Original Article

Treatment Response in Patients with Primary Colonic Lymphomas: Experience in a Single Institute

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Key Words
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B-cell

Purpose. To review the clinical characteristics, treatments and prognosis of the rare malignancy, primary colonic lymphoma at a single-institute in southern Taiwan.
Methods. More than 8953 colon or rectal cancers were reviewed at Chang Gung Medical Center in Kaohsiung from 1989 to 2009, with only 21 cases diagnosed as primary colonic lymphoma. The records of those patients were retrospectively analyzed for age, gender, clinical presentation, location and stage of tumor, operation, adjunctive therapy, survival time and clinical outcome. Cox regression and Kaplan-Meier methods were applied to estimate the prognostic factors for the patient survival time.
Results. Twenty-one patients with primary colonic lymphoma were identified which constituted 0.2% of all reported cases of colorectal cancer in our institute. The mean age at diagnosis was 53.9 years (range, 15-86 years), with a male to female ratio of 16:5. The most common tumor site was the cecum, followed by the ascending colon. All patients had B-cell lymphoma. Seventeen patients had undergone an operation. The chemotherapy was applied to 12 patients out of 21. The overall five-year survival rate was 42.9% (N = 21, median survival time: 12.7 months). Prognostic factors including disease stage, operation method (curative vs. palliative), operation timing (elective vs. emergency) and chemotherapy showed a significant influence on the survival time (all $p < 0.05$).
Conclusion. The choice of treatment for primary colorectal lymphoma is multimodality, adequate curative surgical resection in selected patients followed by adjuvant chemotherapy seems to result in a favorable outcome.
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Primary colorectal lymphoma is a rare disease, amounting to 10-20% of gastrointestinal lymphomas and less than 0.2-0.6% of colorectal malignancies.[1] The sites of gastrointestinal involvement of lymphoma in decreasing order of frequency are the stomach, small intestine, ileocecum, and anorectum.[2,3] Males are more likely to be affected than females. Since 1942, numerous classifications have been used to differentiate non-Hodgkin's lymphoma (NHL). Today, the WHO classification is the latest classification

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system which divides B-cell lymphoma into five subtypes: extranodal marginal lymphoma (MALT lymphoma), follicular lymphoma, mantle cell lymphoma, Burkitt's lymphoma and diffuse large B-cell lymphoma (DLBCL).[4]

Treatments of primary colorectal lymphoma vary from chemotherapy alone to multimodal therapies combining surgery, chemotherapy, and even radiotherapy. The optimal treatment of primary colorectal lymphoma remains unclear due to the small number of cases and variant histologic subtype. Therefore, the purpose of the current study was to examine the presentation, treatment, and outcome of colonic lymphoma in our institute over a 20-year period.

Patients and Methods

The retrospective study of a single-institute in southern Taiwan was performed to analyze patients diagnosed with colorectal NHL (non-Hodgkin's lymphoma). The data was obtained from the cancer registry between 1989 and 2009. The diagnostic criteria of primary colorectal lymphoma was established by Dawson et al. in 1961.[5] There are (1) no superficial enlarged lymph nodes when the patient is first seen; (2) chest radiographs reveal no obvious enlargement of the mediastinal nodes; (3) the total and differential white blood cell counts are within normal limits; (4) only regional lymph nodes are affected at laparotomy; and (5) the liver and spleen are free of tumor. Those patients who matched the diagnostic criteria were selected in our series.

The records of those patients were analyzed for age, gender, clinical presentation, tumor site, stage of tumor, operation method, adjuvant therapy, and clinical outcome. The histology was grouped according to the World Health Organization (WHO) histological classification system. Tumors were staged according to the modified Ann Arbor staging system which was recommended by Carbone (Table 1).[6] Adequate follow-up data on patients was available through most recent examination or at the time of death. Patients who had not returned to our institution had been contacted by telephone to assess their present health, complications and additional therapy. The maximal follow-up period was recorded till 250 months.

The prognostic factors influence on survival time included age, gender, tumor site, tumor staging, tumor size, lymph node involvement, operation method (curative or palliative), operation timing (elective or emergency) and chemotherapy, and the hazard ratios were estimated by the Cox regression method. The survival curves were determined from the Kaplan-Meier method, and the significant difference between groups was estimated by the log-rank test. A p value less than 0.05 was considered statistically significant. Statistical analysis were performed using SPSS software (SPSS Inc., Chicago, IL)

Result

During the period of 1989 to 2009, 21 patients of primary colonic lymphoma were identified in our institution. The incidence of primary colonic lymphoma in our institute was 0.2% of all colorectal cancer (21 of the 8953). The mean age at diagnosis was 53.9 ± 22.2 years (range, 15-86 years). There were 16 men and five women (Table 2). The common presenting symptoms included abdominal pain in 17 cases (81.0%), abdominal fullness in 13 cases (61.9%) and abdominal mass in 11 cases (52.4%) (Table 3). The most common tumor site was the cecum in 11 patients

Table 1. Ann arbor staging system[6]

Stage	Description
I	Involvement of a single nodal group or single extranodal site (IE)
II	Involvement of more than one nodal group on the same side of the diaphragm or single extranodal site and adjacent lymph nodes (IIE)
III	Involvement of multiple nodal sites on both sides of the diaphragm, including extranodal sites (IIIE) or spleen (IIIS)
IV	Diffuse or disseminated involvement of 1 or more extralymphatic organs or tissue without associated lymph node enlargement, such as bone marrow or central nervous system

Table 2. Patients characteristics

	No.	%	
Age (mean ± SD; years)	53.9 ± 22.2		
Range	15-86		
Gender			
Male	16	76.2	
Female	5	23.8	
Ratio M/F	2.6:1		
Lymph node involvement			
Yes	17	81.0	
No	4	19.0	
Operation			
Yes	17	81.0	
Curative resection	10	47.6	
Palliative resection	7	33.3	
No	4	19.0	
Chemotherapy			
Yes	12	57.1	
No	9	42.9	
Histology			
DLBCL	20	95.2	
Burkitt's	1	4.8	
Stage			5 year survival
IE	4	19.0	100%
IIE	9	42.9	55.6%
Curative resection	7		71.4%
Palliative resection	2		0%
IVE	8	38.1	0%

DLBCL – diffuse large B-cell lymphoma.

Table 3. Symptoms/signs, complications and tumor site

Symptoms	No.	Percentage
Abdominal pain	17	81.0
Abdominal fullness	13	61.9
Abdominal mass	11	52.4
Body weight loss	9	43.9
GI bleeding	6	28.6
Bowel habit change	6	28.6
Diarrhea	6	28.6
Nausea/vomiting	6	28.6
Obstruction	3	14.29
Tumor site at diagnosis	**No.**	**Percentage**
Cecum(including ileocecal region)	11	52.4
Ascending colon	7	33.3
Transverse colon	1	4.76
Descending colon	2	9.52
Sigmoid colon	0	0
Rectum	0	0

(52.4%), followed by the ascending colon in 7 patients (33.3%). Abdomen CT was performed in 17 patients, with most interpreted as colon cancer as the initial diagnosis. Colonoscopic examinations were arranged in 10 patients. But only two patients had accurate pathologic diagnosis by colonoscopic biopsy before treatment. Laboratory findings in our patients were unremarkable.

There were 4 (19.0%) patients presented in stage IE, 9 (42.9%) patients in stage IIE, and 8 (38.1%) in stage IVE. All patients in our series had B-cell lymphoma. Most had diffuse large B-cell lymphoma (20/21), and the remaining one had Burkitt's lymphoma. Each tumor stained positively for CD-20 (L26). There was no T-cell lymphoma identified in this series.

Seventeen patients had undergone an operation. Of which, ten had undergone attempted curative resection, and the others (7/17) had a palliative operation. Three patients had post-operative complications. Two patients had wound infection and the other one died of internal bleeding within 30 days of surgery. The adjuvant chemotherapy based on CHOP regimen was applied to 12 patients out of 21. The remaining nine patients did not receive or complete chemotherapy due to patient refusal or poor performance. One patient with stage IE disease had received chemotherapy with R-CHOP regimen alone with no evidence of recurrence during follow up till the time of this analysis (survived 21 months). Only one patient with stage IV disease received radiotherapy as palliative treatment after the operation and died at 6.3 months. Eight of the 21 patients died of the disease due to progression; one patient died of operation complication (internal bleeding). Two patients relapsed, one patient who had received chemotherapy relapsed at 20 months (survived 23.9 months) and the other one who didn't have adjuvant chemotherapy relapsed at 9 months after the operation (survived 11 months). The overall five-year survival rate was 42.9% in our series (N = 21, median survival: 12.7 months, range: 1.1-250) (Fig. 1). The 5-year survival rate of each stage: stage IE: 100% (N = 4, median survival: 103.6 months, range: 17.4-205.0); all stage IIE: 55.6% (N = 9, median survival: 71.2 months, range: 1.1-250); stage IIE with curative resection: 71.4% (N = 7, median survival: 157.4 months, range: 1.1-250); stage IIE with

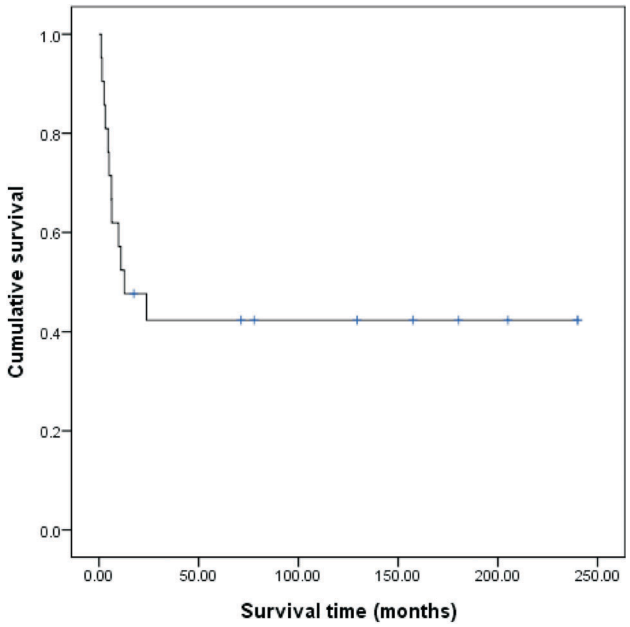

Fig. 1. Overall survival time of patients with primary colonic lymphoma (median survival time: 12.7 months, range 1.1-250).

palliative resection: 0 (N = 2, median survival: 8.65 months, range: 6.3-11); stage IV: 0 (N = 8, median survival: 4.75 months, range: 1.5-12.7). The survival time of patients undergone palliative resection only or with unresectable disease was always less than one year.

Prognostic factors including age, gender, location and lymph node involvement did not have statistically significant result on the survival time, but other prognostic factors including disease stage, operation method (curative vs. palliative), operation timing (elective vs. emergency) and chemotherapy could influence the prognosis ($p < 0.05$, Table 4). Although there was no significant difference in survival time whether operation was undergone ($p = 0.07$; Fig. 2A), but those patients who had undergone attempted curative surgical resection had a better outcome than those with palliative resection or without operation. ($p = 0.02$; Fig. 2B).

Discussion

Primary colorectal lymphoma is a rare disease, being about 0.2 to 0.6% of the colonic malignancies.[1,7-9] The patients in our study were mainly concentrated between the ages of 15 to 86, with a mean age of diagnosis of 53.9. Males were more likely to be affected than females, which correlates with the results of other studies. Most patients experienced abdominal pain, body weight loss, diarrhea, changes in bowel habits as well as gastrointestinal bleeding.[1,10-12] About half of the patients presented with a palpable abdominal mass, suggesting that those tumors can be present for a long period of time without causing symptoms.[13] The most common region for primary colorectal lymphoma is the cecum, most likely due to the

Table 4. Analysis of prognostic factors

	Hazard ratio	95% CI	*p* value
Gender (Male vs. female)	0.72	0.22-2.40	0.592
Age (>= 60 vs. < 60)	2.06	0.66-6.46	0.214
Stage (IE, IIE, IVE)	2.94	1.54-5.61	0.001
Operation (with vs. without)	0.30	0.08-1.18	0.086
Operation method (curative vs. palliative vs. without operation)			
Curative operation	0.05	0.02-0.52	0.012
Palliative operation	0.84	0.21-3.38	0.807
Operation timing			
Elective operation	0.18	0.04-0.77	0.021
Emergency operation	2.54	0.42-15.23	0.307
Chemotherapy	0.09	0.02-0.361	0.001
Lymph node involvement	33.72	0.14-7879.56	0.206
Tumor site (right side vs. left side)	0.54	0.117-2.51	0.433
Tumor size (>= 10 cm vs. < 10 cm)	1.22	0.33-4.52	0.766

$p < 0.05$ = significant difference.

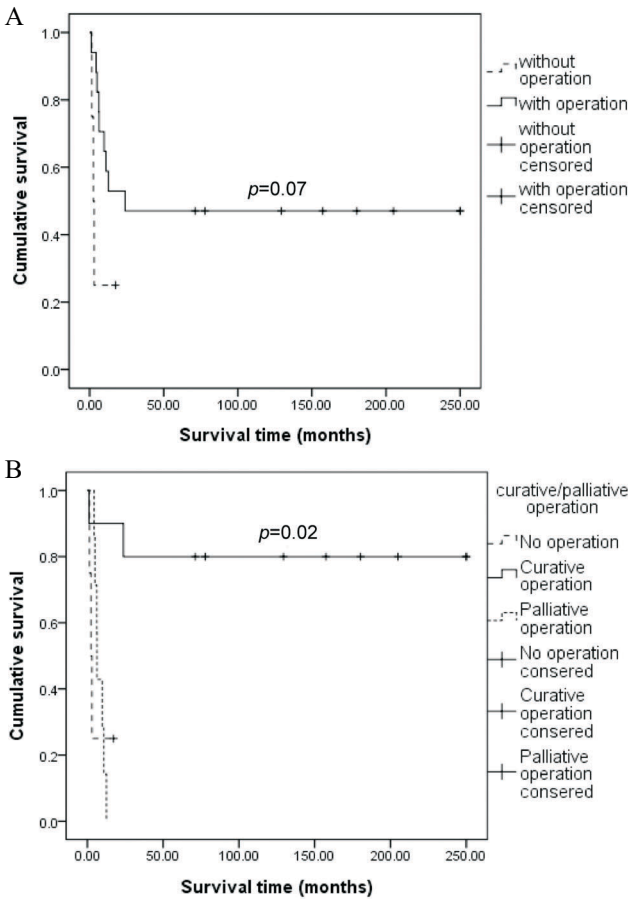

Fig. 2. (A) The difference in survival between patients with colonic lymphoma with operation (N = 17) and without operation (N = 4) (p = 0.07). (B) Patients with curative surgical resection (N = 10) had a better outcome than those received palliative resection only (N = 7) or have no operation (N = 4) (p = 0.02).

massive amount of lymphoid tissue in this region.[8] The rectum is the second most common tumor site.[7,12,14] However, the ascending colon was the second most common tumor site in our series, which is similar to other reports in Taiwan (Table 5).[9,15,16] Most primary colorectal lymphomas have been reported to be of the B-cell lineage. The clinical features differ between B-cell and T-cell lymphoma. Abdominal pain is more common for B-cell lymphomas. Fever, diarrhea and gastrointestinal bleeding are more common for the T-cell lymphoma.[17] Patients who were diagnosed with T-cell lymphoma were younger than those with B-cell lymphoma. Patients with primary T-cell lymphoma seem to have poorer outcome than those with B-cell lymphoma.[14,15,17]

Many series had documented inflammatory bowel disease (IBD) and immunosuppression (immune disorder, status post transplantation or other conditions requiring immunosuppressive medication) as risk factors of lymphoma.[13-19] Further, human immunodeficiency virus (HIV) infection had been mentioned to be associated with an increased incidence of anorectal lymphomas.[20,21] None of those patients in our series had the record of IBD or HIV or other immune disorders, except one patient who was diagnosed as myathesia gravis had received immunosuppressant medicine before the lymphoma became symptomatic (prednisolone for 15 months and cyclophosphamide for 7 months).

Diagnosis of primary colonic lymphoma is difficult due to the absence of specific symptoms. For 33%-65% of the patients, the operative procedure is often emergent because of delayed diagnosis.[16,22,23] Most in over 50% of patients, the lymphoma can reach a diameter beyond 5 cm, which can be detected by palpation or even ultrasonography.[10,16,22,24] Over half of our patients presented with abdominal mass at diagnosis and the tumor size reached beyond 10 cm in size (17/21), our study showed large tumor size was specific for diagnosis. Most patients (17/21) were diagnosed after performing laparotomy. In a non-urgent environment, colonoscopy has proved useful in diagnosing primary lymphoma. The most common colonoscopic manifestations are classified into the mucosal erosive subtype, mucosal ulcerative subtype, polypoid type and the massive type.[15] Sometimes, the tumor may appear as lymphomatous polyposis that could be misinterpreted as familial adenomatous polyposis.[13] However, colonoscopy cannot always achieve a definite diagnosis due to the difficulties in obtaining an adequate specimen for pathologic examination and lack of specific morphology. Ten of our patients had a colonoscopic exam, but only two (2/10) had an accurate pathologic diagnosis before treatment. The radiographic findings associated with lymphoma are generally nonspecific. Double contrast barium enema could reveal the tumor location and gross morphology, but could not distinguish adenocarcinoma or polyposis from lymphoma. Computed tomography (CT) scan finding associated with colorectal lymphoma could be localized or diffuse. If CT

Table 5. Selected series of primary colorectal lymphoma in Taiwan

Author	Case No.	Gender M/F	Mean age	Symptoms/sign	Location	B-/T-cell ratio	Treatment			5 year survival
							Surgery	Radiation	Chemotherapy	
Hwang[14] 1996	16	13/3	34.1 (3.5-76)	Abdominal pain 75% Diarrhea 50% Abdominal mass 43% Body weight loss 37.5%	Cecum 9(60%) Rectum 3(20%)	8 : 5	14/16 (87.5%)	(-)	14/16 (87.5%)	53%
Fan[9] 2000	37	22/15	53.8 (19-79)	Abdominal pain 62% Abdominal mass 54% Body weight loss 43% Bowel habit change 27%	Cecum 17(46%) Ascending colon 8 (21.6%)	not available	35/37 (94.6%)	3 (8%)	21/37 (57%)	39%
Wang[15] 2001	13	9/4	54 (27-86)	Abdominal pain 46% Passage of bloody stool 38% Watery diarrhea 23% Body weight loss 23%	Diffuse involvement 5(38%) Ascending colon 3 (23%)	7:5 1 case unknown	7/13 (53.8%)	(-)	9/13 (69.2%)	20%
Lai[16] 2011	29	19/10	71.6 (23-86)	Abdominal pain 38% Bloody/tarry stool 31% Body weight loss 24%	Cecum 19(48.2%) Ascending colon 7 (24.1%)	28:1	20/29 (69%)	2/29 (6.9%)	22/29 (75.9%)	47.3%
Current series 2011	21	16/5	53.9 (15-86)	Abdominal pain 81% Abdominal fullness 62% Abdominal mass 52% Body weight loss 43%	Cecum 11(52.4%) Ascending colon 7 (33.3%)	21:0	17/21 (81.0%)	1/21 (4.8%)	14/21(66.7%)	42.9%

reveals an infiltrative type tumor accompanied by enlarged lymph nodes in the abdomen or pelvis, lymphoma should be highly suspected in the differential diagnosis and a colonoscopy to precede the operation should be arranged.[25,26] The PET (positron emission tomography) could be used for diagnosis, staging, restaging, and follow up, but the false-positive and false-negative results due to variant metabolic activity should be considered.[27]

In published reports, treatment for primary colorectal lymphoma varies from chemotherapy alone to multimodal therapies combining an operation, chemotherapy, and radiotherapy. Some literature stated chemotherapy alone might be effective for patients with early localized primary colorectal lymphoma, thereby avoiding an operation. However, there are no controlled randomized trials determining the role of chemotherapy alone for surgically resectable colorectal lymphoma. Since advanced malignancy tends to extend beyond local fields encompassed by surgery or radiation, chemotherapy remains the basis of treatment for a rapidly proliferating aggressive disease. The CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) was considered the first line therapy for all moderate and high grade B-cell lymphomas in the past. Currently, several prospective trials have revealed adding rituximab to standard CHOP regimen (R-CHOP) resulted in a better response rate, progression-free disease-free and overall survival.[28,29] But, the physician must recognize the rare potentially fatal complication: rituximab-induced interstitial lung disease (R-ILD).[30] In the absence of disseminated disease, surgical resection is generally performed for colorectal lymphoma.[23] For those symptomatic colorectal lymphoma with bleeding, obstruction or perforation, an operation may be the only option.[9,21,23,24] However, surgery may bring some surgical complications. One of our patients had postoperative internal bleeding and died within 30 days of surgery. Most authors believe surgery could (1) provide important prognostic information, including histology, tumor extent and stage; (2) may offer a chance for cure with or without adjuvant therapy; and (3) prevent complications such as hemorrhage, perforation and obstruction.[1,9,31] Thus, to obtain a better outcome, surgical excision of the tumor remains as a choice of treatment of colorectal lymphoma.[14,16,19,23,31] In Japan, some authors reported endoscopic submucosal dissection (ESD) could be used for en-bloc resection of localized colorectal lymphoma. However, the procedure

is limited to selected patients and there is no long-term outcome data due to the low number of cases.[32] Radiation therapy should be reserved for locally advanced disease after surgical resection as a primary therapy in older patients with a small tumor burden, or in patients with prohibitively high operative risk.[33-35]

Prognostic factors for colorectal lymphoma including stage, chemotherapy, high histologic grade,[9] tumor size (larger than 5 cm, or 10 cm),[7,24] lymph node involvement,[7,12] urgency of operation,[10,23] extension of residual disease, and perforation have been reported in different studies. However, because the number of patients in each study is relatively small, there are still some conflictions in different reports. In our series, prognostic factors including tumor size (larger than 10 cm), tumor site, and lymph node involvement do not have statistical significance for survival time. In general, the disease stage at the initial diagnosis greatly influences the survival, and our analyses disclosed the same finding.[10,22,23] In our series, chemotherapy had significant influence the survival ($p = 0.001$). Zighelboim reported an improvement in median survival from 36 to 53 months in patients who received adjuvant chemotherapy.[31] Aviles et al. noted a 74% rate of relapse with local or disseminated disease in stage IE patients treated with surgery alone, and they described an overall survival of 83% at 10 years in another series of 53 patients with stage IE disease who underwent surgical resection followed by adjuvant chemotherapy.[24] Fan et al. also discovered significant improvement in the median survival from 24 to 36 months in patients with stage IIE who received adjuvant chemotherapy. However, they also detected no significance in adding chemotherapy upon survival of the subgroup of patients with high grade lymphoma in stage I and II.[9] In another recent series in Taiwan, Lai et al. demonstrated surgery followed by chemotherapy had a better survival rate than chemotherapy alone.[16] By combining surgery and adjuvant chemotherapy for primary colorectal lymphoma, the 5-year survival rate has ranged from 20-55%.[7,15,21,31] The overall five-year survival rate in this study was 42.9%. In our series, we found if a curative resection could be performed on patients with colonic lymphoma, there will be a better survival rate than those who had palliative resection with residual disease. Moreover, adjuvant chemotherapy had great impact on prognosis. Therefore, both treatments are highly recommended in selected patients to achieve a better outcome.[9,16,24] Nevertheless, there are some limitations to this study that should be considered. First, this is a retrospective study, so the data could have biases; secondly, the number of our patients is relatively small to achieve any definite conclusion. We feel that a multicentric cooperative analysis might be required to define some prognostic classification that could be useful to achieve a better treatment to avoid the risk of excessive therapies and the presence of acute and late side effect.

Conclusion

Primary colorectal lymphoma is extremely rare compared with colorectal adenocarcinoma. The choice of treatment for primary colorectal lymphoma is multimodality therapy including operation, adjuvant chemotherapy, and even radiation. Adequate curative surgical resection in selected patients with colonic lymphoma followed by adjuvant chemotherapy seems to result in a favorable outcome.

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原　著

原發性結腸惡性淋巴癌單一醫學中心之治療經驗

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目的　原發性結腸惡性淋巴癌為少見惡性腫瘤。本研究回顧高雄長庚紀念醫院過去治療結腸惡性淋巴癌之經驗，並就臨床特徵及預後進行論述。

方法　回顧收集於 1989 至 2009 年間本院結直腸癌登記資料庫中，診斷為結直腸癌之 8,953 名病患裡，病理診斷為惡性淋巴癌者共 21 例。分析上述病患個別醫療紀錄，並就其臨床表徵、病理分類、腫瘤位置、期別、治療成效、復發情形及存活率等進行分析。

結果　統計發現病患以男性居多，男女比為 16 比 5，平均年齡為 53.9 歲。臨床表徵為腹痛或腹脹。腫瘤好發位置為盲腸居多，升結腸次之。只有兩位病人於治療前藉由大腸鏡切片證實為惡性淋巴癌，其餘病人大多是由手術病理診斷確診。病理報告發現主要型態為 B 細胞淋巴癌，在此研究中並無發現 T 細胞淋巴癌。有 17 例病人接受手術，其中 10 例為根除性手術，7 例為緩和性手術。接受化學治療的病人有 12 例。五年存活率為 42.9%。統計結果發現，診斷時的期別、接受根除性手術、非急診手術及化學藥物治療和病人預後有顯著相關 ($p < 0.05$)。

結論　原發性結腸直腸惡性淋巴癌的治療建議為多元整合治療模式，患者若可以接受根除性手術，術後併之輔助性化學治療，對預後是有幫助的。

關鍵詞　惡性淋巴癌、輔助性化學治療、結腸與直腸、B 細胞。