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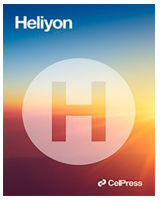

Research article

Overall survival with non-proportional hazards in first-line treatment for patients with metastatic colorectal cancer: Systematic review and network meta-analysis

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ABSTRACT

This study aimed to identify the most effective first-line treatment for patients with metastatic colorectal cancer based on overall survival, identify the most commonly used treatment, and generate a meaningful ranking among all available treatments based on their relative effectiveness. Researchers used the ANOVA parametrization method to fit the second-order fractional polynomial network meta-analysis with a random-effect model. Using a non-proportional hazards network meta-analysis, 46 treatments were compared by considering a combination of direct and indirect evidence extracted from clinical trial studies. Included in the review were 46 trials involving 21350 patients. Between January 2000 and January 2023, researchers conducted a thorough search through Embase, PubMed/Medline, and Scopus. To undertake a secondary analysis of this data, we recreate individual patient data from published Kaplan-Meier (K-M) survival curves and assess the accuracy of that reconstruction. A random-effects model was used to evaluate the pooled overall survival and hazard ratio with a 95 percent confidence interval. The predicted survival curves for the network meta-analysis showed that GOLFIG and FOLFOX + Cetuximab treatments have higher survival, respectively. Our results provide moderate quality evidence and comparative effective estimates for various available first-line treatments for metastasis colorectal cancer based on network meta-analysis.

1. Introduction

One of the most prevalent malignant diagnoses and one of the top three causes of death in developed countries is colorectal cancer (CRC). The five-year survival rate is only 14 percent, and nearly 20 percent of patients receive a diagnosis at the time of metastasis despite the advancement and improvement of screening methods [1]. The liver is the most frequent and often the sole location of metastasis in these individuals [2]. When choosing a treatment, elements connected to the disease, the patient, and the treatment are

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Table 1
Search strategy keywords.

population	outcome	Intervention and control	study
MeSH descriptor: [Colorectal Neoplasms] (colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) adj3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcoma*) Metastatic* or advance*	MeSH descriptor: [survival analysis] explode all trees	first line or first-line initial MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees	randomized controlled trial controlled clinical trial randomized clinical trials as a topic randomly trial

crucial factors to take into account [1].

Based on randomized clinical trials (RCTs), chemotherapy (CT), combined with Bevacizumab or anti-epidermal growth factor receptor agents is the first-line treatment for this illness [2]. First-line treatment for individuals with metastatic CRC now has several alternatives, and combination chemotherapy, like FOLFOX or FOLFIRI, are commonly used [1].

Most research has demonstrated improvements in response rate (RR), progression-free survival (PFS), and overall survival (OS) with effective treatment. When first-line treatment with a high response rate for metastatic CRC is administered, tumor shrinkage may occur, and patients have a higher likelihood of surgery, which can improve PFS and OS [3–5]. According to some studies, patients have exhibited better outcomes with the FOLFOXIRI triple regimen than with FOLFIRI plus Bevacizumab. However, their effect on disease progression is still unclear [5]. Treatment for patients with metastatic CRC has increased the average OS for patients to 30 months, and 70 percent of patients will get at least two lines of therapy. Despite the availability of successful second, third, and, if required, fourth-line regimens, recent research has revealed that the method for selecting the first line of therapy is still important [4].

Using network meta-analysis (NMA), it is possible to estimate and compare the effectiveness of different treatments. This method compares several treatments by considering a combination of direct and indirect evidence extracted from clinical trial studies [6]. The effect size of NMA for survival data is usually reported based on hazard ratio (HR), which should remain constant over time with different covariate levels (different treatments). Most of these models are predicated on the unproven yet underlying assumption of proportional hazard (PH), which declares that the relative hazard should stay constant over time with varying predictor or covariate levels [7,8]. An alternative to an NMA of survival data, where the effect size is represented by a single parameter, i.e., the hazard ratio, is the use of a multidimensional treatment effect. The polynomial fractional model, which offers a more flexible model with numerous parameters and a better analysis of survival shown in the data, is a suitable method [9,7].

The purpose of this study was to perform an NMA to thoroughly assess the effects of first-line therapy for patients with metastatic colorectal cancer based on OS and identify the most often used therapy. We fitted the second-order fractional polynomial NMA with a random-effect model using the ANOVA parameterization approach.

2. Materials and methods

This study was carried out based on reporting guidelines for systematic reviews (PRISMA), a systematic database search, document organization, and selecting studies that complied with standard-defined criteria. On this basis, the researchers extracted information from these studies.

2.1. Data resources and search strategies

To find relevant articles, a systematic search of articles in international databases, Scopus, Web of Science, PubMed, Google Scholar, and Science Direct, was performed until September 14, 2022. To find the appropriate keywords, preliminary published studies and Medical Subject Headings (MESH Terms) in the Pubmed database, as well as the careful examination of the questions of this study, were selected according to PICO criteria. PICO criteria included:

Participants: All patients with metastatic colorectal cancer were examined.

Intervention: First-Line therapy in the papers was chosen since this research aimed to choose the best and most efficient First-Line treatment for patients with metastatic colorectal cancer—any first-line systemic treatment regimen, whether it contains a single medication or many agents.

Control: Evaluating the extent of the effects of each treatment group compared to FOLFIRI + Bevacizumab**.**

Primary Outcome: Overall survival (OS), time from the start of randomization to death by any cause).

Secondary outcome: Hazard ratio (HR)

The chosen keywords were in English. These keywords included colorectal cancer, colorectal neoplasm, metastasis CRC, and first line (Table 1). Boolean search method is used to combine keywords. References to past related studies and the Google Scholar search engine were further explored to find relevant empirical studies.

2.1.1. Inclusion and exclusion criteria

The inclusion criteria for the systematic review and NMA were applied to studies with the following characteristics: (a) RCT studies;

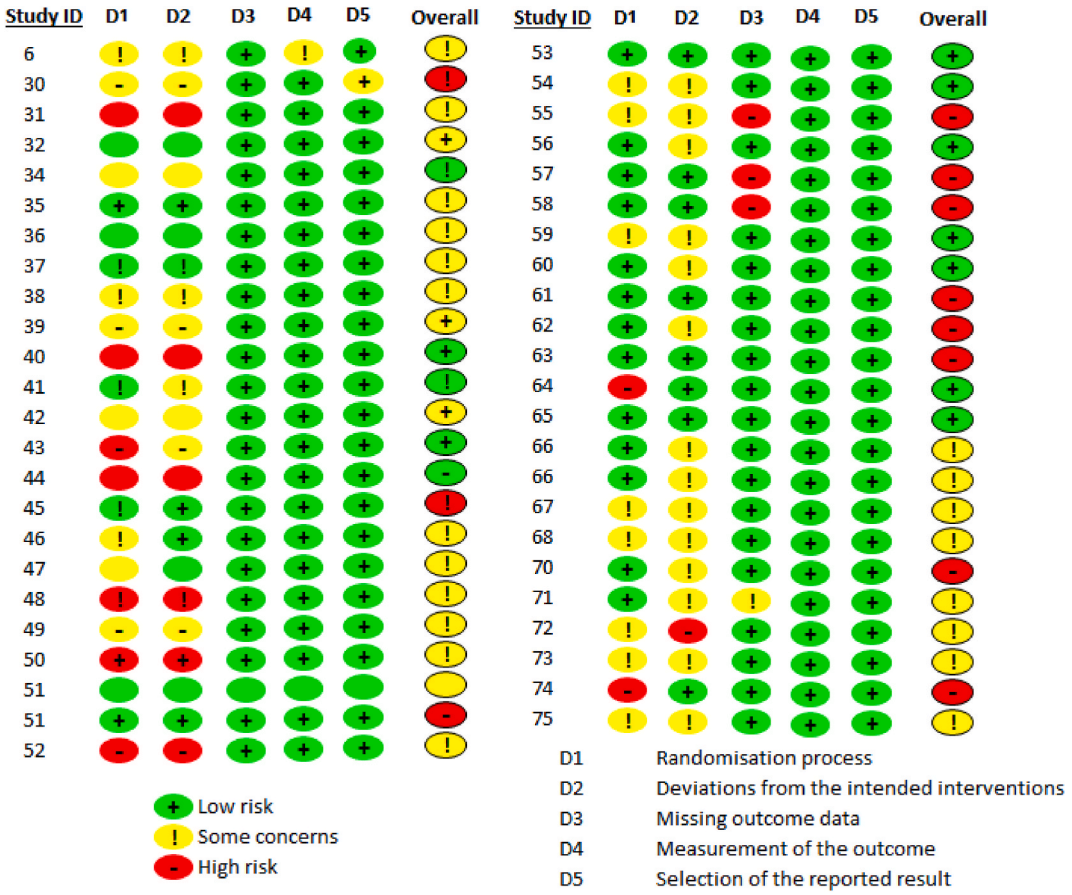

Fig. 1. Considering the risk of bias by Cochrane risk-of-bias tool for randomized trials (RoB 2).

(b) studies that examined the effect of the first-line treatment on the overall survival of patients with metastatic CRC.

The exclusion criteria applied to (a) case-control studies, (b) case reports, (c) letters to the editor, (d) studies for which the full text was not available, (e) unrelated studies, (f) studies with insufficient data, (g) duplicated studies, (h) systematic review and meta-analysis studies.

2.2. Data extraction

The OS follow-up period was considered for an item with several follow-up periods. The survival time and hazard ratio were retrieved for each study's experimental and control groups. ScanIt digitization software was used to digitize the Kaplan-Meier overall survival curves for each treatment arm in each study presented. The fractional polynomial NMA models were used to examine this aggregate data [10]. Two reviewers independently extracted data (double-checking). One author extracted the articles, and the other author reviewed them—the first screening related to titles and abstracts, and the final screening related to the full text. Search results were uploaded to Excel 2013, and duplicates were removed. Both reviewers read the articles. In situations where there was disagreement, a third reviewer was utilized. Independent parallel extraction was also carried out to verify the likelihood of bias. The Cochrane collaboration tool was used by two writers to independently assess the risk of bias.

The tool is structured into five domains through which bias might be introduced into the result [8]. The five domains for individually randomized trials are–

(1) Bias arising from the randomization process.
(2) Bias due to deviations from intended interventions.
(3) Bias due to missing outcome data.
(4) Bias in measurement of the outcome.
(5) Bias in the selection of reported results.

The final score determined whether the study was described as having low concerns of bias, some concerns of bias, or a high risk of bias (Fig. 1). In most examined studies, randomization and the randomization sequence were specified. However, in some of the

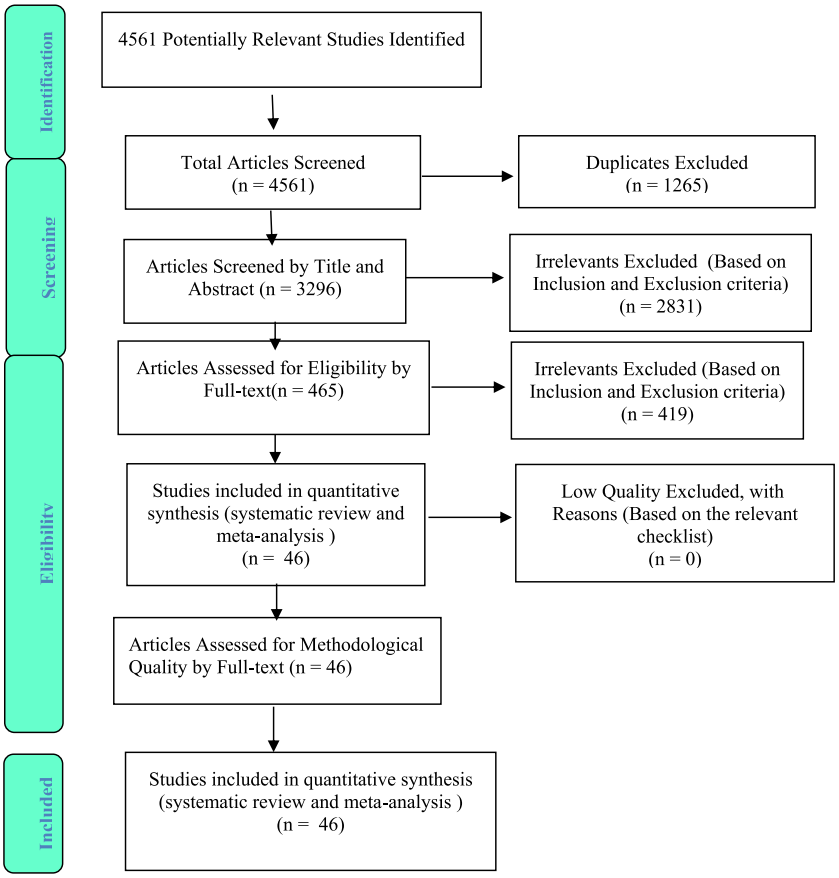

Fig. 2. The flowchart on the stages of including the studies in the systematic review and meta-analysis (PRISMA 2009).

studies, there was no mention of how to implement and how to hide the allocations. Additionally, all of the studies were open-blind. In some studies, it was unclear whether or not the absence of blinding impacted the intervention. The likelihood of reporting bias and other biases (such as baseline imbalances between arms) was not very high.

2.3. Statistical analysis for the NMA with fractional polynomials

To obtain valid NMA results and easier interpretation, it is assumed that network transitivity (potential modifiers of treatment effects are distributed similarly across trials), network consistency (estimates of indirect effects are consistent with direct effects), and homogeneity (interpretation of treatment effects should be homogeneous throughout the trial) should be established.

The so-called Guyot approach enables the approximation of the underlying individual participant data from published Kaplan-Meier curves [11]. It is appropriate to divide this survival time data into time periods to suit this model. Thus, for grouped survival data, we obtain the number of patients at risk n_{jkt} and the number of events that occur to patients r_{jkt} for study j and treatment k in a time interval [t-Δt].

Prentice and Gloeckler showed that grouped survival data can be modeled with a binomial likelihood $r_{jkt} \sim Bin\left(p_{jkt}, n_{jkt}\right)$ and complementary log-log link function, $cloglog\left(p_{jkt}\right) = \eta_{jkt} + \ln\left(\Delta t_{jkt}\right)$ where η_{jkt} is the linear predictor for treatment k in study j at time t, and $\ln\left(\Delta t_{jkt}\right)$ is the offset term accounting for different lengths of time intervals [12]. The hazard function h_{jkt} of an underlying continuous-time model (with survivor function S(t)) relates to the event probability p_{jkt} via $p_{jkt} = \frac{S(t-\Delta t)-S(t)}{S(t-\Delta t)} \cong 1 - e^{-\Delta t\left(h_{jkt}\right)}$. The approximation in the last step above assumes the hazard is constant over the interval $[t - \Delta t]$. Transforming this expression leads to the following approximation [7] $h_{jkt} \cong -\ln\left(1 - p_{jkt}\right)/\Delta t_{jkt}$,which shows that $\ln\left(h_{jkt}\right) \cong cloglog\left(p_{jkt}\right) - \ln\left(\Delta t_{jkt}\right) = \eta_{jkt}$. The fitting of a wide variety of NMA models with time-varying hazard ratios using a generalized linear model approach is provided for grouped survival data.

It has been shown that the optimal status is obtained when arm-based parameterization *NMA* is used [9,10]. The general form for η_{jkt} in a fixed effect NMA with time-varying hazard ratios is $\eta_{jkt} = \sum_{m=0}^{M}\left(\alpha_{mj} + \theta_{mk}\right)g_m(t)$ where α_{mj} are the study-specific coefficients for study j, the θ_{mk} are the treatment coefficients, k is the number of treatments, M is the number of states that vary with time, and $g_m(t)$ are

Table 2
Characteristics of included studies.

row	Authors	Pub year	setting	Phase	Median follow-up	Trt num	treatment	n	Event
1	Cutsem V.E. et al. [14]	2022	52 centers in several European countries, plus Australia and Brazil	II	22.3	1	TT-Bev	77	66
					17.7	2	C-Bev	76	66
2	Qin S. et al. [11]	2021	63 centers in China	III	NE	1	HLX04	338	64
					NE	2	Bev	337	70
3	Denda T. et al. [15]	2021	53 institutions in Japan	III	32.6	1	mFOLFOX6/CapeOX + Bev	243	205
					34.3	2	S-1+irinotecan + Bev	241	209
4	Maiello E. et al. [16]	2020	in 8 Italian centers	II	29.8	1	FOLFOX4+Bev	45	30
					25.0	2	XELOX2+Bev	87	49
5	Cremolini C. et al. [5],	2020	from 58 Italian oncology units	III	27.4	1	FOLFOXIRI + Bev	339	218
					22.5	2	FOLFIRI + Bev	340	241
6	Hurwitz H.I.et al. [13]	2019	in the U.S.	II	34.0	1	cFOLFOXIRI + Bev	93	31
					28.3	2	sFOLFOXIRI + Bev	92	36
					30.7	3	FOLFOX + Bev	95	33
7	Nakayama G. et al. [17]	2018	14 institutions in Japan	II	26.7	1	CapOX + Bev	54	30
					28.7	2	CapIRI + Bev	53	32
8	Bendell J.C. et al. [18]	2017	at 22 sites in the U.S.	II	22.2	1	Onartuzumab + Bev + FOLFOX	97	95
					NA	2	Placebo + Bev + FOLFOX	97	93
9	Baba, H. et al. [19]	2017	at 82 institutions in Japan	III	29.7	1	mFOLFOX6+Bev	255	169
					29.6	2	SOX + Bev	256	174
10	Yamazaki Y. et al. [20]	2016	Japan	III	51.9	1	FOLFIRI + Bev	197	142
					50.8	2	mFOLFOX6+Bev	198	146
11	Folprecht G. et al. [21]	2016	36 centers in Australia, Germany, Italy, Republic of Korea, Russian Federation, Spain, and the UK	II	22.3	1	mFOLFOX6	117	101
					19.5	2	Aflibercept/ mFOLFOX6	119	101
12	Cremolini, C. et al. [22]	2015	Italian oncology units	III	29.8	1	FOLFOXIRI + Bev	252	174
					25.8	2	FOLFIRI + Bev	256	200
13	Kim J.H. et al. [23]	2015	Five institutions in South Korea	II	18.7	1	OS	42	14
					20.1	2	XELOX	44	18
14	Tournigand C et al. [24]	2015	49 centers in France, Austria, and Canada	III	22.1	1	Bev	228	177
					24.9	2	Bev + erlotinib	224	154
15	Heinemann V, et al. [25]	2014	hospitals, outpatient clinics, and private practices in Germany and Austria	III	28.7	1	FOLFIRI + cetuximab	297	158
					25.0	2	FOLFIRI + Bev	295	185
16	Loupakis F et al. [26]	2014	34 Italian centers	III	31.0	1	FOLFOXIRI + Bev	252	131
					25.8	2	FOLFIRI + Bev	256	155
17	Kim S.T [27].	2014	11 institutions in Korea	III	19.0	1	SOX	168	134
					18.4	2	CapeOX	172	145
18	Correale P,et al. [28]	2014	5 Italian Medical Oncology Units	III	25.4	1	GOLFIG	62	46
					21.6	2	FOLFOX-4	62	42
19	Douillard J.Y et al. [29]	2014	at 51 centers in 13 countries	II	18.4	1	FOLFOX4 +Cetuximab	150	99
					16.8	2	UFOX + Cetuximab	152	84
20	G. Folprecht et.,al [30]	2014	16 centers in Germany and 1 in Austria	II	35.8	1	FOLFOX/cetuximab	56	44
					29.0	2	FOLFIRI/cetuximab	55	42
21	Tabernero J et al. [31]	2013	centers in Belgium, Romania, Russia, Spain, the United Kingdom, and the United States	III	17.6	1	Sorafenib + mFOLFOX6	97	62
					18.1	2	Placebo + mFOLFOX6	101	61
22	Infante J.R.et al. [32]	2013	in the United States	II	19.4	1	Axitinib + FOLFOX	42	30
					24.5	2	Bev + FOLFOX	43	42
					20.7	3	Axitinib + Bev + FOLFOX	41	34
23	Ducreux M et al. [33]	2013	15 centers in France	II	36.0	1	Bev + XELIRI	72	49
					36.0	2	Bev + FOLFIRI	73	49
24	Yamada Y. et al. [34]	2013	in 82 sites in Japan	III	29.6	1	mFOLFOX6+Bev	255	105
					30.9	2	S-1 + oxaliplatin + Bev	256	109
25	Pectasides D et al. [35]	2012	Australian New Zealand Clinical Trials Registry	III	20.0	1	XELIRI + Bev	143	93
					25.3	2	FOLFIRI + Bev	142	109
26	Souglakos J et al. [36]	2012	23 institutions throughout Greece.	II	25.7	1	FOLFIRI + Bev	167	143
					27.5	2	CAPIRI + Bev	166	138
27	Diaz-Rubio E et al. [37]	2012	MACRO TTD Study Spain	III	23.2	1	XELOX + Bev	239	175
					20	2	Single-agent Bev	241	171
28	Sang Hong Y et al. [38]	2012	11 institutions in South Korea	III	20.5	1	CapeOX	168	84
					21.2	2	SOX	172	90
29	Van Cutsem E et al. [39]	2011	Europe	III	18.6	1	FOLFIRI	599	502
					19.9	2	Cetuximab + FOLFIRI	599	487

(*continued on next page*)

Table 2 (*continued*)

row	Authors	Pub year	setting	Phase	Median follow-up	Trt num	treatment	n	Event
30	Guan Z.Z et al. [40]	2011	12 centers in China	III	13.4	1	mIFL	64	49
					18.7	2	Bev + mIFL	139	93
31	Hecht J.R et al. [41],	2011	USA	III	21.4	1	PTK/ZK + FOLFOX4	585	398
					20.5	2	Placebo + FOLFOX4	583	419
32	Cassidy J et al. [42]	2011	Study NO16966 Europe, USA, and Africa	III	31	1	XELOX	317	266
					17.7	2	FOLFOX4	317	284
					19.0	3	XELOX + placebo	350	246
					18.9	4	FOLFOX4+placebo	351	273
					21.6	5	XELOX + Bev	350	274
					21.0	6	FOLFOX4+ Bev	349	274
33	Tebbutt N.C et al. [43]	2010	6 institutions in Australia, two in New Zealand, and three in the United Kingdom	III	18.9	1	Capecitabine	156	35
					18.9	2	CB	157	42
					16.4	3	CBM	158	33
34	Tol J et al. [44]	2009	79 centers in the Netherlands	III	20.3	1	CB	368	193
					19.4	2	CBC	368	214
35	Van Cutsem E et al. [45]	2009	184 centers inWestern Europe, Eastern Europe and outside Europe	III	19.9	1	Cetuximab + FOLFIRI	599	412
					18.6	2	FOLFIRI	599	416
36	Hecht J.R et al. [46]	2009	American Society of Clinical Oncology, 200 US centers	III	19.4	1	Pmab + Bev/OX-Ct	413	143
					24.5	2	Bev/OX-Ct	410	108
					20.7	3	Pmab + Bev/Iri-CT	115	26
					20.5	4	Bev/Iri-CT	115	18
37	Cunningham D et al. [47]	2009		III	15.9	1	Oxaliplatin+ 5-FU	362	
					15.2	2	5-FU	363	
38	Hochster H S et al. [48]	2008	33 United States centers	III	19.2	1	mFOLFOX6	50	49
					17.9	2	bFOL	50	50
					17.2	3	CapeOx	50	48
					26.1	4	mFOLFOX6 + Bev	75	71
					20.4	5	bFOL + Bev	74	70
					24.6	6	CapeOx + Bev	74	72
39	Porschen R et al. [49]	2007	68 institutions in Germany and one institution in Austria	III	16.8	1	CAPOX	241	194
					18.8	2	FUFOX	233	176
40	Falcone A et al. [50]	2007	15 Italian centers	III	16.7	1	FOLFOXIRI	122	65
					22.6	2	FOLFIRI	122	81
41	Díaz-Rubio E et al. [51]	2007	at 29 Spanish centers	III	18.1	1	XELOX	171	113
					20.8	2	FUOX	171	101
42	Fuchs CS. et al. [52]	2007	99 sites and four countries (United States, Canada, Australia, and New Zealand)	III	23.1	1	FOLFIRI	144	115
					17.6	2	mIFL	141	117
					18.9	3	CapeIRI	145	119
					NA	4	FOLFIRI + Bev	57	31
					19.2	5	mIFL + Bev	60	44
43	Souglakos J et al. [53]	2006	11 institutions in Greece	III	19.5	1	FOLFIRI	146	135
					21.5	2	FOLFOXIRI	137	122
44	Kabbinavar,F.F. et al. [54]	2005	60 sites in the United States and Australia/New Zealand	II	12.49	1	FU/LV + Placebo	105	64
					16.56	2	FU/LV + Bev	104	44
45	Paulo M. et al. [55]	2001	from 61 centers: 48 in the United States, nine in Canada, two in Brazil, and two in Mexico	III	12.5	1	Capecitabine	302	260
					13.3	2	5-FU/LV	303	273
46	Giacchetti et al. [56]	2000	France, Italy and Belgium	III	47	1	FOLFOX	100	84
					47	2	FU/LU	100	81

Abbreviation:
bFOL (bolus FU and low-dose LV with oxaliplatin), Bev(Bevacizumab), CapeOx(capecitabine with oxaliplatin), CapeIRI(irinotecan plus oral capecitabine), CB(capecitabine; capecitabine plus bevacizumab), C–B(capecitabine plus bevacizumab), CBC(capecitabine, oxaliplatin, bevacizumab and cetuximab), CBM(capecitabine, bevacizumab, and mitomycin), FOLFOXIRI (fl uorouracil, leucovorin, oxaliplatin, and irinotecan), cFOLFOXIRI (concurrently FOLFOXIRI), sFOLFOXIRI(sequentially FOLFOXIRI), FOLFOX (5-fluorouracil/leucovorin/oxaliplatin), FOLFOX4(5-fluorouracil/folinic acid plus oxaliplatin), FOLFOX-6(5-fluorouracil/leucovorin plus oxaliplatin), mFOLFOX6 (bolus and infusion fluorouracil and leucovorin with oxaliplatin), FOLFIRI(fl uorouracil, leucovorin, and irinotecan), FU (fluorouracil), FUOX(fluorouracil plus oxaliplatin), GOLFIG(Gemcitabine, Oxaliplatin, Levofolinate, 5-Fluorouracil, Granulocyte-Macrophage Colony-Stimulating Factor, and Interleukin-2), Iri-CT (fluorouracil, leucovorin, and irinotecan-based chemotherapy), LV(leucovorin), mIFL (irinotecan plus bolus fluorouracil/leucovorin), OS(Oxaliplatin plus S-1), Ox-CT (fluorouracil, leucovorin, and oxaliplatinbased Chemotherapy), Pmab (Panitumumab), UFOX (UFT, leucovorin, and oxaliplatin), SOX(S-1 plus oxaliplatin), TT-B(trifluridine/tipiracil plus bevacizumab), XELIRI (oral capecitabine plus irinotecan), XELOX (capecitabine plus oxaliplatin), XELOX-2 (capecitabine plus oxaliplatin).

baseline functions for time-varying variables. Assuming $g_m(t) = t^{p_m}$ for a set of predefined exponents p_m we obtain the fractional polynomial (of Mth order) NMA models introduced in Jansen [7]. The vectors $(\theta_{0k}, \theta_{1k}, \ldots, \theta_{Mk})$ model the $M+1$ dimensional treatment effect to compare the treatment k to a reference treatment and $\theta_{m1} = 0$ for all m for identifiability. We fitted frequentist fixed effect NMA model with second-order fractional polynomials $(p_1 = -2, p_2 = 1)$ model with reference treatment FOLFIRI +

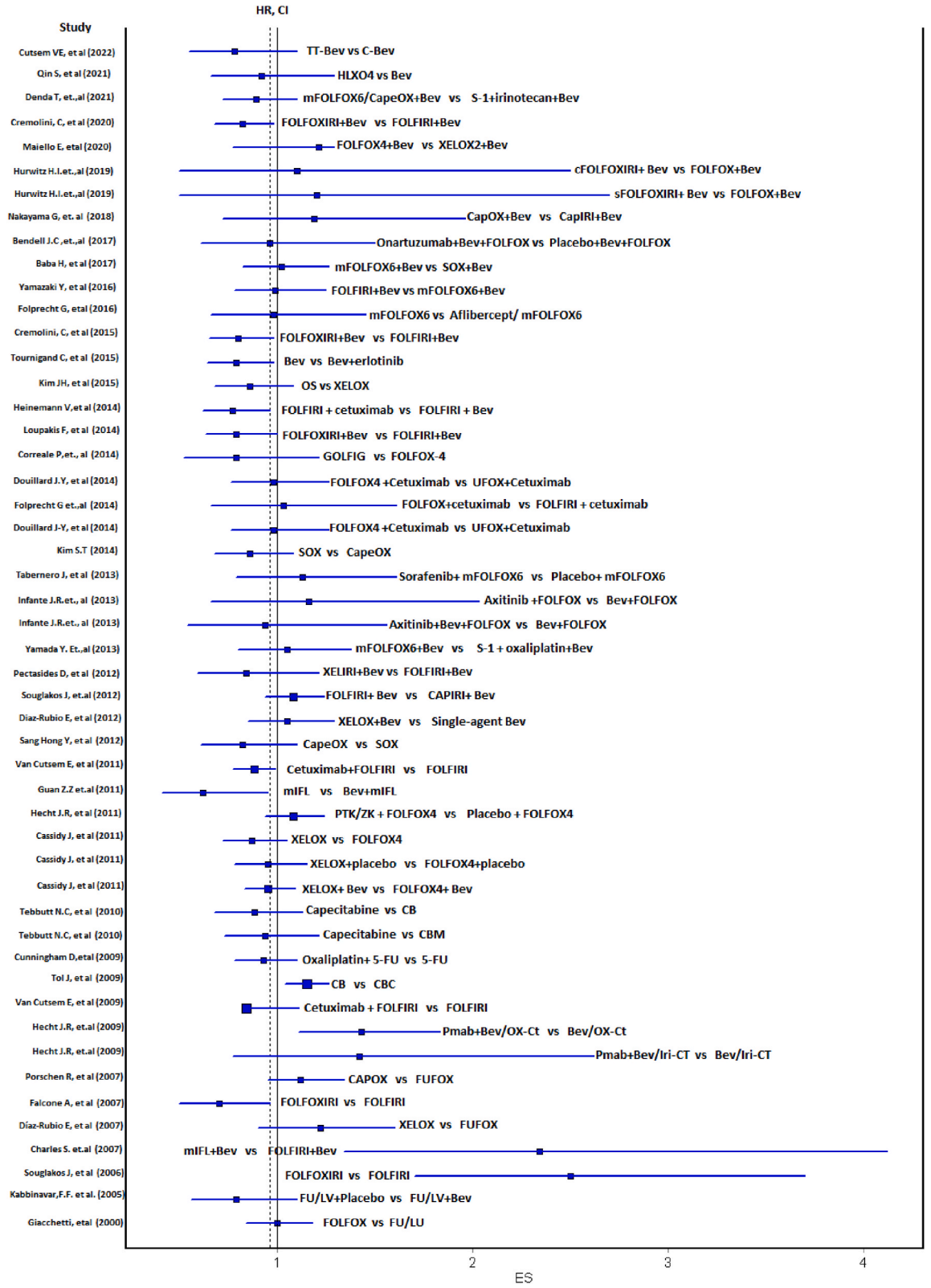

Fig. 3. Pairwise treatment effect (HR reported with confidence interval) meta-analysis for all pairwise comparisons in the previous studies.

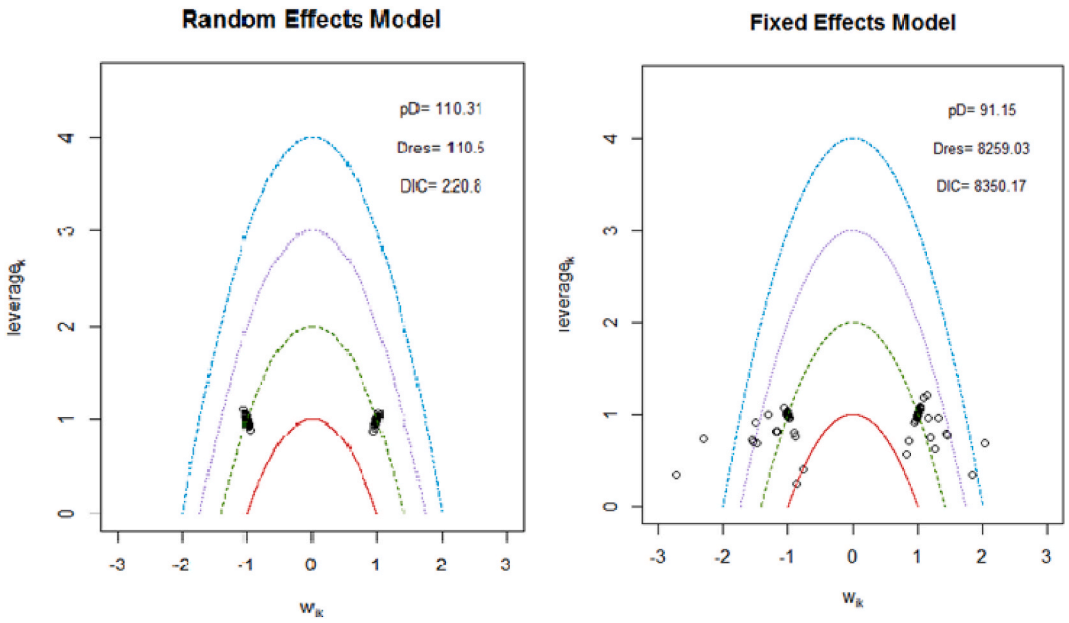

Fig. 4. Leverage plots and fit statistics produced by the nma.fit(.) Function in BUGSnet for survival outcome.

Bevacizumab.

Applied models with less than 1 or 2 time-dependent variables provide great flexibility in the shape of the hazard ratio so that we can analyze hazard ratios with a monotonically decreasing or increasing trend, bathtub, and inverted bathtub. For most practical purposes, M = 1 or 2 will suffice [7]. Since we have individual patient data (IPD) regarding time to death and censoring for all trials included in the NMA, we can estimate these hazard functions using a statistical model and avoid inconsistency in the clinical evidence synthesis [13]. R code for Scan IPD KM, Heatmap, and estimated parameters for fractional polynomial network meta-analysis are provided in supplementary files.

3. Results

3.1. Database search

Database search includes 4561 article abstracts (Scopus n = 2001, Google Scholar n = 981, Science Direct n = 573, PubMed n = 380, Web of Science n = 618). Of these, 465 studies were included in the systematic review, while 46 were included in the NMA. The study selection flowchart is reported in Fig. 2.

3.2. Descriptive information

Table 2 provides an overview of the research included in the NMA. There were 46 studies that were included. The papers under examination were released starting in 2000 and ending in 2022. The mean follow-up median overall survival time in the examined studies was 23.43, with a standard deviation of 7.43. The total number of evaluated patients was 21350, of which 13737 (64.31 %) experienced the event.

The hazard rate is the most recommended single summary statistic for quantifying the treatment effect in studies using survival data. This statistic is chosen because it can be calculated from time-to-event data with censoring and because it measures the size of the difference between two Kaplan-Meier curves. By dividing the hazard rate under treatment by the hazard rate under control, the Cox-Mantel estimate of the hazard ratio is created. Fig. 3 displays the study population's estimated HR and a confidence interval. As can be seen, in most of the studies, the HR is close to one, and there is no significant difference among the treatments.

We compared the fit of both a fixed and random effects model. Based on a visual examination of the leverage plots and comparison of the DIC values produced by the nma.fit(.), the random effects model would be preferred over the fixed effects model for this particular dataset because the DIC value is lower and there are fewer outliers in the leverage plot (Fig. 4).

3.3. Fitting network meta-analysis

Based on the interventions and outcome measures, including OS, the network was based on 1035 pairwise comparisons and 46 interventions. The net graph is shown in Fig. 5. The researchers fit the second-order fractional polynomial random-effect models using ANOVA parametrization in a frequentist framework for this network. By using the average of study-specific estimates with FOLFIRI +

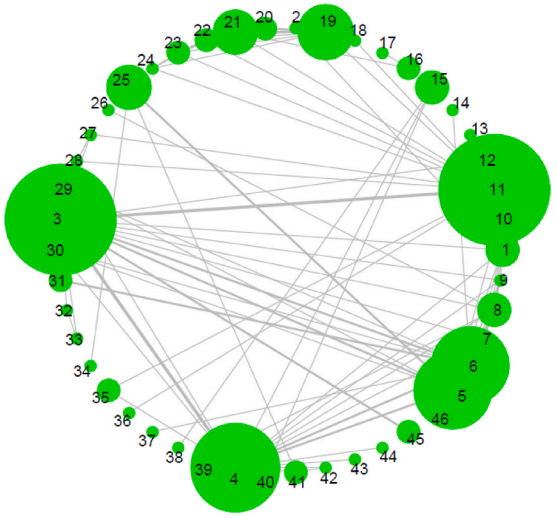

Fig. 5. Network plots for OS outcome.
Treatment:
1 (FOLFOX + bevacizumab + placebo),2 (FOLFOX + bevacizumab + onartuzumab), 3 (FOLFOX + bevacizumab), 4 (Capeox + bevacizumab), 5 (FOLFOX), 6 (Capeox), 7 (Capeox + placebo + bevacizumab), 8 (FOLFOX + placebo), 9 (Capeox + placebo), 10 (GOLFIG), 11 (FOLFIRI + bevacizumab), 12 (FOLFOXIRI + bevacizumab), 13 (S-1 + irinotecan + bevacizumab), 14 (FUOX), 15 (Bevacizumab), 16 (FOLFOX + Cetuximab), 17 (UFOX + Cetuximab), 18 (Bevacizumab + XELIRI), 19 (FOLFIRI), 20 (FOLFOXIRI), 21 (FOLFIRI + Cetuximab), 22 (MIFL), 23 (MIFL + bevacizumab), 24 (CapeIRI), 25 (FU-LV), 26 (PTK/ZK + FOLFOX), 27 (Panitumumab + bevacizumab + FOLFOX), 28 (Panitumumab + bevacizumab + FOLFIRI), 29 (BFOL), 30 (BFOL + bevacizumab), 31 (SOX), 32 (FOLFOX + Axitinib), 33 (bevacizumab + FOLFOX + Axitinib), 34 (Bevacizumab + FU-LV), 35 (CapIRI + bevacizumab), 36 (XELIRI + bevacizumab), 37 (FUFOX), 38 (HLX04), 39 (Sorafenib + placebo), 40 (Bevacizumab + erlotinib), 41 (Capecitabine), 42 (Capecitabine + bevacizumab + mitomycin), 43 (Capeox + bevacizumab + Cetuximab), 44 (Trifluridine + tipiracil + bevacizumab), 45 (SOX + bevacizumab), 46 (FOLFOX + Aflibercept).

Table 3
Parameter estimates (std error) for second-order fractional polynomial model for the 10 best treatment.

treatment	θ_0	θ_1	θ_2
GOLFIG	0.548(1.447)	58.567(66.612)	−0.023(0.07)
FOLFOX + Cetuximab	−0.187(0.807)	14.989(14.028)	−0.012(0.035)
UFOX + Cetuximab	−0.743(0.721)	18.861(13.606)	0.013(0.029)
CapIRI + Bev	−0.254(0.326)	5.039(2.823)	0.004(0.012)
Panitumumab + Bev + FOLFIRI	−0.404(0.789)	4.179(4.088)	0.044(0.066)
FOLFIRI + Cetuximab	0.071(0.251)	2.792(2.454)	−0.016(0.012)
FOLFOXIRI + bev	−0.156(0.2)	1.983(2.377)	−0.001(0.009)
Panitumumab + Bev + FOLFOX	0.25(0.445)	1.695(2.884)	0.013(0.035)
Capecitabine	0.332(0.359)	1.175(3.099)	0.002(0.02)
Capeox + Bev + Cetuximab	−0.248(0.539)	1.056(3.913)	0.042(0.027)

Bev as the reference, the expected θ_0, θ_1 and θ_2 for the comparisons were calculated using the relative treatment effects. The results of fitting the top 10 treatments against the reference treatment FOLFIRI + Bev using the baseline-contrast parameterization in a frequentist framework are given in Table 3.

The corresponding hazard and survival functions for each intervention are presented in Figs. 6 and 7. Fig. 6 shows the hazard ratios over time for the second-order fractional polynomial, and Fig. 7 presents the predicted survival curves for the model using Maiello, E [57] as the baseline study. GOLFIG and FOLFOX + Cetuximab treatments have higher survival, respectively.

4. Discussion

To compare the comparative efficacy evidence for first-line therapy for patients with metastatic colorectal cancer, the researchers

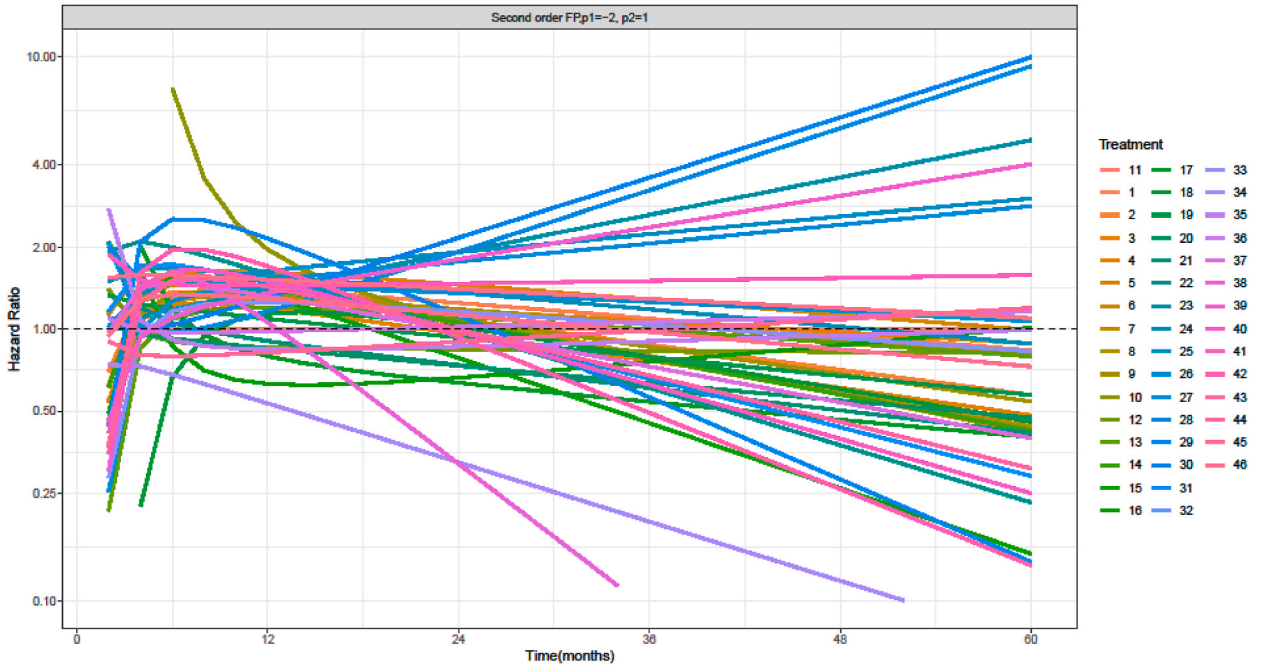

Fig. 6. Hazard ratio over time for each of the interventions relative to FOLFIRI + Bev as obtained with frequentist random effects second order fractional polynomial NMA model(p1 = −2, p2 = 1).
Treatment:
1 (FOLFOX + bevacizumab + placebo),2 (FOLFOX + bevacizumab + onartuzumab), 3 (FOLFOX + bevacizumab), 4 (Capeox + bevacizumab), 5 (FOLFOX), 6 (Capeox), 7 (Capeox + placebo + bevacizumab), 8 (FOLFOX + placebo), 9 (Capeox + placebo), 10 (GOLFIG), 11 (FOLFIRI + bevacizumab), 12 (FOLFOXIRI + bevacizumab), 13 (S-1 + irinotecan + bevacizumab), 14 (FUOX), 15 (Bevacizumab), 16 (FOLFOX + Cetuximab), 17 (UFOX + Cetuximab), 18 (Bevacizumab + XELIRI), 19 (FOLFIRI), 20 (FOLFOXIRI), 21 (FOLFIRI + Cetuximab), 22 (MIFL), 23 (MIFL + bevacizumab), 24 (CapeIRI), 25 (FU-LV), 26 (PTK/ZK + FOLFOX), 27 (Panitumumab + bevacizumab + FOLFOX), 28 (Panitumumab + bevacizumab + FOLFIRI), 29 (BFOL), 30 (BFOL + bevacizumab), 31 (SOX), 32 (FOLFOX + Axitinib), 33 (bevacizumab + FOLFOX + Axitinib), 34 (Bevacizumab + FU-LV), 35 (CapIRI + bevacizumab), 36 (XELIRI + bevacizumab), 37 (FUFOX), 38 (HLX04), 39 (Sorafenib + placebo), 40 (Bevacizumab + erlotinib), 41 (Capecitabine), 42 (Capecitabine + bevacizumab + mitomycin), 43 (Capeox + bevacizumab + Cetuximab), 44 (Trifluridine + tipiracil + bevacizumab), 45 (SOX + bevacizumab), 46 (FOLFOX + Aflibercept).

performed a systematic review and NMA. In reality, despite many of these therapies being tested in different randomized clinical studies, it is still unknown how successful they compare to one another. Instead, therapy efficacy is often reported exclusively based on patient characteristics and particular tumor features. Therefore, the comparison and ranking all these treatments based on therapeutic effects may be helpful for confirmation in prospective clinical trials.

We compared present treatments using NMA for survival analysis and estimated the effects of direct and indirect treatment comparisons and the effectiveness order of treatments. The transitivity assumption must hold for the relevant relative effect measure for NMA. Although breaches of the assumption of the proportional risk across trials might lead to erroneous indirect comparisons of survival over time, this assumption still holds for the constant hazards ratio. Therefore, to estimate the effects with higher accuracy and to consider the changes in HR over time in different treatments, the researchers used the multidimensional fractional polynomial model, which, according to previous studies, is the best power of the model for estimation are *p1 = -2, p2 = 1*. This approach essentially represents the treatment effects with multiple parameters rather than a single parameter or outcome.

This study and similar studies in NMA, if performed at the patient level, have more power to estimate effects, therefore reducing inconsistency and discovering differences among the treatments with higher accuracy. In this analysis, we utilized aggregate-level data and scanned Kaplan-Meier curves to compare all therapies since getting patient-level information for all RCTs in a network was not feasible. The NMA showed that the average survival time of patients treated with GOLFIG (HR = 58.75) is higher than that of other treatments. GOLFIG is a combined regimen developed in preclinical methods that includes gemcitabine + FOLFOX with multiple low-dose chemotherapies [58–60]. Previous studies have shown the anti-tumor effects of this treatment in patients with metastatic CRC, and such studies explain that the GOLFIG regimen is a reliable treatment option for patients and provides strong evidence for designing further clinical trials [61]. Therefore, 9 best treatments, FOLFOX + Cetuximab (HR = 18.86), UFOX + Cetuximab (HR = 14.99), CapIRI + Bev (HR = 5.04), Panitumumab + Bev + FOLFIRI (HR = 4.179), FOLFIRI + Cetuximab (HR = 2.79), FOLFOXIRI + bev (HR = 2.98), Panitumumab + Bev + FOLFOX (HR = 1.69), Capecitabine (HR = 1.75) and Capeox + Bev + Cetuximab (HR = 1.056) were introduced in the order of their priority. Other treatment order is shown in supplement1.

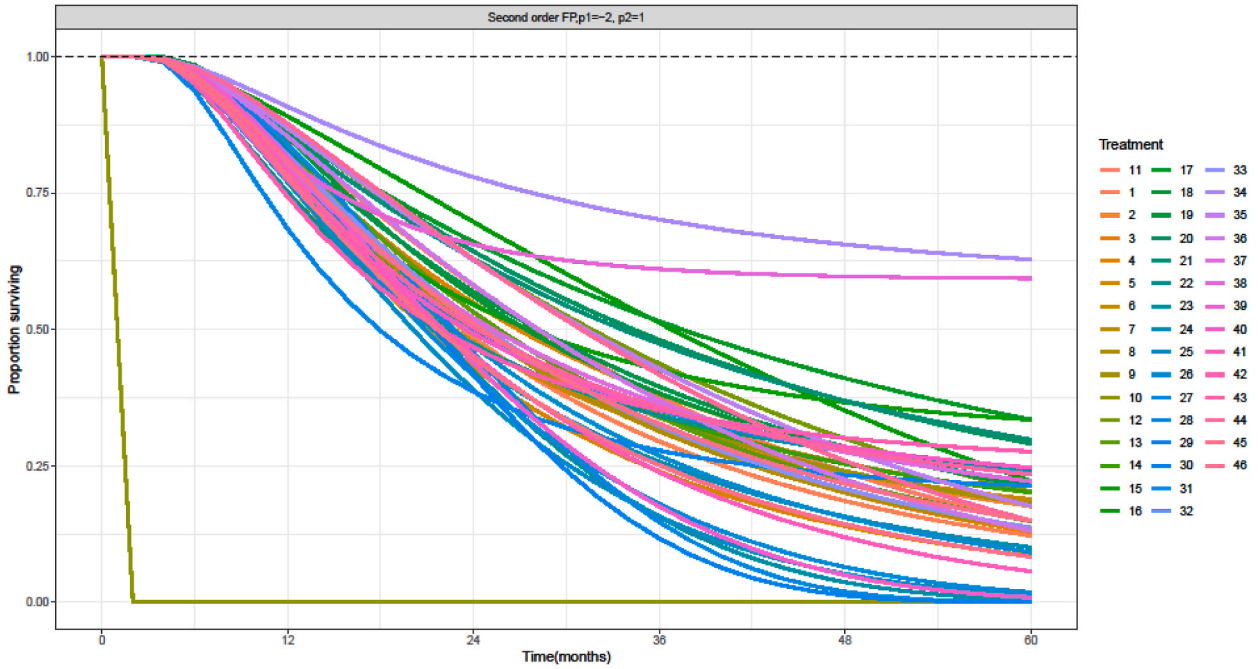

Fig. 7. Survival over time for each intervention as obtained with frequentist random effects second order fractional polynomial (p1 = −2, p2 = 1) NMA model: Treatment ranks from random treatment effect NMA model.
Treatment:
1 (FOLFOX + bevacizumab + placebo),2 (FOLFOX + bevacizumab + onartuzumab), 3 (FOLFOX + bevacizumab), 4 (Capeox + bevacizumab), 5 (FOLFOX), 6 (Capeox), 7 (Capeox + placebo + bevacizumab), 8 (FOLFOX + placebo), 9 (Capeox + placebo), 10 (GOLFIG), 11 (FOLFIRI + bevacizumab), 12 (FOLFOXIRI + bevacizumab), 13 (S-1 + irinotecan + bevacizumab), 14 (FUOX), 15 (Bevacizumab), 16 (FOLFOX + Cetuximab), 17 (UFOX + Cetuximab), 18 (Bevacizumab + XELIRI), 19 (FOLFIRI), 20 (FOLFOXIRI), 21 (FOLFIRI + Cetuximab), 22 (MIFL), 23 (MIFL + bevacizumab), 24 (CapeIRI), 25 (FU-LV), 26 (PTK/ZK + FOLFOX), 27 (Panitumumab + bevacizumab + FOLFOX), 28 (Panitumumab + bevacizumab + FOLFIRI), 29 (BFOL), 30 (BFOL + bevacizumab), 31 (SOX), 32 (FOLFOX + Axitinib), 33 (bevacizumab + FOLFOX + Axitinib), 34 (Bevacizumab + FU-LV), 35 (CapIRI + bevacizumab), 36 (XELIRI + bevacizumab), 37 (FUFOX), 38 (HLX04), 39 (Sorafenib + placebo), 40 (Bevacizumab + erlotinib), 41 (Capecitabine), 42 (Capecitabine + bevacizumab + mitomycin), 43 (Capeox + bevacizumab + Cetuximab), 44 (Trifluridine + tipiracil + bevacizumab), 45 (SOX + bevacizumab), 46 (FOLFOX + Aflibercept).

5. Conclusions

In recent decades, acceptable progress has been observed in treating metastatic colorectal cancer. When multiple cytotoxic agents and targeted treatments were combined, the average overall survival of patients with this cancer increased from about one year to about 30 months. Using efficient treatment combinations with surgical treatments also increased overall survival from about one year to about 30 months. Such treatments have often boosted these patients' chances of living longer than five years [22]. Therefore, identifying more effective combined treatments can help increase these patients' survival and life expectancy. Studies, particularly those using NMA, which compare different treatments in different studies, are useful in this field.

5.1. Limitations

Practical experience shows that fractional polynomial models for use in a Bayesian framework can be time-consuming and complex. Even convergence of models for a simple network of limited studies and treatments takes several minutes. By focusing on the structure of the model, which is a frequency-oriented approach, our method removes the complexity of the network meta-analysis model from the consequences of time to the occurrence of the event in which the hazard ratio is variable with time.

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Informed consent statement

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Ethics approval and consent to participate

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Data availability statement

All data generated or analyzed during this study are included in this published article.

CRediT authorship contribution statement

Fatemeh Keshavarzi: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Nader Salari:** Writing – original draft, Formal analysis. **Sara Jambarsang:** Formal analysis. **Seyyed Mohammad Tabatabaei:** Writing – original draft, Formal analysis, Conceptualization. **Soodeh Shahsavari:** Writing – original draft, Formal analysis, Conceptualization. **Andrew J. Fournier:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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