REVIEW

Role of endoglin and VEGF family expression in colorectal cancer prognosis and anti-angiogenic therapies

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Abstract

Colorectal cancer (CRC) is one of the cancer models and most of the carcinogenic steps are presently well understood. Therefore, successful preventive measures are currently used in medical practice. However, CRC is still an important public health problem as it is the third most common cancer and the fourth most frequent cause of cancer death worldwide. Nowadays, pathologic stage is a unique and well-recognized prognostic indicator, however, more accurate indicators of the biologic behavior of CRC are expected to improve the specificity of medical treatment. Angiogenesis plays an important role in the growth and progression of cancer but its role as a prognostic factor is still controversial. Probably the most important clinical implication of tumor angiogenesis is the development of anti-angiogenic therapy. The goal of this review is to critically evaluate the role of angiogenic markers, assessed by either endoglin-related microvessel density or expression of vascular endothelial growth factor family members in the CRC setting and discuss the role of these angiogenic markers in anti-angiogenic therapies.

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Key words: Angiogenesis; Colorectal cancer; Colorectal cancer treatment; Endoglin; Prognosis; Vascular endothelial growth factor

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COLORECTAL CANCER EPIDEMIOLOGY

Colorectal cancer (CRC) is the third most common cancer and the fourth most frequent cause of cancer death worldwide[1-3]. Globally, CRC incidence varies widely, with higher rates in North America, Australia and Western Europe and lower rates in developing countries[4], although, in recent years, high CRC rates have also been reported in these countries[5]. In terms of mortality, geographic disparities have also been observed[6]. In Western countries, CRC is

the second most common cause of death from malignant disease, and despite improvements in treatment mortality remains high with metastatic spread to the liver occurring in about 50% of patients[7].

European countries rank highest in the global statistics, both in terms of CRC incidence and mortality. From 1998 to 2002, the incidence of CRC in Europe for men and women was 38.5 and 24.6 (world age standardization (ASR-W)) per 100 000 inhabitants and mortality over the same period was 18.5 and 10.7 (ASR-W) per 100 000 inhabitants, respectively[8]. However, over the past twenty-five years, mortality rates among Caucasians have steadily declined[9]. Data from the World Health Organization (WHO), between 1997 and 2007 have revealed that mortality from CRC declined by around 2% per year from 19.7 to 17.4/100 000 for men (world standardized rates), and from 12.5 to 10.5/100 000 for women, and these recent decreases in CRC mortality rates in several European countries are likely due to improvement in earlier diagnosis and treatment, with a consequent higher survival[10].

CRC incidence is generally higher in men, and the risk increases with age, as the majority of cases are diagnosed in patients older than 50 years[1, 3, 8], with only 5% of cases recorded in patients younger than 40 years[1]. A large nationwide study identified CRC as one of the 10 most commonly diagnosed cancers among men and women aged 20-49 years[11]. The prevalence of advanced CRC also increases with age and is higher among men than women[12].

COLORECTAL CANCER PROGNOSIS AND DISEASE PROGRESSION

The main prognostic factors in CRC are tumor size (T), lymph node involvement (N), grade of differentiation (G) and distant disease spread (M)[1-3,9,13,14]. Other important factors include invasion of blood and/or lymphatic vessels and penetration or perforation of the bowel wall[14].

Long-term survival correlates with stage of the disease[9, 15-17], and this is the most important predictor of mortality. The five-year survival rate for localized disease is 90.4%, but only 39% of CRC is diagnosed at this early stage[9, 16]. Approximately 15-20% of patients die as a consequence of CRC in early stages compared with 40-80% in advanced stages[15]. The overall 5-year survival rate varies among studies but is approximately 60%[9, 15, 16]. Stage-specific survival rates are 96%, 87%, 55%, and 5% for TNM stage Ⅰ, Ⅱ, Ⅲ, and Ⅳ, respectively[9,17,18].

One third of the patients submitted to curative intent surgery die of local and/or distant tumoral recurrence[15]. Among the sites of metastasis, liver is the organ most frequently involved (38%-60% of cases), followed by abdominal lymph nodes (38%), lung (38%) and peritoneum (28%)[14]. Of those diagnosed with metastatic disease, less than 10% are still alive after 5 years[16]. The 5-year overall survival rates for patients in whom hepatic resection was technically feasible and who had metastasis confined to the liver was only 25%-40%[7,19,20]. Better results were reported by Abdalla *et al* and Choti *et al*, with a 5-year overall survival rate of 58% following resection[21] and a rate of 67% described by de Haas *et al*[22]. These higher survival rates likely reflect improvements in patient selection, perioperative and postoperative care, multidisciplinary treatment, and an appropriately aggressive approach to safe hepatic resection[21]. Therefore, early diagnosis is critical to improve survival rates in CRC[23] and owing to its typically slow growth, there is a large potential for reducing the burden of the disease by early detection and removal of precancerous lesions or early cancer stages[24].

On the other hand, the pathologic clinical stage is currently the single most well-established prognostic indicator, but it does not fully predict individual clinical outcome[7, 25, 26]; also, the response of clinically-identical tumors to the same treatment may be vastly different[1]. This is particularly contentious for those tumors with intermediate stage disease (Stage Ⅱ, T3-T4N0M0)[7], where one third of patients with tumor-free lymph nodes have recurrences, and therefore, adjuvant chemotherapy may be beneficial[27]. In this group, carcinoma cells are not detected in lymph nodes by conventional staging methods in 24% of patients. Surgical technique and specific pathological staining may improve staging accuracy and the appropriate selection of patients for chemotherapy[27]. Furthermore, the identification of cancer penetration or perforation is particularly important in defining CRC aggressiveness[14]. Accordingly, identification of prognostic molecular markers capable of categorizing those patients at high-risk, would be very helpful for improving treatment strategies mainly in lymph node negative patients, determining the characteristics of patients' outcome, predicting cancer dissemination and recognizing which patients might benefit most from adjuvant chemotherapy and those unlikely to benefit thus sparing them the toxicities of treatment[14, 27-29].

Molecular markers may improve clinicopathologic staging and provide a basis to guide novel therapeutic strategies which target specific tumor-associated molecules according to individual tumor biology[1, 2, 7, 14], however, so far, no ideal molecular marker has been found to predict disease progression[29].

HIGHLIGHTS OF THE ANGIOGENESIS PHENOMENON

Angiogenesis plays a key role in tumorigenesis and metastatic processes[1, 28, 30]. It consists of the formation of new blood vessels from the endothelium of pre-existing vasculature[2, 30]. Sprouting from existing blood vessels is the principal process of angiogenesis and involves proliferation of activated endothelial cells, migration of endothelial cells to reach remote targets, assembly of endothelial cells into new capillary tubes, followed by synthesis of a new basement membrane and maturation of vessels with formation of a vascular lumen[30]. However, recruitment and *in situ* differentiation of bone marrow-derived endothelial

progenitor cells are also involved[30].

Tumor angiogenesis is essential to allow neoplastic mass development favoring access to the blood components, and also strengthening the vascular routes in the metastatic process[25, 31-33]. Neovascularization as a whole promotes tumor growth by supplying nutrients, oxygen and releasing growth factors that promote tumor cell proliferation[25, 30, 34-36]. Hypoxia in solid tumors occurs at a distance of $\geq 70\ \mu m$ from functional blood vessels and it is generally accepted that tumors do not exceed a volume of 1-2 mm^3 without induction of angiogenesis[36]. Intra-tumoral vasculature density is believed to be associated directly with cancer cell entrance into the systemic blood circulation, with the ability of cancer cells to invade locally normal anatomic structures, and the establishment of blood-borne metastases in distant organs[32, 37]. Regulation of tumor angiogenesis is the result of a complex balance between many stimulatory and inhibitory factors, which are secreted by both tumor cells and host-infiltrating cells as well as by tumoral stroma-cells activity[2, 30, 34]. Malignant neoplastic cells promote angiogenesis by secreting growth factors such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF) and platelet-derived growth factor (PDGF), among others that stimulate endothelial migration and proliferation[2,25,31,33,37,38].

The role of angiogenesis as a prognostic factor, however, is still controversial[13, 39]. Weidner et al first reported a direct correlation between the incidence of metastasis and the number and density of blood vessels in invasive breast cancers. Similar studies have endorsed this correlation in gastrointestinal cancers[33] and in a variety of malignancies[2, 7, 13, 25, 35, 37]. An association between increased angiogenesis and an increased incidence of metastases and a subsequent decrease in survival curve rates was observed for the vast majority of solid tumors[2, 7, 3, 25, 35, 37].

Several studies revealed high angiogenic activity in CRC, which was more likely correlated with aggressive histopathological features that included parietal invasion, tumor stage, grade of tumor differentiation, metastatic potential and poor patient survival[1, 13, 32]. Tanigawa[35] et al confirmed this premise, although a significant variation in patient populations and techniques was used, which can explain, in part, the inverse relationship between tumor vascularity and patient survival observed by these authors. Gurzu[13] et al added that augmented angiogenesis in CRC was higher in early-stages of tumoral proliferation but was not a progressively increasing process, having rather an oscillating character.

However, other studies revealed that angiogenesis does not provide any significant information[13, 28, 30]. These controversial statements may be credited to the lack of standardization of the different methods of counting tumoral blood vessels and to the different cut-offs used to define relevant parameters to consolidate the results and, lastly, to the different antibodies used to highlight the blood vasculature[13, 28, 30].

Despite the debates, assessment of tumor angiogenesis may be particularly useful in prognostic classification of patients with apparent early cancer by conventional tumor staging, some of which may still develop early recurrence or metastasis (despite being staged as having early cancers by conventional parameters such as tumor size)[30].

De Vita[37] et al observed that highly angiogenic tumors were associated with the presence of lymph node invasion. Nevertheless, a higher percentage of patients with node-positive colon cancer than those without will experience recurrence and might benefit from anti-angiogenic adjuvant therapy. Thus, angiogenesis can be used to identify a subset of patients at high risk for recurrence regardless of their lymph node involvement[35].

There is evidence that blood vessel density is also important in predicting cancer response to chemotherapy or radiotherapy[20]. Angiogenic tumors have a more aggressive phenotype and the degree of intra-tumoral microvessels is significantly predictive of poor response to platinum-based chemotherapy in terms of complete response, as seen in two studies, one in squamous cell carcinoma patients[40] and the other in patients with epithelial ovarian cancers[41]. In addition, Takagi[42] et al observed that blood vessel density was a valid predictor of the effects of intra-arterial targeted carboplatin chemotherapy and concurrent radiotherapy for treating human oral and oropharyngeal squamous cell carcinomas. Zhang[43] et al, trying to identify reliable predictive factors for local control of hypopharyngeal cancer (HPC) treated by radiotherapy, observed that microvessel density (MVD) in biopsy specimens was closely correlated with local control of HPC treated by radiotherapy. In one study of 28 patients with advanced gastric cancer treated by paclitaxel and carboplatin, tumors with medium MVD showed a significantly higher response rate compared with those with either a high or low MVD[44]. Long course of radiotherapy significantly decreased angiogenesis in rectal cancer tissue. MVD have been found to be a favorable marker for tumor behavior during radiotherapy and a predictor of overall survival after a long course of radiotherapy. Further investigations are now needed to determine the changes in angiogenesis during a shorter course of radiotherapy[1]. However, the most important clinical implication of tumor angiogenesis is probably the development of anti-angiogenic therapy, targeting tumor vessels instead of cancer cells[30].

ENDOGLIN AND ASSESSMENT OF MICROVESSEL DENSITY AS ANGIOGENIC MARKERS

Microvessel density (MVD) assessment is the most common technique used to quantify intratumoral and peritumoral angiogenesis in cancer[2, 7, 28, 30, 39]. It was first developed by Weidner et al in 1991 who used pan-endothelial immunohistochemical staining of blood microvessels, mainly with Factor VIII related antigen (F. VIII Ag or von Willebrand's factor), CD31 or CD34, and rarely CD105[2].

Measurement of angiogenesis is complicated by the

fact that it is a dynamic process. Intra-tumoral micro-vessels can be identified by immunostaining of endothelial cells by two categories of human endothelial cell-specific antibodies: the pan-endothelial cell markers and specific antibodies that bind selectively to proliferating endothelium[44, 45]. CD31 is utilized as the pan-endothelial marker of choice; it is characterized by equal intensity of staining for small and large vessels. The disadvantages associated with staining for CD31 antigen include co-staining of inflammatory cells. The selective antibodies, such as endoglin, distinguish quantitatively between tumor neovascularization and pre-existing vessels with no or poor staining of lymphatics and normal quiescent blood vessels[46]. Most studies revealed that high MVD predicts occurrence of metastatic disease[2, 7, 13, 25, 32, 35, 37], and although tumor angiogenesis is unlikely to be the only factor responsible, it provides large numbers of leaking blood vessels for vascular invasion[25].

Endoglin (CD105) is a receptor for the TGF-β1 molecule that is up-regulated in tumor angiogenesis[13, 25, 29]. Its secretion is induced by hypoxia[29] and, as it is present mainly in new vessels, it is very useful in the assessment of newly formed vessels in malignant neoplasms[13, 25, 29]. It is also currently accepted as a potential target for anti-angiogenic therapy, especially in cancer patients at risk of developing metastases[29]. The endoglin antibody binds preferentially to the activated endothelial cells that participate in tumor angiogenesis, however, endoglin expression is weak/or negative in vascular endothelium of normal tissues; accordingly, it is a more specific and sensitive marker of tumor angiogenesis than the others commonly used such as pan-endothelial markers[25, 29]. Intra-tumoral MVD determined by immunohistochemical staining for endoglin has been reported to be an indicator of poor prognosis in many types of solid neoplasia such as breast carcinoma, cervical cancer, endometrial carcinoma, gastric carcinoma, melanoma, some testicular tumors, non-small cell lung cancer, prostate cancer, renal cell carcinoma and squamous cell carcinoma[29].

In CRC, many reports indicate that endoglin assessed immunohistochemically correlates not only with MVD, but also with survival curves, and it has also been identified as a valuable parameter for predicting increased risk of developing metastatic disease[25, 29,42]. Yan[47] et al reported that MVD was higher in CRC patients with metastases than in those without and observed that the specificity and sensitivity of MVD in predicting metastatization in CRC was 66.22% and 51.72%, respectively. In other studies, the presence of endoglin also had a prognostic meaning, showing a positive correlation with the presence of angio-lymphatic invasion, lymph node metastases, tumor stage and hepatic metastases, reinforcing the premise that endoglin might be considered for further therapeutic trials as anti-angiogenic therapy[25, 29].

Endoglin is not only expressed on the cell surface but its soluble form can also be detected in the blood[29, 48]. Myśliwiec[29] et al demonstrated an apparent continuous endoglin rise in plasma from patients with metastatic colorectal cancer, and Li[48] et al reported that circulating endoglin levels positively correlated with CRC Dukes' stage and survival; patients with a high MVD, above the median 3.10 × 250, showed the worst prognosis. Takahashi[49] et al observed that increased serum endoglin was associated with metastasis in patients with solid tumors including colorectal and breast carcinomas; and, in CRC patients, the difference in endoglin levels between the metastasis-negative patients and the metastasis-positive patients was statistically significant. Conversely, it was recently demonstrated that assessment of endoglin in plasma is not a useful maker of CRC, but might be helpful in selecting patients with metastatic diseas[29].

VASCULAR ENDOTHELIAL GROWTH FACTOR FAMILY AND CRC

Quantification of angiogenic factors in solid malignant tumors provides an alternative to MVD evaluation in assessing tumor angiogenic activity[28, 30]. Numerous studies have demonstrated that tumor overexpression of vascular endothelial growth factor (VEGF) correlates with high tumor MVD and is associated with advanced tumor stage or tumor invasiveness in various common human cancers[30, 37, 50, 51] and, its overexpression in colon cancer tissue indicates poor prognosis[51]; although paradoxically, some data showed that MVD might have a significant prognostic value in colon cancer tissue, whilst VEGF has not[52].

VEGF is the most widely studied angiogenic factor; it increases vascular permeability and is the most potent, direct acting, angiogenic protein known[28, 29, 36, 37, 52]. Normally, VEGF is weakly expressed in a wide variety of human and animal tissues; however, high levels of VEGF expression can be detected at sites where physiologic angiogenesis is required, such as fetal tissue or placenta, or in the vast majority of human tumors and other diseases i.e., chronic inflammatory disorders, diabetes mellitus, and ischemic heart disease[37]. Furthermore, both VEGF and its receptors are expressed at high levels in metastatic human colon carcinomas and in tumor-associated endothelial cells, respectively[37]. Consequently, VEGF is recognized as a prominent angiogenic factor in colon carcinoma and the assessment of VEGF expression may be useful for predicting metastasis from CRC[37]. In fact, VEGF expression was found to be higher in patients with metastatic tumors than in those with non-metastatic tumors[37,38], and high levels of VEGF expression were associated with advanced cancer stage and related with unfavorable prognosis[51-53].

De Vita et al [37] reported that preoperative serum VEGF levels might be useful for predicting the outcome of colon cancer patients following surgery. After surgery, VEGF levels tend to decrease compared with preoperative concentrations[30, 37]. Conversely, elevated VEGF levels after surgery may indicate significant residual disease, even

if it is not evident macroscopically[37].

Other studies have shown that VEGF is also a useful marker for prognosis by significantly correlating with angio-lymphatic invasion, lymph node status and depth of invasion, notwithstanding it was not an independent prognostic factor[25, 29].

Although numerous publications dealing with the measurement of circulating VEGF for diagnostic and therapeutic monitoring have been published, the relationship between the production of tissue VEGF and its concentration in blood is still unclear[31]. Some of the controversies regarding the clinical value of VEGF serum level measurement are related to the well-known fact that circulating VEGF is largely found in platelets, and as a consequence an open debate is ongoing to clarify if VEGF serum levels truly reflect tumor expression of VEGF or whether there are other potential sources of circulating VEGF, such as blood cells[30]. Cressey[31] et al noted that the cell-associated isoform (VEGF189), but not the soluble isoforms (VEGF121 and VEGF165) appear to play an important role in tumor progression. In addition, Serum VEGF protein levels are a prognostic parameter for progression-free and overall survival in CRC. Patients with high soluble VEGF levels might have a more aggressive disease, and the improved outcome observed in their series might be a reflection of the disease biology[54,55].

The effect of VEGF depends not only on tumor cell expression of VEGF, but also on the VEGF receptors in the endothelial cells[30]. The ligands of the VEGF family include VEGF-A, VEGF-B, VEGF-C, VEGF-D and VEGF-E; and the receptors are VEGFR-1, R-2 and R-3[56].

VEGF-A is commonly overexpressed by a wide variety of human tumors, and this overexpression has been correlated with progression, invasion and metastasis, MVD, and poorer survival and prognosis[56]. In CRC, VEGF-A is the ligand of the VEGF family most abundantly expressed[29]. VEGF-A promotes angiogenesis through enhancement of permeability, activation, survival, migration, invasion, and proliferation of endothelial cells[57]. VEGF-A and VEGF-B play a role in early tumor development at the stage of adenoma formation[7, 58].

Myśliwiec[29] et al found a strong positive association with VEGF-A plasma concentrations assessed postoperatively and the presence of distant metastases. Zlobec[59] et al also correlated high VEGF expression with response to preoperative radiotherapy in patients with rectal tumors.

VEGF-C and -D are glycoproteins structurally similar and sharing areas of sequence homology with VEGF-A. In CRC, augmented VEGF-C expression has been found to correlate with lymphatic invasion and lymph node metastasis[60]. Elevated levels of serum VEGF-C have been found in patients with breast cancer, lung cancer and cervical cancer and it appears to be an independent marker for early diagnosis of cancer metastasis. Moreover, increased VEGF-C mRNA expression in tumor tissues correlates positively with lymphatic metastasis and poor prognosis[61]. A correlation between VEGF-D expression levels in the primary tumor and lymph node metastasis is still disputable, with controversial data reported[62].

Another important fact is that through the development of anti-angiogenic therapy, CRC prognosis is improving[30, 63-65]. Median survival of patients with metastatic CRC (mCRC) treated with best supportive care is approximately 6 mo. Palliative chemotherapy considerably improves treatment outcome, with fluorouracil (FU) plus irinotecan and/or oxaliplatin extending median overall survival to approximately 20 mo[66]. Thus, in the past decade, the median overall survival of patients with mCRC has increased from 12 mo to approximately 20 mo, mainly due to the development of new combinations with standard chemotherapy[67]. Currently, anti-angiogenic treatment can prolong the survival time by some months, however, the results are not reproducible for all cases[13]. There have been clinical trials which show as many as 94% of invasive carcinomas and 88% of in situ carcinomas having a complete response[68]. Unfortunately, there are no tumor characteristics or molecular markers at present that help to identify patients who are likely to benefit from anti-angiogenic treatment[69].

Bevacizumab (BV) is a monoclonal antibody against VEGF with anti-angiogenic properties, and several clinical trials supported the use of BV in the first-line treatment of mCRC[70]. BV is typically used in combination with other chemotherapeutic agents such as oxaliplatin, irinotecan, leucovorin, and 5-fluorouracil (5-FU) for treatment of patients with mCRC[70, 71]. In addition to its direct anti-angiogenic effects, BV may also improve the delivery of chemotherapy by changing tumor vasculature and decreasing the elevated interstitial pressure in tumors[69]. When combined with standard chemotherapy regimens, it has been associated with significant improvements, compared with chemotherapy alone, in the efficacy end points of overall survival, progression-free survival, and response rates in patients with mCRC and for some facilitates secondary resections[72]. Jubb[73] et al demonstrated that in patients with mCRC, the addition of BV to irinotecan, 5-FU/leucovorin (IFL) improves survival regardless of the level of VEGF expression, or MVD. In a review by Tappenden[74] et al, the addition of BV to IFL resulted in a statistically significant increase in median overall survival (OS) of 4.7 mo, and in a median progression-free survival (PFS) of 4.4 mo. An overall tumor response rate of 44.8% was reported for BV plus IFL compared with 34.8% for IFL plus placebo within one study. In a pivotal, placebo-controlled, phase III trial in patients with mCRC (Genentech Study 2107), the addition of BV to IFL resulted in a significantly longer survival time (20.3 vs 15.6 mo) and progression-free survival time (10.6 vs 6.2 mo) than with IFL plus placebo[73, 75-78]. In a placebo-controlled, phase II trial (Genentech Study 2192), adding BV to 5-FU plus LV resulted in a significantly longer progression-free survival time than with 5-FU and LV plus placebo in

Table 1 The main results of CD105 and VEGF studies

Study	n	High levels of CD105 were associated with	High levels of VEGF were associated with
Barozzi et al[7]	101	M1	M1
Saad et al[25]	150	M1, N1 and angiolymphatic invasion	N1, angiolymphatic and depth of invasion
De Vita et al [37]	81	NE	NCs (serum levels)
Cascinu et al[38]	121	NE	RR
Myśliwiec et al[29]	48	M1	Colorectal cancer patients (plasma levels)
Li et al[48]	111	Dukes' stages and survival	NE
Takahashi et al[49]	34	M1	NE
Liang et al[51]	114	NE	N1, TNM staging and poor prognosis
Zheng et al[52]	97	NE	Poorly differentiated adenocarcinoma
Cressey et al [31]	76	NE	TNM
Cao et al[53]	71	NE	N1, M1, TNM, and OS
Miyazaki et al[58]	127	NE	RR, DF, OS (plasma levels)

DF: Disease-free; M1: Positive distant metastasis; N1: Positive lymph node metastasis; NCs: Non-curative surgery; NE: Not evaluated; OS: Overall survival; RR: Recurrence rate

patients with mCRC who were unsuitable candidates for first-line therapy with irinotecan (9.2 *vs* 5.5 mo). There was also a trend towards a longer survival time in patients receiving 5-FU, LV, and BV (16.6 *vs* 12.9 mo)[77]. BV was also tested in mCRC combined with an oxaliplatin-based regimen in the second-line setting. In this randomized phase III trial (E3200), patients with previously treated CRC were randomized into 3 arms: FOLFOX4 plus BV, FOLFOX4 and BV only. Results showed superior survival and progression-free survival in the FOLFOX4 plus BV arm. In this study, BV was equally effective with the oxaliplatin-based regimen[78].

BV ultimately achieved FDA approval in 2004 as a first-line treatment for mCRC in combination with chemotherapy, based on its statistically and clinically meaningful benefits on progression-free survival and OS and has since garnered additional approval[79]. BV is the most used VEGF inhibitor with clear proof of efficacy in CRC, however, optimal use of this agent at various stages of the disease is still under investigation. Additionally, there are numerous other angiogenic agents targeting VEGF and other pro-angiogenic systems in clinical development[80]. These novel targeted agents inhibit the VEGF pathway by targeting the VEGF ligand, its receptors or by blocking downstream signaling pathway components. Anti-angiogenic agents include antibodies, small molecule tyrosine kinase (TK) inhibitors, antisense oligonucleotides and aptamers[81].

Table 1 summarized the main results of CD105 and VEGF studies.

CONCLUSION

Despite major advances, in terms of knowledge and treatment of CRC in recent years, the single most well-documented prognostic marker of pathologic stage remains the gold standard for disease stage at diagnosis. Angiogenesis plays an important role in the growth and progression of cancer but its role as a prognostic factor is still controversial. Most studies report that endoglin and vascular endothelial growth factor family expression are indicators of poor prognosis in CRC patients. Beyond these controversies, the ultimate clinical implication of tumor angiogenesis is the development of anti-angiogenic therapy, targeting tumor vasculature.

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