particularly in colorectal cancer, EpCAM overexpression may be linked to cancer development and worse prognosis (Boesch et al., 2018).

In our study, there was no relationship between EpCAM expression and histopathological grade (Table 2). This finding is in line with reports (Kuhn et al., 2007; Lugli et al., 2010) which showed no relationship of EpCAM expression with tumor grade and stage. However, in other study report a very significant correlation where high EpCAM expression and positive CD44 expression correlated with grade and clinical staging, depth of invasion and metastasis (Liu et al., 2014). Due to the complex multistep molecular etiology of CRC, which includes numerous genetic and epigenetic alterations, there are variances in EpCAM expression (Kalantari et al., 2022). EpCAM expression is significantly regulated by epigenetic modifications such histone modification and methylation of gene promoters (van der Gun et al., 2010). Compared to healthy colonic mucosa, tumor tissue has more prominent EpCAM expression. Increased expression of EpCAM in tumor tissue indicates its involvement in the process of carcinogenesis (Liu et al., 2014). In malignant tumor cells, EpCAM mainly intracellular domain (EpICD), binds and causes β-catenin activation which in turn activates EMT genes and reprogramming promoters factor (OCT4, SOX2, NANOG and c-MYC) result in tumor cell proliferation (Lin et al., 2012).

Even while EpCAM expression was frequently seen in the majority of CRCs, some CRCs had no EpCAM expression. Recent research has linked germline EpCAM deletions and lack of EpCAM expression in CRC with Lynch syndrome-associated MSH2-deficiency. Deletion of the 3' end of the *EpCAM* gene can result in complex transcription and trigger promoter hypermethylation of the *MSH2* gene in EpCAM-expressing cells (Kim et al., 2014). The dedifferentiation of tumor cells may also have an impact on the decrease of EpCAM expression. The decreased level of EpCAM expression in tumor cells may indicate dedifferentiation because EpCAM is a hallmark of epithelial differentiation (Went et al., 200 Kim et al., (2016) in their study also stated that foci of EpCAM loss were mostly detected in poorly differentiated metastatic CRC tumor groups. These findings may be related to the un-expression of EpCAM in one of the high-grade adenocarcinoma samples in our study. However, it still needs to be demonstrated through additional research to understand how EpCAM interacts with other molecules that control how its expression is regulated. Therefore, the some reason why the EpCAM expression has no associated with histopathological grade is the variety of EpCAM expression due to the complex epigenetic process of CRC and also other molecular involvement in genetic mutation syndromes that we did not examine in this study.

We also assessed EpCAM expression with their relationship to lymphovascular invasion and metastasis (Table 2). Data from this study showed a significant relationship between EpCAM expression and lymphatic invasion and metastasis. EpCAM expression was higher in colorectal adenocarcinoma with lymphovascular invasion and metastasis than in noninvasive and nonmetastatic ones. This is consistent with studies by Abdelaziz et al., (2017) who found that positive CD44 and EpCAM expression correlated with higher stage and grade of cancer, presence of lymphatic and nodal invasion, and distant metastasis.

EpCAM controls the adhesion, proliferation, migration, invasion, stemness, and epithelial-to-mesenchymal transition (EMT) of cancer cells as the disease progresses (Eslami-S et al., 2020). The progression, metastasis, and recurrence of CRC are all positively influenced by EpCAM overexpression (Han et al., 2017). EpCAM has both oncogenic and tumor-suppressive biologic features, functioning as a double-edged sword protein (Kalantari et al., 2022). The role of EpCAM in prospectively activated oncogenic through the release of its intracellular domain, which is capable for giving signaling into the nucleus and then activating the Wnt pathway (Munz et al., 2009).

Overexpressed of EpCAM provides a strong growth stimulus for tumor cells thereby enabling proliferation, as well as causing tumor cell invasion and migration due antagonism to E-cadherin and upsetting the balance between α-catenin and F-actin. EpCAM is a prometastatic molecule because intercellular adhesion damage encourages proliferation, migration, and differentiation (Boesch et al., 2018).

The ability of cancer cells to temporarily alter their morphological and functional characteristics at the location of metastasis is one of their distinguishing characteristics (Sacchetti et al., 2021). Epigenetic modifications may be the foundation of phenotypic plasticity due to their ability to propagate through the milieu and produce metastases in other organs. This might be the mechanism of metastatis (Teeuwssen and

Fodde, 2019). The epithelial to mesenchymal transition (EMT), which involves the loss of epithelial characteristics and the acquisition of a more migratory mesenchymal phenotype, can be seen to exh phenotypic plasticity. This transition is thought to be a key step in the invasion and dissemination of tumor cells (Nieto et al., 2016).

EpCAM overexpression may encourage EMT in tumor cells by increasing Slug levels and activating the PTEN/Akt/mTOR signaling pathways, which are all involved in cell proliferation. (ang et al., 2018) Under hypoxic conditions, EpCAM overexpression in b st cancer cells encourages EMT and the production of stem cell markers (NANOG, SOX2, and OCT4). EpCAM's capacity to regulate and encourage invasion and migration is explained by EpICD signaling. Through the activation of the catenin pathway, EpICD serves as a signaling molecule in the nucleus and encourages the development of EMT. (Brown et al., 2021)

EpCAM affects the composition and function of tight junctions (TJ), which in turn regulates E-cadherin-mediated adhesion and the regulation of epithelial integrity. Although Ep M does not build up in TJ, it physically binds to claudin-7 and claudin-1, two significant TJ cell surface protein constituents. Through a direct contact between the EpCAM domain and claudin-7, the association of EpCAM-claudin-1 is dependent on claudin-7. EpCAM may play a significant role by reducing TJ aversion. Invasion and metastasis can occur as a result of the TJ framework losing its cohesiveness (Wu et al., 2013).

The limitation in this study is that it is only using one type of CSC marker with only one modality of protein detection through immunohistochemistry, so it is still less accurate in analyzing the complexity of the relationship between the EpCAM and various other molecules involved in the regulation of its expression, as well as its relationship to colorectal adenocarcinoma invasion and metastasis.

In conclusion, there is significant relationship between EpCAM expression and lymphovascular invasion and also metastasis in colorectal adenocarcinoma. EpCAM expression in the lymphovascular invasion group are higher than in wi out lymphovascular invasion group. While, EpCAM expression in the metastatic group are higher than in the non-metastatic group. There is no relationship between EpCAM expression and histopathological grade. EpCAM expression affects the invasion and metastasis of colorectal carcinoma but does not play a role in histopathological grading.

Author Contribution Statement

LOG, UAM, and MHC were involved in the method's conceptualization and design; LOG and M were involved in laboratory sample processing. LOG and AAZ were involved in data curation, analysis, and interpretation. UAM, MHC, GA and SW gave it a thorough conceptual and editing evaluation; The final version of the essay was revised and approved by all authors.

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Study Approval

This work was permitted by the research committee of the Faculty of Medicine, Hasanuddin University.

Ethical approval

The Faculty of Medicine's Ethics Committee waived informed consent for this study (Protocol #UH21090565 – Registry No. 605/UN4.6.4.5.31/PP36/2021).

Availability of Data

On reasonable request, the associated author will release the datasets used in this work.

Conflict of Interest

All authors state that they have no conflicting interests.

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