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Making Progress: Impact of Diabetes on Metastatic Colon Cancer Disease Progression

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Abstract

Background: Diabetes is a risk factor for the development of colon cancer and is associated with worse cancer-specific outcomes in a non-metastatic disease. However, it remains unclear whether diabetes clinically impacts cancer-specific outcomes in metastatic colon cancer. This study aimed to determine if diabetes conferred an increased risk of disease progression as measured by progression-free survival in diabetics compared to nondiabetics, as well as to determine whether A1Cor diabetes medication clinically impacted disease progression.

Methods and Findings: We performed a single-institution retrospective chart review comparing radiographic progression-free survival of 42 diabetics to 149 non-diabetic patients with newly diagnosed metastatic colon cancer. Cox proportional hazard models were used to compare progression-free survival. Models controlled for chemotherapy, surgical interventions, gender, age, and ethnicity. Diabetics experienced significantly shorter mean progression-free survival (0.84 versus 1.27 years, p=0.028) and experienced significantly increased risk of disease progression [HR 1.68 (1.16-2.41), p=0.0054] compared to non-diabetics. No significant benefit or harm to progression-free survival was found by A1Cor diabetic regimen.

Conclusion: Our results suggest diabetes is associated with an increased risk of disease progression in newly diagnosed patients with metastatic colon cancer. These results seem to suggest that diabetes is a poor prognostic indicator in newly diagnosed metastatic colon cancer and that improved management of diabetes may lead to delay in disease progression.

Keywords: Diabetes; Metastatic colon cancer; Progression-free survival; Tumor progression; Cancer specific outcomes; A1C; Insulin

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Introduction

Diabetes is an important risk factor for the development of colon cancer, the third most common cancer worldwide. Specifically, Larsson et al. showed that diabetics have a 30% increased relative risk of developing colon cancer compared to non-diabetics [1]. Additionally, having diabetes seems to play an important role in the outcomes of colon cancer [2]. Numerous studies have shown diabetes modestly increased the risk of all-cause mortality, cancer-specific mortality, recurrence, and operative mortality in non-metastatic colon cancer [3-6].

However, the clinical relationship between diabetes and cancer-specific outcomes in metastatic colon cancer remains less well understood. Little research exists specifically examining whether diabetics with metastatic colon cancer have worse cancer-specific outcomes. Multiple studies have found insulin and Insulin Growth Factor (IGF) stimulate significantly greater cellular proliferation of mice variants of metastatic colon cancer. Further, others have found insulin and IGF significantly promoted cellular proliferation and migration ability in human colon cancer cells [7,8]. However, the only study with a large sample size failed to demonstrate inferior cancer-specific outcomes in diabetics with metastatic colon cancer, however, this cohort only included Asian patients, which may not be generalizable to other ethnicities [9,10]. Additionally, no studies to date have specifically examined whether diabetes clinically impacts the risk of disease progression in patients being actively treated for metastatic colon cancer [6].

Thus, we performed a single-institution retrospective study to examine whether having diabetes conferred an increased risk of progression of metastatic colon cancer as measured by progression-free survival. Additionally, we examined whether A1C or diabetic regimen impacted progression-free survival.

Methods

Our study design was reviewed and approved by the University of Pennsylvania Institutional Review Board. The patient cohort from Pennsylvania Hospital was obtained from the UPHS Cancer Registry with a diagnosis of stage four colon cancer between 2014-2018. A retrospective chart review was conducted using electronic medical records.

Progression-free survival was determined the first date of documentation diagnosis of metastatic colon cancer to the first date of radiographic chart documentation or clinical chart documentation of the date of radiographic progression of the disease. Patients that had not progressed by December 31st 2018 were censored at this point and treated as if they had progressed at this date. Patients diagnosed with metastatic colon cancer in 2018 who had not progressed by December 31 2018 were excluded from analysis in an attempt to standardize the documentation of follow up time to at least one year.

Patients were considered diabetic if they had an active chart diagnosis of diabetes mellitus, documentation of insulin use, and/or had documentation of Hemoglobin A1C>6.4 within the treatment period. Patients who were considered prediabetic (active chart diagnosis of prediabetes, no active insulin use, and A1C 5.7-6.4) were included within the non-diabetic cohort.

A total of 243 charts were reviewed, including 185 non-diabetics and 58 diabetics. Of these, 31 non-diabetic and 16 diabetic patients either were placed on hospice or expired before radiographic disease progression was assessed and were excluded from analysis, leaving 149 non-diabetic and 42 diabetic patients for final analysis. Patient age at diagnosis, sex, ethnicity, chemotherapy (categorized as yes/no cumulative throughout the oncologic course), surgical interventions (categorized as yes/no cumulative over the oncologic course of therapy), and A1C (if available) were recorded for all patients. The patient's diabetic regimens were recorded. Chemotherapeutic agents were in keeping with current NCCN 2013 guidelines for initial lines of therapy.

Unadjusted incidence ratios were calculated for all variables. Multivariable Cox regressions examining the adjusted hazard ratio of cancer progression were performed with all included variables. Two-sided confidence intervals of 95% were used. Values were determined to be statistically significant for $p \leq 0.05$. Chi-squared was used to determine significant differences between groups. Two-tailed t-test was used to analyze for the significant difference within A1C cohort. SAS 9.4 was used fordata analysis.

Results

Most baseline characteristics were matched as seen in **Table 1.** A significant difference did exist in sex between diabetics and non-diabetics (54.8 *vs* 37.6% Male, p=0.045), however, multivariable cox regression showed sex to have no significant impact on the risk of progression (HR 0.87, p=0.41) **(Table 2)**. Additionally, multivariable cox regression showed undergoing chemotherapy had non-significant trend towards decreased risk of progression [HR 0.65 (0.35-1.21), p=0.17] while non-white race [HR 1.21 (0.87-1.71), p=0.26] and age [HR 1.01 (1.00-1.02), p=0.237) had non-significant trends towards increased risk of progression. Unadjusted patient characteristics can be found in **Tables 3 and 4**.

After adjusting for other variables, diabetics had significantly increased risk of disease progression compared to non-diabetics [HR 1.68 (1.16-2.41) p =0.0054], with diabetics progressing at an average of 0.84 years compared to 1.27 years in non-diabetics (p=0.0281), further demonstrated by **Figure 1.** Within diabetics, the diabetic regimen did not appear to significantly impact progression-free survival **(Table 5)**. Of medications used, lack of metformin appeared to have the closest association progression-free survival, with the non-significant trend towards harm [IRR 1.39 (0.75-2.58), p=0.301]. Insulin use did not significantly impact progression-free survival [IR 1.16 (0.75-1.81), p=0.907]. While limited in sample size due to many patients lacking charted A1C's within the study period, there was a non-significant trend of elevated A1C towards increased risk of progression [t(60)=1.47, p=0.148].

Discussion

Our study seems to demonstrate that diabetes significantly increases the risk of disease progression in metastatic colon cancer. Additionally, the degree to which diabetes increased disease progression appeared to be clinically significant (approximately 5 months). Intriguingly, diabetes was a stronger, more significant predictor of disease progression than having undergone chemotherapy, having received surgical intervention,

Table 1: Baseline characteristics of patients with metastatic colon cancer.

Characteristic	Diabetics	Non-Diabetics	p-value
Less than 60	19	59	0.51
Older than 60	23	90	
Male	23	56	0.046
Female	19	93	
White	27	108	0.3
Non-White	15	41	
Chemotherapy	39	139	0.92
No Chemotherapy	3	10	
Undergone Surgery	27	100	0.73
No Surgery	15	49	

Table 2: Multivariable adjusted cox regression models examining risk of progression.

Characteristic	HR (95% CI)	p-value
Diabetes	1.68 (1.16-2.41)	0.0054
Male	0.87 (0.63-1.21)	0.41
Age	1.01 (1.00-1.02)	0.24
Non-White Race	1.21 (0.87-1.70)	0.26
Undergone Chemotherapy	0.65 (0.35-1.21)	0.17
Undergone Surgery	0.86 (0.62-1.20)	0.38

Table 3: Unadjusted non-diabetics metastatic colon cancer patient characteristics.

Characteristic		Patients	%	Total Follow-up Years	Total Events	Mean Years to Progression	IR (95% CI)	IR Ratio (95% CI)	p-value
All Patients		149	100%	175.35	135	1.27	0.77 (0.65-0.91)		
Sex	Female	93	62.42%	108.89	86	1.23	0.79 (0.64-0.98)	1.07 (0.75-1.52)	0.701
	Male	56	37. 58%	66.46	49	1.32	0.74 (0.56-0.98)		
Age									
Mean 62.8	Under 60 Years	59	39.60%	72.78	53	1.34	0.73 (0.56-0.95)	0.91 (0.64-1.29)	0.596
STD 13.94									
Race	Over 60 Years	90	60.40%	102.56	82	1.2	0.80 (0.64-0.99)		
	Non-White	41	27.52%	42.23	39	1.05	0.92 (0.67-1.26)	1.28 (0.88-1.86)	0.1929
	White	108	72.48%	133.11	96	1.35	0.72 (0.59-0.88)		
Chemotherapy	No	10	6.71%	9.54	10	0.95	1.05 (0.56-1.95)	1.39 (0.73-2.65)	0.3161
	Yes	139	93.29%	165.8	125	1.3	0.75 (0.63-0.90)		
Surgery	No	49	32.89%	55.98	45	1.2	0.80 (0.60-1.08)	1.07 (0.75-1.52)	0.7261
	Yes	100	67.11%	119.36	90	1.29	0.75 (0.61-0.93)		

Table 4: Unadjusted diabetic metastatic colon cancer patient characteristics.

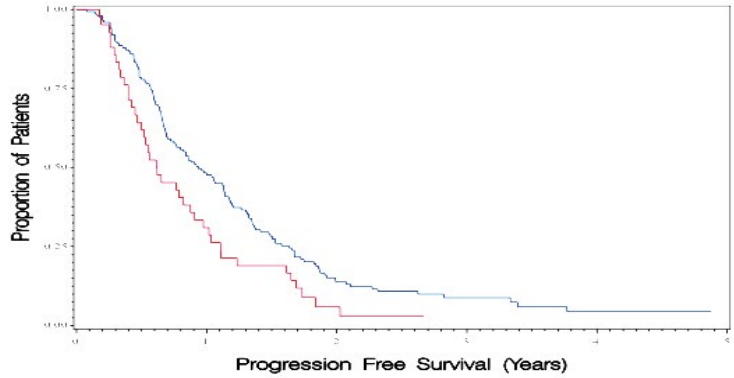
Characteristic		Patients	%	Total Follow-up Years	Total Events	Mean Years to Progression	IR (95% CI)	IR Ratio (95% CI)	p-value
All Patients		42	100.00%	34.99	40	0.84	1.14 (0.84-1.56)		
Sex	Female	19	45.24%	15.22	17	0.85	1.12 (0.69-1.80)	0.96 (0.51-1.80)	0.8984
	Male	23	54.76%	19.77	23	0.86	1.16 (0.77-1.75)		
Age									
Mean- 60.9 STD 10.14	Under 60 Years	19	45.24%	17.28	17	0.94	0.98 (0.61-1.58)	0.76 (0.40-1.42)	0.3853
	Over 60 Years	23	54.76%	17.71	23	0.77	1.30 (0.86-1.95)		
Race	Non-White	15	35. 71%	9.97	14	0.66	1.40 (0.83-2. 37)	1.35 (0.71-2.59)	0.3643
	White	27	64.29%	25.02	26	0.93	1.04 (0.71-1.53)		
Chemotherapy	No	3	7.14%	0.98	3	0.33	3. 06 (0.99-9. 49)	2.81 (0.87-9.12)	0.0849
	Yes	39	92.86%	34.01	37	0.88	1.09 (0.79-1.50)		
Surgery	No	15	35.71%	11.69	15	0.78	1.28 (0.77-2. 13)	1.20 (0.63-2.27)	0.5828
	Yes	27	64.29%	23.3	25	0.88	1.07 (0.72-1.59)		

Table 5: Unadjusted diabetic regimen impact on progression-free survival.

Characteristic		Patients	Percent	Total Follow-up Years	Total Events	Mean Years to Progression	IR (95% CI)	IR Ratio (95% CI)	p-value
Insulin	No	21	50.00%	17. 82	20	0.85	1.12 (0.72-1.74)	0.96 (0.52-1.79)	0.9066
	Yes	21	50.00%	17. 17	20	0.83	1.16 (0.75-1.81)		
Metformin	No	19	45.24%	13. 81	19	0.73	1.38 (0.88-2.16)	1.39 (0.75-2.58)	0.301
	Yes	23	54.76%	21.18	21	0.94	0.99 (0.65-1.52)		
Sulfonylureas	No	35	83.33%	27. 88	33	0.81	1.18 (0.84-1.66)	1.20 (0.53-2.72)	0.6586
	Yes	7	16.67%	7. 11	7	1.02	0.98 (0.47-2.07)		
DPP4 Inhibitors	No	39	92.86%	32. 74	37	0.85	1.13 (0.82-1.56)	0.85 (0.26-2.75)	0.7817
	Yes	3	7.14%	2. 25	3	0.75	1.33 (0.43-4.14)		

age, sex, or ethnicity. Altogether, these results are interesting, as they may suggest that improved management of diabetes may lead to a significant delay in disease progression in metastatic colon cancer.

However, it remains to be elucidated as to how this could be best accomplished. While limited by sample size, our study did not find any significant benefit (or harm) by the degree of A1C elevation or specific diabetic agent. Others have found that metformin was



Diabetic --- Non-diabetic ---

	0 Years	0.5 Years	1 Year	1.5 Years	2 Years	2.5 Years	+3 Years
Non-diabetics	149 (100%)	117 (78.5%)	73 (49%)	39 (26.2%)	18 (12.1%)	13 (8.9%)	10 (6.7%)
Diabetics	42 (100%)	26 (61.9%)	12 (28.6%)	8 (19%)	2 (4.8%)	1 (2.4%)	0

Figure 1 Diabetic *vs* Non-diabetic progression free survival.

associated with improved survival in colorectal cancer patients, which may be mediated through glucose metabolism, the effect on cancer stem cells, or growth factors. Unfortunately, they failed to show a survival benefit of metformin use in metastatic disease [11,12]. It may be that other factors may lead to an increased risk of disease progression in metastatic colon cancer for diabetics [11]. For instance, studies have found hyperglycemia can lead to decreased tumor cell chemosensitivity to 5-FU and Oxaliplatin in colon cancer, which could potentially lead to inferior cancer-specific outcomes in diabetics. However, another study failed to show a survival benefit with improved blood glucose control in diabetics with metastatic disease [13,14]. It may be that maybe the IGF may be what drives advanced colon cancer growth [15]. For instance, one study showed that elevated IGFBP-2 levels correlated with worse survival in colon cancer, as well as the loss of imprinting within IGF-II in the metastatic disease was significantly associated with worse overall survival. Another showed IGF1-R levels strongly correlated with higher stage disease [16,17].

While our results are interesting, our study has limitations. Due to population limits, our diabetic cohort was relatively small, which limits its generalizability. Additionally, the lack of many recorded A1C's limited our ability to assess their relationship with disease progression. Furthermore, while our study did not find a relationship between sex and risk of disease progression, our populations had a significant gender difference which may also limit its generalizability.

Conclusion

Our results suggest that diabetes is associated with clinically hastened disease progression in newly diagnosed metastatic colon cancer. These results could have numerous implications. First and foremost, they suggest that even in advanced malignancy, diabetes is clinically relevant. Diabetics with metastatic colon cancer may need to be approached and managed differently than non-diabetics, potentially via new targeted therapies versus simple lifestyle modification. This could prompt heightened surveillance of diabetes status in metastatic disease, as well as in other stages of the disease to potentially optimize long-term cancer outcomes. These results should prompt prospective replication with a larger population to further assess the impact of diabetes on colon cancer progression through certain factors, such as IGF, blood glucose, and A1C. If verified, they may suggest that diabetics with metastatic colon cancer hopefully could derive clinical cancer-directed benefit from improved management of their diabetes.

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We report no funding assistance or conflicts of interest.

References

1 Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, et al. (2015) Cancer incidence and mortality worldwide: Sources, methods, and major patterns in Globocan 2012. Int J Cancer 136: 359-386.

2 Larsson SC, Orsini N, Wolk A (2005) Diabetes mellitus and risk of colorectal cancer: A meta-analysis. JNCI 97: 1679-1687.

3 Mills KT, Bellows CF, Hoffman AE, Kelly TN, Gagliardi G (2013) Diabetes and colorectal cancer prognosis: A meta-analysis. Dis Colon Rectum 56: 1304-1319.

4 Stein KB, Snyder CF, Barone BB, Yeh HC, Peairs KS, et al. (2010) Colorectal cancer outcomes, recurrence, and complications in persons with and without diabetes mellltus: A systematic review and meta-analysis. Dig Dis Sci 55: 1839-1851.

5 Coughlin SS, Callie EE, Teras LR, Petrelli J, Thun MJ (2004) Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol 159: 1160-1167.

6 Huang YC, Lin JK, Chen WS, Lin TC, Yang SH, et al. (2011) Diabetes mellitus negatively impacts survival of patients with colon cancer, particulary in stage II disease. J Cancer Res Clin Oncol 137: 211-220.

7 Koenuma M, Yamori T, Tsuruo T (1989) Insulin and insulin-like growth factor 1 stimulate proliferation of metastatic variants of colon carcinoma 26. Jpn J Cancer Res 80: 51-58.

8 Wu Y, Yakar S, Zhao L, Henninghausen L, LeRoith D (2002) Circulating insulin-like growth factor-i levels regulate colon cancer growth and metastasis. Cancer Research 62: 1030-1035.

9 Lu CC, Chu PY, Hsia SM, Wu CH, Tung YT, et al. (2017) Insulin induction instigates cell proliferation and metastasis in human colorectal cancer cells. Inter J Onco 50: 736-744.

10 Frasca F, Pandini G, Scalia P, Sciacca L, Mineo R, et al. (1999) Insulin receptor isoform a, a newly recognized, high-affinity insulin-like growth factor ii receptor in fetal and cancer cells. Mol Cell Biol 19: 3278-3288.

11 Garrett C, Hassabo H, Bhadkamkar N, WenS, Baladandayuthapani V, et al. (2012) Survival advantage observed with the use of metformin in patients with type II diabetes and colorectal cancer. Br J Cancer 106: 1374-1378.

12 Rattan R, Fehmi RA, Munkarah A (2012) Metformin: An emerging new therapeutic option for targeting cancer stem cells and metastasis. J Oncol 92: 8127.

13 Bergandi L, Mungo E, Morone R, Bosco O, Rolando B, et al. (2018) Hyperglycemia promotes chemoresistance through the reduction of the mitochondrial damage, the Bax/Bcl-2 and Bax/Bcl-XL Ratio, and the Cells in Sub-G1 phase due to antitumoral drugs induced-cytotoxicity in human colon adenocarcinoma cells. Front Pharmacol 9: 866.

14 Yang IP, Miao ZF, Huang CW, Tsai HL, Yeh YS, et al. (2019) High blood sugar levels but not diabetes mellitus significantly enhance oxaliplatinchemoresistance in patients with stage III colorectal cancer receiving FOLFOX6 chemotherapy. Ther Adv Med Oncol 11: 1-13.

15 Hong YJ, Han HS, Jeong Y, Jeong J, Lim SN, et al. (2014) Impact of hyperglycemia on survival and infection-related adverse events in patients with metastatic colorectal cancer who were receiving palliative chemotherapy. Cancer Res Treat 46: 288-296.

16 Liou JM, Shun CT, Liang JT, Chiu HM, Chen MJ, et al. (2010) Plasma insulin-like growth factor-binding protein-2 levels as diagnostic and prognostic biomarker of colorectal cancer. J Clin Endocrinol Metab 95: 1717-1725.

17 Hakam A, Yeatman T, Lu L, Mora L, Marcet G, et al. (1999) Expression of insulin-like growth factor-1 receptor in human colorectal cancer. Hum Pathol 30: 1128-1133.