Reviews

Cost-effectiveness of healthcare interventions for rare cancers: Evidence from a systematic literature review and meta-analysis

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ABSTRACT

Background: Rare cancers account for 20–24% of all cancer diagnoses in Europe and have been recently recognized as a public health issue due to the lower survival compared to common cancers. However, the evidence about the cost-effectiveness of interventions for rare cancers remains unclear. The aim of this study was to review economic evaluation studies of these interventions, assess their quality, and provide policy-makers with summary estimates about the value-for-money of these interventions.

Methods: We systematically searched Medline, EMBASE and governmental reimbursement agencies by following the PRISMA guidance and selected economic evaluations of healthcare interventions for rare cancers based on predefined criteria. A template was developed to extract study and patient characteristics as well as reported outcomes and costs. The CHEERS checklist was used to assess the quality of the studies and costs were inflated to 2016 prices and converted to British Pound. A random effects meta-analysis, using study quality scores as weights, was performed to pool outcomes and costs and to explore differences between types of rare cancer and study origin.

Results: Out of 1991 screened studies, 32 economic evaluations of interventions for sarcoma, malignant pleural mesothelioma and thyroid carcinoma were selected. Almost all of them evaluated drug treatment and surgeries (n = 30; 94%) and were originated from North America (n = 8; 49%) and Europe (n = 7; 43%). Half of these studies were NICE reports and their results ranged from £20300 to £59000 per quality adjusted life year (QALY). The 16 published studies were assessed to be of mediocre quality, particularly in describing the assumptions underpinning decision-analytic models and the methods used to handle uncertainty or population heterogeneity. The meta-analysis of their results showed that the pooled incremental cost of these interventions was £3410 (95% CI £821–£7642) per patient per year. In term of outcomes, the pooled incremental QALY was 0·20 (95% CI 0.04–0.37).

Conclusion: Compared to NICE suggested thresholds and cost-effectiveness ratios of reimbursed interventions for common cancers, interventions for rare cancers seem to be value-for-money. More collaborative research is needed to realise their full potential for improving efficiency and equity in healthcare.

Research in context

Evidence before this study

There are approximately 200 types of rare cancers that account for 20–24% of all cancer diagnosis in Europe (1). Over half a million patients are annually diagnosed per year in Europe, and incidence rate rises every year (1). Rare cancers have been recently recognized as a public health issue due to the lower survival compared to common cancers.

Despite advances in the prevention, diagnosis, treatment, and follow-up care of rare cancers, the cost-effectiveness of the provided interventions has received much less attention by healthcare providers than interventions for common cancers. Economic evidence in this area is needed and expected when considering the relatively significance of rare cancer in terms of cancer care as a whole, and inequalities of outcomes for rare cancer patients. Some of the key issues contributing to the relative inefficiencies in rare cancer pathways include delayed and incorrect diagnosis, limited access to clinical expertise, less

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effective standard treatments and inadequate funding for preclinical and clinical research.

Added value of this study

To our knowledge, this is the first study to provide a systematic overview of cost-effectiveness studies of interventions for rare cancers, assess their study quality and support decision makers with summary estimates about the value-for-money of these interventions.

Implications of all available evidence

More collaborative research is needed to realise their full potential of interventions for rare cancers to improve efficiency and equity in healthcare. Equal access should be provided to healthcare facilities and to high quality therapeutic interventions to all cancer patients, regardless of the rarity of their disease.

1. Introduction

According to international/European agreement, cancer histiotypes with an incidence of less than 6 cases per 1,00,000 people per year are classified as rare [1]. Currently there are at least 200 different types of rare cancer, although it is expected that molecular re-classification may amend the categorisation of many cancers from common to rare [1,5]. Despite their individual rarity, when combined, rare cancers pose a substantial threat to population health and burden healthcare systems

[2]. They account for about one fifth of all newly diagnosed cancers and 30% of all cancer mortality [3]. They also have 20% lower survival comparing to common cancers [4]. This disparity is not to be attributed only to the heterogeneity and clinical complexity of rare cancers; studies confirm that delays in diagnosis, limited research and treatment options and inequality of access to expert care affect the course of the disease [1,6–8].

As with many rare diseases, lobbying has driven the placement of rare cancers on top of the European health policy agenda. One of the important initiatives has been the establishment of the European Reference Network (ERN) for rare diseases by the European Commission. As part of this initiative, the first federated network of endorsed healthcare providers for rare solid tumours (EuraCan), haematological diseases and childhood cancers (PaedCan) was developed in 2017 [9–11]. Through centralized guidelines and referral networks, it is anticipated that the ERNs will facilitate better access and delivery of appropriate use of technology, drugs and care. Moreover, the European Medicine Agency (EMA) and US Food and Drug Administration (FDA) have provided financial incentives (e.g. orphan designation to industry), in an effort to stimulate investment in drug and technology development.

Despite the prioritisation of the health policy agenda for rare cancers, it remains necessary to identify cost-effective interventions for rare
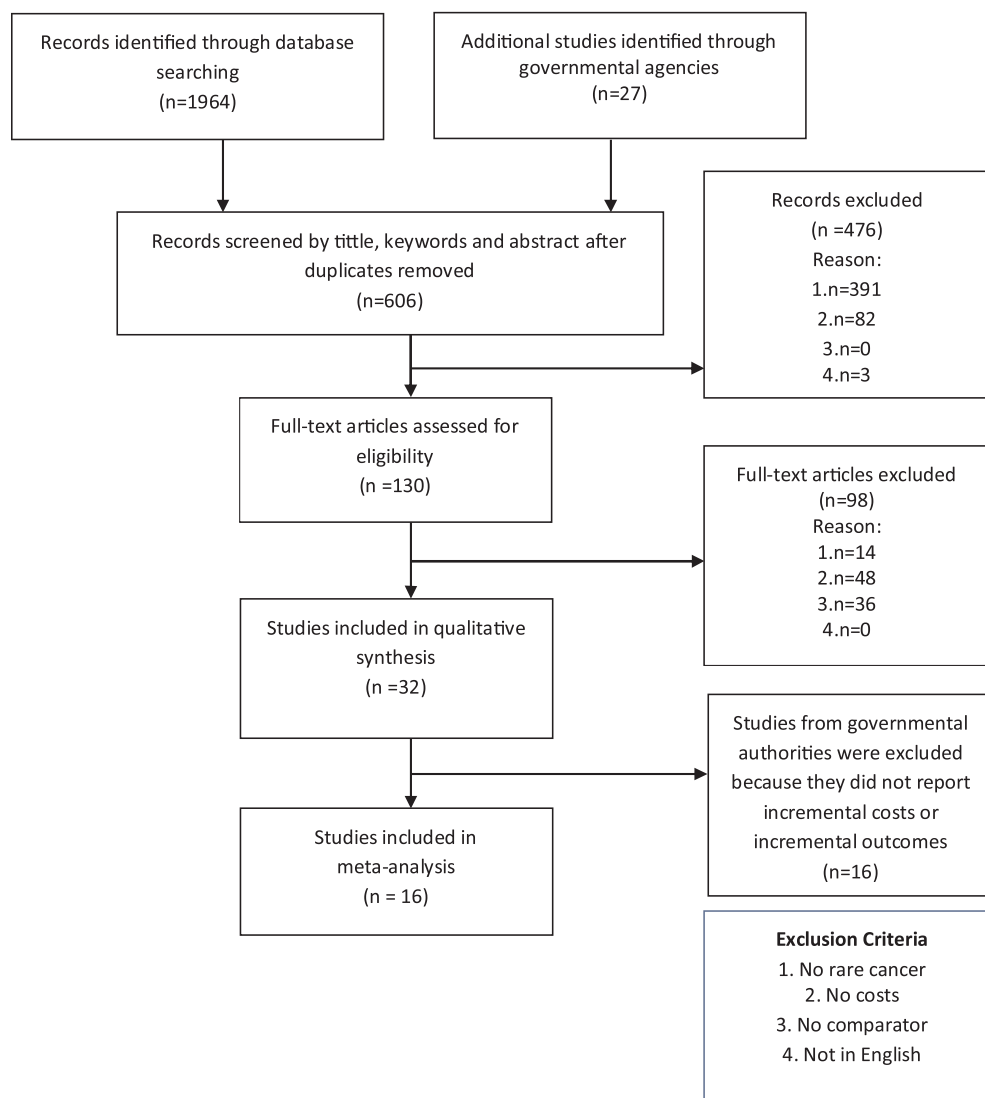

Fig. 1. Study selection.

Table 1
Study characteristics.

Citation	Type of cancer	Type of intervention	Economic Evaluation	Country	Study Design	Economic Model	Perspective
[17]	Sarcoma	Treatment	CEA	UK	Simulation Cohort Phase III trial	Multistate	HC
[19]	Sarcoma	Treatment	CEA	Canada	Simulation Cohort Phase III trial	Partitioned Survival	HC/SP
[22] (IT)	Sarcoma	Treatment	CEA	Italy	Simulation Hypothetical cohort	Markov	HC
[22] (SP)	Sarcoma	Treatment	CEA	Spain	Simulation Hypothetical cohort	Markov	HC
[22] (SW)	Sarcoma	Treatment	CEA	Sweden	Simulation − hypothetical cohort	Markov	HC
[26]	Sarcoma	Treatment	CEA	USA	Clinical Trial − cohort	Decision Tree	
[27]	Sarcoma	Treatment	CEA	Canada	Simulation hypothetical cohort	Markov	
[29]	Sarcoma	Treatment	CEA	Spain	Simulation cohort	Partitioned Survival	HC
[28]	Sarcoma	Treatment	CEA	Finland	Simulation- hypothetical cohort	Markov	HC/Payer
[20]	Sarcoma	Diagnostic	CUA	USA	Clinical Trial − cohort		HC
[30]	Sarcoma	Treatment	CEA	USA	Simulation hypothetical cohort	Markov	
[25]	Sarcoma	Treatment	CMA	USA	Clinical Trial − cohort		
[18]	MPM	Treatment	CEA	UK	Simulation − randomized Cohort		HC
[32]	MPM	Treatment	CEA	UK	Simulation − randomized cohort	Partitioned Survival	HC/SP
[24]	Thyroid carcinoma	Diagnostic	CUA	USA	Simulation hypothetical cohort	Markov	HC/SP
[21]	Thyroid carcinoma	Treatment	CUA	USA	Simulation hypothetical cohort	Markov	SP
[23]	Thyroid carcinoma	Treatment	CMA	China	Simulation hypothetical cohort	Decision Tree	Payer
[31]	Thyroid carcinoma	Treatment	CUA	China	Simulation hypothetical cohort	Markov	Payer
[33]	MPM	Treatment	CEA	UK	single bird cohort		HC
[34]	NHL	Treatment	CEA	UK	Controlled Open Label Phase III Study	Markov	HC
[35]	CML	Treatment	CEA	UK			
[36]	Sarcoma	Treatment	CEA	UK	RCT	State Transition	
[37]	GST	Treatment	CEA	UK	RCT	Markov	HC
[38]	CML	Treatment	CEA	UK		State Transition	
[39]	CML	Treatment	CEA	UK		Markov	HC
[40]	Lymphoma	Treatment	CEA	UK	RCT	Markov	HC and patient
[41]	Myelofibrosis	Treatment	CEA	UK	RCT		
[42]	GST	Treatment	CEA	UK		Markov	HC, patient, and SP
[43]	CML	Treatment	CEA	UK			
[44]	Sarcoma	Treatment	CEA	UK		Health State transition	HC
[45]	HGG	Treatment	CEA	UK		Markov	
[46]	CML	Treatment	CMA	UK			HC
[47]	CML	Treatment	CEA	Canada			HC
[48]	Sarcoma	Treatment	CEA	Canada		Partitioned Survival	

MPM: Malignant Pleural Mesothelioma; CML: Chronic Myeloid Leukaemia; NHL: Non Hodgkin Lymphoma; HGG: High Grade Glioma, GST: Gastrointestinal Stromal Tumour, CEA: Cost Effectiveness Analysis, CUA: Cost Utility Analysis, CMA: Cost Minimisation Analysis, TT: Total Thyroidectomy, pCND:, BSC: Best Supportive Care; RCT: Randomized Control Trial; HC: Healthcare perspective; SP: societal.

cancers and to highlight consistencies and discrepancies with common cancers. This would help decision makers to improve efficiency in care for rare cancers. However, the overall evidence about the cost-effectiveness of the relatively limited interventions for rare cancers remains unknown. It is likely that this evidence is fragmented across many specific types of rare cancer, and its quality is uncertain. The aim of this study is to systematically review economic evaluations of interventions for rare cancers, assess their quality, and provide policy-makers with summary estimates about the value-for-money of these interventions.

2. Methods

2.1. Search strategy and selection criteria

A systematic review was performed by following the PRISMA guidance [12]. We used a four-step scheme that adapted the validated Patient or Problem, Intervention, Comparator and Outcome (PICO) criteria to select search terms. The RARECARE List of Rare Cancers was used to identify clinical search terms associated with rare cancers [13]. The economic search terms were selected based on previews reviews of economic evaluations of complex health interventions [14,15]. Free search terms were preferred to MeSH terms in order to locate the papers. The search strategy was validated with a trained university librarian.

Searches for scientific papers published in English were performed on Medline (OVID version) and EMBASE (OVID version) on the 30th of January 2017. All records were inserted in Mendeley and duplicates were deleted. Studies were excluded based on the following criteria: rare cancer not subject of the study, not an economic evaluation (i.e.

including assessment of (at least) costs and outcomes), no comparative analysis (i.e. including two alternatives), and study language other than English. Reviews and meta-analyses were also excluded but they were eye-ball scanned for relevant articles.

In the first screening step, records of interest were selected based on title, keyword and abstract and in the second screening step; full-text articles were reviewed. In both steps; records were screened by two reviewers independently (ARM and PZ). A rare cancer expert (ABH) and a health economist (AT) provided advice throughout the selection process when needed. Discrepancies were solved by consensus.

In addition, governmental authorities' websites that use cost-effectiveness as a criterion for reimbursement were searched for relevant reports. These authorities included National Institute for Health and Care Excellence (NICE) in England, Canadian Agency for Drugs and Technologies in Health (CADTH), National Health Care Institute in the Netherlands, Dental and Pharmaceutical Benefits Agency (TLV) in Sweden, Best Practice Advocacy Centre (BPAC) in New Zealand, and Pharmaceutical Benefits Scheme (PBS) in Australia. We also looked for studies that met our selection criteria in international organisations such as Portal for Rare Diseases and Orphan Drugs (Orphanet), European Medicines Agency (EMA), and European Network for Health Technology Assesment (EUnetHTA).

2.2. Data extraction and synthesis

A standardized template was used to extract information from all full-text studies selected for inclusion about type of rare cancer, publication year, study origin, study design, type of intervention (categorised in prevention diagnostic, treatment and follow-up

Table 2
Reported costs and outcomes in scientific literature.

PANEL A: Reported mean costs

	Cost Base Year	Reported Costs		Costs in 2016 British Pounds		
		Intervention	Comparator	Intervention	Comparator	Incremental Cost
[17]	NR	£22,086	£14,110	£23,856	£15,314	£8542
[19]	2012	CA$40,177	CA$19,337	£25,214	£12,115	£13,099
[22](IT)	2010/2011	€ 38,922	€ 40,614	£35,135	£37,213	−£2078
[22](SP)	2010/2011	€ 30,700	€ 34,196	£27,729	£30,887	−£3158
[22]SW	2010/2011	€ 36,507	€ 39,780	£32,526	£35,442	−£2916
[26]	2001	US$119,372	US$0	£124,880	£0	£124,880
[27]	2016	US$26,633	US$28,028	£20,555	£21,632	−£1077
[29]	2014	US$21,861	US$45,338	£19,035	£35,256	−£16,221
[28]	2008	€ 40,384	€ 7568	£39,120	£7331	£31,789
[20]	2009	US$1334	US$162	£1152	£140	£1012
[30]	2015	US$65,273	US$65,486	£55,449	£55,630	−£181
[25]	2012	US$24,613	US$12,129	£19,858	£9786	£10,072
[18]	NR	£11,410	£7662	£14,059	£9441	£4618
[32]	2009	£7112	£1358	8276	1580	6696
[24]	2010	US$863,249	US$862,448	£733,324	£732,643	£681
[21]	2013	US$13,738	US$10,604	£11,670	£9008	£2662
[23]	2013	US$19,888	US$22,761	£15,814	£18,098	−£2284
[31]	2013	US$11,366	US$11,332	£9299	£9271	£28

PANEL B: Reported outcomes

	Intervention					Comparator					Incremental Outcomes				
	QALY	LY	OS	PFS	PPS	QALY	LY	OS	PFS	PPS	QALY	LY	OS	PFS	PPS
[17]	0.719	1.375		0.503		0.519	1.262		0.211		0.2	0.113		0,292	
[19]	0.713	1.362		0.502	0.859	0.585	1.25		0.211	1.309	0.128	0.112		0,291	−450
[22](IT)	0.595					0.53					0.065				
[22](SP)	0.59					0.55					0.04				
[22]SW	0.608					0.584					0.024				
[26]			43					13					30		
[27]	3	4,09				2.86	3.95				0.14	0.14			
[29]	0.705					0.686					0.019				
[28]		1.76					0.596					1.164			
[20]															
[30]	9.095					6.798					2.297				
[25]															
[18]	0.83	1.219				0.689	1.001				0.141	0.218			
[32]	0.89	1.37				0.68	1.08				0.21	0.29			
[24]															
[21]	1					1									
[23]															
[31]	14					13.67					0.33				

QALY: quality-adjusted life year; LY: life-years; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival.

interventions), type of economic evaluation(i.e. cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-minimisation analysis (CMA)), type of economic model, perspective of cost analysis (i.e. healthcare perspective(HC), societal perspective (SP), payer perspective or patient perspective), type of health care costs (i.e. hospital and other), type of non-health care costs (i.e. productivity loss and informal caregiving), cost base year and currency unit, and type of outcome (i.e. quality-adjusted life years (QALY), life years (LY), overall survival (OS), progression free survival (PFS) and post progression survival (PPS). The reported incremental cost-effectiveness ratio (ICER) was extracted from scientific literature and governmental reports.

2.3. Study quality assessment

The Consolidated Health Economic Evaluation Reporting Standard (CHEERS) statement was used to assess the quality of the studies on 24 key items of good reporting practice based on a yes/no response option [17]. The total quality score of a study was calculated as the proportion of positive responses on all applicable items (maximum score was 100%). The assessment process was performed by ARM and PZ by using an Excel spreadsheet following the CHEERS statement. Considering that this statement is relevant to scientific papers only, governmental reports were assumed to have a quality score equal to the maximum score of the selected studies.

2.4. Meta-analysis

We used a random-effects model to pool the extracted costs and outcomes and estimate incremental costs (i.e. difference between mean costs of intervention and mean costs of comparator) and incremental outcomes. The scores of the study quality assessment were used to weight the contribution of each study to the pooled estimates. This was performed to prioritise higher quality studies and to overcome the unreported uncertainty in the mean estimates. Unit costs from intervention and comparator groups were inflated to 2016 prices by using the consumer price index in each study's country of origin and converted, when necessary, to GBP (£) by using purchasing power parities (PPPs).

2.5. Role of funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding

Table 3
Reported incremental cost-effectiveness ratios.

Scientific Literature			Grey Literature	
Reference	Cost/QALY	Cost/LY	Reference	Cost/QALY
[17]	£62,162		[33]	£37,000
[19]	CA$163,336	CA$186,502	[34]	£22,000
[22](IT)	€ − 26,308		[35]	£32,000
[22](SP)	€ − 87,423		[36]	£34,500
[22] (SW)	€ − 136,396		[37]	£31,800
[26]		US$51,159	[38]	£47,200
[27]	DOMINANT		[39]	£26,000
[29]	DOMINANT		[40]	£20,300
[28]		€28,192	[41]	£31,200
[20]	–	–	[42]	£26,000
[30]	US$93		[43]	£43,000
[25]	–		[44]	£36,000
[18]	£26,437	£17,156	[45]	£57,000
[32]	£27,360	£19340	[46]	–
[24]	–	–	[47]	CA$167,782
[21]	–	–	[48]	CA$142,843
[23]	–	–		
[31]	US$105.96			

author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Results of the literature review

As Fig. 1 shows, the search strategy resulted in 1964 published studies and 27 reports. After exclusion of duplicate studies, 606

potentially relevant studies remained for screening. There were 476 papers excluded in the first step of selection (i.e. title and abstract assessment) and 98 papers excluded in the second screening step (i.e. full-text assessment) were excluded based on the four criteria previously mentioned. The main reason for exclusion in the first selection step were studies that referred to common cancers (n = 391) and in the second selection step were studies without costs included in the analysis (n = 48). The selection process resulted in 32 studies eligible for review (note that one multi-national study reported economic evaluations in three different European countries).

The characteristics of selected studies are summarized in Table 1. Of the 32 studies, 16 (50%) were scientific publications and 16 (50%) governmental reports. Most studies regarded sarcoma (n = 13; 40%) followed by chronic myeloid leukaemia(CML) (n = 6; 19%), thyroid carcinoma (n = 4; 13%), malignant pleural mesothelioma (n = 3; 9%), gastrointestinal stromal tumours (GST) (n = 2; 6%), high-grade glioma (HGG) (n = 1; 3%), non-hodgkin lymphoma (n = 1; 3%), lymphoma (n = 1; 3%) and myelofibrosis (n = 1; 3%).

The vast majority of the studies evaluated treatment interventions, distinguishing between drug treatment and surgeries (n = 30; 94%), while only 2 (6%) studies evaluated diagnostic procedures. Most economic evaluations were originated from North America (United States (n = 6; 37%) and Canada (n = 2; 12%)) and Europe (United Kingdom (n = 3; 19%), Spain (n = 2; 12%), Finland (n = 1; 6%), and Sweden (n = 1; 6%). The selected governmental reports were from United Kingdom (n = 14; 88%) and Canada (n = 2; 12%).

Economic evaluations were based on randomised clinical trials (n = 10; 30%) or simulations alongside cohort studies (n = 13; 40%). Most economic evaluation studies were cost-effectiveness analysis (n = 26; 79%) followed by cost-utility analysis (n = 4; 12%) and cost minimisation analysis (n = 3; 9%). Markov modelling was the most common approach to assess costs and effects up to the time-horizon in

Table 4
Results of the study quality assessment of scientific literature.

| SECTION	ITEM	[17]	[19]	[22]	[26]	[25]	[27]	[29]	[28]	[20]	[30]	[18]	[32]	[24]	[21]	[23]	[31]	Frequency per item
Title		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	–	✓	–	88%
Abstract		–	✓	–	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	88%
Introduction	Background and objectives	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
Methods	Target Population and subgroups- −Reporting and Reasoning	–	✓	✓	✓	✓	✓	✓	✓	✓	–	✓	✓	✓	✓	✓	✓	88%
	Setting and Location −−Reporting and Reasoning	–	✓	✓	✓	✓	–	✓	–	✓	–	–	–	–	–	–	–	38%
	Study Perspective −Reporting and Reasoning	–	✓	–	–	–	–	✓	✓	–	–	–	–	–	–	–	–	19%
	Comparators	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
	Time Horizon − Reporting and Reasoning	✓	✓	–	–	–	✓	–	✓	–	✓	✓	✓	✓	✓	–	✓	63%
	Discount Rate	✓	–	✓	–	–	–	✓	–	–	–	–	–	–	✓	✓	✓	31%
	Choice of Health Outcomes	–	✓	✓	–	NA	–	✓	✓	–	–	–	–	✓	NA	–		36%
	Measurement of Effectiveness	✓	✓	✓	–	NA	✓	✓	✓	–	–	–	–	✓	✓	NA	–	57%
	Measurement and valuation of preference-based outcomes	✓	✓	–	–	NA	–	✓	–	–	–	✓	–	✓	–	NA	–	36%
	Estimating Resources and cost	✓	✓	✓	✓	✓	✓	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	94%
	Currency, price data and conversion	✓	✓	✓	✓	✓	✓	✓	✓	–	✓	–	✓	✓	✓	✓	–	75%
	Choice of model	–	–	✓	✓	–	✓	–	✓	–	–	–	–	✓	✓	✓	✓	50%
	Assumptions	–	–	–	–	–	–	–	–	–	–	–	–	✓	✓	✓	✓	25%
	Analytic methods	–	–	–	–	✓	–	–	✓	–	–	–	–	–	–	–	–	13%
Results	Study Parameters	–	–	–	–	–	✓	✓	–	–	–	–	–	✓	✓	✓	✓	38%
	Incremental cost and outcome	✓	✓	–	✓	✓	–	–	–	–	–	✓	✓	✓	✓	–	–	56%
	Characterizing uncertainty	✓	✓	✓	✓	–	✓	✓	✓	✓	–	–	–	✓	✓	✓	✓	75%
	Characterizing heterogeneity	–	–	✓	–	–	✓	–	–	–	–	–	–	✓	–	–	–	25%
Discussion	Study Findings, limitations, generalizability and current knowledge	✓	✓	✓	✓	–	✓	✓	✓	–	✓	✓	✓	–	✓	✓	✓	75%
Others	Source of funding	✓	✓	✓	–	–	–	✓	✓	–	✓	✓	✓	–	–	–	–	50%
	Source of interest	✓	✓	✓	–	–	–	✓	✓	–	✓	–	✓	✓	✓	–	–	56%
	Study Quality Score (%)	58%	75%	67%	50%	43%	58%	75%	75%	29%	42%	46%	46%	71%	63%	67%	50%	

NA: Not aplicable.
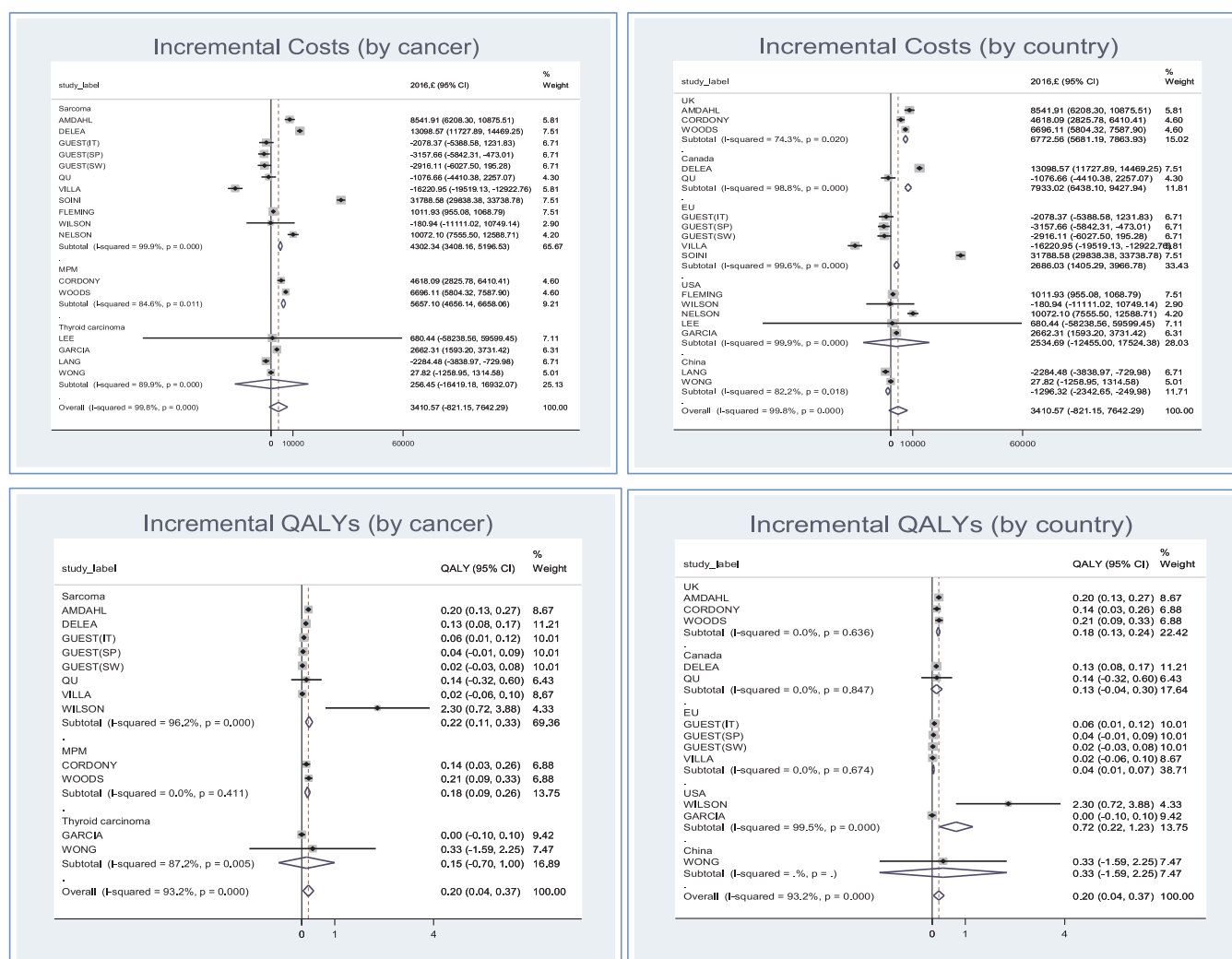
Fig. 2. Forest plots with the results of meta-analysis.

each study (n = 12; 36%), followed by partitioned survival model (n = 5; 15%), state transition model (n = 4; 12%) and decision tree models (n = 2; 6%). From the studies that reported the evaluation perspective (n = 20; 61%), 12 studies adopted only a healthcare perspective (60%), 5 studies adopted a combination of healthcare, social or payers perspective (25%), 2 studies adopted only a payer perspective (10%), and 1 adopted only a social perspective (5%). More details about patient characteristics (i.e. sample size, age, gender) and study characteristics (i.e. cycle length, time horizon, and discount rate) are presented in Table B1 in Appendix B.

The reported mean costs and mean outcomes of patients in the intervention and comparator groups in each study are reported in Table 2. Outcomes and costs of the comparators were not reported in the selected governmental reports and are therefore, not reported in this table.

After inflating and converting the reported costs to 2016 British pounds, the incremental costs ranged from −£16221 to £124880. Panel B in Table 2 reports the outcomes in terms of QALY, LY, OS, PFS, PPS. The total difference in QALYs between the intervention and control group ranged from 0.019 to 0.33. The total difference in LYs between the intervention and control group ranged from 0.14 to 1.16.

The incremental cost-effectiveness ratios reported in the 32 scientific studies and reports are presented in Table 3. In scientific studies the ICERs are positive, one study [22] reports a negative ICER and two studies [27,29] demonstrate that ICER is dominant, whereas in technological appraisal guidance's the reported ratios are all positive and the UK based are all above £20000 per QALY gain.

3.2. Results of the study quality assessment

The study quality scores of the published studies (governmental reports were not assessed) are presented in Table 4. Cost-Minimisation analyses [25,23] were excluded from choice of health outcomes, measurement of effectiveness, measurements and valuations of preference based outcomes evaluation. The quality score of the 16 selected studies ranged between 29% and 75% with an overall mean quality score of 57·2%. One study [20], was found to be of very low quality (29%), mainly due to the lack of information provided on the assessment and analysis of preference-based outcomes. Moreover, in many studies there was poor information on reporting values, ranges, references or probability distribution for all given study parameters. Most studies did not provide any descriptions of the analytic method supporting the evaluation (13%), a description of the relationship of the study perspective with the evaluated costs (19%), a description of the assumptions underpinning the decision-analytic model (25%),or the methods used to handle uncertainty or population heterogeneity (25%).

3.3. Results of the meta-analysis

The results of the meta-analysis by type of rare cancer (i.e. sarcoma, malignant pleural mesothelioma and thyroid carcinoma) and country (i.e. UK, Canada, USA, EU, China) are presented in Fig. 2. Based on all 16 studies used in the meta-analysis, interventions for rare cancers led on average to £3411 (95% CI: −821-7642) higher costs and 0·20 QALY

(95% CI 0·04–0·37) gain compared with their comparators (see Table B1 in Appendix B for the comparator in each selected study). The increase in hospital costs was predominantly driven by higher costs in the area of MPM (mean: £5657, 95% CI 4656–6658, n: 2) and sarcoma (mean: £4302, 95% CI 3408–5197, n: 11). Similar, the highest QALY gains were from interventions for sarcoma (mean: 0·22, 95% CI 0·11–0·33, n: 8) and MPM (mean: 0·18, 95% CI 0·09;0·26, n: 2).

Looking at the results of the meta-analysis by country, interventions for rare cancers led on average to an increase in hospital cost by £6772·56 (95% CI £5681·19–£7863·93) in the UK, £7933·01 (95% CI £6438·10–£9427·94) in Canada, £2686·03 (95% CI £1405·29 to £3966·78) in Europe while, both Chinese studies reported costs savings. Interventions for rare cancer led to QALY gains in all countries ranging from 0·04 (95% CI 0·01–0·07) in Europe to 0·72 (95% CI 0·22–1.23) in USA.

4. Discussion

Our study shows that there is a limited and of mediocre quality economic evidence of interventions for rare cancers. The published evidence shows that these interventions led on average to QALY gains (mean 0·20; 95% CI 0.04–0.37) at likely higher hospital costs (mean 3411; 95% CI −821 to −7642). All published scientific studies (n = 16), reported positive health outcomes (expressed in QALYs and survival) while, some of them reported cost savings indicating therefore, dominance of the evaluated interventions over their comparators.

The ICERs reported in the NICE reports (n = 16, 50% of all selected studies) ranged from £20300 to £59000 per QALY which is not excessively higher than the range of ceiling ratios (i.e. £20000 to £30000) suggested by NICE in England [49]. A study in England concluded that healthcare interventions costing £40000 per QALY had 50% chance to be recommended by NICE [50]. Considering this, interventions for rare cancers seem to provide reasonable value-for-money besides treating patients with rare cancers who are frequently children and adolescents with high severity of illness. These factors may increase the likelihood of NICE recommendation [51].

Moreover, the ICERs of rare cancer interventions included in our study fall within the range of ICERs of interventions for common cancers such as metastatic colorectal cancer (from £41310 to £67057) [52], metastatic breast cancer (from €1983 to €86174) [53], and lung cancer [54]. This implies that interventions for rare cancers are similar to interventions for common cancers with regards to cost-effectiveness. However, our study highlights the limited number of economic studies in rare cancers. The reasons for this are not clear but they might include the lesser need for economic evidence in the reimbursement of interventions for rare cancers. Decision-making for this type of interventions may rely on other criteria, such as effectiveness and equity, than on cost-effectiveness. Considering that cost-effectiveness studies in rare cancers are frequently complicated and expensive, the limited number of such studies may also imply inequality in public funding for research.

The vast majority of cost-effectiveness studies were focused on sarcoma treatments showing therefore, small variation in economic evidence among different types of rare cancer. This may be because there have been more than 70 histologic subtypes of sarcoma identified with higher prevalence and mortality than other rare cancers [55]. Sarcoma clinical trials provide a strong opportunity to potentially improve treatment and economic evaluations are frequently conducted alongside clinical trials. The many misconceptions about clinical trials for rare cancer interventions may be another explanation of the limited study variation. Conducting clinical trials and economic evaluations in most rare cancers may be perceived as difficult and expensive. This may be reflected in the fact that all selected studies in this review were conducted in high income countries. More international collaborations, such as the European Reference Network for rare diseases, are needed to make interventions for rare cancers more attractive to investors, governments and academic community.

The mediocre quality of the selected studies in this review also calls for more research funds and collaboration to assess the cost-effectiveness of rare cancer interventions. Poor clarification on the assumptions and analytic methods as well as the narrow scope of costs included in the published economic evaluations make the reliability of the existing evidence questionable. International guidelines of good-practice in economic evaluation should lead health economic research in rare cancers too.

Certainly, more and better economic evidence should be provided by researchers and governmental agencies worldwide aiming to highlight the noticeable need for conventional reimbursement for rare cancer interventions. This evidence is needed in decision-making more now than ever considering the increasingly tight health budgets.

Contributors

ARM was involved in the study design, literature search, review of the articles, and extraction of the data. PZ participated in the review of the articles and data extraction. ARM and PZ drafted the initial manuscript. AT contributed in the study design, literature search, review of the articles, interpretation of the data, and performed the meta-analysis. BH contributed to the study design, funding and clinical research experience to ensure relevance of the findings. AT and BH reviewed and revised previous versions of the manuscript. All authors have approved the final manuscript.

Declaration of interests

We declare not competing interest.

Study registration

This study is registered as PROSPERO CRD42017068539.

Conflict of interest

None.

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Appendix A. Search term strategy

((rare cancer or uncommon cancer or uncommon carcinoma or mesothelioma or thymoma or adrenal cancer or sarcoma or soft tissue sarcoma or classical hodgkin lymphoma or neuroendocrine carcinoma or rare lymphoma or rare leukemia or myelodysplastic neoplasm or head neck carcinoma or thyroid carcinoma or parathyroid carcinoma) and (cost effectiveness or cost benefit analysis or cost-effectiveness or cost effectiveness analysis or cost utility or cost-utility or cost)), ti.ab.

Appendix B

Table B1
Additional characteristics of selected studies.

	Intervention	Comparator	Study Population			Cycle Length	Time Horizon	Discount Rate
			Mean age	Gender (%Females)	Individuals			
[17]	Pazopanib	Placebo			n = 369	1 month	10 years	3.5%
[19]	Pazopanib	Placebo			n = 369	1 month	10 years	5%
[22]	Doxorubicin+ Lipoamide	Trabectedin	65			1 month	2 years	3%
[26]	Pulmonary Resection (PR) + Systemic Chemotherapy	No Treatment			n = 1124		1 year	3%
[27]	Preoperative Radiation Therapy	Post-operative Radiation Therapy				3 months	5 years	3%
[29]	Pazopanib	Trabectedin			n = 369	1 month	10 years	3%
[28]	Trabectedin	End Stage Treatment				1 month	5 years	
[20]	CxR +CT	CxR	44	47.2%	n = 125	1 month	76 months	
[30]	Osteoarticular graft reconstruction	Endoprosthetic reconstruction	20			1 year	10 years	
[25]	Functional Restoration Surgery	Soft Tissue Excision	51,6	64,17%	n = 67			
[18]	Pemetrexed + cisplatin	Vinorelbine			n = 448	1 month	29 months	
[32]	Raltitrexed + cisplatin	Active Symptom Control				21 days	5 years	3.5%
[24]	BRAF Testing	No BRAF Testing	40	0%		1 year	42 years	3%
[21]	TT + pCND	TT	40	0%	N = 100,000	1 year	42 years	3%
[23]	TT	pCND	50	0%	N = 100,000	1 year	20 years	3%
[31]	TT + pCND	TT	50	0%	N = 100,000	1 year	20 years	3%
[33]	Pemetrexed + cisplatin	Standard Care	448			29 months		
[34]	Pixantrone	BSC	67			6 months	23 years	
[35]	Imatinib	BSC					10 years	
[36]	Trabectedin	BSC				1 month	5 years	
[37]	Sunitinib	BSC				6 weeks	6 years	
[38]	Azatidine	BSC			207	35 days	Lifetime	
[39]	Imatinib	IFN-alpha			600	1 month	30 years	
[40]	VR-CAP	RCHOP				21 days	20 years	
[41]	Ruxolonitib	BSC						
[42]	Imatinib	No adjuvant treatment				1 month	50 years	
[43]	Bosutinib	Hydroxicarbamide						
[44]	Mifamurtide + Cisplatin + Doxorubicin +methotrexate + ifosfamide	Mifamurtide + Cisplatin + Doxorubicin + methotrexate			604	6months	60 years	
[45]	Carmustine Implants	Placebo				1 week	5 years	
[46]	Dasatinib	Imatinib						
[47]	Bosutinib	Nilotinib			546			
[48]	Pazopanib	Placebo						

MPM: Malignant Pleural Mesothelioma; CML: Chronic Myeloid Leukaemia; NHL: Non Hodgkin Lymphoma; HGG: High Grade Glioma, GST: Gastrointestinal Stromal Tumour, CEA: Cost Effectiveness Analysis, CUA: Cost Utility Analysis, CMA: Cost Mfinimisation Analysis, TT: Total Thyroidectomy, pCND; Best Supportive Care; RCT: Randomized Control Trial.

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