RESEARCH ARTICLE

Telomere length as a prognostic marker in colorectal cancer: a scoping review [version 1; peer review: 2 approved with reservations]

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Abstract

Background: Telomeres are protective structures at both ends of a chromosome, which consist of repetitive DNA sequences (TTAGGG). Maintenance of telomere length is known to have important roles in carcinogenesis. However, there is no consensus about the prognostic role of telomere length in colorectal cancer.

Methods: We conducted a scoping review using Pubmed and EMBASE as information sources through April 2019. Inclusion criteria were studies investigating telomere length and prognosis of colorectal cancer. Selected studies were reviewed to reevaluate the significance of telomere length in the prognosis of colorectal cancer. The aim of the study was to summarize the previous studies, to find consistent results, and to suggest future research.

Results: In total, 12 studies were identified and 1955 patients were included from 2004 to 2019. Among 10 studies with tissue samples, two studies revealed better prognosis in patients with longer telomere length, and only stage IV patients were recruited in these two studies; four studies revealed better prognosis in patients with shorter telomere length or lower ratio of telomere length between cancer and normal tissue; four studies did not show any significant association between tumor length and prognosis. Two studies with blood samples presented contradictory results regarding the correlation between telomere length and survival rate.

Conclusions: There was no consistent evidence to prove the prognostic value of telomere length in colorectal cancer. However, in a subgroup with the metastatic disease only, longer telomere length of tumor tissue was significantly associated with superior prognosis. Multicenter prospective studies with a large sample size are needed to verify the prognostic value of telomere length in colorectal cancer.

Keywords

Telomere length, colorectal cancer, prognosis, biomarkers

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide. Estimated number of newly diagnosed CRCs is 1,849,518 in 2018, according to the [World Health Organization GLOBOCAN database](#). Moreover, CRC is the second-leading cause of cancer mortality worldwide. The number of deaths from CRC in 2018 is 880,792 according to the [GLOBOCAN database](#). Clinical outcomes of CRC have been improved because of the introduction of regular screening, the advancement of surgical skills, and development of neoadjuvant therapy and adjuvant therapy¹. However, the prognosis of stage IV CRC is poor, with fewer than 15% of patients surviving for 5 years². Nowadays, personalized treatment is considered as a new strategy to improve clinical outcomes and effort is being made to explore appropriate biomarkers to identify patients who would respond to certain therapies¹.

Although numerous biomarkers have been studied in laboratories so far, only a couple of them are currently being used in practice. Telomere length might be considered as a potential biomarker to predict prognosis of CRC¹. However, a limited amount of research has been conducted so far and there is a lack of solid evidence to support its prognostic role consistently³.

Telomeres are protective structures at both ends of a chromosome. They consist of repetitive DNA sequences (TTAGGG) with associated proteins, and they protect the genome from degradation, recombination, and fusion⁴. Telomeres shorten with each cell division by loss of DNA termini, and finally, cells undergo senescence or apoptosis following activation of the DNA damage response, when telomeres become too short to protect chromosome ends after repeated cell divisions. However, cancer cells overcome senescence or apoptosis and acquire immortality by maintaining telomere length. There are two mechanisms for telomere maintenance: 1) transcriptional activation of telomerase and 2) activation of alternative lengthening of telomeres (ALT). Telomerase is expressed in 85–95% of all cancer cells and the ALT pathway is activated in 5–15%⁵.

Maintenance of telomere length is considered to have important roles in carcinogenesis and researchers studies about the role of telomere length as a prognostic marker in CRC. However, conflicting results have been published and there is currently no consensus. Thus, this study aimed to review all the published studies including the newest one and to evaluate the significance of telomere length as a prognostic marker for CRC.

Methods

Search strategy

Pubmed and Embase were systemically searched to identify studies investigating telomere length and CRC prognosis in adherence with the Preferred Reporting Items for Systematic review and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist⁶. MeSH terms including “telomere”, “colorectal neoplasms”, “colonic neoplasms”, and “rectal neoplasms” were used for Pubmed search. Emtree terms including “telomere length”, “colorectal cancer”, “colon cancer”, and “rectum cancer” were used for Embase search. Studies were

selected for review if they met all of the following criteria: 1) human CRC cancer patients were included; 2) telomere length from a tissue sample or from blood sample was measured; 3) clinical outcomes were reported as survival rate or disease relapse. The latest search was performed on April 22, 2019. No date limits were imposed and there was no language limitation.

Review of studies

Two researchers (G.K. and K.Y.L.) reviewed all included studies and extracted the following data independently: author, year, country, origin of samples, cancer site, sample size, mean (or median) age of involved patients, tumor stage, assay or detection method for telomere length, follow up period, and survival outcome. A pilot test for three articles to check the data extraction form and to ensure consistency was performed before data extraction.

A detailed review protocol is available as *Extended data*⁷.

Results

Studies identified

In total, 533 studies were initially screened from Pubmed database and 815 studies were screened from Embase. Among 1,348 studies, 1,336 studies were excluded and 12 studies were finally identified to report the association between telomere length and prognosis of CRC between 2004 and 2019. The included cases from 12 studies were 1,955. Of these studies, ten measured telomere length from tissue samples ([Table 1](#)) and two measured telomere length from peripheral leukocytes ([Table 2](#)). There were seven studies from Europe, three from Asia, one from the USA, and one from Australia.

Studies finding associations between telomere length and CRC prognosis

In brief, the results from 12 studies are contradictory. First, two of ten studies analyzing tissue samples showed better prognosis of patients with longer telomere length, especially in patients with metastasis^{8,9}.

Balc'h *et al.* measured telomere length from 125 CRC tissue samples⁸. A significant shortening of telomere length in the tumor tissue compared with the normal tissue was observed. They reported that the overall survival rate was significantly correlated with telomere length in metastatic disease ($n=28$, $p=0.03$). In metastatic disease, patients with longer telomeres survived longer than those with shortened telomeres. However, there was no statistically significant difference in overall survival rate between the maintained telomere length group and shortened telomere length group when analyzing localized disease group ($n=97$) or the entire group ($n=125$). In addition, they observed that telomere length was significantly associated with the occurrence of mutation in KRAS. They found that the shorter the telomeres in healthy tissue were, the longer the telomeres in tumor tissue were. They suggested that telomere length in healthy normal tissue might influence telomere maintenance mechanisms in a tumor.

Augustine *et al.* measured telomere length from 75 CRC tissue samples and explored the efficacy of telomere length as a predictor

Table 1. Summary of studies analyzing the prognosis of CRC by measuring telomere length in tissue samples (n=10).

Author	Year	Country	Sample origin	Cancer site	Sample size (n)	Mean/median age (years)	Tumor stage	Assay/detection method	Follow up period (months)	Outcome	Result
Balc'h <i>et al.</i> ⁸	2017	France	Tissue	Right colon 50 (40%), left colon 70 (56%), rectum 5 (4%)	125	Mean 72	I-IV	Southern blot	103	OS	Longer TL, better prognosis (in metastatic disease)
Augustine <i>et al.</i> ⁹	2015	USA	Tissue	Colon 55 (73%), rectum 20 (27%)	75	Median 60	IV	qPCR	Not reported	DFS	Longer TL, better prognosis (in metastatic disease)
Fernández-Marcelo <i>et al.</i> ¹⁰	2016	Spain	Tissue	Right colon 34 (26%), left colon 30 (23%), rectum 61 (46%), unspecified 7 (5%)	132	Median 71	Dukes stage A-D	qPCR	Median 60	DFS	Shorter TL, better prognosis; lower TL ratio, better prognosis
Valls <i>et al.</i> ¹¹	2011	Spain	Tissue	Colon 85 (58%), rectum 62 (42%)	147	Not reported	I-IV	Southern blot	Mean 45	OS	Lower TL ratio, better prognosis
García-Aranda <i>et al.</i> ¹²	2006	Spain	Tissue	Right colon 23 (25%), left colon 13 (14%), rectum 55 (60%)	91	Average 68.60	Dukes stage A-D	Southern blot	Median 43.86	DFS	Lower TL ratio, better prognosis
Getler <i>et al.</i> ¹³	2004	Germany	Tissue	Colon 27 (47%), rectum 30 (53%)	57	Mean 64.6	I-IV	Southern blot	Median 75.5	OS	Lower TL ratio, better prognosis
Bae <i>et al.</i> ¹⁴	2019	Korea	Tissue	Not reported	60	Not reported	I-IV	qPCR	Median 80	OS, DFS	No association between TL and prognosis
Suraweera <i>et al.</i> ¹⁵	2016	Australia	Tissue	Right colon 195 (47%), left colon 142 (34%), rectum 82 (20%)	419	Median 70	I-IV	qPCR	Median 45.2 for OS; median 41.6 for PFS	OS, DFS	No association between TL and prognosis (only in stage II-III, n=246)
Lopez-Doriga <i>et al.</i> ¹⁶	2018	Spain	Tissue	Right colon 12 (29%), left colon 30 (71%)	42	Median 70	II	qPCR	36	Recurrence	No association between TL or TL ratio and prognosis
Kojima <i>et al.</i> ¹⁷	2011	Japan	Tissue	Colon 56 (53%), rectum 50 (47%)	106	Not reported	Dukes stage A-C	Southern blot	Mean 41	Non-specified survival	No association between TL and prognosis; Shorter 3'-OH, better prognosis

OS, overall survival rate; DFS, disease-free survival rate; TL, telomere length; TL ratio, ratio of telomere length between cancer and normal tissue.

Table 2. Summary of studies analyzing the prognosis of CRC by measuring telomere length in blood samples (n=2).

Author	Year	Country	Sample origin	Cancer site	Sample size	Mean/median age (years)	Tumor stage	Assay/detection method	Follow up period (months)	Outcome	Result
Chen <i>et al.</i> ¹⁸	2014	China	Peripheral leukocytes	Colon 266 (47%), rectum 305 (53%)	571	Median 60	I-IV	qPCR	Median 28	OS, DFS	Longer TL, better prognosis
Svenson <i>et al.</i> ¹⁹	2016	Sweden	Peripheral leukocytes	Right colon 42 (32%), left colon 44 (34%), rectum 44 (34%)	130	Mean 70	I-IV	qPCR	Median 202	OS	Shorter TL, better prognosis

OS, overall survival rate; DFS, disease-free survival rate; TL, telomere length.

for response to anti-TGFR therapy in metastatic disease⁹. They first measured telomere length in 21 human-derived CRC cell lines. When the cell lines were treated with cetuximab, a monoclonal antibody to EGFR, growth of cell lines with a longer telomere length was inhibited to a significantly larger degree than cell lines with a shorter telomere length ($p=0.02$). When the analysis was limited to K-ras wild-type cell lines only, growth of cells with a longer telomere length was more inhibited by cetuximab treatment compared with cells with a shorter telomere length ($p=0.04$), which was similar to above. Next, they analyzed telomere length in patients' tumor samples. In the analysis of all human CRC samples, progression-free survival after anti-EGFR therapy was significantly longer in patients with longer telomere length compared with that of patients with shorter telomere length ($n=75$, $p=0.026$). Furthermore, when the analysis was narrowed down to the patients with K-ras wild-type tumors only, again, patients with longer telomere length showed longer progression-free survival than patients with shorter telomere length ($n=43$, $p=0.012$). The authors suggested that telomere length could play a role as a marker for predicting the benefit of anti-EGFR treatment in metastatic CRC.

The two aforementioned studies suggested the telomere length as a prognostic marker in metastatic CRC^{8,9}. The longer the telomere, the better the prognosis was. On the contrary, the next four studies among the ten to examine tissue samples showed better prognosis of patients with shorter telomere length^{10–13}.

Fernández-Marcelo *et al.* analyzed 132 CRC tissue samples and corresponding noncancerous normal tissue samples, and measured telomere length, a ratio of telomere length in cancer to normal tissue (TL ratio), and telomerase activity¹⁰. Patients with shorter telomere length showed a significantly longer disease-free survival compared with those with longer telomere length ($p<0.001$). Moreover, patients with the lowest TL ratio never experienced recurrence during the follow-up period (median 60 months, $p=0.043$). Cox multivariate analysis also showed that mean telomere length was an independent prognostic factor for disease-free survival ($p=0.017$). The authors suggested the use of telomere status as an independent prognostic factor.

Valls *et al.* analyzed 147 CRC tissue samples and paired normal tissue samples. The authors measured the telomere length of the samples and calculated the TL ratio, which is defined as a ratio of telomere length in cancer to normal tissue¹¹. Univariate analysis and multivariate Cox regression analysis both showed a significant relationship between TL ratio and overall survival rate. Patients with lower TL ratios exhibited a significantly longer overall survival rate ($n=125$, $p=0.014$). The TL ratio was an independent prognostic factor for overall survival in CRC. However, there was no significant correlation between TL ratio and the disease-free survival rate.

García-Aranda *et al.* explored 91 CRC tissue samples¹². They measured telomere length in CRC tissue samples and paired normal tissue samples. They also accessed telomerase activity and expression level of telomeric repeat-binding factor (TRF1), which is one of six subunits of the shelterin complex. Patients

with longer telomeres showed a significantly shorter disease-free survival rate ($p=0.02$). Cox regression analysis also proved that telomere length was an independent prognostic factor ($p=0.04$). In patients with Dukes stage C tumors, both longer telomere length and higher TL ratio were significantly associated with shorter disease-free survival rate ($p=0.03$ and $p=0.04$, respectively). Additionally, patients with shortened telomeres expressed higher TRF1 levels than patients without telomere shortening. Furthermore, among patients with telomerase-positive tumors, lower TL ratio and TRF1 over-expression was associated with longer disease-free survival ($p=0.03$ and $p=0.05$, respectively).

Getler *et al.* analyzed telomere length and hTERT expression in 57 CRC tissue samples and adjacent normal tissue samples¹³. Patients with longer TL ratio showed a significantly shorter overall survival rate compared with patients with shorter TL ratio ($p<0.002$). In multivariate Cox regression analysis, TL ratio was an independent prognostic factor; longer TL ratio predicted shorter overall survival ($p<0.03$). Additionally, telomere length and hTERT expression correlated significantly in cancer tissues and normal tissues ($p<0.001$ and $p<0.001$, respectively), and telomere length was shorter in cancer tissue compared with normal mucosa ($p<0.001$). The authors suggested that hTERT-mediated telomere stabilization might play a role in the progression and prognosis of CRC.

Studies finding no association between telomere length and CRC prognosis

The following four studies did not prove an association between telomere length and prognosis of CRC^{14,15–17}. Bae *et al.* analyzed telomere length in 60 CRC tissue samples and corresponding nonmalignant normal tissue samples¹⁴. In the survival analysis, there was no association between telomere length and overall survival rate or disease-free survival rate. They also evaluated the expression level of telomeric repeat-containing RNA (TERRA) in cancer tissue and normal tissue. TERRA refers to a class of long noncoding RNAs which forms an integral component of telomeric heterochromatin²⁰. TERRA is also known to regulate telomere length and telomerase activity²¹. The analysis showed a significant association between TERRA expression and telomere length ($p<0.05$). However, it did not prove any statistical significance of TERRA as a prognostic factor for overall survival or disease-free survival although there was a tendency that survival was better in TERRA high group.

Suraweera *et al.* analyzed telomere length in 419 CRC tissues and adjacent normal tissues¹⁵. Telomere length was significantly shorter in cancer tissues than in normal tissues ($p<0.001$). Survival analysis was performed only in stage II and III CRC ($n=281$). There was no significant association between overall survival ($n=281$) or disease-free survival ($n=246$) and tumor length or TL ratio.

Lopez-Doriga *et al.* analyzed telomere length in cancer tissues and adjacent normal tissues from 42 patients with stage II colon cancer¹⁶. Significant shortening of telomere length was identified in cancer tissues as compared to their adjacent normal tissues ($p<0.01$). No significant relationship was observed between the recurrence rate and telomere length or TL ratio.

Kojima *et al.* measured telomere length, length of telomere 3'-overhang (3'-OH) and telomerase activity from 106 CRC tissue samples and corresponding noncancerous normal mucosa¹⁷. There was no significant association between telomere length and prognosis. However, patients with shortened 3'-OH showed a significantly increased survival rate compared with those without 3'-OH shortening among patients with telomerase-activated cancers, ($p=0.018$). Additionally, expression levels of telomere binding proteins (TBPs) were analyzed in cancer samples and normal mucosa samples. The analysis revealed all TBPs, except for protection of telomeres 1 (POT1), which is one of six subunits of the shelterin complex, were downregulated in cancers. In the telomerase-activated cancers, there was a significant correlation between the length of 3'-OH and expression level of POT1. The authors suggested that elongation of telomeric 3'-OH could increase malignant potential in CRC and that might be regulated by POT1.

Telomere length in peripheral leukocytes and CRC prognosis

Lastly, there were two studies analyzing telomere length in peripheral leukocytes from CRC patients^{18,19}. The two studies presented conflicting results. Chet *et al.* analyzed telomere length of peripheral leukocytes from 571 CRC patients, who were followed up for 28 months¹⁸. Patients with longer telomere length presented significantly longer overall survival and longer disease-free survival ($p<0.001$ and $p<0.001$).

Svenson *et al.* analyzed 130 blood samples of CRC patients and followed up the patients for 202 months¹⁹. On the contrary to the previous study, patients with shorter telomere length showed significantly longer overall survival ($p=0.030$).

Discussion

This study reviewed the data of 1,955 CRC patients from 12 publications. Survival outcome according to the telomere length was the primary endpoint. Before this study, there were two review articles to evaluate the prognostic value of telomere length for CRC^{22,23}. All the literature analyzed by these two articles was included for review in our study.

In 2016, Jia *et al.* reviewed five studies and performed meta-analysis²². Among the five studies initially included in the review, two studies were excluded because Chen's study used blood samples to measure telomere length¹⁸ and Kojima's study did not report hazard ratios and 95% confidence intervals¹⁷. Thus, only three studies with 279 patients were meta-analyzed finally. The result was that longer telomere length was significantly associated with poorer overall survival ($HR=2.70$, 95% 1.51 to 4.84, $p=0.001$) and the authors concluded that some evidence exists for telomere length as a prognostic factor for overall survival in CRC.

In 2017, Wang *et al.* reviewed eight studies and performed a meta-analysis to investigate the association between telomere length and prognosis of CRC²³. Two of the studies used blood samples as materials^{18,19}, unlike the others which used tissue samples; however, the pooled analysis included all the eight studies. As a result, there was no significant association between telomere length and survival for CRC patients.

Although Jia *et al.* concluded telomere length had a prognostic value for overall survival in CRC patients, only three studies were included in the meta-analysis and consequently, high risk of bias could not be avoided. And their study did not assess the association between telomere length and disease-free survival²². Following Jia's study, Wang *et al.* performed meta-analysis with eight studies only to fail to prove any association between telomere length and survival outcome²³.

Therefore, there has been no solid evidence to confirm the role of telomere length as a prognostic marker in CRC so far. Three more studies were published after Wang's study and we planned a new literature review to reevaluate the significance of telomere length in CRC. The aim of our study was to summarize the results of previous studies; to find consistency from the previous studies; to aid further research by analyzing the strengths and weaknesses of the previous studies.

In our review, as summarized in Table 1 and Table 2, the studies were categorized according to the sample material. The majority of the included studies used cancer specimen for measuring telomere length and two studies used blood sample of patients. In the first category with tissue samples, the results varied. Two studies revealed better prognosis in patients with longer telomere length, and only stage IV patients were recruited in these two studies^{8,9}; four studies revealed better prognosis in patients with shorter telomere length or lower TL ratio^{10–13}; four studies did not show any significant association between tumor length and prognosis^{14,15–17}. In the next category with blood samples, two studies presented contradictory results regarding the correlation between telomere length and survival rate^{18,19}.

In conclusion, we found no consistency in the literature. There was no consistent evidence to prove the prognostic value of telomere length in colorectal cancer. However, in a subgroup with the metastatic disease only, longer telomere length of tumor tissue was significantly associated with superior prognosis.

More evidence is needed to support the significance of telomere length in the prognosis of CRC. To avoid the risk of bias, multicenter prospective studies with a large number of patients are warranted. Additionally, presenting data as being categorized by certain clinical characteristics such as TNM stages, tumor locations, or genders is encouraged to facilitate subgroup analyses. And finally, providing original data with statistics could be a support for future research even if study results are insignificant or discouraging.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Figshare: review protocol.docx. <https://doi.org/10.6084/m9.figshare.8075207.v17>.

Extended data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

Reporting guidelines

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Rajiv Kumar

Germany Cancer Research Center, Helmholtz Association, Heidelberg, Germany

The study described in the manuscript is based on data available for association between telomere-length and the disease prognosis in patients with colorectal cancer. The data presented are curated from published studies on the topic.

General comments:

The idea of the study is to ascertain whether telomere length can be a biomarker of the disease outcome in colorectal cancer. The studies reviewed include those that have measured telomere length in tumor tissues, tumor tissues/adjacent normal tissues or in peripheral leukocytes. The methodology used in the studies included ranged from qPCR to Southern blotting. And outcomes in those studies, not surprisingly, are not concordant. The reasons for that are multi-fold. One of the prime reasons can be the lack of enough statistical power, which hampers many such studies. The other reasons could be methodological or quality of tissues screened. All those issues should be part of consideration for the discussion in this study.

Suggestions:

I think in a study of this scope, it is important to provide a context for the potential of telomeres as biomarkers of cancer risk and as outcome predictors. There have been several studies, which have shown association of leukocyte telomere length with increased risk of several cancers¹. In a majority of cancers, the increased risk has been associated with longer telomeres and in some cancers with shorter telomeres^{1,2}. And many later studies have used Mendelian randomization to provide genetic basis for such association as barring some exogenous factors, the telomere length is genetically determined^{1,3}. Similarly, several studies have shown that shorter leukocyte telomeres associate with poor outcome in different cancers⁴. It will give the paper an overall uplift and provide readers the necessary context. And accordingly, the results can be discussed within that context and provide a space to highlight the shortcomings in the studies included in the analysis.

It is also pertinent to discuss the methodology. Most of the studies included in the analysis have used quantitative PCR that actually measures a ratio between telomere content and the albumin

gene content in a given DNA sample⁵. That method itself has several versions that could impact the results. Two studies have used Southern blot that actually gives the measure of telomere length in kilo-bases.

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cancer genetics with specific interest in genetics of telomerases and telomeres.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 07 October 2019

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The study aims to summarize the evidence regarding the role of telomere length as a prognostic biomarker in colorectal cancer. It is a systematic, non-quantitative review of the literature, that concludes that there is inconsistent evidence regarding the utility of this biomarker for predicting survival. The paper provides very helpful summary tables, describing pertinent clinical information about the patients included in individual studies, along with the methods used to measure telomere length or ratio. Below are some comments that we think could strengthen this manuscript and the discussion regarding these biomarkers.

General comments

At least three biomarkers are reviewed: 1) tumor telomere *absolute length*, 2) tumor vs non-tumor telomere length *ratio* and 3) peripheral leukocyte absolute telomere *length*. Age-adjustment and additional variables (e.g. telomere 3'-overhang) are also included in some of the studies reviewed. Although correlations between these metrics may exist ¹, we think each one should be discussed and evaluated separately, unless evidence to justify their grouping is presented.

The review concludes that "multicenter prospective studies with large numbers of participants are warranted". Such studies may be warranted if these biomarkers showed consistent or aggregated independent prognostic value; had been suggested to improve current clinical prognostication methods (e.g. the Immunoscore) or have therapeutic relevance (e.g. MSI); and could be prospectively measured and interpreted (e.g. values can be prospectively classified as good or poor prognosis). The data presented does not seem to suggest that any of the three main telomere-related biomarkers meet these criteria.

It would also be helpful to briefly discuss why a quantitative meta-analysis of the different telomere-related biomarkers was not performed. It seems like the heterogeneity of the studies would not lend itself well to such an analysis, and could lead to inaccurate conclusions; this is worthwhile mentioning.

Introduction

The introduction could benefit from discussion of telomere length across the spectrum of colon

pre-malignancy to metastatic disease^{2,3}. It would also be helpful to briefly summarize the data regarding the association between telomere length and other prognostic and molecular features of colorectal cancer (e.g. stage, MSI status, sidedness, *KRAS/BRAF*), as well as how these associations may impact the independent prognostic value of telomere length. For example, shorter telomere length has been associated with early-stage tumors, right-sided tumors and microsatellite unstable (MSI-H) tumors in some studies^{2,3}.

Minor comment: references 1 and 2 do not seem to be supporting the sentences preceding them. 1 is referring to improved outcomes in CRC but the reference is about telomeres and 2 is regarding outcomes in stage IV disease but the reference is about genetic alterations.

Methods

Minor comment: if the authors update their publication, they could consider including another paper that has since been published².

Results

The study by Suraweera *et al.* is the largest study in the review, and seemingly the most comprehensive and rigorous. It would be helpful to discuss this study more in detail, including its use of age-adjusted variables.

It is worth noting that Lopez-Doriga *et al.* did not directly measure telomere length. Rather, their length and ratio estimates are based on whole-exome sequencing data in MSS tumors. They found an association with somatic mutation rate and with gene expression of several immune-related pathways that is also worth noting⁴.

Minor comment: the PRISMA flow diagram⁵ or a slightly more detailed description of the study inclusion/exclusion process would be helpful to include. It would be unusual to have 1,348 unique studies with no overlap between PubMed and Embase, for example.

Minor comment: there is a typo mentioning anti-TGFR instead of anti-EGFR.

Discussion

Focusing the discussion on the current literature review, its limitations and the reliability of the results may be more informative than an extensive discussion of previous meta-analyses (these could be briefly summarized).

The authors note that Wang *et al.* included very different (tumor and blood-based) studies in their meta-analysis. As mentioned above, unless the authors provide evidence to the contrary, these should likely not be grouped together and thus the conclusions in the paper by Wang *et al.* seem to not be applicable. The following sentences in the discussion do not seem to reflect this major limitation of the meta-analysis of Wang *et al.*: "As a result, there was no significant association between telomere length and survival for CRC patients." and "Wang *et al.* performed meta-analysis with eight studies only to fail to prove any association between telomere length and survival outcome".

It would be helpful to discuss the associations between telomere length and clinical/molecular characteristics found in several studies, and how these can potentially confound the study of telomeres as prognostic biomarkers. Given the importance of the immune response to colorectal cancer in predicting survival⁶⁻⁸, it may be worthwhile to summarize any data regarding the relationship between telomere length and the immune response to colorectal cancer.

If possible, it would be helpful to suggest which of the telomere-related biomarkers is the best candidate for further studies (based on CRC studies or studies in other cancers). If none of the markers is preferable, we would mention that as one of the challenges in validating the role of telomere-related biomarkers.

The conclusion regarding patients with metastatic disease (in the discussion and abstract) is based on a subgroup analysis of 28 patients in the study by Balci *et al.* and another study where all patients were treated with anti-EGFR therapy. We would be hesitant to draw such a strong conclusion based on these data.

Minor comment: The sentence "This study reviewed the data of 1,955 CRC patients from 12 publications" may be misinterpreted as having performed a patient-level analysis as opposed to aggregated data analysis.

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Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Molecular epidemiology of colorectal cancer; colorectal cancer and premalignant tumor immunology; hereditary colorectal cancer

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

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