Original Article

Horizontal Tumor Size is Inversely Related to Prognosis in Nodal-positive Stage III Colorectal Cancer

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Key Words
Colorectal cancer;
Horizontal tumor size;
Prognosis

Purpose. Vertical tumor growth, reflected by the T classification, is the most important prognostic variable in colorectal cancer. However, the data regarding the prognostic impact of horizontal tumor size are limited and contradictory. In the present study, we aimed to investigate the effect of maximal horizontal tumor size on patient outcome in patients with nodal-positive stage III colorectal cancer.
Methods. We retrospectively reviewed the medical records from 1996 to 2009. We included individuals diagnosed with nodal-positive stage III colorectal cancer who underwent surgical resection, and for whom complete medical records were available. In our analysis, the cut-off values for tumor size were set at 1.0 cm and 0.5 cm. A Kaplan-Meier survival analysis and the Cox proportional hazard model were applied to the data for further analysis.
Results. In total, 939 nodal-positive stage III colorectal cancer specimens were reviewed retrospectively. We classified the patients into two groups: those with a maximum horizontal tumor size of < 1.0 cm (57 patients; 6%) and those with a maximum horizontal tumor size of > 1.0 cm (887 patients; 94%). With regard to the TNM classification, the group of patients with tumors < 1.0 cm in size had a greater number of T1-2 stage tumors compared to the group with tumors > 1.0 cm in size (42.1% vs. 27%, p = 0.02). With regard to the primary tumor site, the group of patients with tumors < 1.0 cm in size had a greater number of rectal tumors compared to the group with tumors > 1.0 cm in size (61.7% vs. 45%, p = 0.01). The median disease-free-survival was shorter in patients with tumors < 1.0 cm in size than in patients with tumors > 1.0 cm in size (6.96 months vs. 17.64 months, p = 0.003). Survival was significantly different between these two groups of patients as well (p = 0.008). Using a Cox proportional hazard model, the hazard ratio was found to be 2.29 for patients with tumors < 0.5 cm in size and 1.224 for those whose tumor measured 0.5-1.0 cm in size. Further multivariate analysis also demonstrated that small tumor size is a significant risk factor for a negative prognosis (p = 0.01).
Conclusion. In nodal-positive stage III colorectal cancer, tumor size is inversely related to prognosis. We postulated that smaller nodal-positive tumors would display significantly more aggressive tumor behavior as compared to larger tumors. However, these interesting findings require further investigation to corroborate the results.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2014;25:65-73*]

Received: January 27, 2014. Accepted: June 25, 2014.
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In Taiwan, more than 10000 individuals are diagnosed with colorectal cancer (CRC) annually,[1] and it represents one of the most challenging diseases for clinical physicians. Accurate prediction of the prognosis of patients with CRC follows a specific approach. Surgical intervention is not only the most promising therapeutic approach to CRC, but it is also useful in determining the appropriate treatment plan for this disease.[2,3] The prognosis of CRC is strongly correlated to the tumor stage. The TNM classification is the internationally accepted standard for colorectal cancer staging, and considers the depth of tumor invasion, the involvement of regional lymph nodes, and the presence of distant metastatic spread. The most important parameter in identifying patients at high risk for treatment failure is the T classification, which is based on vertical tumor penetration across the different layers of the bowel wall.[4]

However, data regarding the prognostic impact of horizontal tumor size are limited and contradictory. Some studies have shown that tumor size plays no prognostic role,[5-10] whereas other studies have found that larger tumors are associated with several negative prognostic effects.[11-16]

In stage III CRC, we observed that the smaller the tumor size, the poorer the prognosis. We assumed that tumor behavior is aggressive in small tumors with lymph node metastasis. In a retrospective database study of patients from one institution, we investigated the clinical significance of horizontal tumor size on patient outcome, which appears to be the first such study on this topic.

Materials and Methods

A retrospective chart review initially identified all patients with nodal-positive stage III CRC who were treated with surgical intervention at Kaohsiung Veterans General Hospital between January 1996 and August 2009. The exclusion criteria were: (1) recurrent cancer; (2) secondary neoplasm; (3) metastatic disease; (4) tumor stage other than stage III CRC; and (5) history of neoadjuvant chemotherapy due to presumptive treatment-related changes in T classification. Among the patients with CRC, only those who underwent radical resection and had a final pathology report finding of regional lymph node metastasis were enrolled in the final study. Clinicopathologic patient data were recorded from hospital charts and electronic medical records, and included cell type, tumor cell differentiation, T stage, tumor site, and follow-up information. In the pathology report, tumor size was recorded as length (cm) × width (cm) × height (cm). We chose the largest values to represent the maximal horizontal tumor size. The cut-off values for tumor size were set at 1.0 cm and 0.5 cm. Tumors located from the cecum to the transverse colon were defined as right-sided cancers, and tumors located from the splenic flexure to the sigmoid colon were defined as left-sided cancers. Tumors originating from the rectosigmoid junction or from within the rectum were characterized as rectal cancers.

Patients had a follow-up examination every three months during the first two years after surgery, every six months during the third year after surgery, and annually thereafter. Disease-free survival (DFS) was measured from the date of diagnosis to the date of relapse, progression, death, or last follow-up.

Statistical analysis

The statistical significance of the association between CRC tumor size and other categorical tumor variables was determined using the Chi-square test. The Kaplan-Meier survival curve and Cox proportional hazards regression analyses were used to study patient survival and to identify the independent factor for survival. Variables that appeared to be significantly associated with worse prognosis were entered into the stepwise Cox proportional hazards model. Statistical analyses were performed with the use of SPSS 12.0 (SPSS, Inc., Chicago, IL). A two-sided p value < 0.05 was considered statistically significant.

Results

In total, we identified 1001 patients. After a review of medical records, 62 patients were excluded

due to various causes (20 had recurrent cancer, 8 had a secondary neoplasm, 12 had metastatic disease, and 22 had missing medical records data). Thus, a total of 939 patients were enrolled; of these, 317 (33.8%) were women, and the mean age of patients was 66.4 years (standard deviation [SD], 12.6; range, 21-93 years). The clinicopathologic data from these patients are summarized in Table 1. The median DFS was 19.1 months (SD 16; range 0-149 months).

With regard to tumor type, 876 patients (93.3%) had tumors classified as adenocarcinoma, 33 (3.5%) had tumors classified as mucinous carcinoma, 11 (1.2%) had tumors classified as signet ring-cell carcinoma, and 19 (2%) had tumors classified as other rare tumor types such as adenosquamous carcinoma or carcinoid tumor. With regard to tumor cell differentiation, 17 tumors (1.8%) were well differentiated, 843 (89.8%) were moderately differentiated, 44 (4.7%) were poorly differentiated, and 35 (3.7%) were undifferentiated. With regard to the depth of tumor invasion, 269 patients (28.6%) had tumors classified as T1-2 and 670 (71.4%) had tumors classified as T3-4. With regard to tumor localization, 192 patients (19.6%) had tumors in the right colon, 308 patients (31.9%) had tumors in the left colon, and 439 patients (46%) had tumors in the rectum. Overall, the median tumor size was 4.59 cm (SD, 2.44; range, 0.2-30 cm). The distribution of tumors according to size is shown in Fig. 1.

Table 1. Clinicopathologic characteristic of 939 patients with nodal-positive stage III colorectal cancer

Categorical variables*	No. of patients (%)
Sex	
Male	622 (66.2)
Female	317 (33.8)
Cell type	
Adenocarcinoma	876 (93.3)
Mucinous carcinoma	33 (3.5)
Signet ring cell carcinoma	11 (1.2)
Other	19 (2)
Tumor cell differentiation	
WD	17 (1.8)
MD	843 (89.8)
PD	44 (4.7)
Undifferentiated	35 (3.7)
T stage	
T1-2	269 (28.6)
T3-4	670 (71.4)
Tumor site	
Right colon	192 (19.6)
Left colon	308 (31.9)
Rectum	439 (46)
Continuous variables**	
Age (years)	66.4 ± 12.66 (21-93)
Median DFS (months)	19.1 ± 16 (0-149)

SD standard deviation, LN lymph node, WD well differentiated, MD Moderately differentiated, PD poorly differentiated; DFS, disease-free survival.

* Values are presented as numbers and percentages in parentheses, unless otherwise indicated.

** Values are presented as mean ± standard deviation (range).

Receiver operating characteristic analysis showed that the median tumor size of 1.0 cm had the strongest discriminatory capacity (maximum sum of sensitivity and specificity) with respect to predicting patient outcome. Therefore, we classified the patients into two groups based on the maximum horizontal tumor size: those with a maximum horizontal tumor size of < 1.0 cm (57 patients; 6%) and those with a maximum horizontal tumor size of > 1.0 cm (882 patients; 94%). These results are summarized in Table 2. With regard to the TNM classification, the number of T1-2 stage tumors was greater in the group of patients with tumors < 1.0 cm in size than in the group of patients with tumors > 1.0 cm in size (42.1% vs. 28.1%, p = 0.02). With regard to primary tumor site, the number of rectal tumors was greater in the group of patients with tumors < 1.0 cm in size than in the group with tu-

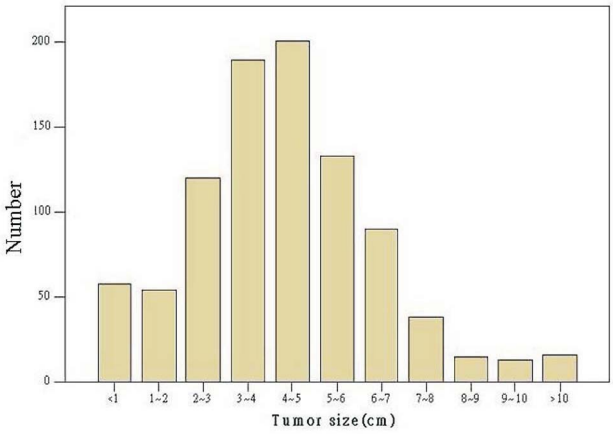

Fig. 1. Distribution of nodal-positive stage III colorectal cancers according to horizontal tumor size.

Table 2. Characteristics of patients with tumors < 1 cm in size and tumors > 1 cm in size

Categorical variables*	Tumors < 1 cm in size (n = 57, 6%)	Tumors > 1 cm in size (n = 882, 94%)	*p* value
Sex			0.269
Male	35	576	
Female	22	306	
Cell type			0.063
Adenocarcinoma	53	827	
Mucinous carcinoma	0	33	
Signet ring cell carcinoma	1	10	
Other	3	12	
Tumor cell differentiation			0.07
WD	1	16	
MD	46	803	
PD	3	41	
Undifferentiated	7	22	
T stage			0.02
T1~2	24 (42.1%)	244 (27%)	
T3~4	33 (57.9%)	638 (73%)	
Tumor site			0.01
Right colon	3 (5%)	187 (20.1%)	
Left colon	18 (31.3%)	291 (32.1%)	
Rectum	36 (61.7%)	404 (45.2%)	
Continuous variables**			
Age (years)	65.7 ± 13.2	66.4 ± 12.6	0.683
Number of positive LN	2.6 ± 2.0	2.8 ± 1.7	0.781
Median DFS (months)	6.96	17.64	0.003

LN lymph node, WD well differentiated, MD moderately differentiated, PD poorly differentiated, DFS disease-free survival.
* Chi-square test was performed, as appropriate.
** Values are presented as mean ± standard deviation. Student's *t*-test was performed, as appropriate.

mors > 1.0 cm in size (61.4% vs. 45.2%, $p = 0.01$). The median DFS was shorter in patients with tumors < 1.0 cm in size than in patients with tumors > 1.0 cm in size (6.96 months vs. 17.67 months, $p = 0.003$).

Moreover, DFS was significantly different between these two groups of patients as well (Fig. 2A, $p = 0.003$). Using Cox proportional hazards regression models, the hazard ratio was determined to be 1.708 for patients with tumors < 1.0 cm in size compared to those with tumors > 1.0 cm in size (Fig. 2A). The percentage of those with rectal cancer was significantly higher in the group of patients with tumors < 1 cm in size, and multivariate analysis indicated that a tumor size of < 1.0 cm in size was a significant predictor of worse prognosis (hazard ratio = 1.919; $p = 0.01$) (Table 3).

Due to these interesting results, we subgrouped 57 patients who had tumors < 1.0 cm in size into two groups for further analysis: those with tumors < 0.5 cm in size (34 patients) and those with tumors 0.5-1.0 cm in size (23 patients).

DFS was found to be different among patients with tumors < 0.5 cm, 0.5-1.0 cm, and > 1.0 cm in size (Fig. 2B, $p < 0.001$). Using Cox proportional hazards regression models, the hazard ratio was found to be 2.29 in patients with tumors < 0.5 cm in size compared to those with tumors > 1.0 cm in size (Fig. 2B).

Discussion

According to our data, the size of a tumor in patients with nodal-positive stage III colorectal cancer is inversely related to the prognosis. In 1983, Wolmark et al[17] stated that Dukes' B tumors were larger than Dukes' C lesions in colon and rectal cancer.

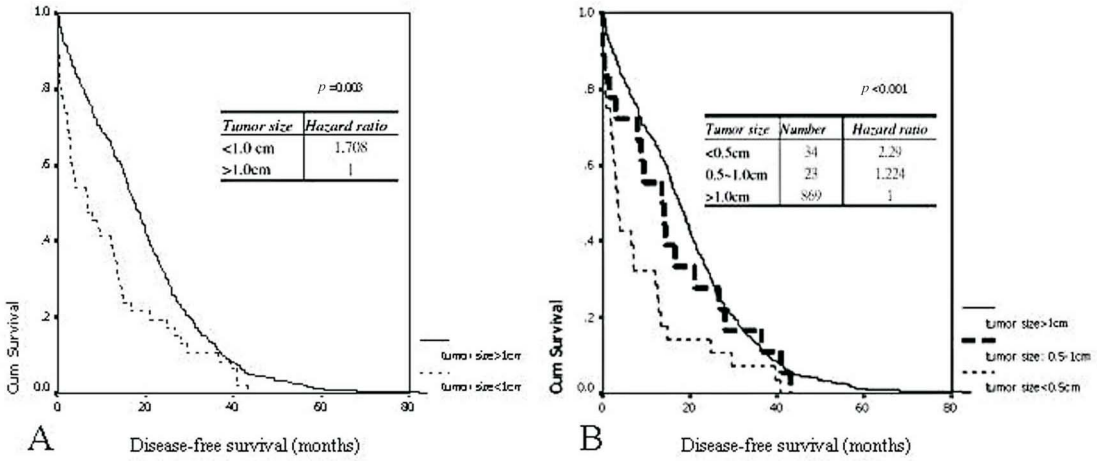

Fig. 2. Disease-free survival between tumor size < 1.0 cm and > 1.0 cm (A, $p = 0.003$, log-rank test) and disease-free survival between tumor size < 0.5 cm, 0.5-1.0 cm, and > 1.0 cm (B, $p < 0.001$ log-rank test). In Cox proportional hazards regression models, the hazard ratio was 1.708 in tumor size < 1.0 cm compared with tumor size > 1.0 cm (A). The hazard ratio was 2.29 in tumor size < 0.5 cm compared with tumor size > 1.0 cm (B).

Table 3. Multivariate analyses of the tumor size and tumor site for the disease-free survival in nodal-positive stage III colorectal cancer

Factor	Hazard ratio	95% CI	*p* value
Tumor < 1 cm	1.919	1.462-2.519	0.01
Rectum	1.089	0.957-1.241	0.197

CI, confidence interval.

In 1984, Wolmark et al[18] reported that the depth of tumor penetration was related to both tumor size and the number of positive regional lymph nodes in Dukes' C colorectal cancer. Bjerkeset et al[12] demonstrated that tumor size had a significant impact on survival for patients with stage I-III colorectal cancer. In 1999, Li et al[19] demonstrated a significant positive correlation between tumor size and Dukes stage. Adachi et al[20] found that although there were a greater number of positive nodes in patients with tumors larger than 6 cm in size (42% vs. 22%), tumor size was not an independent predictor of local lymphatic spread. Wang et al[9] determined that while tumor size was a prognostic variable in univariate analysis, it had no prognostic significance in multivariate Cox analysis. In 2009, Yun et al[21] demonstrated that having a tumor > 5 cm in size is a poor prognostic factor in T3N0M0 colon cancer.

Overall, published data regarding the prognostic significance of tumor size are contradictory, and multivariate analyses have only rarely been performed. In some studies, tumor size — in particular, the horizontal tumor diameter — did not have any prognostic impact,[5-10] whereas in other studies, tumor size was significantly associated with patient outcome.[11-16]

We postulated that smaller nodal-positive tumors would show significantly more aggressive tumor behavior as compared to larger tumors. A review of scientific literature shows that some genomic markers are useful for determining the prognosis of patients with colorectal cancer. The most common mutation in colorectal cancer inactivates the gene that encodes the APC protein. In the absence of functional APC — which acts as a negative regulator of β-catenin — Wnt signaling is inappropriately and constitutively activated, leading to cellular activation.[22] Germ-line mutations in the *APC* gene lead to a very high risk of colorectal cancer and may help in guiding the frequency of colorectal cancer surveillance and establishing recommendations for prophylactic surgery.[23] A germ-line mutation in mismatch-repair genes, such as *MLH1*, *MSH2*, or *MSH6*, is indicative of hereditary nonpolyposis colon cancer and is associated with a 40-80% lifetime risk of colorectal cancer.[24-26] Methylation-associated silencing of *MLH1* in primary colorectal cancers can be detected either through the detection of

DNA microsatellite instability or loss of tumor MLH1 protein expression on immunohistochemical analysis. This repression of *MLH1* is more frequent in early-stage colorectal cancers than in advanced disease. *MLH1* inactivation may be a marker of more indolent disease or a better prognosis in the absence of adjuvant chemotherapy.[27,28] The somatic loss of heterozygosity at chromosomal location 18q — a site containing genes associated with colorectal cancer (e.g., *SMAD4* and *SMAD2*) — is associated with a poorer outcome in patients with stage II or stage III colon cancer; patients with tumors that retain both parental alleles at 18q[29] have a comparatively better outcome.

Gene expression profiles, as detected by cDNA microarray, differ between lymph node-positive and lymph node-negative colorectal cancers.[30] These differences are primarily related to the upregulation of genes responsible for apoptosis (*STK17A*, *CSE1*) and metabolism (*AMD1*, *ATP5D*, *UCP2*). In lymph node-positive samples, the most frequently altered genes belong to the functional category of signal transduction (i.e., *ZNF173*, *TCEA2*, *HSPCA*, *PIK3R1*). In 2007, Grade et al[31] identified 68 genes by microarray that showed differential expression that was significantly different between lymph node-negative and lymph node-positive tumors ($p < 0.001$) The functional component of this study revealed a preponderance of genes that play a role in cellular immune response and surveillance.

However, from the viewpoint of tumor biology, it is still unclear whether the genetic makeup of a solid tumor determines its metastatic potential. Based on a class prediction analysis of the primary tumors from our study, we were not able to reliably distinguish between those tumors from which cells had infiltrated to the lymph node and those from which cells had not. Therefore, it remains to be determined whether the capability of a primary tumor to metastasize requires additional mutations, or whether this metastatic capability is inherent in its specific gene expression profiles. Although the findings of this retrospective analysis are promising, we plan to investigate the above-mentioned genes in both small and large tumors in order to elucidate direct evidence of our results at the molecular level. Efforts to conduct these types of tests are already ongoing at Kaohsiung Veterans General Hospital.

There are several limitations to our study. First, the present study is a retrospective analysis, and has limitations inherent with such a study design. Second, colon cancer and rectal cancer should ideally be separated for analysis. When examining patient prognosis, Kornprat et al[32] indicated that the cut-off value of tumor size was different for colon cancer (5 cm) and rectal cancer (3.4 cm), which indicates that the tumors behave differently in these two cancers. However, due to the limited number of patients in our study who had tumors < 5 cm in size (n = 34), separation and further analysis would have been impractical. Third, the overall survival was not analyzed in this study due to the different treatment modalities used after recurrence or metastasis in stage III colorectal cancer, which does not permit the analysis of prognosis using overall survival.

Conclusion

Decreasing tumor size is a negative prognostic factor in nodal-positive stage III colorectal cancer. We postulated that smaller nodal-positive tumors might be significantly more aggressive than larger tumors. However, further investigation of these interesting findings is needed to corroborate the results.

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原　著

第三期大腸直腸癌之橫向腫瘤大小為臨床預後之反向預測因子

吳志謙　王瑞和　金台明　張敏琪　許詔文

高雄榮民總醫院　外科部　大腸直腸外科

目的　腫瘤之垂直向生長程度是影響大腸直腸癌預後的重要因子，但腫瘤之橫向大小對預後影響之研究仍然有限且存在爭議。我們在此探討第三期大腸直腸癌有淋巴腺轉移之橫向腫瘤大小與其臨床預後之關係。

方法　從 1996 年至 2009 年間，第三期有淋巴腺轉移之大腸直腸癌術後且有完整病歷記錄的病患被回溯性分析。腫瘤大小分別以 0.5 和 1 公分為分界，利用相關統計方法分析其預後之差異。

結果　共 939 位病患被收錄。其中原發腫瘤大小小於 1 公分者共有 57 位，大於 1 公分者共 882 位。腫瘤小於 1 公分組之 TNM 分期為 T1~2 之比例大於腫瘤大於 1 公分組 (42.1% vs. 27%，p = 0.02)。腫瘤小於 1 公分組之原發腫瘤位置也較腫瘤大於 1 公分組多位在直腸 (61.7% vs. 45%，p = 0.01)。腫瘤小於 1 公分組之無疾病存活期中位數也顯著地短於腫瘤大於 1 公分組 (6.96 個月 vs. 17.64 個月，p = 0.003)。利用 Cox 比例風險迴歸模式分析，相對于腫瘤大小大於 1 公分者，腫瘤大小小於 0.5 公分之風險比值為 2.29，腫瘤大小介於 0.5 至 1 公分則為 1.224。進一步加入腫瘤位置作多變數分析後也顯示類似的結果。

結論　對於第三期有淋巴腺轉移之大腸直腸癌患者，其腫瘤之大小可反向預測其臨床預後。我們推測腫瘤大小較小時即發生淋巴腺轉移，可能因其腫瘤行為相對腫瘤大小較大者來的具侵略性。這個發現更需要許多層面之研究來支持。

關鍵詞　大腸直腸癌、橫向腫瘤大小、預後。