Peer Review File

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Comment 1*: Fix grammar in first sentence*

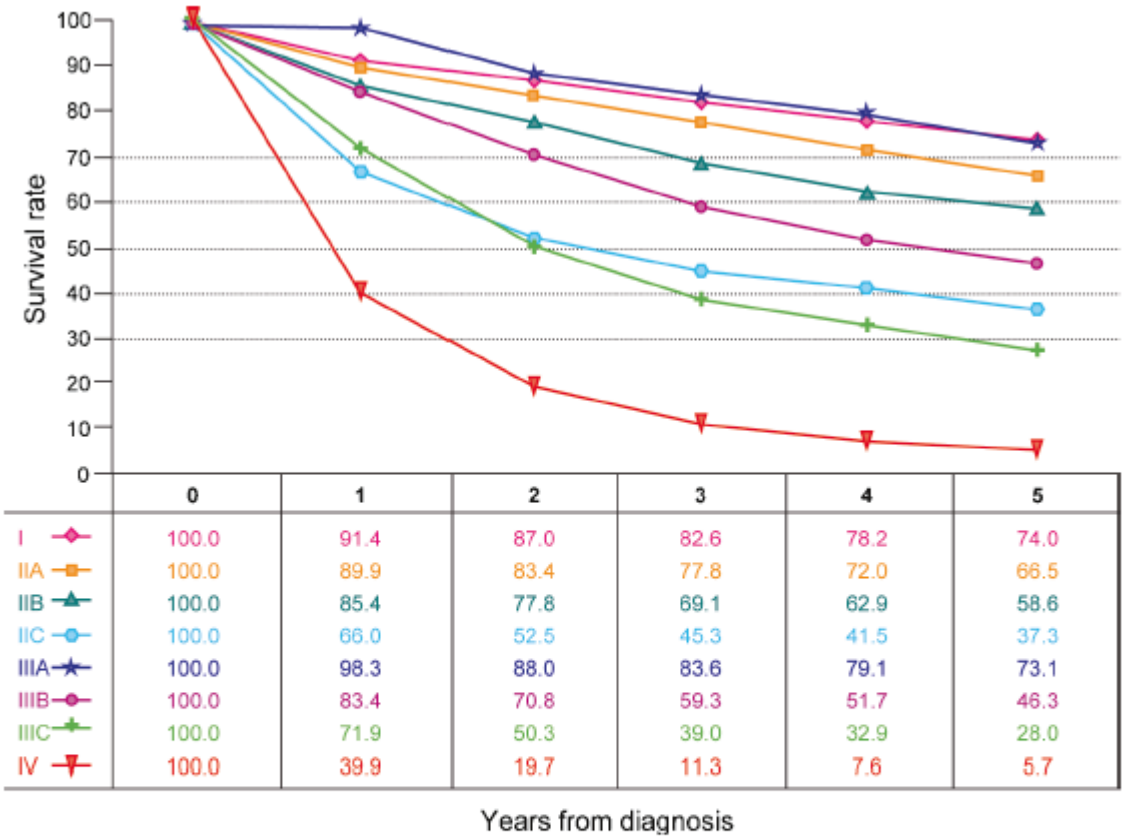
Reply: Done

Changes in text: We modified the text as advised. See the first sentence.

Page 4, line 15 and 16. Colorectal cancer is the second leading cause of cancer death in men and the third leading cause of death in women the United States each year(1).

Comment 2: *The second sentence does not appear accurate. 5 year survival for individuals with regional CRC is 71.8% per SEER*

Reply: Thank you for the comment. The second sentence includes data that clinical oncologists routinely refer to from the AJCC 7th edition and uses seer data up through 2005 (graph below). While the average survival in stage III disease is now reported at 71.8%, there is a significant difference within each stage based on tumor and lymph node characteristics, which we feel is important to highlight (table below). The 18th edition only gives 2 year survival data and references the 7th edition.



	0	1	2	3	4	5
I	100.0	91.4	87.0	82.6	78.2	74.0
IIA	100.0	89.9	83.4	77.8	72.0	66.5
IIB	100.0	85.4	77.8	69.1	62.9	58.6
IIC	100.0	66.0	52.5	45.3	41.5	37.3
IIIA	100.0	98.3	88.0	83.6	79.1	73.1
IIIB	100.0	83.4	70.8	59.3	51.7	46.3
IIIC	100.0	71.9	50.3	39.0	32.9	28.0
IV	100.0	39.9	19.7	11.3	7.6	5.7

FIGURE 14.4. Observed survival rates for 28,491 cases with adenocarcinoma of the colon. Data from the SEER 1973–2005 Public Use File diagnosed in years 1998–2000. Stage I includes 7,417; Stage IIA, 9,956; Stage IIB, 997; Stage IIC, 725; Stage IIIA, 868; Stage IIIB, 1,492; Stage IIIC, 2,000; and Stage IV, 5,036.

TABLE 14.7. Colon cancer: Expanded changes in AJCC substaging for stage II and III based on expanded SEER data

Category[a]	*SEER*				*SEER*	
TN	*Relative Survival, 5-year*	*SE*	*TNM Stage, 6th ed*	*TNM stage, 7th ed*[b]	*Observed Survival, 5-year*	*SE*
T1N0	97.4	0.6	I	I	78.7	0.5
T2N0	96.8	0.6	I	I	74.3	0.4
T3N0	87.5	0.4	IIA	IIA	66.7	0.3
T4aN0	79.6	1.0	IIB	IIB	60.6	0.8
T4bN0	58.4	1.3	IIB	**IIC**	45.7	1.0
T1-2N1a	90.7	1.5	IIIA	IIIA	73.7	1.2
T1-2N1b	83.0	2.0	IIIA	IIIA	67.2	1.6
T1-2N2a[a]	79.0	3.6	IIIC	**IIIA/IIIB**[a]	64.7	3.0
T3N1a	74.2	0.8	IIIB	IIIB	58.2	0.6
T4aN1a	67.6	2.0	IIIB	IIIB	52.2	1.5
T3N1b	65.3	0.8	IIIB	IIIB	51.7	0.6
T1-2N2b	62.4	6.5	IIIC	**IIIB**	51.8	5.3
T4aN1b	54.0	1.9	IIIB	IIIB	42.1	1.5
T3N2a	53.4	1.0	IIIC	**IIIB**	42.8	0.8
T4aN2a[c]	40.9	2.1	IIIC	IIIC	32.5[c]	1.7
T3N2b	37.3	1.2	IIIC	IIIC	30.4	0.9
T4bN1a	38.5	2.2	IIIB	**IIIC**	30.6	1.8
T4bN1b	31.2	2.0	IIIB	**IIIC**	25.4	1.6
T4bN2a	23.3	2.1	IIIC	IIIC	18.3	1.6
T4aN2b	21.8	2.2	IIIC	IIIC	17.5	1.7
T4bN2b	15.7	1.9	IIIC	IIIC	12.9	1.5

Bold print and gray screen indicate change from AJCC 6th edition.

[a] T2N2a colon lesions did better than rectal T2N2a (both categories placed in stage IIIB).

[b] Change in substaging of stages II/III (bold type and gray-screened items) based on expanded outcomes in SEER data analyses.

[c] T4aN2a colon lesions did worse than rectal T4aN2a (both categories placed in Stage IIIC).

Changes in text: pg 4 lines 17-19.

Despite advances in adjuvant therapy, the observed 5 year overall survival in patients with stage III disease range from 12.9- 73.7 percent (2) depending on tumor and nodal pathologic features, with average survival of 71.8% (2–5).

Comment 3: *Background is long and detailed. I wonder if some of the mechanism text could be summarized more succinctly.*

Reply: Thank you for the feedback. As suggested we have shortened this section by removing the below text.

Changes in the text: removed page 5- lines 23, 24, page 6 lines 1-3 and lines 5,6

Removed: Elevated levels of glucose, insulin and c-peptide have been associated with increased risk of colon cancer (6,10,14,20). Increased levels of IGF-I and IGF-II are associated with increased risk of colorectal cancer (14–18,21), while decreased levels of IGFBP-1 and to a lesser extent IGFBP-2 have been shown to inversely affect the risk of colorectal cancer (14,21)…. Removed phrase: “various cancers including”

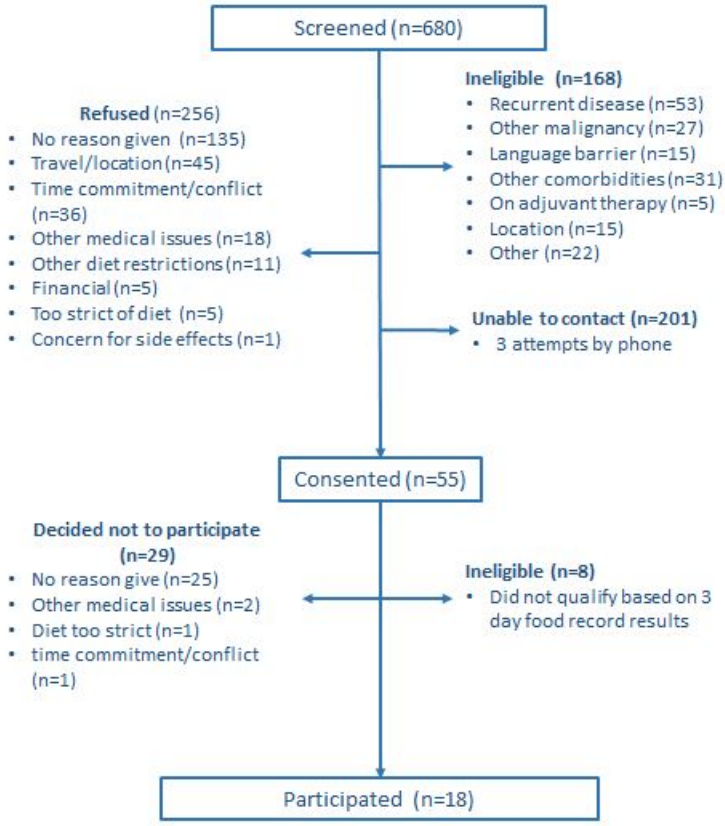
Comment 4: *I see in the figure that there were language and treatment criteria when determining eligibility. Please add to text when you describe eligibility criteria.*

Reply: The text lists inclusion criteria for eligible patients and the information in the figure references the same criteria through exclusion criteria.

Text:

Eligible patients were 18 years or older, with a history of stage I-III colon or rectal cancer who had undergone definitive therapy (surgery with or without chemotherapy and/or radiation therapy) and regularly consumed a diet with a daily glycemic load (using white bread reference) >150, as estimated through a 3 day self-reported food record.

Figure:



A participant was not eligible if they had:

Recurrent/metastatic disease: as this is not stage I-III disease

Other malignancy: not colon or rectal cancer. On review of tumor registry, tumors were included in the registry by mistake and were in fact a different histologies such as neuroendocrine carcinoma.

On adjuvant therapy: they were not done with definitive therapy

Language barrier: non-English speaking.

Location: they were included in tumor registry as surgery done at one of the participating hospitals but the person in fact lived hours away from site or for some came from a different state and could not participate in in-person visits.

Other comorbidities: which would limit their ability to travel and "be readily able to participate in study over 3 month time period" that was actually an eligibility criteria in the study protocol, which I added to text below. This was subjective on review of patient chart and/or discovered on calling to discuss the study, the caller would find a participant not living independently, able to care for self or consent in some situations. If this is felt to be too subjective these can be removed from the number and figure of those screened.

Changes in the text: Page 7, lines 5-10; added English speaking and last sentence.

Eligible patients were 18 years or older, English speaking, with a history of stage I-III colon or rectal cancer who had undergone definitive therapy (surgery with or without chemotherapy and/or radiation therapy), and regularly consumed a diet with a daily glycemic load (using white bread reference) >150, as estimated through a 3 day self-reported food record. They also needed to be readily available for a 3 month period and agreeable to participate in regular dietary adherence assessments.

Comment 5: *A flow chart in the supplemental material showing the planned 2 stage study design would be of interest. This is a really interesting concept and could be useful for other studies to consider.*

Reply: Thank you for your interest in the study design, the schema is in the protocol, which highlights to the 2 stage design, and has been included as part of the supplemental material. It is also described in detail in the statistical analysis of protocol.

Changes in text: Page 8. Line 8. Each cohort was intended to follow a 2 stage study design with early termination of a cohort if the primary endpoint of feasibility was not met, and plan to close once the feasibility endpoint was met (Schema and flow chart included in supplemental material).

Comment 6: *What was the rationale for obtaining non-consecutive days for the screening 3 day diet record? Did the potential participants choose which 3 days to record? Was this screening tool a barrier to enrollment?*

Reply: The 3 day food record is a validated dietary assessment tool, routinely used to assess intake and considered the optimal amount of time for estimation of macronutrients. Three non-consecutive days were used because individual intake can vary day-to-day, and dietary intake and glycemic load was averaged over that 3 day period. In order to minimize common errors with self-reported dietary recall, such as under-reporting, detailed oral and written instructions were reviewed with the participants by a dietician and they were instructed on how to choose the days, which included 1 weekend day. All food and beverage entries were reviewed with the participant for clarity and portion sizes. A strength of the tool is it does not rely on long term memory and is readily available to record intake real time. We do

not believe the tool was a barrier to enrollment as patients seemed to base their decision to participate on the logistics of the study time period itself and daily logistics related to that. We felt use of this tool was essential to get an accurate representation of a participants average daily glycemic load.

Changes to text: see page 9, lines 11-21.

Changed line 19, added: including instruction on how to choose the days.

Comment 7: *Did participants get to choose whether they had a 1 –on- 1 session with dietitian at the first meeting vs group? For groups, was it whoever was enrolled at that time or was there any effort to make the groups homogeneous with regards to participant age, stage of disease, time since diagnosis, gender or race?*

Reply: Participants did not get to choose the number in their group. We attempted to get 3 participants in a group, which was the case for all groups, except for 1. There was 1 group of 4. Only 1 participant who had 1 on 1 sessions with the dietician, which was due to slow enrollment at the site, the nutritionist's ability to accommodate the sessions, and the participants plan to live in another state for the winter months, and desire to complete the study prior leaving. The nutritionist would sometimes accommodate individual sessions for participants in the groups of 3-4 if there was personal conflict with a day or time, but in general the groups of 3-4 met together. There was no attempt to make the groups homogeneous. Groups were based on when participants were approached/enrolled and a group of at least 3 reached.

Changes in text: Added: pg 10 line 5-7: Participants did not get to choose their group size, and group participants were random based on the timing of their enrollment. It was attempted to get at least 3 participants in a group.

Comment 8: *Were the survey data collected using paper, by phone or electronically.*

Reply: The 3 day food record, baseline patient information, food acceptability survey, program improvement survey were paper forms that the patients filled out. The data for the 24 hour recalls were a combination of phone and in-person questions completed by the nutritionist.

Changes in text:

Page 10 line 19: added text: which the dietitian reviewed in-person and by phone

page 11, lines 9-10; added text: It was a self-administered, paper survey.

Page 11, lines 12: added text: self-administered paper survey.

Comment 9: *Why did the 1 patient withdraw?*

Reply: she was an emergency room nurse and due to work and family obligations (she became the primary caregiver of a grandchild) she was not able to accommodate the study schedule.

Changes in text: none.

Comment 10: *How did you calculate the dietician's time for group visits? Was the same amount of time considered for each participant or did you divide by the number of the people in session?*

Reply: The dietician recorded the time spent at each in-person/group visit and phone visit. For the group visits the same amount of time was considered for each participant in a particular group. We provided the average for each in- person group session (initial and subsequent); the nutritionist spent an average of 60-90 minutes on the initial session and 30-60 min on subsequent sessions, which varied slightly per group.

Changes in text: added: page 13, lines 14-15: The dietician recorded the time spent at each in-person and phone session and this was averaged for each participant.

Comment 11: *I am not sure about the somewhat arbitrary cut –point for defining compliance and then comparing outcomes in those who complied and those who did not. Can you examine whether change in mean GL, adjusting for baseline GL was associated with weight change and or biomarker levels?*

Reply: We appreciate the inquiry. The definition of compliance was determined a priori and defined based upon expert consensus of the study team. We concluded that a participant being able to follow the diet ~ 75% of time over the 12 week study period represented compliance with the diet. The primary predefined outcome of our study was compliance as this was a feasibility study and our primary purpose was to determine if colorectal cancer patients were able to follow the diet. The other outcomes such as changes in physical parameters and the potential biomarkers were all predefined exploratory endpoints, which we reported on what we felt was meaningful, but otherwise feel this is too small of a sample to pursue that level of analysis.

Changes in text: none