Original Article

Impact of Diabetes Status on Long Term Oncological Outcome of Stage II Colorectal Cancer

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Key Words
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Purpose. Colorectal cancer and diabetes shared similar dietary and lifestyle risk factors. Many studies showed higher prevalence and poor overall survival of colorectal cancer among diabetes patients. However, the long term oncological outcome of colorectal cancer among diabetes patients was limited and non-conclusive.
Methods. We presented a consecutive case series from our database of colorectal cancer from 1999 to 2002. Stage II colorectal cancer patients with curative resection were included and radiation therapy were excluded. Clinicopathological factors, long-term overall survival and oncological outcome were analyzed and compared between diabetes and non-diabetes patients.
Result. Comparing the diabetes to non-diabetes group, DM patients had elder ages, higher BMI, higher rates of moderate to severe chronic renal failure (19 vs. 7.5%, $p < 0.001$), CEA elevation over 5 ng/ml (55.2% vs. 33.6%, $p < 0.001$), myocardial infarction (16.1% vs. 5.7%, $p = 0.043$) and congested heart failure (4.8% vs. 1.2%, $p = 0.008$) were significantly higher in diabetes group. Although overall survival showed no difference between DM and non-DM patients, the 5-year disease specific survival and 3-year disease free survival rates of diabetes group were 91% and 88%, significantly higher than 81% and 78% of non-diabetes group ($p = 0.025$ and 0.015, respectively). Diabetes showed improved disease free survival (hazard ratio = 0.192, $p = 0.023$) in multivariate Cox-regression modelafter adjusted with age, metformin using and other clinicopathological factors. On the other hand, diabetes only showed borderline improvement in disease specific survival after adjusted by metformin and other clinicopathological factors (HR = 0.258, $p = 0.064$).
Conclusions. Diabetes presented to be a protective factor in oncological outcome against accompanied higher serum CEA level in stage II colorectal cancer with curative resection only.
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Colon rectal cancer (CRC) is the third most common cancer in men, the second most common cancer in women and also the fourth common cause of death related with cancer worldwide.[1,2] Diabetes mel-

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litus (DM) patients was a common disease with 382 million people globally in 2013 and is projected to growth to 592 million by 2035.[3]

Both CRC and DM share similar facts, such as western diets, obesity, physical inactivity and smoking. However, DM and CRC are not merely share similar risk factors. In one meta-analysis comprise of 8 case-control and 16 cohort studies, DM is related to CRC with a relative risk of 1.26 than those without DM.[4] DM was also correlated to not only short-term perioperative mortality but overall mortality such as cardiovascular disease among all CRC patients.[5,6]

Although DM related to higher risk of CRC and a negative impact on overall survival among CRC patients, the impact of DM on oncological outcome, especially long term oncological outcome was varied. In one meta-analysis including 26 articles and 216,981 participants reveled a significantly negative impact of DM on both disease specific survival and disease free survival in both colon and rectal cancer, but heterogeneity was found between studies and long term follow up was lacking.[7] In one cancer registry analysis including 10862 stage I to III CRC patients (6974 with colon cancer, 3888 with rectal cancer), higher long term disease-specific mortality was found among rectal cancer patients but not colon cancer patients.[8] Another study focused on long-term outcome of high-risk stage II and stage III colon cancer patients (3759 patients, 287 with DM) undergoing curative intent treatments showed significantly worse overall survival and disease-free survival in patients with DM.[9]

However, studies focused on association between DM and long term oncological outcome, especially on the early stage of CRC was limited and inconclusive. One study based on Taiwan Cancer Registry database showed association between DM patients and poor overall survival in stage I and II CRC but not disease specific survival.[10] One case series including 241 DM patients out of 1116 patients with stage II colon cancer showed no impact on overall survival or recurrence rate except lower rate of receiving adjuvant chemotherapy with similar complete rate.[11] In contrast, another case series including 150 DM patients out of 836 patients with stage II colon cancer patients showed not only poor overall survival but poor disease specific survival in after adjustment (HR: 2.11, $p = 0.005$).[12]

Therefore, we presented data from our prospective CRC database on a consecutive series focusing on the interaction of both DM and adjuvant chemotherapy in stage II CRC patients and compare the long term oncological outcome between high and low risk of stage II CRC patients.

Materials and Methods

Study population

Data collected from a prospective colorectal cancer database was based on a single medical center (Chang Gung Memorial Hospital, Linkou). All consecutive stage II CRC patients underwent curative resection between January 1, 1999 and December 31, 2002 were included and analyzed. All patients had routine pre-operative evaluations such as computerized tomogram of chest, abdomen and pelvis. Post operation follow-up visits were arranged on standardized protocol. Any recurrence or other primary cancer was recorded prospectively along with disease status, date and cause of mortality. The subgroup of type 2 diabetes was then defined by diabetes medication, the hospital pharmacy database and medical records. Baseline renal function was assessed at the time of pre-operative assessment. This study was approved by Chang-Gung medical foundation institutional review board.

We selected to focus on patients with stage II colorectal cancers due to partial impact from chemotherapy. Stage I colon cancers was excluded due to the low recurrence rate by surgical excision only. Node positive CRC was excluded due to variation in the adjuvant chemotherapy may be influenced by the patient's overall condition and other associated comorbidities, which might influence choice and dose of chemotherapy. Patients with radiation therapy was excluded in this study due to pre-operative or post-operative radiation therapy may confound the impact between adjuvant chemotherapy and DM status. Diabetes patients were compared with non-diabetes patients in stage II CRC patients and subgroups divided by

adjuvant chemotherapy or not. Operation related mortality (within 30 days after operation) was excluded in comparison of long term overall and oncological outcome.

Statistical significance was analyzed using SPSS Statistics Data Editor 17.0 (SAS institute Inc, Cary, NC, USA). Descriptive statistics including frequencies were used to describe the study population between DM and non-DM groups. Pearson chi square test was used to analyze categorical variables, in which student *t* test was used to analyze mean variables such as age and BMI. Kaplan-Meier method was used to analyze overall survival, disease specific survival and disease-free survival. The Cox proportional hazards model was used for univariate and multivariate analyses of clinicopathological factors for disease specific survival and disease free survival. *p* value less than 0.05 represents statistical significance.

Result

There were 871 stage II CRC patients included in the selected duration underwent curative resection without radiation therapy, with 7 patients were excluded for other pathology report other than colon cancer (lymphoma, sarcoma and squamous cell carcinoma) and 16 DM patients were excluded for inadequate DM medication record (Fig. 1). After exclusion, 848 patients were included; 55.9% were male and average age was 63.99 years. A number of 105 patients (12%) with type 2 diabetes were identified. The mean follow-up time in overall patients was 71.2 months.

Elder age, higher BMI score, elevated serum CEA level (more than 5 ng/ml), higher rate of chronic renal failure, history of myocardial infarction and congested heart failure with statistical significance were found in DM patients (Table 1).

Clinicopathological factors in DM patients between chemotherapy and non-chemotherapy showed higher T4 staging, circumferential involvement and younger age in patients receiving chemotherapy (Table 2).

Overall survival in total patients and in both subgroups showed no statistical difference between DM and non-DM patients after a maximum of 176 months of follow-up (Fig. 2). However, DM patients presented with significantly higher disease specific survival and disease free survival in overall patients and subgroup of non-adjuvant group. The 5-year disease specific survival and 3-year disease free survival rates of diabetes group both were 94% and 88%, significantly higher than 90% and 77% of non-DM group ($p = 0.022$ and 0.021, respectively) (Fig. 3). On the other

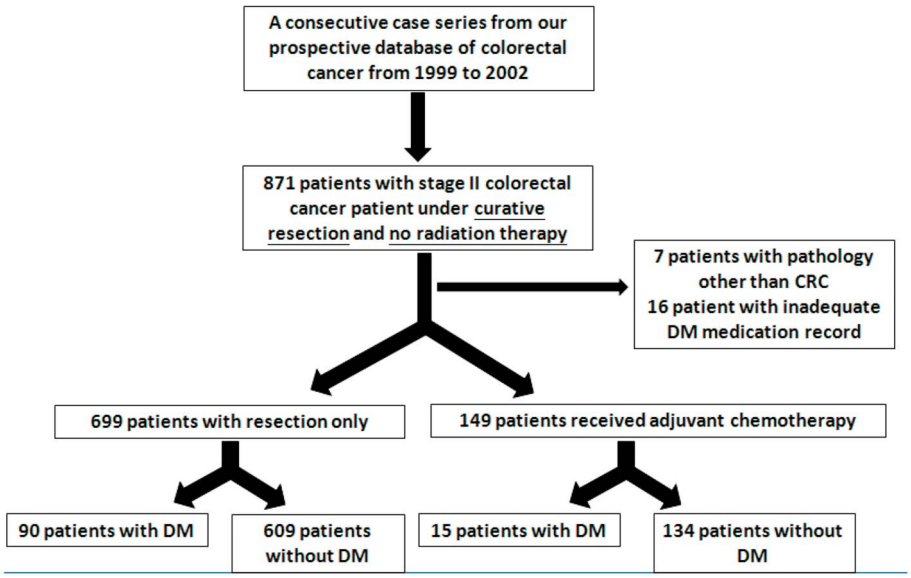


Fig. 1. Flow chart — study population.

Table 1. Overall demographic data

	Non-DM	DM	*p*-value
Case number	743	105	
Age (Std. dev)	63.44 (13.43)	67.94 (10.1)	0.0325
Sex			0.325
M (%)	420 (56.5%)	54 (51.4%)	
F (%)	323 (43.5%)	51 (48.6%)	
BMI (Std. dev)*	23.17 (3.76)	24.01 (3.69)	0.032
Organ			0.846
Colon (%)	445 (59.9%)	64 (61%)	
Rectum (%)	294 (39.6%)	40 (38.1%)	
Both (%)	4 (0.5%)	1 (0.8%)	
Moderate to severe CKD	56 (7.5%)	20 (19%)	< 0.001
MI (%)	6 (5.7%)	17 (16.1%)	0.043
CHF (%)	9 (1.2%)	5 (4.8%)	0.008
CVA (%)	25 (3.4%)	8 (7.6%)	0.093
COPD (%)	10 (1.3%)	3 (2.9%)	0.238
Liver disease (%)	29 (3.9%)	4 (3.8%)	0.963
T4 stage (%)	419 (56.4%)	67 (63.8%)	0.150
Circumferential involvement	240 (32.3%)	33 (31.4%)	0.858
Poorly differentiation (%)	27 (3.6%)	1 (1%)	0.150
Histologic type (%)			0.625
Adenocarcinoma	682 (91.8%)	99 (94.3%)	
Signet ring cell	2 (0.3%)	0	
Mucinous	59 (7.9%)	6 (5.7%)	
Metachronous tumor	29 (3.9%)	5 (4.8%)	0.442
CEA > 5 ng/ml	250 (33.6%)	58 (55.2%)	< 0.001
< 12 Lymph nodes (%)	184 (24.8%)	25 (23.8%)	0.832
Emergent operation (%)	15 (2%)	5 (4.8%)	0.083
Obstruction or perforation (%)	91 (12.2%)	11 (10.5%)	0.601
Adjuvant chemotherapy (%)	134 (18%)	15 (14.3%)	0.345
OP mortality (%)	9 (1.2%)	2 (1.9%)	0.557
Complication (%)			
Infection	22 (3%)	2 (1.9%)	0.541
CV	5 (0.7%)	0	0.399
GI	56 (7.5%)	6 (5.7%)	0.502
Anastomosis leakage	14 (1.9%)	1 (1.0%)	0.498
Bladder dysfunction	25 (3.4%)	7 (6.7%)	0.097

* 11 patients had inadequate BMI data (4 DM patients, 7 non-DM patients).

hand, DM patients showed similar survival curve with non-DM patients in subgroup of adjuvant chemotherapy (Fig. 4).

When the patients were assorted by receiving adjuvant chemotherapy or surgical resection only, non-DM patients showed improved overall survival by adjuvant chemotherapy (5-year survival: 90% vs. 79%, $p = 0.009$), but improvement of disease specific survival was not significant (5-year survival: 80% vs. 84% $p = 0.531$) (Table 3). In contrast, chemotherapy showed no significant difference in overall survival, 5-year disease specific survival and 5-year disease free survival among DM patients (Table 3).

Cox proportional-hazards regression revealed lower risk of DM in disease free survival after adjusted with other clinicopathological factors including metformin and insulin using (HR: 0.192, $p = 0.023$) (Table 4). On the other hand, DM showed decreased risk of disease specific survival in univariate regression only (HR: 0.433, $p = 0.046$), but borderline im-

Table 2. Demographic data of DM patients with or without chemotherapy

	Chemotherapy	No chemotherapy	*p*-value
Case number	15	90	
Age (Std. dev)	62.47 (10.1)	68.86 (9.86)	0.023
Sex			0.130
M (%)	5 (33.3%)	49 (54.4%)	
F (%)	10 (66.7%)	41 (45.6%)	
Organ			0.258
Colon (%)	12 (80%)	52 (57.8%)	
Rectum (%)	3 (20%)	37 (41.1%)	
Moderate to severe CKD	0	20 (22.2%)	0.042
MI	0	6 (6.7%)	0.303
CHF	0	5 (5.6%)	0.350
CVA	1 (6.7%)	7 (7.8%)	0.609
COPD	0	3 (3.3%)	0.473
Liver disease	0	4 (4.4%)	0.405
T4 staging (%)	13 (86.7%)	54 (60%)	0.047
Circumferential involvement	8 (53.3%)	25 (27.8%)	0.048
Poorly differentiation (%)	0	1 (1.6%)	0.682
Histologic type(%)			0.170
Adenocarcinoma	13 (86.7%)	86 (95.6%)	
Mucinous	2 (13.3%)	4 (4.4%)	
CEA > 5 ng/ml	9 (60%)	9 (54.4%)	0.689
< 12 Lymph nodes (%)	2 (13.3%)	23 (25.6%)	0.304
Emergent operation (%)	1 (7.7%)	3 (3.3%)	0.092
Obstruction or perforation (%)	1 (6.7%)	10 (11.1%)	0.603
OP mortality (%)	0	2 (2.2%)	0.560
Complication (%)			
Infection	0	2 (2.2%)	0.560
CV	0	0	n/a
GI	0	6 (6.7%)	0.303
Anastomosis leakage	1 (6.7%)	6 (6.7%)	1
Bladder dysfunction	1 (6.7%)	6 (6.7%)	1
DM control			
No control	6 (46.2%)	42 (52.5%)	0.671
Metformin	4 (28.6%)	20 (30.8%)	0.871
Sulfonylurea	5 (35.7%)	34 (50%)	0.330
Insulin	1 (7.1%)	9 (13.4%)	0.515
Other * OHA	0	3 (4.7%)	0.426

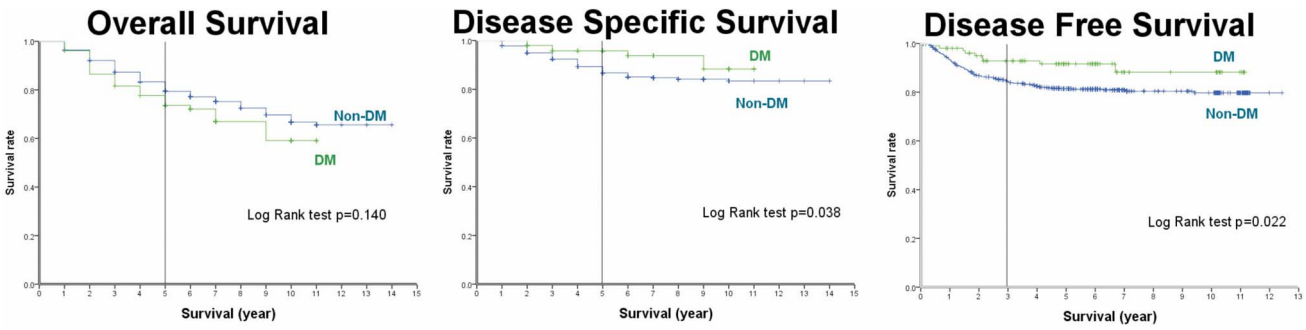
* OHA: oral hypoglycemic agent.

provement after adjustment in multivariate regression (HR: 0.258, $p = 0.064$) (Table 5).

Discussion

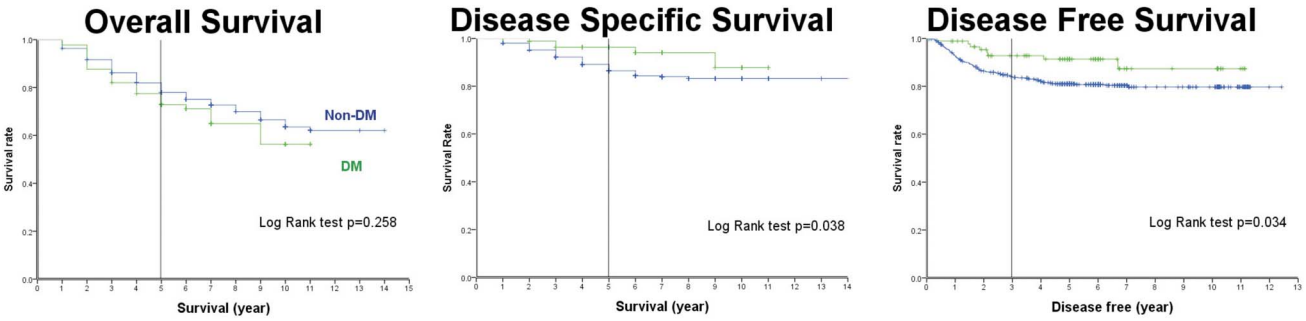
DM is associated with multiple macrovascular and microvascular complications which cost patients' life other than cancer itself. In our study, more comorbid diseases such as myocardial infarction and congested heart failure were found among CRC patients with DM and were identical with the studies mentioned above.[5,6]

Current oncological outcomes of DM patients focused on stage II colorectal cancer were divergent. According to our study, improved disease free survival was presented among DM patients in stage II colorectal cancer with curative resection only but overall survival was similar. The improvement of cancer specific survival was borderline after adjustment, but there was no survival benefit of DM in the patients with adjuvant chemotherapy. In contrast to our study, one population-based case series of stage II colon cancer by Bae, S. et al. showed similar overall survival



	5-year Overall Survival	5-year Disease-Specific Survival	3-year Disease-Free Survival
DM	61%	91%	88%
Non-DM	67%	81%	78%
p-value	0.135	0.025	0.015

Fig. 2. Survival rate of stage II CRC between DM and non-DM patients.

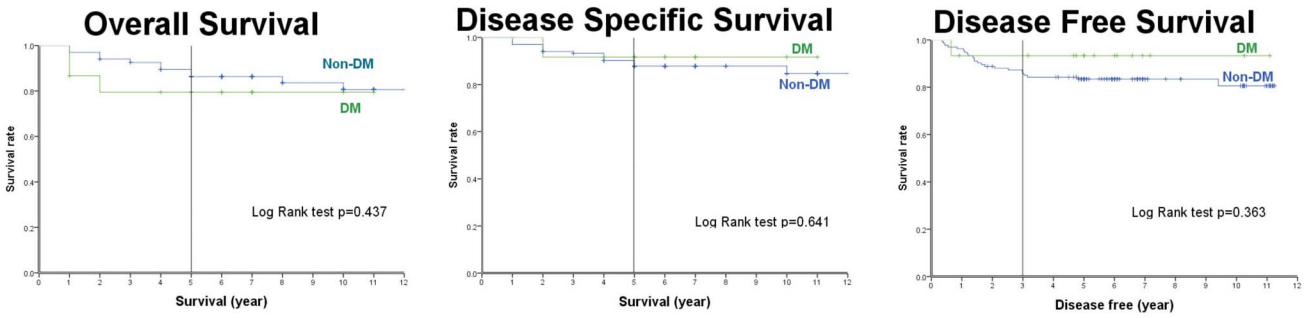


	5-year Overall Survival	5-year Disease-Specific Survival	3-year Disease-Free Survival
DM	76%	94%	88%
Non-DM	79%	90%	77%
p-value	0.268	0.022	0.021

Fig. 3. Survival rate of stage II CRC without adjuvant chemotherapy between DM and non-DM patients.

and recurrence rate.[11] However, another case series including 836 stage II colon cancer showed worse overall and disease specific survival.[12] In comparison to our report, both studies by Bae, S., et al. and Huang, Y.C., et al. recruited colon cancer patients only and did not compare between adjuvant chemotherapy or curative resection only, but there is still diverse in the outcome of survival.

The underlying pathophysiological mechanism by which DM impacts on survival in stage II CRC pa-



	5-year Overall Survival	5-year Disease-Specific Survival	3-year Disease-Free Survival
DM	80%	92%	93%
Non-DM	79%	84%	80%
p-value	0.340	0.701	0.406

Fig. 4. Survival rate of stage II CRC with adjuvant chemotherapy between DM and non-DM patients.

Table 3. Survival between chemotherapy and resection only

	5-year overall survival	5-year disease specific survival	3-year disease free survival
Non-DM patients			
Chemotherapy	90%	80%	93%
Resection only	79%	84%	92%
p value	0.009	0.531	0.437
DM patients			
Chemotherapy	79%	92%	93%
Resection only	59%	91%	87%
p value	0.842	0.519	0.922

tients remains non-conclusive. Current consensus such as advanced stage due to under screening, less aggressive treatment plan by clinical decision and poor response to chemoradiotherapy, were not presented in our study.[13-15] Factors of high risk stage II colon cancer (T4 staging, obstruction or perforation, poorly differentiated histology), adjuvant chemotherapy rate showed no significant difference between DM and non-DM patients and radiation therapy was

Table 4. Univariate and multivariate analysis by the Cox proportional hazard model to demonstrate the adjusted hazard ratios of potential factors on disease free survival

Clinicopathological variable	Univariate HR	*p* value	Multivariate HR	*p* value
Age ≥ 70 years	1.369	0.059	1.235	0.331
Male sex	1.026	0.877	0.552	0.879
Rectum origin	1.294	0.002	2.217	< 0.001
MI	0.483	0.306	0.297	0.233
CHF	0.427	0.450	< 0.001	0.955
Diabetes	0.463	0.025	0.192	0.023
Moderate to severe CKD	1.136	0.349	1.033	0.846
T4 stage	1.441	0.035	1.690	0.019
Lymph node < 12	1.812	0.001	1.662	0.029
Poor differentiate	0.800	0.661	1.613	0.429
CEA > 5 ng/mL	2.065	< 0.001	2.468	< 0.001
Obstruction or perforation	1.393	0.152	1.615	0.106
Adjuvant chemotherapy	1.020	0.532	1.012	0.782
Metformin	0.526	0.368	2.240	0.426
Insulin	0.586	0.595	4.242	0.248

MI: myocardial infarction; CHF: congested heart failure; CKD: chronic kidney disease.

Table 5. Univariate and multivariate analysis by the Cox proportional hazard model to demonstrate the adjusted hazard ratios of potential factors on disease specific survival

Clinicopathological variable	Univariate HR	*p* value	Multivariate HR	*p* value
Age ≥ 70 years	1.499	0.035	1.3557	0.227
Male sex	1.033	0.865	0.831	0.468
Rectum origin	1.269	0.014	1.799	0.027
MI	0.678	0.586	0.360	0.320
CHF	0.636	0.653	< 0.001	0.984
Diabetes	0.433	0.046	0.258	0.064
Moderate to severe CKD	1.233	0.172	1.069	0.731
T4 stage	1.564	0.028	1.952	0.014
Lymph node < 12	1.818	0.003	1.690	0.055
Poor differentiate	1.119	0.825	2.366	0.161
CEA > 5 ng/mL	2.133	< 0.001	3.131	< 0.001
Obstruction or perforation	1.467	0.146	1.397	0.348
Adjuvant chemotherapy	1.020	0.590	1.046	0.395
Metformin	0.276	0.047	< 0.001	0.978
Insulin	0.473	0.049	< 0.001	0.989

MI: myocardial infarction; CHF: congested heart failure; CKD: chronic kidney disease.

excluded before hand in our study.

Hyperinsulinemia, elevation of insulin-like growth factor I (IGF-I) and decreased insulin growth factor binding proteins (IGFBPs) may play an important role in the carcinogenesis of colon cancer. Hyperinsulinemia was considered as a growth factor in colon tumor in whites and African Americans.[16] One prospective study of colonoscopy screening on 210 patients with acromegaly and accompanied hyperinsulinemia showed elevated rate of colonic lesions (38.6%) and adenocarcinoma (2.8%).[17] Current studies also showed possible association between hyperinsulinemia and following elevated IGF-I with cell proliferation and, peptide and blood sugar itself may also played a role in development of colorectal cancer. One prospective study from 14916 cancer-free man showed association of elevated plasma C-peptide and colorectal cancer and was independent from BMI, IGF-I or IGFBP-3 levels.[18] One meta-analysis showed linear dose-response relationship of fasting blood glucose with the risk of CRC (HR: 1.015, $p < 0.001$ for each 20 mg/dl elevation of fasting blood sugar), which implied the blood sugar itself may played the role of carcinogenesis than DM.[19]

On the other hand, metformin using in DM patients may showed positive impact on colorectal cancer. One meta-analysis studies including 5 observational studies, 1546 patients revealed a significant reduction of mortality of colon cancer with metformin using (HR = 0.65, $I^2 = 0\%$).[20] Another meta-analysis including 108,161 type 2 DM patients showed lower risk of colorectal cancer with metformin using (HR: 0.63, $p = 0.002$).[21] For non-diabetes patients, metformin using was associated with reduced aberrant crypt formation in rectal pre-euplastic tumors.[22] The mechanism of metformin was complex, including reducing serum insulin level from improving insulin sensitivity and acting directly on AMPK/mTOR pathway.[20] Although metformin using showed no difference in oncological outcome due to limited numbers, it also showed no confounding in the disease free survival among DM patients.

Even though DM patients showed better disease free survival in our study, chemotherapy showed better improvement in overall outcome among non-DM patients than other groups. The impact of DM on chemotherapy was mainly on organ system damage, such as chronic renal insufficiency, myocardial failure, heart failure and neuropathy.[23,24] Hyperglycemia was also associated with higher rate of infection.[25] However, study of DM on chemotherapy decision, especially on stage II colorectal cancer, was limited. A report including 3759 high-risk stage II and stage III colon cancer patients showed higher incidence of diarrhea in DM patients undergone adjuvant chemotherapy.[9] A series of 1116 patients showed fewer adjuvant chemotherapy in DM patients (13.7% versus 24.8%, $p = 0.002$), but complete rate (69.7 versus 67.7%, $p =$

1.00) are equal with similar disease specific and recurrent free survival.[11]

The limitations of our study including limited case number of metformin and insulin using, lack of C-peptite, IGF-1 and IGFBPs data, adjuvant chemotherapy in the studying period was mainly 5-FU based without the using of oxaliplatin, lack of length or interaction of different DM medications.

Conclusions

Although overall survival was equivalent, DM patients have better disease free survival and borderline disease specific survival in stage II CRC, especially in the sub-group without adjuvant chemotherapy. In contrast, the patients without DM showed better response to adjuvant chemotherapy. Factors of radiation therapy, combined chemotherapy with radiotherapy and different DM and chemotherapy regimens on the long-term outcome of stage II colorectal cancer may need further studies.

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原　著

糖尿病對第二期大腸直腸癌長期預後之影響

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目的　糖尿病與大腸直腸癌有相似的飲食及生活因子。目前許多研究均顯示糖尿病病患有較高的大腸直腸癌發生率及較差的總存活率，但是長期存活率及癌症相關存活率的研究卻相對有限且無一致的結論。

方法　挑選本院 1999 年至 2002 年第二期大腸直腸癌接受根除性切除但排除接受放射治療之病患。比較糖尿病及非糖尿病病患之臨床病理表現、長期總存活率及癌症相關存活率，另外則比較不同糖尿病治療方式之癌症相關存活率之異同。

結果　在大腸直腸癌病患中，罹患糖尿病的病患有較高的年齡、BMI、慢性腎衰竭 (19% vs. 7.5%, $p < 0.001$)、心肌梗塞 (16.7% vs. 5.7%, $p = 0.043$)、心衰竭病史 (4.8% vs. 1.2%, $p = 0.008$) 及癌胚抗原數值 (CEA > 5 ng/ml, 55.2 vs. 33.6%, $p < 0.001$)。兩組間總體存活率並無顯著差異，但糖尿病病患比非糖尿病病患有顯著較高的 5 年癌症相關存活率 (91% vs. 81%, $p = 0.025$) 及 3 年疾病無復發率 (88% vs. 78%, $p = 0.015$)。在多變數分析中排除 metformin 使用及其他因子後糖尿病仍有顯著較低之疾病復發率風險 (HR = 0.192, $p = 0.023$)，然而多變數分析中糖尿病之癌症死亡率風險卻達邊緣性統計顯著 (HR = 0.258, $p = 0.064$)。

結論　糖尿病在第二期大腸直腸癌病患中雖有較高的癌胚抗原值，但排除 metformin 使用後糖尿病對於第二期大腸直腸癌之癌症預後為明顯保護因子。

關鍵詞　糖尿病、大腸直腸癌、癌症相關存活率。