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Literature Review

Association between Lymphovascular Invasion and Carcinoembryonic Antigen as a Prognostic Factor in Post Colorectal Cancer Surgery Patients: Literature Review

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Background: Several prognostic factors have been proposed to reflect the course of the disease, such as demographic, histopathological, immunological, molecular and multidisciplinary interventions. Histological examination is widely used to predict prognosis and optimize adjuvant treatment, such as LVI and CEA.
Purpose and objectives: This study is a literature review that aims to see the correlation of LVI and CEA as a postoperative porgnostic indicator which is a development from previous studies regarding CEA levels on chemotherapy response
Methods: This study was a literature review focusing on the association between lymphovascular invasion and carcinoembryonic antigen as prognostic factors in post-colorectal cancer surgery patients. Two authors independently conducted searches of the PubMed, ScienceDirect, and British Medical Journal databases to identify relevant studies. Selected articles were reviewed and analyzed to synthesize current evidence on the topic.
Results: CEA normalized in more than 70% of patients after surgery, and the outcomes of patients with postoperative CEA who returned to normal were similar to those with normal preoperative CEA. Lymphovascular invasion is an independent poor prognostic marker for survival in colorectal cancer. Node negative patients, particularly stage II, are the most important group that could benefit from identification of LVI.
Conclusion: Serum CEA and LVI levels have the potential to be better biomarkers for the prognosis of colorectal cancer patients.

Keywords: Lymphovascular invasion, carcinoembryonic antigen, prognosis, colorectal cancer

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Background

Colorectal cancer is a common disease but contributes to a high mortality rate. According to the 2018 GLOBOCAN data, colorectal cancer is the third highest morbidity cancer and the fourth most frequently diagnosed cancer worldwide. Nearly 2 million new cases and around 1 million deaths are expected in 2018.[1,2] The incidence of colorectal cancer continues to increase worldwide, especially in developing countries that adopt a western lifestyle.[3] In 2018 in Indonesia, the incidence of colorectal cancer was ranked third highest with a proportion of 10.2% of all cancer cases and with 1.8 million new cases, and was ranked second as the type of cancer with the highest mortality. The risk of colorectal cancer is influenced by environmental and genetic factors. Obesity, lack of physical activity, consumption of red meat, alcohol, and smoking are considered to be the driving factors behind the high incidence of colorectal cancer.[4]

At the time of initial diagnosis, approximately two-thirds of patients with colorectal cancer undergo resection with curative goals, but 30%-50% of these patients experience recurrence and die. The main goal of postoperative monitoring of patients with colorectal cancer is to improve survival. Most colorectal cancer recurrences occur within a short period of time, with 60%-80% of recurrences occurring within the first 2 years after resection and 90% within the first 4 years. Survival in cases of early recurrence is poor. In both recurrence and metastases, if detected early, it may be possible to undergo surgical resection which is potentially curative and this will increase the patient's chances of survival.[5]

Several prognostic factors have been proposed to reflect the course of the disease, such as demographic, histopathological, immunological, molecular and multidisciplinary interventions. Histological examination is widely used to predict prognosis and optimize adjuvant treatment. However, there is still no consensus regarding the role of these tests in colorectal cancer.[6]

The lymphatic system is the main route for cancer metastasis because of its loose epithelial junctions and the absence of a basement membrane. Lymphovascular invasion is a marker of the presence of cancer cells in the lymphatics or blood vessels and is considered an early step in lymph node metastasis and cancer spread.[7] Previous studies have shown that LVI is associated with more aggressive tumor behavior and increased mortality in some cancers, such as breast cancer, bladder, and stomach.[8] The rate of lymphovascular invasion in colorectal cancer has been reported to vary from 4.1 to 89.5%.[9] Lymphovascular invasion has been reported to be useful in identifying patients with high-risk stage II colorectal cancer who may benefit from adjuvant chemotherapy.[9,10]

Carcinoembryonic Antigen Serum (CEA) is an important biomarker for the diagnosis, prognosis, recurrence, metastasis, and evaluation of the effects of chemotherapy in colorectal cancer.[10] Since its introduction in 1965, CEA has become a tumor marker recommended by the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology, and the European Group on Tumor Markers for preoperative examination in patients with non-metastatic colorectal cancer. Recently, CEA has been recommended as part of colorectal cancer postoperative monitoring screening. Carcinoembryonic antigen is reported to be superior to other prognostic biomarkers.[11]

High preoperative serum CEA levels are reported not to return to normal after surgery in approximately one third of

patients with colorectal cancer. This indicates the presence of persistent disease and the need for further evaluation(Huang et al., 2020). Meta-analysis studies have also confirmed that early postoperative CEA levels are a better biomarker for the prognosis of stage II colorectal cancer patients than preoperative CEA. LVI also shows a significant relationship with increasing CEA levels to increasing tumor differentiation and staging.[12] Recent studies have highlighted the potential prognostic role of lymphovascular invasion (LVI) and carcinoembryonic antigen (CEA) in patients who have undergone colorectal cancer surgery. However, evidence remains scattered, and it is unclear how these factors can be used to guide post-operative prognosis, tailor adjuvant therapy, and ultimately improve patient survival. Therefore, a comprehensive review of the existing literature is important to clarify their prognostic significance. This review aims to synthesize current evidence on the association between LVI and CEA as prognostic factors in post-colorectal cancer surgery patients.

Colorectal Cancer

Etiology

There is epidemiological and preclinical evidence for an association between diet, lifestyle, and colorectal cancer incidence. Population studies and animal studies have been conducted to describe the effects of various fats and proteins, carbohydrates, vegetable and fiber components, micronutrients, and lifestyle on colon cancer development. In general, a "healthy" diet pattern characterized by a high intake of fruit and vegetables, whole grains, nuts and legumes, seafood, milk and dairy products was associated with a lower risk of colorectal cancer, whereas a diet high in meat red and highly processed, refined grains and alcohol intake are associated with a higher risk of colorectal cancer.[13]

The environmental risk profile may also differ according to the type of colorectal cancer precursor lesion (conventional adenomas versus serrated polyps) and according to the molecular subtype of the cancer. The predisposing genetic factors and molecular changes underlying colorectal cancer have been extensively studied. The most common inherited forms of colorectal cancer are Lynch syndrome, which is caused by mutations in the DNA mismatch repair gene, and familial adenomatous polyposis (FAP), which is caused by germline mutations in the adenomatous polyposis coli (APC) gene.[14]

Pathophysiology

Most cancers start as polyps. This process begins with crypt aberrations which then progress to neoplastic precursor lesions (polyps), and eventually develop into colorectal cancer over a period of about 10-15 years. The cells of origin of most colorectal cancers are currently assumed to be stem cells or stem cell-like cells. Cancer stem cells are the result of a progressive accumulation of genetic and epigenetic changes that inactivate tumor suppressor genes and activate oncogenes. Cancer stem cells reside at the base of the colonic crypts and are critical for tumor initiation and maintenance.[15]

There are two main distinct pathways of precursor lesions: the adenoma-carcinoma pathway (also known as sequence chromosomal instability) which causes 70-90% of colorectal cancers, and the serrated neoplasia pathway (10-20% of colorectal cancers). This pathway represents several distinct genetic and epigenetic events in a somewhat sequential

order. Chromosomal instability phenotypes usually develop following genomic events initiated by APC mutations, followed by RAS activation or loss of TP53 function. In contrast, the serrated neoplasia pathway is associated with RAS and RAF mutations, and epigenetic instability, characterized by a CpG island methylation phenotype, leading to stable and unstable microsatellite cancers.[16]

Most carcinomas are initially exophytic (i.e. protruding into the lumen) and then ulcerate on the surface and progressively invade the muscular wall of the intestine. Finally, the tumor involves the serosa and surrounding structures. Stromal fibrosis can lead to luminal narrowing, which is responsible for the common acute presentation of large bowel obstruction.[15,16]

Colorectal carcinoma metastasizes via the lymphatics and bloodstream, and at the time of diagnosis, as many as 25% of patients already have distant metastases. Lymphatic spread occurs sequentially, first to the mesenteric glands and then to the paraaortic glands. Involvement of the paraaortic glands may manifest as a palpable mass or cause duodenal obstruction. Other enlarged lymph nodes can compress the bile ducts at the porta hepatis causing jaundice (Figure 1).[17]

Figure 1.Colorectal cancer signs and symptoms(Quick et al., 2019)

Diagnosis

History and Physical Examination

Colorectal cancer can present as an emergency or with well-recognized chronic symptoms. Diagnostic triggers for colonoscopy were blood per rectum (37%), abdominal pain (34%) and anemia (23%). The most common indications for emergency surgery were obstruction (57%), peritonitis (25%) and perforation (18%). A thorough physical examination should be performed for signs of ascites, hepatomegaly, and lymphadenopathy. A comprehensive family history is highly relevant for identifying family groups and patterns of inheritance that will change the evaluation and treatment of high-risk patients.[18]

Generalized examination may reveal features suggestive of disseminated malignancy, such as marked cachexia or enlargement of the supraclavicular glands. Abdominal examination is often found within normal limits, but there may be palpable masses in the colon, hepatomegaly caused by metastases, or ascites. Unfortunately, all of these signs represent a late and often incurable disease.[17,18]

Rectal examination is mandatory in all suspected cases, as most carcinomas occur in the lowest 12 cm and can be reached with the examiner's finger. In addition, intraperitoneal tumor spread into the pouch of Douglas can be palpated anteriorly through the rectal wall. The degree of fixation of the rectal tumor to surrounding structures can also be evaluated digitally to provide some indication of the need for neoadjuvant radiotherapy and the difficulty of surgery. Gloves should also be checked for stool color and consistency, as well as blood and mucus.[19]

Supporting investigation

Laboratory examination of the patient is to determine whether there are comorbid conditions that may affect perioperative morbidity and mortality. Standard laboratory evaluations include

hemogram, blood clotting, liver and kidney function, fasting blood sugar, electrolytes, urine analysis, and measurement of carcinoembryonic antigen (CEA) levels. Other laboratory studies are determined by a history of past medical problems and a thorough system review.[18,19]

Rigid or flexible proctoscopy and sigmoidoscopy are usually performed at the initial consultation. Approximately 50% of colorectal cancers are within the range of the rigid sigmoidoscope and 75% are within the range of the flexible sigmoidoscope. A history of rectal bleeding should be fully examined in patients over 45 years of age and in any patient if symptoms or signs suggest malignancy. This is true even if local causes, such as hemorrhoids are found. Flexible sigmoidoscopy is a minimal initial examination for rectal bleeding because the causative lesion may be in the left colon.[19]

If there is a change in bowel habits (particularly looser stools) or unexplained anemia, intestinal lesions may occur in the right colon, and thus the entire colon should be examined by colonoscopy or radiological imaging (Fig. 2).[20]

When colorectal malignancy is diagnosed, colonic surgery may be needed to relieve symptoms. Staging is performed to guide oncologist planning and counseling. Liver and lung metastases are evaluated (and possibly surgical curative resection) along with evidence of other spread within the abdomen or to the bone. Computed tomography (CT) of the thorax, abdomen and pelvis is the most useful examination. Magnetic resonance imaging (MRI) is performed if liver metastases are suspected (or ultrasound if an MRI is not available). A CT positron emission tomography scan is sometimes used. An MRI scan adds important information regarding the local extent of rectal cancer spread.[21]

In patients presenting as an emergency patient with total bowel obstruction, plain abdominal radiograph often shows the colon dilated with gas, descending to the level of the obstruction and empty of gas beyond it. CT scanning is very important to confirm the possible diagnosis of carcinoma, nodal staging and metastases. 'Instant' (ie, without bowel preparation) Gastrografin enemas can confirm the diagnosis and at the same time exclude pseudoobstruction. Endoscopic ultrasound provides an accurate view of the lining of the rectal wall. The tumor most often appears as a hypoechoic mass that encroaches on the lining of the rectum. MRI accurately predicts T stage and status of circumferential resection margins and is considered the technique of first choice for primary staging and restaging of colorectal cancer.[22]

Classification

The histological classification of colorectal cancer has been proposed by the World Health Organization (WHO):

- Adenocarcinoma
- *Cribriform comedo-type adenocarcinoma*
- Medullary Carcinoma
- Micropapillary carcinoma
- Mucinous adenocarcinoma
- *Serrated adenocarcinoma*
- *Signet ring cell carcinoma*
- Adenosquamous carcinoma
- Spindle cell carcinoma
- Squamous cell carcinoma
- Undifferentiated carcinoma
- *Neuroendocrine carcinoma*(NEC): large NEC, small NEC
- Mixed adenoneuroendocrine carcinoma

According to this classification, most colorectal cancers are adenocarcinomas of no particular type.

Special subgroups are noteworthy because they may be associated with specific genotypes and prognoses. Mucinous, medullary, and signet ring cell subtypes were more likely to be associated with the microsatellite–high instability (MSI-H) genotype; signet ring cell variant, when microsatellite stable (MSS) usually has a more poor clinical course. Serrated adenocarcinomas are associated with BRAF mutations, and the serrated and cribriform phenotypes are more likely to enter into the CpG hypermethylator genotype. NEC has a different staging and prediction scheme than traditional TNM systems, with high-level NEC having an aggressive behavior.[23]

Consensus molecular subtype s(CMS) colorectal cancer is a new classification system that integrates six classifications based on the comprehensive gene expression level of stage I-IV colorectal cancer into four CMS:

- CMS1 (MSI-immune, 14%), hypermutation burden, dMMR, unstable microsatellite and strong immune activation
- CMS2 (canonical, 37%), high chromosomal instability, epithelium, activation of WNT and MYC signaling
- CMS3 (metabolic, 13%), epithelial metabolic dysregulation and apparent, KRAS . mutation
- CMS4 (mesenchyme, 23%), CpG hypermethylation, prominent transforming growth factor-beta activation, stromal invasion and angiogenesis.

CMS classification has prognostic value, CMS1 is good, CMS2/3 is moderate, and CMS4 is bad.[24]

Staging

The tumor, node, metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) 8th edition is the preferred staging system for colorectal cancer. The AJCC classification for colorectal cancer is:

- Limited to the mucosa-submucosa (stage I)
- Invasion of the muscularis propria (stage II)
- Local gland involvement (stage III)
- Distant metastases (stage IV)

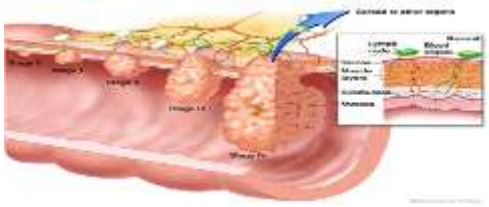

Figure 2. Colorectal Cancer Stage

Stage*	Criteria†
0	Carcinoma in-situ: intraepithelial tumor or invasion of the lamina propria‡ (Tis N0 M0)
I	Tumor invades submucosa (T1 N0 M0) [Dukes A] Tumor invades muscularis propria (T2 N0 M0) [Dukes A]
II	Tumor invades through the muscularis propria into pericolorectal tissues (T3 N0 M0) [Dukes B] Tumor penetrates the surface of the visceral peritoneum (T4a N0 M0) [Dukes B] Tumor directly invades or is adherent to other organs and structures (T4b N0 M0) [Dukes B]
III	Any degree of bowel wall penetration with regional lymph node metastasis N1: metastasis in 1-3 regional lymph nodes N1a: metastasis in 1 regional lymph node N1b: metastasis in 2-3 regional lymph nodes N1c: tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastases N2: metastasis in ≥4 regional lymph nodes N2a: metastasis in 4-6 regional lymph nodes N2b: metastasis in 7 or more regional lymph nodes Any T N1 M0 [Dukes C] Any T N2 M0 [Dukes C]
IV	Any invasion of the bowel wall with or without lymph node metastasis, but with evidence of distant metastasis Any T Any N M1a: metastasis confined to 1 organ or site (liver, lung, ovary, non-regional node) Any T Any N M1b: metastasis in more than 1 organ/site or the peritoneum

Figure 3. TNM staging

Management

Surgical resection is the definitive and curative initial treatment for stage I to III colorectal cancer. Certain patients (stage II high risk, all stage III) are recommended to receive adjuvant chemotherapy.

Microsatellite instability can be used in conjunction with clinicopathological factors in stage II and III colorectal cancer to guide therapy.[25]

The preferred surgical treatment for resectable non-metastatic colorectal cancer is colectomy with en-bloc removal of regional lymph nodes. The extent of resection is determined by the blood supply and distribution of regional lymph nodes. Resection should include a segment of the colon at least 5 cm on either side of the tumor, although wider margins are often included due to ligation of the arterial blood supply. The American Joint Committee on Cancer and the American College of Pathologists and the NCCN recommend examination of a minimum of 12 lymph nodes to accurately identify stage II disease (i.e., no lymph node involvement). Minimally invasive laparoscopic assisted surgery may be an acceptable alternative to open surgery for colon cancer in certain patients.[26,27]

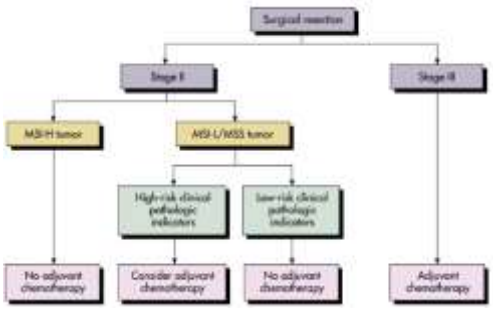

Figure 4.Colorectal cancer surgical resection algorithm

The standard chemotherapy regimen for adjuvant treatment of resected colorectal cancer is the combination of oxaliplatin with fluoropyrimidine (5-fluorouracil or capecitabine) for a period of 3 to 6 months. Older patients and patients with significant co-morbidities are more likely to experience toxicity with combination chemotherapy; treatment with single-agent fluoropyrimidine therapy is only recommended in these patients.[28]

Neoadjuvant chemotherapy and radiation therapy are used to shrink and downgrade rectal cancer before definitive resection and improve overall survival and local disease control in stage II and III cancer. Adjuvant chemotherapy in stage II disease provides a slight increase in overall survival of 3% to 4%, with 5-year survival rates currently in the 80% range. Thus, current guidelines recommend considering adjuvant chemotherapy only in high-risk stage II patients. The magnitude of the survival benefit was significantly higher in stage III patients, and combination chemotherapy was associated with an overall 5-year survival rate in the 70% range with wide variation within subgroups.[29]

Chemotherapy agents used in metastatic states include 5-fluorouracil (5-FU), capecitabine, irinotecan, oxaliplatin, and mitomycin. Chemotherapy regimens using combined antimetabolites (5-FU or capecitabine) in combination with oxaliplatin or irinotecan form the 'backbone' of systemic chemotherapy. Patients undergoing resection of isolated liver or lung metastases should also be considered for neoadjuvant therapy (capecitabine/oxaliplatin or 5-FU/leucovorin (LV)/oxaliplatin for 2 to 3 months) and adjuvant chemotherapy (6 months total perioperative treatment).[29,30]

Epidermal growth factor receptor (EGFR) inhibitors prevent cell growth and have shown benefit in the treatment of metastatic colorectal cancer, either used as a single agent or in combination with chemotherapy. Antiangiogenic agents (bevacizumab, aflibercept, and ramucirumab) and EGFR inhibitors (cetuximab and panitumumab) are used in combination with standard chemotherapy regimens in patients with metastatic colorectal cancer.[30]

Role of Carcinoembryonic Antigen, and Lymphovascular Invasion in Colorectal Cancer

Available evidence supports the use of CEA in colorectal cancer surveillance, particularly in postoperative follow-up. However, there is no evidence to support its use in screening and diagnosis of colorectal cancer, because CEA can be elevated in patients with other pathologies and many colorectal cancer patients will have normal CEA. Elevated CEA levels have been associated with a number of benign and malignant conditions. Carcinoembryonic antigen is most frequently used in colorectal cancer, but CEA is also a tumor marker in mucinous adenocarcinoma of the endocervix and ovary, and in keratinizing squamous cell carcinoma of the cervix. Because CEA is mainly metabolized in the liver, hepatic dysfunction and biliary obstruction can be associated with elevated CEA levels. When the liver metabolizes CEA, Liver damage can impair CEA clearance and cause elevated circulating levels. Increased concentrations of CEA have been observed in some patients after radiation and chemotherapy treatment.[31]

Figure 5. Factors affecting CEA concentrations

Carcinoembryonic antigen secreted by a variety of solid tumors, including 90% of colorectal cancers. As the single most important and reliable serum prognostic biomarker in colorectal cancer, elevated preoperative CEA levels were found to be associated with a poorer colorectal cancer prognosis.(Becerra et al., 2016; Wu & Gu, 2020). Carcinoembryonic antigen has been associated with cancer cell adhesion and innate immunity in colorectal cancer. In addition, CEA has also been reported to facilitate the attachment of colorectal cancer cells to the site of metastasis and support tumor development.[32]

Ona study found that after curative surgery, meaning resection, CEA levels would decrease exponentially. Carcinoembryonic antigen was measured preoperatively and on the 7th and 30th postoperative days. In the group of patients in which the CEA level had decreased exponentially, survival was significantly greater than in the group in which the CEA remained high, with a trend toward increased disease-free survival. Similarly, in patients with stage 4 colorectal cancer who underwent R0 resection, increased postoperative CEA was associated with reduced disease-free survival. Failure of the CEA to return to normal after surgery is indicative of residual or recurrent disease, with a CEA of greater than 10 ng/mL strongly associated with metastatic disease.[31,32] The National Comprehensive Cancer Network has recommended a serum CEA examination every 3 months after surgery as an indicator of recurrence.[32]

American Joint Committee on Cancerhave classified prognostic factors into four categories reflecting their strength of prognostic value, and LVI is listed among the first category prognostic factors that adversely affect patient survival, along with local tumor area (T), nodal involvement (N), distant metastases (M). , tumor budding, and residual tumor after surgical resection. Currently LVI is widely accepted as a strong poor prognostic factor and is listed by the NCCN guidelines as a

high-risk feature for colorectal cancer, along with positive margins, bowel obstruction, examination of <12 lymph nodes, perineural invasion, localized perforation, and differentiated histology.[33]

Lymphovascular invasionis a common histopathological finding and serves as an unfavorable prognostic factor in many cancers. Invasion of tumor cells into the vascular canal is thought to be a mandatory step in tumor progression to metastasis. The findings of LVI in colorectal cancer vary widely, from 10.0% to 89.5%, which may be due to differences in diagnostic techniques and patient populations in different studies. In one study, increased LVI findings were associated with tumor stage, with stage I found in 5.5% and increasing to 24.4% in stage IV. Lymphovascular invasion is closely associated with aggressive tumor features, such as higher histologic grade and advanced tumor stage. Thus, some findings suggest that the presence of LVI should be an indication for more extensive surgical resection.[29,30]

Lymphovascular invasion has been associated with several other criteria including advanced T and N stage tumor, high grade, budding tumor, perineural invasion, and mucinous histology. Among patients with lymph node involvement, tumors with LVI had a higher number of lymph node metastases, which roughly means that, in most cases, LVI positive and LVI negative patients show different stages of TNM at pathology. Such association of LVI and N status would, to some degree, confirm the hypothesis suggesting that LVI could be considered a precursor to, and therefore associated with, lymph node metastases, including occult ones, defining LVI as a potential predictor of patient outcome.[31,32]

Lymphovascular invasion is an independent poor prognostic marker for survival in colorectal cancer. Patients with negative nodes, especially stage II, are the most important group who can benefit from identification of LVI. Patients in this group may not be considered candidates for adjuvant chemotherapy, but may benefit substantially from it. Current NCCN clinical practice guidelines list LVI among the factors that should be considered when determining whether adjuvant therapy should be given in stage II disease. In patients with LVI(+) tumors were significantly more likely to metastasize to lymph nodes systemically than in patients with LVI(-). Wang et al's study conducted at Wuhan Hospital where LVI results were significant as an indicator of aggressive tumors and strongly correlated with poor prognosis in colorectal cancer.[33,34]

Conclusion

Serum CEA levels and LVI have the potential to be better biomarkers for the prognosis of colorectal cancer patients, where LVI also shows a significant relationship with increased CEA levels to increased tumor differentiation and staging.

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