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Impact of geography on prognostic outcomes of 21,509 patients with metastatic colorectal cancer enrolled in clinical trials: an ARCAD database analysis

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Abstract

Background: Benchmarking international cancer survival differences is necessary to evaluate and improve healthcare systems. Our aim was to assess the potential regional differences in outcomes among patients with metastatic colorectal cancer (mCRC) participating in international randomized clinical trials (RCTs).

Design: Countries were grouped into 11 regions according to the World Health Organization and the EUROCARE model. Meta-analyses based on individual patient data were used to synthesize data across studies and regions and to conduct comparisons for outcomes in a two-stage random-effects model after adjusting for age, sex, performance status, and time period. We used mCRC patients enrolled in the first-line RCTs from the ARCAD database, which provided enrolling country information. There were 21,509 patients in 27 RCTs included across the 11 regions.

Results: Main outcomes were overall survival (OS) and progression-free survival (PFS). Compared with other regions, patients from the United Kingdom (UK) and Ireland were proportionaly over-represented, older, with higher performance status, more frequently male, and more commonly not treated with biological therapies. Cohorts from central Europe and the United States (USA) had significantly longer OS compared with those from UK and Ireland ($p = 0.0034$ and $p < 0.001$, respectively), with median difference of 3–4 months. The survival deficits in the UK and Ireland cohorts were, at most, 15% at 1 year. No evidence of a regional disparity was observed for PFS. Among those treated without biological therapies, patients from the UK and Ireland had shorter OS than central Europe patients ($p < 0.001$).

Conclusions: Significant international disparities in the OS of cohorts of mCRC patients enrolled in RCTs were found. Survival of mCRC patients included in RCTs was consistently lower in the UK and Ireland regions than in central Europe, southern Europe, and the USA, potentially attributed to greater overall population representation, delayed diagnosis, and reduced availability of therapies.

Keywords: cancer survival, colorectal cancer, country, healthcare system, meta-analysis, randomized trial

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Introduction

Healthcare systems vary significantly across the world and have a major impact upon disease burden and outcomes.[1,2] Colorectal, lung, breast, and prostate cancers account for 18–50% of the total cancer burden and, not surprisingly, patients treated in countries with a high deprivation index, in which healthcare systems are less well developed, appear to have worse outcomes.[1,3] Benchmarking of regional or national systems allows healthcare providers and policy makers to critically appraise outcomes in order to understand trends, and potentially to intervene and improve the provision of healthcare, especially patient treatment, locoregionally.[4]

Evaluation may focus upon specific areas relevant to the providers, i.e. regional variations seen within a country, in which nominally the systems are similar [e.g. the United Kingdom (UK)] or on socioeconomic factors that significantly influence healthcare systems within a country [e.g. the United States (USA)].[5] The EUROCARE model exemplifies a system attempting to compare a large number of countries based upon registry data, publishing a fifth edition (EUROCARE-5) in 2014. This comprehensive report examined data from more than 10 million patients from 107 population-based registries from 29 countries grouped into five regions (EUROCARE-5).[6] While such data identify an overall summary, distilling the components that impact upon survival as an outcome is critically important when revisions to national healthcare systems are being considered. For this to be most effective, we needed to explore the outcomes in cancer subpopulations and treatment modalities that affect survival.[7] Several studies (EUROCARE, CONCORD) have shown disparities in the survival of colorectal cancer patients according to where they reside in different regions of the world. The observed cancer survival deficit in the UK has been attributed to a higher number of excess deaths occurring among older patients in the first 3 months after diagnosis, which is hypothesized to relate to a slower speed of cancer diagnosis, which leads to shorter survival after diagnosis.[8,9] Several other population-based studies have attempted to define potential variations in the patient management that could possibly account for apparent differences in cancer survival across countries. In a recent population study based on three cancer registries from France and one from England, the observed poorer survival among patients diagnosed with colorectal cancer in England was largely attributed to a larger proportion dying during the first year after diagnosis.[11] The authors further noted large variations in treatment modalities within 6 months of diagnosis, such as surgical resections, which were performed more frequently in France. Gatta *et al.*[12] observed how large variations in management were observed across European countries, with a large proportion of patients not receiving treatment in accordance with guidelines based upon published clinical trials.

Apart from management issues, several other factors have been proposed to account for the observed country-by-country differences in survival. Many factors have been suggested to explain these differences, such as the differences in cancer registration modalities (including whole-population representation), co-morbidities, stage of presentation, accessibility to state-of-the-art treatment, and quality of care. These variables are not usually captured in population-based studies, making it difficult to identify the causal factors responsible for the outcomes observed in those studies. Furthermore, most population-based studies looking at the question of country-based differences in cancer survival have done so prior to the introduction of biological agents in the treatment paradigm of patients with advanced colorectal cancer.

ARCAD is a pooled database of individual patient data from recent therapeutic trials in advanced colorectal cancer conducted worldwide. Using this database, we aimed to determine differences, if any, in prognostic outcome among patients with metastatic colorectal cancer (mCRC) diagnosed in different countries, and participating in international clinical trials, in the era of biological therapy.

Methods

Study population

Individual patient data from 21,509 patients enrolled in 27 first-line mCRC trials between 1997 and 2012 were included[13,15,22–46] (Supplemental Table 1). Collectively, 51 countries contributed participating patients. These countries were grouped into 11 regions (Supplemental Table 2), based on access to healthcare by the population and the sophistication of the healthcare systems. Specifically, we followed the categories determined by the EUROCARE consortium[6] to group

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the European countries into central Europe, northern Europe, Eastern Europe, southern Europe, and UK and Ireland, designated UK + Ireland for convenience (Supplemental Table 3). In Asia, countries were grouped into one group including countries other than China and Thailand, and the second group including China and Thailand. Kenya and South Africa were grouped together as Africa. Argentina, Brazil, Chile, Costa Rica, Guatemala, Mexico, and Panama were grouped as South America. Australia, New Zealand, and Canada were grouped as ANZC. The USA was evaluated as a separate entity because of its population size and geographic territory. Accrual to trials per 100,000 population is presented in Supplemental Table 4 as an estimate of inclusivity of patients in the trials. This was calculated by dividing the total accrual in this time period (15 years) by the summated population from the region in 2010, and therefore only offers a relative estimate. The following analyses were based on regions instead of countries.

Individual trials were approved through countries' mechanisms at the time trials were done. All patients provided written, informed consent at enrollment in the respective trials. The ARCAD database collaboration research protocol was approved by the Mayo Clinic Institution Review Board. Individual patient data of all trials were collected and the analyses were done at an independent statistical center at the Mayo Clinic, Rochester, MN, USA.

Statistical analyses

Patient characteristics were summarized descriptively within each region and statistically compared using chi-square tests for categorical variables and two sample *t*-tests for continuous variables. The majority of studies only enrolled patients from a subset of 51 countries (11 grouped regions). Hence, head-to-head comparisons between all regions within studies were not feasible, and the common pooled analysis by stratified Cox model is suboptimal. For example, only 1 out of 27 trials included both USA and UK + Ireland patients, which could be used to make a direct comparison between the 2 countries. Therefore, meta-analytic approaches were used to synthesize the evidence across studies and treatment groups in a two-stage model. In stage 1, overall survival (OS) and progression-free survival (PFS) estimates (median times and rates at 6, 12, or 24 months, as well as associated sandard deviations) per region in each treatment arm were estimated using adjusted Kaplan–Meier methods, after adjusting for age, sex, performance status (PS), metatastic site count, and time period (<2005 or $\geqslant 2005$). These estimates were further synthesized across trials using a random-effects model[10] in stage 2 to estimate the regional treatment effect, accounting for variability across both arms and trials. Regions with less than 5% of the patient population were not included in the primary comparisons due to their limited sample sizes. This resulted in six regions being included in the primary comparisons involved, including central, southern, and Eastern Europe, UK + Ireland, the USA, and ANZC. Sensitivity analysis with all regions included is presented in the Supplemental material (Supplemental Tables 5–7; Supplemental Figures 1 and 2). Bonferroni adjustment was applied to adjust for multiplicity with $p < 0.01$ considered statistically significant (five comparisons in total in the primary analysis). Subgroup analyses were conducted by sex, age, PS, and treatment type.

Results

Patient demographics and disease charactersitics

Among the 20,707 patients included in the current analysis, median follow-up time was 39.4 months. Patients had a median age of 63 years, 62% male, 96% with a baseline PS 0–1 (Supplemental Table 5). The majority had colon cancers only (69%) and, most commonly, liver metastasis (77%), while 38% had lung metastasis. Compared with other regions, UK + Ireland patients were more likely to be male than female, older, had higher PS at baseline, and were less likely to be treated with biological therapies. Eastern European patients were more likely to be younger and treated with anti-epidermal growth-factor receptor (anti-EGFR) agents only. Patients in the USA studies were more likely to have low PS at baseline and to be treated with anti-vascular endothelial growth factor (anti-VEGF) agents only. Notably, UK + Ireland patients were more frequently enrolled in strategy-based studies, including intermittent therapy or studies testing dose-reduction approaches for the treatment of older or frailer patients. A higher proportion of patients were enrolled in advanced trials in colorectal cancer (CRC) in the UK + Ireland (7.84/100,000) compared with other regions

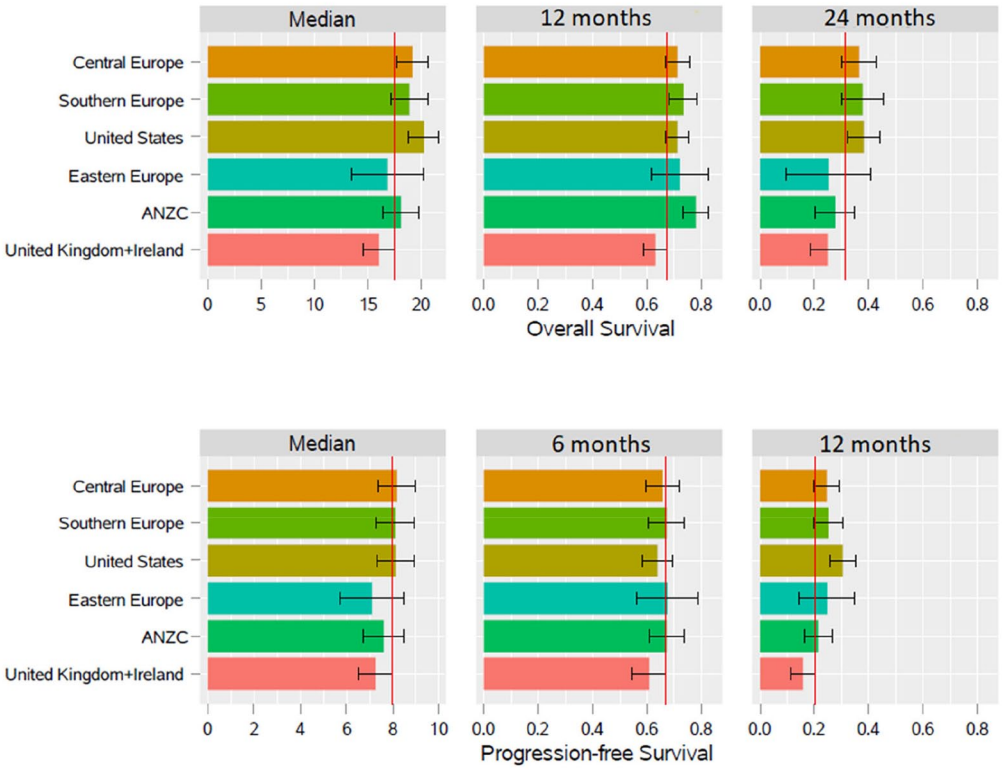

Figure 1. OS and PFS median and point estimate bars by region.
(a) Median, 12-month, and 24-month OS survival estimates by region; (b) median, 6-month, and 12-month PFS survival estimates by region.
ANZC, Australia, New Zealand, and Canada; OS, overall survival; PFS, progression-free survival.

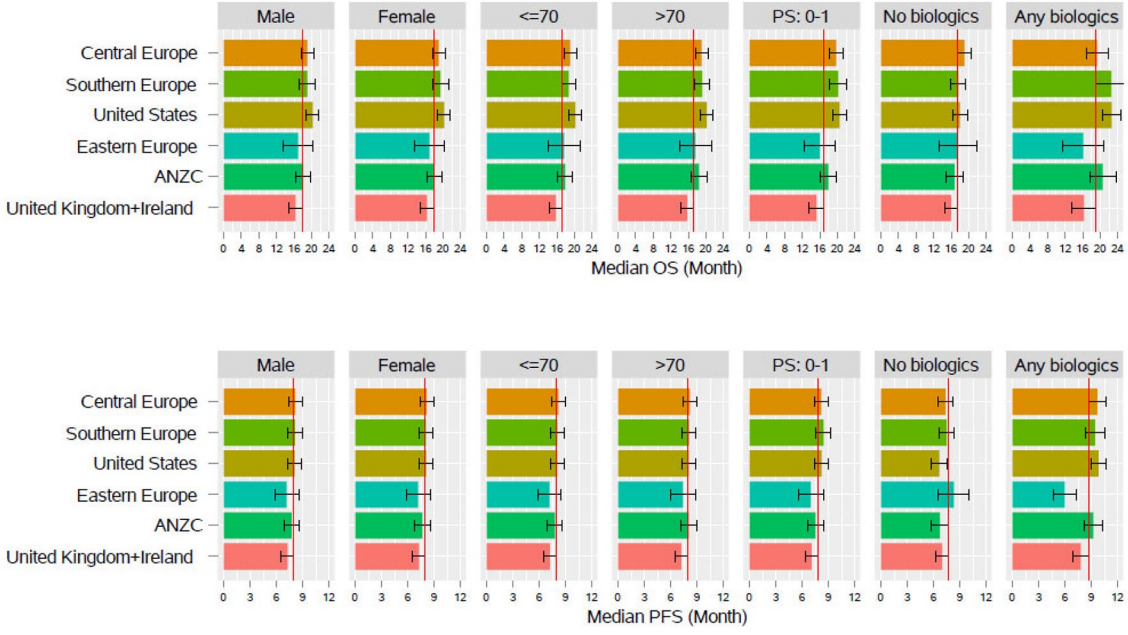

Figure 2. Median OS and PFS bars by region in subgroups.
(a) Median OS by region in subgroups; (b) median PFS by region in subgroups.
ANZC, Australia, New Zealand, and Canada; OS, overall survival; PFS, progression-free survival; PS, performance status.

(ANZC 2.76, central Europe 2.20, USA 1.84). Relating this on a global scale, given the varied age distributions within regions, equates to 50.05/100,000 age 65+ for UK + Ireland *versus* other regions (ANZC 20.35, central Europe 12.28, USA 14.21; Supplemental Table 4).

Overall survival and progression-free survival

The OS varied between regions, with median OS highest in the USA (20.2 months), central Europe (19.1 months), and southern Europe (18.9 months), followed by ANZC (18.1 months), Eastern Europe (16.8 months), and UK + Ireland (16 months; Table 1; Figure 1). Patient cohorts from central Europe and the USA had significantly longer OS compared with those from UK + Ireland ($p = 0.0034$ and $p < 0.001$, respectively), with a range of median difference between 3 months and 4 months. Most of the difference arose in the first year. The survival deficit in UK + Ireland patients, compared with the other five regions, was at most 15% lower at 1 year and 13% lower at 2 years (Table 1; Figure 1), after adjusting for baseline age, sex, PS, number of metastatic sites, and time period.

Similar patterns were observed for PFS, with median PFS highest in central Europe (8.2 months), southern Europe (8.1 months), the USA (8.1 months), followed by ANZC (7.6 months), UK + Ireland (7.2 months), and Eastern Europe (7.1 months; Table 1; Figure 1), but no significant differences were found in median PFS after Bonferroni adjustment for multiplicity. The difference was not significant in the first 6 months, but became apparent at 1 year, where 1-year PFS was signifantly lower in UK + Ireland [16%, 95% confidence interval (CI) 11–20%, $p < 0.01$] compared with the USA (30%, 95% CI 26–35%). It is likely the significant difference in 1-year PFS was triggered by deaths and not progression events.

Subgroup analyses

The geographic patterns differed among subgroups, but some features were generally consistent (Figure 2). Comparing OS within treatment groups, central Europeans had significantly longer OS than the UK + Ireland cohort among patients receiving chemotherapy only without biological therapies ($p = 0.0057$). Southern Europeans ($p = 0.0076$) and the USA ($p = 0.0005$) had significantly longer OS than UK + Ireland patients among those receiving any type of biological therapies (anti-VEGF and/or anti-EGFR agents). Among other subgroups, a consistent pattern was observed where central Europe, southern Europe, and USA cohorts had the longest survival, significantly longer than UK + Ireland cohort in all subgroups (Supplemental 7; Figure 2).

Comparing PFS among subgroups, there was no significant difference overall between regions, except among patients with baseline PS 0–1 and those treated with biological therapies. Among PS 0–1 patients, only the southern European cohort had a significantly longer PFS compared with those from UK + Ireland ($p = 0.007$). Central European and USA patients treated with biological therapies had better PFS than the UK + Ireland cohort ($p = 0.0044$ and $p = 0.0015$, respectively).

Time-trend analyses

To further investigate the survival trend over time, we dichotomized the patient enrollment period into two cohorts: older (1997–2004) *versus* newer (2005–2012) eras. The cut-off points were chosen to reflect the changes in the standard of care due to the introduction of biologic agents around 2004. The trend for 1-year OS was mostly flat for all regions except for southern Europe where a substantial upward trend was observed with a 8.4% increase in 1-year OS [Figure 3; Supplemental Table 8(a)]. An upward trend for 2-year OS was observed for all regions.

The trend for 6-month and 1-year PFS varied among regions, with an upward trend observed for both southern and central Europe, a flat trend for ANZC, and a decreasing trend over time for UK + Ireland [Figure 3; Supplemental Table 8(b)].

Discussion

Several population-based studies have investigated differences in cancer survival across countries;[11,12] however, no studies so far have investigated the regional disparity in patients enrolled in clinical trials. Many factors have been suggested to explain cancer survival differences, such as differences in cancer registration modalities (including whole-population representation), in stage of presentation, and in accessibility to state-of-the-art treatment modalities, and quality of care. These variables are not usually captured in population-based studies, but are rigorously collected in randomized clinical trials. Additionally, for trials enrolling patients from multiple countries, patients

Table 1. Overall OS and PFS estimates by region.

	Central Europe (*n* = 4305)	Southern Europe (*n* = 2759)	United States (*n* = 5728)	Eastern Europe (*n* = 1004)	ANZC (*n* = 1681)	United Kingdom + Ireland (*n* = 5230)
Overall survival						
Median OS in month (95% CI)	19.1 (17.6, 20.6)	18.9 (17.1, 20.6)	20.2 (18.8, 21.6)	16.8 (13.5, 20.2)	18.1 (16.4, 19.8)	16.0 (14.6, 17.5)
Difference *versus* UK + Ireland	3.12	2.86	4.2	0.82	2.06	REF
p value (*versus* UK + Ireland)	0.0034	0.0137	<0.0001	0.6617	0.0748	REF
12-month OS (95% CI)	0.71 (0.67, 0.76)	0.73 (0.68, 0.79)	0.71 (0.67, 0.75)	0.72 (0.62, 0.83)	0.78 (0.73, 0.83)	0.63 (0.59, 0.67)
Difference *versus* UK + Ireland	0.08	0.1	0.08	0.09	0.15	REF
p value (*versus* UK + Ireland)	0.0113	0.0027	0.0084	0.1198	<0.0001	REF
4-month OS (95% CI)	0.37 (0.30, 0.43)	0.38 (0.30, 0.45)	0.38 (0.32, 0.44)	0.25 (0.10, 0.41)	0.28 (0.20, 0.35)	0.25 (0.18, 0.31)
Difference *versus* UK + Ireland	0.12	0.13	0.13	0	0.03	REF
p value (*versus* UK + Ireland)	0.0116	0.0113	0.0026	0.9663	0.5718	REF
Progression-free survival						
Median PFS in month (95% CI)	8.2 (7.4, 9.0)	8.1 (7.3, 8.9)	8.1 (7.3, 8.9)	7.1 (5.7, 8.5)	7.6 (6.7, 8.5)	7.2 (6.5, 8.0)
Difference *versus* UK + Ireland	0.94	0.86	0.88	−0.15	0.35	REF
p value (*versus* UK + Ireland)	0.0918	0.1310	0.1146	0.8543	0.5524	REF
6-month PFS (95% CI)	0.66 (0.60, 0.72)	0.67 (0.60, 0.74)	0.64 (0.58, 0.69)	0.67 (0.56, 0.79)	0.67 (0.61, 0.74)	0.61 (0.55, 0.67)
Difference *versus* UK + Ireland	0.05	0.06	0.03	0.07	0.07	REF
p value (*versus* UK + Ireland)	0.2525	0.1578	0.4584	0.3072	0.1478	REF
12-month PFS (95% CI)	0.25 (0.20, 0.29)	0.25 (0.20, 0.30)	0.30 (0.26, 0.35)	0.25 (0.14, 0.35)	0.21 (0.16, 0.26)	0.16 (0.11, 0.20)
Difference *versus* UK + Ireland	0.09	0.09	0.15	0.09	0.05	REF
p value (*versus* UK + Ireland)	0.0103	0.0103	<0.0001	0.1231	0.1200	REF

ANZC, Australia, New Zealand, and Canada; CI, confidence interval; OS, overall survival; PFS, progression-free survival; REF, reference group for comparison.

entering trials are required to fulfill specific eligibility criteria and follow the same study protocol for treatment, patient care, and data follow up. Hence the patient population is more homogeneous than in population-based studies because of the rigorous inclusion criteria and prescribed therapies associated with randomized trials. Furthermore, most population-based studies looking at the question of country-based differences in cancer survival have done so prior to the introduction of biological

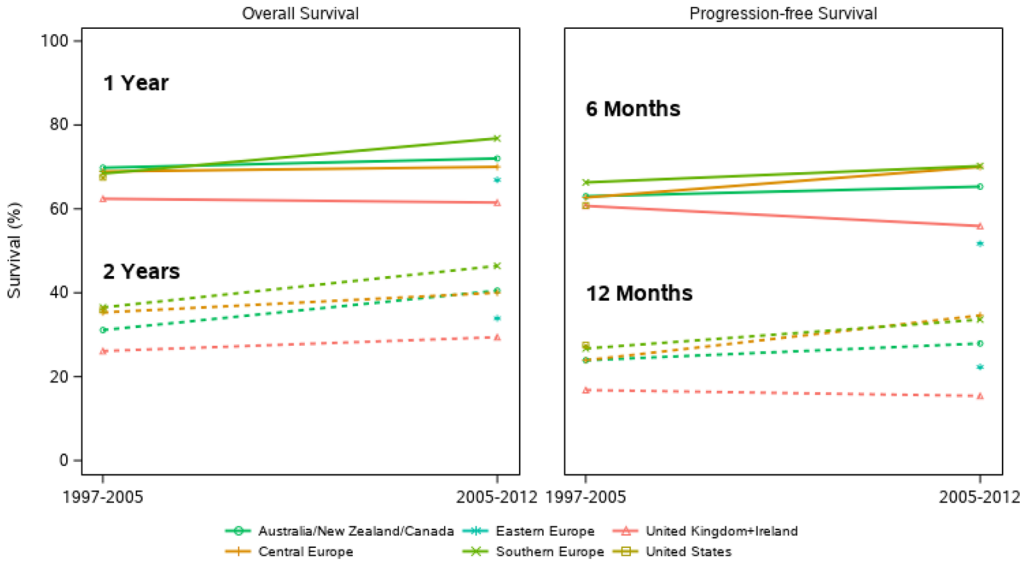

Figure 3. Overall survival and progression-free survival estimates by time period and region.

agents, where clinical trials are more likely to include biological agents as experimental therapy. There are clear advantages of investigating regional disparity using a clinical trial database. To our knowledge, the ARCAD database is the only large database collecting individual-level patient data from completed studies, and future, large, phase III randomized mCRC trials conducted worldwide can provide meaningful and sufficient data to evaluate this important question.

In addition to rigorous and standardized data collected in clinical trials, another strength of our study was the statistical methods we adopted. Specifically, we used a two-stage meta-analysis based on individual patient data, where outcomes were consistently estimated across all trials at the first stage, and compared using a random-effects model at the second stage to account for trial and treatment heterogeneity. With indiviudal-level patient databases such as ARCAD, we were able to achieve a large sample size comparable with population registries, and superior to literatured-based meta-analysis due to consistent adjustments of relevant potential confounders across studies.

In no small measure, the findings from our study continuously demonstrated the value of international data-sharing consortia to address critical issues that no single trial or group alone can address. Our findings were significant in that we not only confirmed the existence of international disparity in mCRC patient outcomes, as seen in population studies,[16,17] but our data further suggested that the disparity was mainly driven by a difference in survival after first-line therapy, since no significant differences were observed in first-line median PFS. These findings were consistent in subpopulations defined by age, sex, race, PS, location of metastastic sites, and treatment classes (i.e. whether biological agents were involved or not). Our study results suggested that some determinants of early mortality from mCRC were not controlled by clinical trial inclusion criteria. Cancer management also mattered, such as access to innovative, active treatments, newer drugs, or secondary surgeries for metastatic disease, which might explain, at least in part, persistant disparities within randomized trials.[18–20]

However, our study was not without limiations. One limitation was that countries included in the same geographic region might have different systems of oncology service delivery. One important reason for presenting data by region in the main manuscript was due to the limited sample size when an individual country was considered. However, we have conducted the same analysis at a country level. In stage 1 of the meta-analysis, model outcomes were estimated from patients available within each country in each treatment arm of a study (not pooling all patients from the same country across trials). This was due to the need to account for heterogeneities due to treatment within each trial. As a result, patient

enrollment per country in each arm of a study was too low to have enough number of events to have a robust estimation.

It is important to point out that the observed survival deficit in the UK region was driven from the COIN[13,14] and the FOCUS (1 and 2) studies[15] that enrolled only UK patients. We discovered that these trials were predominantly 'strategy based,' though not entirely, evaluating a reduced-therapy approach among more frail populations, with a focus on the benefit in quality of life outcomes. By design, the COIN trial accepted a non-inferiority boundary for intermittent therapy of 1.162 (i.e. a 16% difference in OS outcome). Additionally, we further acknowledge that the UK group was more representative of the general population by conducted additional analysis on trial accrual. Supplemental Table 4 shows that 7.84/100,000 people were enrolled in the trials in this analysis from UK + Ireland compared with a mean of 0.51/100,000 across all other regions. This high level of accrual into trials with relative permissive eligibility criteria inevitably resulted in entry of a less fit but more representative group, as reflected in the higher age and poorer PS metrics reported in the study. These are possible reasons for this particular finding.

It is widely acknowledged that the optimal route to improving national and global cancer outcomes are through prevention and early diagnosis, including national screening programs, where appropriate. It is also important that improved data collection enables the appropriate scrutiny of national healthcare systems. Recent work within the UK has focused on routes to diagnosis leading to publication of data for all cancer types between 2006 and 2013.[21] Improvements of cancer survival in the UK over the past 2 decades have been reported following the launch of the National Health Service Cancer Plan for England and the establishement of the National Cancer Research Networks, with improvements in cancer detection, diagnostic routes, and access to tertiary specialized cancer units.[4,7,8] It must also be recognized that patients will, for the foreseeable future, continue to develop or present with metastatic disease. In order to improve outcomes in these individuals, it is critical to appraise differences in service provision that may influence the survival of these patients. This will allow us to more effectively appraise the role of aspects including: supportive care, surgical interventions, ablative techniques, and access to newer drugs in survival outcomes.

To conclude, significant international disparities in the OS of cohorts of mCRC patients enrolled in randomized clinical trials were found. Survival of mCRC patients included in randomized clinical trials was consistently lower in the UK + Ireland regions than in central Europe, southern Europe, and the USA, which can be potentially attributed to greater overall population representation, delayed diagnosis, and reduced availability of therapies.

Author contributions

Dr Shi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Jun Yin, Shaheenah Dawood, Romain Cohen, Qian Shi, Axel Grothey, Richard Adams.

Acquisition, analysis, or interpretation of data: all co-authors.

Drafting of the manuscript: Jun Yin, Jeff Meyers, Romain Cohen, Qian Shi, Richard Adams.

Critical revision of the manuscript for important intellectual content: all co-authors.

Statistical analysis: Jun Yin, Jeff Meyers, Qian Shi.

Obtained funding: Qian Shi, Axel Grothey.

Administrative, technical, or material support: Qian Shi.

Supervision: Qian Shi.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Data sharing

Data sharing of the individual patient data from each randomized clinical trial included in this

analysis is subject to the policy and process of each trial contributor.

Supplemental material

Supplemental material for this article is available online.

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