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Application of the systematic review and bibliometric network analysis (SeBriNA) methodology contextualizes evidence. Part 2: rituximab for non-Hodgkin's lymphoma

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Abstract

Objective: We conducted a *s*ystematic r*e*view and *b*ibliomet*ric* *n*etwork *a*nalysis (SeBriNA) of rituximab for non-Hodgkin's lymphoma.

Study Design and Setting: We searched three primary data sources (1997−2003) for five document types: original research, reviews, guidelines, editorials, and media reports. We conducted cumulative meta-analysis on three outcomes (mortality, tumor response, safety) and used GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) to classify evidence quality. Direct citation relationships between original research documents and other documents were analyzed and visually represented.

Results: Of 6,798 documents, 757 met inclusion criteria. The 317 original research documents represented 209 study clusters and 8,483 evaluated patients. Of 209 study clusters, 2.9% were randomized controlled trials (RCTs) and reported data on outcomes of interest. The quality of evidence was moderate. We identified 1,571 direct citations to the 317 original research documents. The first RCT reporting relevant outcomes appeared in 2000, whereas the first guidelines appeared in 1999. Of 212 media reports, 92% cited no original research.

Conclusions: Of 757 rituximab documents, RCTs of comparisons and outcomes represented $<3\%$ of original research. In contrast, review articles, guidelines, editorials, and media reports each outnumbered the relevant original research. The SeBriNA review facilitated the analysis, contextualization, and interpretation of these complex relationships.

Keywords: Evidence-based medicine; Bibliometrics; Systematic reviews; Non-Hodgkin's lymphoma; Publication bias; Rituximab

1. Introduction

The *s*ystematic r*e*view and *b*ibliomet*ric* *n*etwork *a*nalysis (SeBriNA) is a new methodology that aims to help decision makers conceptualize, interpret, and visualize the quantity, quality, and relevance of original research data within a network of related documents. We developed and tested our methodology on a new technology, rituximab for non-Hodgkin's lymphoma (NHL) because it was the first monoclonal antibody approved for cancer treatment, is expensive ($11,550 CDN per treatment course) [1], and demonstrated variable use in academic cancer centers [2]. Rituximab represented an important advancement for patients with NHL because of its limited toxicity profile compared with existing chemotherapy regimens. Thus, it was an ideal case study to demonstrate the value of the new SeBriNA methodology.

2. Methods

Below, we describe key steps of the SeBriNA and present results from our case study. Appendix A on the journal's Web site at www.jclinepi.com contains an expanded version of the methods, results, and discussion.

2.1. Research questions and selection of eligible documents

Our question for original research was as follows: For adult patients (>18 years) with newly diagnosed,

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What is new?

Key finding

The systematic review and bibliometric network analysis (SeBriNA) facilitated the analysis, contextualization, and interpretation of complex relationships among original research, reviews, guidelines, and media reports of rituximab, a first-in-class, expensive treatment for non-Hodgkin's lymphoma (NHL).

What this adds to what was known?

We conducted a SeBriNA of rituximab for NHL to understand the quality of patient-centered outcomes and context of this evidence represented by related documents. Of 757 documents of rituximab for NHL (1997−2003), original research of randomized controlled trials (RCTs) representing comparisons and outcomes of interest represented <3% of original research. The quality of evidence was moderate. The first RCT reporting response, mortality, or adverse events appeared in 2000, whereas the first guidelines appeared in 1999. Of 212 media reports, 92% cited no original research.

What is the implication and what should change now?

Practice pattern analysis identified variable and widespread use of rituximab for NHL in academic cancer centers before guideline recommendations and RCT results were released. The systematic review and bibliometric network analysis aims to help decision makers conceptualize, interpret, and visualize the quantity, quality, and relevance of original research data within a network of related documents. Potential applications of this methodology include prospective support for clinical and policy decisions, particularly in situations of uncertainty, and identification of research gaps.

relapsed, or refractory NHL, what is the effect of rituximab as a single agent or in combination with other therapies, regardless of study design, on mortality, tumor response, safety/adverse events, and quality of life? For review articles, guidelines, editorials, and media reports, we sought all documents that discussed rituximab as a treatment for NHL, and examined specific relationships between the documents and original research.

We defined a document as a ''written record, including published and unpublished material'' [3]. For original research, we included conference abstracts and peer-review literature. We included four types of related documents: reviews (systematic or narrative), clinical practice guidelines (guidelines), editorials (letters to the editor and editorials), and media reports. Throughout this article, we use the term ''document'' to represent the smallest unit of analysis of any of the foregoing reports.

Two independent reviewers (see acknowledgments) reviewed each document, discussed disagreements, and resolved differences by consensus. We noted reasons for exclusion and calculated inter-rater reliability using the Kappa statistic and 95% confidence interval [4,5]. Table 1 outlines our search strategies and eligibility criteria. Appendix B on the journal's Web site at www.jclinepi.com outlines each of our search strategies in detail.

2.1.1. Results

The search identified 6,798 documents, and 757 met inclusion criteria. The K by data source varied from 0.77 to 0.81. Table 2 outlines results of our document search and inter-rater reliability.

2.2. Original research data extraction and analysis

We abstracted a core data set from each document. Using original research documents, we identified all study clusters by matching authors' descriptions of the study sample and intervention [6]. We defined a ''study cluster'' as a metric to describe how one original research study may present different results and outcomes in a series of separate publications and forms over time. We conducted further analyses on study clusters with similar interventions.

We used GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) to assess the quality of evidence by outcome for all studies contributing to an outcome's estimate of effect [7]. We focused on four outcomes (mortality, tumor response, adverse events, and quality of life). We determined the evolving quality of the evidence over time; for each year, we calculated the estimate of effect through cumulative meta-analysis. Appendix C on the journal's Web site at www.jclinepi.com outlines the risk of bias items, operational definitions, and rating criteria.

2.2.1. Results

Of the 757 documents, we identified 317 (41.9%) original research, 160 (21.1%) reviews, 9 (1.2%) guidelines, 59 (7.8%) editorials, and 212 (28.0%) media reports. Of 317 original research documents, 202 (63.7%) appeared as conference abstracts, and the remainder, peer-review publications. Of 160 review articles, 9 (5.6%) were systematic reviews. Almost half of all media reports originated in the United States (97 (45.8%)), and the most common media source was the New York Times (34 (16%)). Table 3 outlines characteristics of the different documents.

Of 317 original research documents, we identified 209 study clusters. The median (interquartile range [IQR]) study cluster size was 1 (1−2) document; 155 study clusters were one document, and 54 study clusters were represented by 162 documents. Across 209 study clusters, 119 (56.7%)

Table 1. Document inclusion criteria

Document type	Original research documents	Reviews, practice guidelines, editorials	Media reports
Description	Any study reporting patients receiving rituximab for NHL, including case reports, prospective and retrospective cohort studies, single-arm studies (regardless of phase), and randomized controlled trials	*Reviews:* Narrative and systematic (citing a literature search strategy) *Guidelines:* Documents providing specific recommendations for patient's care, were developed by an organization or society, and included a reference list *Editorials/letters to the editor*	Media reports available to a layperson audience
Research question	*For adult patients (> 18 yr) with newly diagnosed, relapsed, or refractory NHL, what is the effect of rituximab as a single agent or in combination with other therapies, regardless of study design, on mortality, tumor response, safety/adverse events, and quality of life?*	*Review articles:* What original research did review articles cite? *Guidelines:* Did the practice guideline cite a systematic review? If not, what original research did the practice guideline cite? *Editorials/letters to the editor:* What original research did letters to the editor or editorials cite?	What original research did media reports cite?
Database source(s)	• Web of science • American Society of hematology proceedings • MEDLINE • EMBASE	• MEDLINE • EMBASE • Additional sources for guidelines: SUMSEARCH database, National Guidelines Clearinghouse (NGC) (www.guidelines.gov), known prominent oncology guideline developers not in the NGC (e.g., National Comprehensive Cancer Network)	• Factiva • LexisNexis
Inclusion criteria	*Population:* Adult humans (age >18 yr) with follicular (grade 1, 2, 3, or not otherwise specified), diffuse large cell, or mantle cell lymphoma low grade, indolent, or aggressive lymphoma *Intervention:* Rituximab for treatment of newly diagnosed, previously treated, or relapsed NHL as a single agent or in combination with other therapies *Comparison:* Any, including radioimmunotherapy *Outcomes:* Mortality, response, safety/adverse events, and quality of life	*Population:* Adult humans *Intervention:* Rituximab for treatment of newly diagnosed, previously treated, or relapsed NHL as a single agent or in combination with other therapies *Comparison:* Any	Newspapers Magazines and journals Unclassified documents
Exclusion criteria	• Use of rituximab in the preclinical setting (e.g., animal studies, studies of cell lines) • Rituximab use as a part of a radioimmunotherapy treatment regimen, rituximab as a part of a conditioning regimen for stem cell transplant, and treatment for non–lymphoma-related conditions (e.g., posttransplant lymphoproliferative disorder)	• Review articles that did not specifically mention the use of rituximab for NHL (e.g., overviews of monocolonal antibodies for cancer) • Guidelines developed by individuals • Editorials where the primary focus was not rituximab (e.g., drug approvals).	• Trade publications • Wire reports (not all wire reports are picked up by newspapers or magazines)

Abbreviation: NHL, non-Hodgkin's lymphoma.

appeared only as conference abstracts, 32 (15.3%) as conference abstracts and peer-review publications, and 58 (27.8%) as peer-review publications alone. From the 209 study clusters, authors evaluated 8,483 patients (median per study 20, IQR, 5–41), and most of the study clusters were case series (129, 61.7%). Randomized trial data represented 15 (7.2%) of all study clusters. Fig. 1 outlines the study designs of each of the 209 study clusters at first presentation.

Of the 209 study clusters, single-arm studies of single-agent rituximab or rituximab plus chemotherapy accounted for 131 (62.7%) of all the studies (Table 3). Multiple-arm designs accounted for 21 (10.0%) of all the studies; of these, 18 were randomized controlled trials (RCTs), eight had potentially relevant outcomes, and seven reported data on the outcomes of interest. No study clusters reported data on quality of life. Outcome reporting in conference abstracts was inconsistent, and at times, authors did not report the number of patients in each arm; we developed data assumptions for proof-of-concept analysis (Appendix D on the journal's Web site at www.jclinepi.com). Of seven study clusters reporting outcomes of interest, six study clusters, represented by 11 conference abstracts and one

Table 2. Kappa statistics for included studies

Source	American Society of Hematology Proceedings	OVID	LexisNexis, Factiva
Document type(s)	**Primary studies**	**Primary studies, reviews, guidelines, editorials**	**Media reports**
Identified	**490**	**5,781**	**523**
Excluded	0	5,102	226
Exclusion reasons			
Duplicates	0	487	0
Not applicable	0	2,960	0
Ineligible histology	0	686	0
Not rituximab	0	485	0
Radioimmunotherapy	0	155	0
Study of cell lines	0	135	0
Stem cell or bone marrow transplant	0	102	0
Pediatric	0	36	0
Animal study	0	24	0
Other	0	32	0
Ineligible publications	0	0	226
Candidates for full-text duplicate review	**490**	**679**	**297**
Excluded	0	51	0
Exclusion reasons			
Duplicates	0	10	0
News report	0	34	0
Trade publication	0	6	0
Personal account	0	1	0
Full-text reviewed in duplicate	**490**	**628**	**297**
Excluded	288	293	85
Exclusion reasons			
Duplicates	2	3	30
Not applicable	53	139	18
Unable to retrieve article	0	4	0
Ineligible histology	90	18	32
Not rituximab	2	88	0
Radioimmunotherapy	7	12	0
Study of cell lines	39	10	0
Stem cell or bone marrow transplant	84	14	0
Pediatric	1	1	0
Animal study	9		0
Not English	0	4	0
Other	1	0	5
Included	**202**	**335**	**212**
K **[95% CI]** **Final**	**0.80 [0.76, 0.83]**	**0.77 [0.72, 0.80]**	**0.81 [0.76, 0.85]**

Note: In this table, we outline our exclusion reasons and K statistics for each of the three literature searches. Bold numbers represent the total number of documents for each stage of document review.

peer-review publication (3.7% of 317 original research documents) contributed data. Table 4 outlines original research study clusters by intervention and study design.

Fig. 2 outlines the risk of bias assessments for the six study clusters contributing data to the outcomes of interest. Most of the studies did not report sufficient information to make a judgment. The study best reporting risk of bias characteristics was the peer-review publication [8].

We rated the overall quality of evidence as moderate. We downgraded the quality of RCTs from high to moderate because many trials had insufficient reporting to assess the risk of bias attributes, particularly allocation concealment and intention-to-treat analyses, two factors empirically associated with larger estimates of treatment effect [9,10]. Overall, the effect estimates for mortality and response consistently favored rituximab. However, for safety estimates, conclusions were less certain. Table 5 outlines the cumulative meta-analysis results and quality of evidence by outcome, over time. Appendix E on the journal's Web site at www.jclinepi.com outlines the detailed summary of findings tables for each outcome.

2.3. Document network relationships

To understand the context of original research, we conducted a direct citation analysis between reviews,

Table 3. Characteristics of included documents

Document type	*N* (% of document type)		
	Conference abstracts (202)	Peer-review publications (115)	Total (%)
Original research (*N* = 317)			
Year			
1997	6	2	8 (2.5)
1998	8	4	12 (3.8)
1999	21	10	31 (9.8)
2000	32	17	49 (15.5)
2001	42	23	65 (20.5)
2002	42	32	74 (23.3)
2003	51	27	78 (24.6)
Study design			
Randomized controlled trial	29	12	41 (12.9)
Nonrandomized comparative	5	0	5 (1.6)
Before-after	1	0	1 (0.3)
Case series	135	62	197 (62.1)
Case study	8	29	37 (11.7)
Database/outcomes study	24	12	36 (11.4)
Number of patients evaluated (median, interquartile range)	28 (12, 53)	26 (1, 52)	27 (9, 53)
Reported outcomes			
Mortality	67	45	112 (35.3)
Response	154	79	233 (73.5)
Adverse events	133	78	211 (66.6)
Quality of life	0	1	1 (0.3)
Any author affiliated with industry	43	24	67 (21.1)
Disease status of enrolled patients			
Newly diagnosed or previously untreated	54	29	83 (26.2)
Relapsed or refractory	114	58	172 (54.2)
Newly diagnosed or previously untreated and relapsed or refractory	25	19	44 (13.9)
Not reported	9	9	18 (5.7)

Document type	*N* (% of document type)
Conference presentation type (*N* = 202)	
Oral	36 (17.8)
Poster	81 (40.0)
Publication only	85 (42.1)
Review articles (*N* = 160)	
Systematic	9 (5.6)
Narrative	151 (94.4)
Any author affiliated with industry	19 (11.9)
Editorials (*N* = 59)	
Editorial	32 (54.2)
Report of clinical data	22 (37.3)
Commentary on published research	4 (6.8)
Research letter	1 (1.7)
Any author affiliated with industry	2 (3.3)
Clinical practice guidelines/guidance statements (*N* = 9)	
Citing a systematic review	6 (66.7)
Any author affiliated with industry	1 (11.1)
Media reports (*N* = 212)	
Country	
United States of America	97 (45.8)
United Kingdom	77 (36.3)
Australia	14 (6.6)

(*Continued*)

Table 3. Continued

Document type	*N* (% of document type)
Canada	10 (4.7)
New Zealand	7 (3.3)
France	3 (1.4)
Israel	2 (0.9)
Spain	1 (0.5)
Switzerland	1 (0.5)
Source	
The New York Times	34 (16.0)
Financial Times	17 (8.0)
The Times (London)	13 (6.1)
Daily Mail (London)	11 (5.2)
The Globe and Mail (Canada)	9 (4.2)
The Wall Street Journal	8 (3.8)
The San Diego Union-Tribune	6 (2.8)
Business Week	6 (2.8)
The Boston Globe	6 (2.8)
The Washington Post	5 (2.4)
Other	156 (73.6)

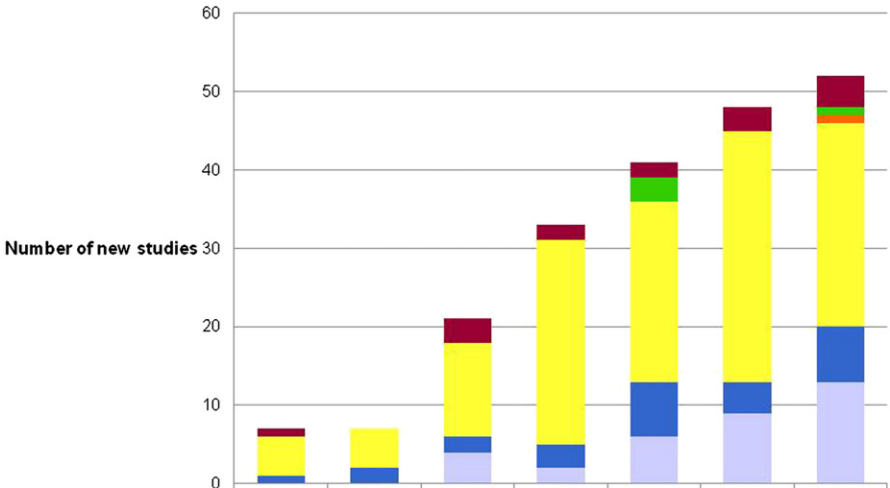
In this table, we describe the characteristics of the 757 documents included in our case study exemplar. Of the 757 documents, we identified 317 (41.9%) original research, 160 (21.1%) reviews, 9 (1.2%) practice guidelines, 59 (7.8%) editorials/letters to the editor, and 212 (28.0%) media reports.

guidelines, editorials, and media reports and all original research documents in our cohort [3].

2.3.1. Results

We identified 1,571 direct citations to the 317 original research data documents. The 160 reviews accounted for 1,421 (90.4%) citations; the nine guidelines, 25 (1.6%) citations; the 59 editorials, 108 (6.9%) citations; and the 212 media reports, 17 (1.1%) citations. The 160 review articles cited a median (IQR) of 5 (3–11) original research documents; of these, 96 (60.0%) cited both peer-review publications and conference abstracts, 47 (29.4%) cited peer-review publications alone, 7 (4.4%) cited conference abstracts alone, and 10 (6.2%) cited nothing from our cohort of original research data reports.

Of nine practice guidelines, six cited systematic reviews, all completed specifically for the practice guideline. Overall, the nine guidelines cited a median (IQR) of 8 (5–11) original research documents. Six practice guidelines cited peer-review and conference abstract documents, three cited



	1997	1998	1999	2000	2001	2002	2003
Randomized controlled trial	1	0	3	2	2	3	4
Non-randomized comparative study	0	0	0	0	3	0	1
Before-after study	0	0	0	0	0	0	1
Case series	5	5	12	26	23	32	26
Database / outcomes study	1	2	2	3	7	4	7
Case report	0	0	4	2	6	9	13
Total new studies	7	7	21	33	41	48	52

Fig. 1. Study design for 209 original research study clusters on rituximab for non-Hodgkin's lymphoma. In this figure, we demonstrate the number of new study clusters, by year, and by study design.

Table 4. Original research studies of rituximab for NHL (1997–2003)

Intervention	1997	1998	1999	2000	2001	2002	2003	Total (%)
Single-arm trials								188 (90.0)
Single-agent rituximab	5	7	8	12	10	15	10	67 (32.1)
Rituximab + CHOP[a]	0	0	3	3	3	4	5	18 (8.6)
Rituximab + other chemotherapy (non-CHOP)	0	0	3	10	8	13	12	46 (22.0)
Rituximab + other therapy (nonchemotherapy)[b]	1	0	3	3	10	3	6	26 (12.4)
Rituximab + ≥2 therapies[c]	0	0	1	1	1	8	8	19 (9.1)
Rituximab + unknown[d]	0	0	0	1	4	2	5	12 (5.7)
Nonrandomized comparative, before-after studies or randomized trials[e]								21 (10.0)
Rituximab vs. chemotherapy or placebo	0	0	0	0	0	0[f]	0	0
Rituximab + chemotherapy vs. chemotherapy	0	0	0	2	2[e]	3	4[e]	11 (5.3)
New therapy vs. Rituximab	0	0	1	0	0	0	0	1 (0.5)
Rituximab in both arms	1	0	2	1	3	0	2	9 (4.3)
Total of all studies	7	7	21	33	41	49	52	209

Abbreviation: NHL, non-Hodgkin's lymphoma.

In this table, we summarize the original research studies of rituximab for NHL by study intervention. We included studies from the American Society of Hematology proceedings and journals indexed by MEDLINE or EMBASE. If authors reported a study at multiple time points, we included the first study report.

[a] CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone.

[b] Other therapies included growth factor, interleukin-2, interferon, radioimmunotherapy, thalidamide, other monocolonal antibodies, vaccines, and experimental therapies.

[c] Combined therapies were primarily chemotherapy and growth factor.

[d] Within each of these studies, the patients did not receive the same treatments with rituximab or the authors did not describe the additional therapies.

[e] Two studies were nonrandomized comparative trials (2001, 2003); one study was a before-after study (2003); all other numbers represent randomized trials (total randomized trials = 8).

[f] One three-arm randomized controlled trial included rituximab alone vs. rituximab plus chemotherapy vs. chemotherapy alone. We included this study in the rituximab plus chemotherapy vs. chemotherapy category.

peer-review publications only, and none cited conference abstracts alone. The 59 editorials cited a median (IQR) of 1 (0–3) original research data reports.

Of 212 media reports, 195 (92.0%) cited nothing from our cohort of original research; the remaining 17 (8.0%) media citations represented two study clusters of three documents—an interim analysis of the first RCT comparing rituximab plus chemotherapy vs. chemotherapy alone [11] ($n = 5$; 2.4%), its subsequent peer-review publication [8] ($n = 11$; 5.2%), and a peer-review publication of an RCT comparing rituximab against a new therapy [12] ($n = 1$; 0.5%). Across document types, authors cited conference abstract data in 77.5% of all documents.

The most influential original report, measured by the greatest number of citations by other sources, was a 166 person, single-arm case series of single-agent rituximab with 111 (7.1%) citations, published as a peer-review publication in 1998 [13]. Table 6 outlines the top 10 influential studies; all of these documents were peer-review publications.

2.4. Document network visualization

To develop and visualize the document network, we used social network analysis techniques. We visualized two types of relationships: [1] Study clusters–relationships between original research documents, and [2] Direct citation relationships between other documents and original research documents.

2.4.1. Results

Foundations: The foundations represent the volume of documents by document type and year. In Fig. 3, we highlight five main features of the document cohort by document type. Among the 317 original research documents, there were many case series and few RCTs. Among the 160 review documents, there were many review articles, but few systematic reviews. Of nine practice guidelines, six cited a systematic review. The first of 59 editorials appeared in 1998, and there was a lot of media "buzz," starting as early as 1997 as demonstrated by the 212 media documents.

Relationships among foundations: The relationships represent the links among the original research documents and reviews, guidelines, editorials, and media reports. Fig. 4 is a common output from a bibliometric network analysis and exposes the complexity of relationships among different documents. Within the original research documents (gray and red), the relationships between the 317 original research documents and 209 study clusters are complex. At times, the network is so complex that the individual line pathways are no longer clearly visible. Of the 54 study

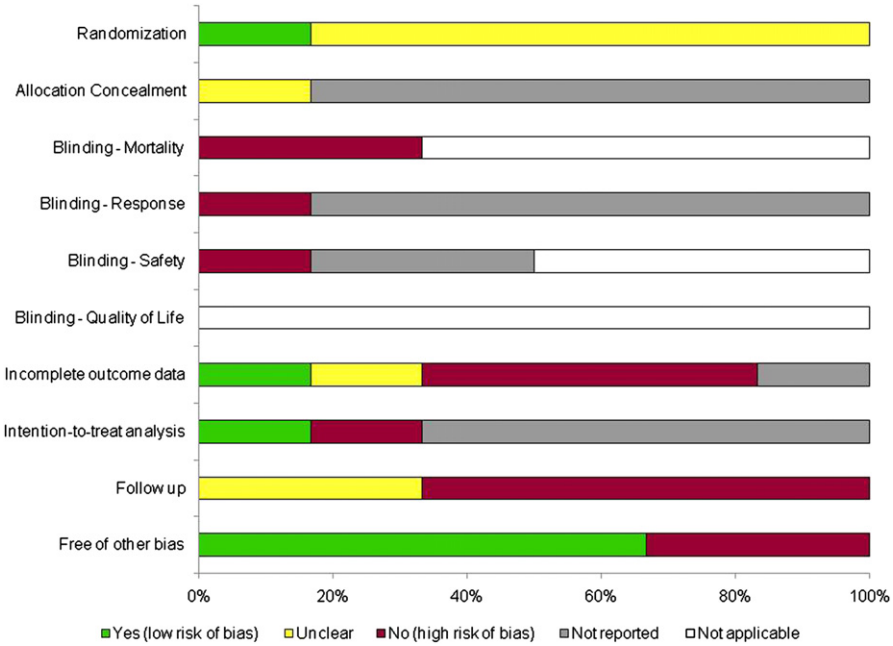


Fig. 2. Risk of bias assessments for the six randomized controlled trials comparing rituximab + chemotherapy vs. chemotherapy alone and reporting data on our outcomes of interest. In this figure, we display the risk of bias assessments for the six study clusters reporting original research data on our outcomes of interest (mortality, tumor response, safety, or quality of life). Green bars indicate the study reported and executed the item to minimize risk of bias. Red bars indicate the study reported and executed the item to increase risk of bias. Yellow bars indicate authors did not report sufficient detail to judge yes or no. Gray bars indicate the item was not reported. White bars indicate the item was not applicable because the authors did not include this outcome in their analysis.

clusters represented by multiple documents, 59% progressed from conference abstract to peer-review publication. Lines from review articles, practice guidelines, and editorials to original research data documents highlight citations of both conference abstracts and peer-review publications. Very few lines connect the 212 media reports to original research data reports. Where relationships do exist, the media reports all report on the same conference abstract RCT in 2000 [11], or two peer-review RCTs in 2002 [8,12].

SeBriNA outputs: The SeBriNA outputs juxtapose the quality of evidence by outcome and cumulative meta-analysis results with the citation relationships among documents. Figs. 5 and 6 build on the previous figures, and add information about the estimate of effect and quality of the

Table 5. Estimate of effect and quality of evidence (RCTs of rituximab + chemotherapy vs. chemotherapy alone)

Year	1997	1998	1999	2000	2001	2002	2003
Mortality, two studies total	No comparative studies			0.53 [0.36, 0.80] ⊕⊕⊕◯ One study	0.67 [0.51, 0.90] ⊕⊕⊕◯ Two studies	0.70 [0.54, 0.92] ⊕⊕⊕◯ Two studies	0.70 [0.54, 0.92] ⊕⊕⊕◯ Two studies
Response, six studies total	No comparative studies			1.26 [1.08, 1.47] ⊕⊕⊕◯ One study	1.35 [1.01, 1.81] ⊕⊕⊕◯ Two studies	1.14 [1.03, 1.25] ⊕⊕⊕◯ Four studies	1.24 [1.02, 1.52] ⊕⊕⊕◯ Six studies
Safety, one study total	No comparative studies			No studies reporting outcome	1.30 [0.75, 2.77] ⊕⊕⊕◯ One study[a]	0.60 [0.38, 0.96] ⊕⊕⊕◯ One study[b]	0.60 [0.38, 0.96] ⊕⊕⊕◯ One study[b]
Total new study clusters (RCT/non-RCT)	7 (1/6)	7 (0/7)	21 (3/18)	33 (2/31)	41 (2/39)	48 (3/45)	52 (4/48)

In this table, we outline the yearly cumulative meta-analysis estimate of effect (top row of each cell), quality of evidence by outcome (middle row of each cell), and number of studies contributing to each estimate of effect (bottom row of each cell). The symbols within the table represent the overall quality of the evidence for each important outcome (◯= very low quality evidence; ⊕⊕⊕⊕=High quality evidence). For mortality and safety outcomes, numbers less than 1 favor rituximab plus chemotherapy. For response outcomes, numbers greater than 1 favor rituximab plus chemotherapy.

[a] This study appeared as a conference abstract and reported grade 3 or 4 adverse events in aggregate.

[b] This study was the peer-review publication of the 2001 conference abstract. The estimate of effect represents the proportion of grade 3 or 4 infections. Authors did not report grade 3 or 4 adverse events in aggregate.

Table 6. Top 10 influential original research documents

Author	Year	Number of direct citations	Study design	Number of evaluable patients	Intervention	Any author industry affiliation	Survival	Response	Safety
McLaughlin [13]	1998	111	Case series	165	Single-agent rituximab	Y	x	x	x
Czuczman [21]	1999	90	Case series	40	Rituximab + CHOP	Y	x	x	x
Coiffier [22]	1998	86	RCT	54	Rituximab in both arms	Y	x	x	x
Maloney [23]	1997	71	Case series	37	Single-agent rituximab	Y		x	x
Coiffier [8]	2002	68	RCT	399	Rituximab + CHOP vs. CHOP	N	x	x	x
Maloney [24]	1997	56	Case series	20	Single-agent rituximab	Y		x	x
Vose [25]	2001	46	Case series	33	Rituximab + CHOP	Y	x	x	x
Piro [26]	1999	43	Case series	37	Single-agent rituximab	Y		x	x
Colombat [27]	2001	41	Case series	50	Single-agent rituximab	Y		x	x
Davis [28]	1999	40	Case series	31	Single-agent rituximab	Y	x	x	x

Abbreviations: Y, Yes; N, No; x, outcome reported in original research document; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone—CHOP is a type of chemotherapy; RCT, randomized controlled trial.

In this table, we outline the top 10 influential documents, based on the number of direct citations by review articles, practice guidelines, editorials or letters to the editor, and media reports.

evidence for patient-centered comparisons and outcomes from Table 4. Fig. 5 focuses on the relationships within original research documents, juxtaposed against all original research data in our cohort. Despite 209 study clusters, most of the patient-centered evidence appeared across seven study clusters, and only 6 (2.9%) reported information on the same outcome, tumor response. Because of unclear reporting, the overall quality of the evidence was moderate. This information about the quantity, quality, and consistency of the original research data are important considerations as we discuss the subsequent figures.

Fig. 6 adds the synthesis documents (reviews, green), guidance documents (practice guidelines, orange), editorials (lavender), and media reports (blue) to Fig. 5, all juxtaposed against the original research. We identified a high ratio (1:1.3) of review articles ($n = 160$) compared with original research study clusters of *any* study design ($n = 209$), and the first clinical guidance preceded any publicly available information of our comparisons or outcomes of interest. Of 212 media reports of rituximab for NHL, 8% ($n = 17$) cited original research data. Of the 317 original research documents, media reports cited three original research documents of two study clusters.

Fig. 7 is the ultimate output of the SeBriNA, visually integrating all information from the previous figures. We added the marketing approval dates by three jurisdictions: United States (1997) [14], the European Union (1998) [14], and Canada (2000) [15]. From this figure, the first marketing approvals occurred before any publicly available data on patient-centered comparisons and outcomes. Although Canada approved the drug in 2000, approval occurred before the first peer-reviewed publication of patient-centered comparisons and outcomes, yet 1 year after the first practice guideline recommending its use.

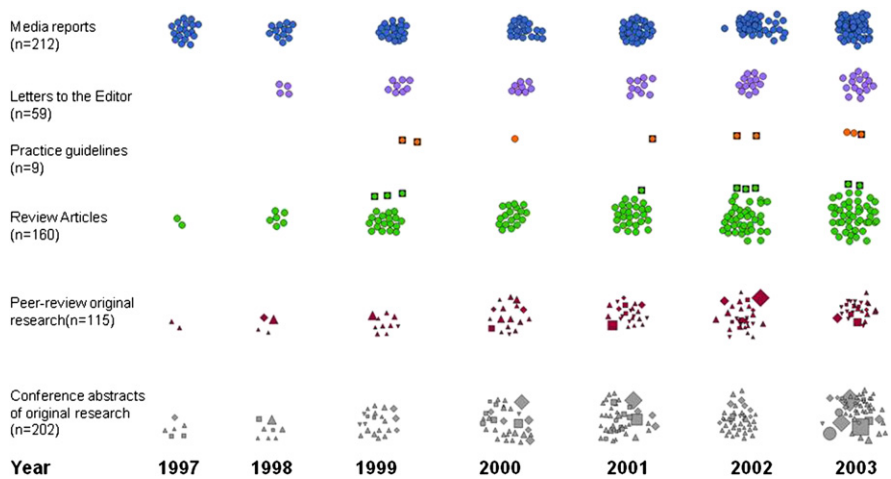


Fig. 3. Visualization of 757 rituximab documents by year (1997–2003). In this figure, we demonstrate the foundational visualization of 757 rituximab documents by year and document type. Each point represents one original research document. Gray = conference abstracts of original research; red = peer-review original research; green = review articles (green with black boxes = systematic reviews; all other represent narrative reviews); orange = practice guidelines (orange with black boxes = practice guidelines citing a systematic review); lavender = letters to the editor or editorials; blue = media reports. For original research documents (gray or red), symbols represent study design: ◆ = randomized controlled trial; ▲ = case series; ▼ = case study; ■ = database study; ● = other. Symbol size represents number of enrolled patients.

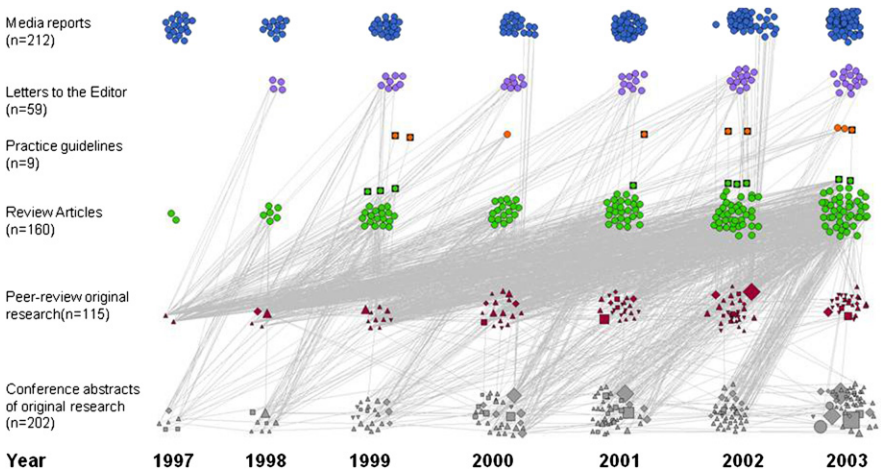
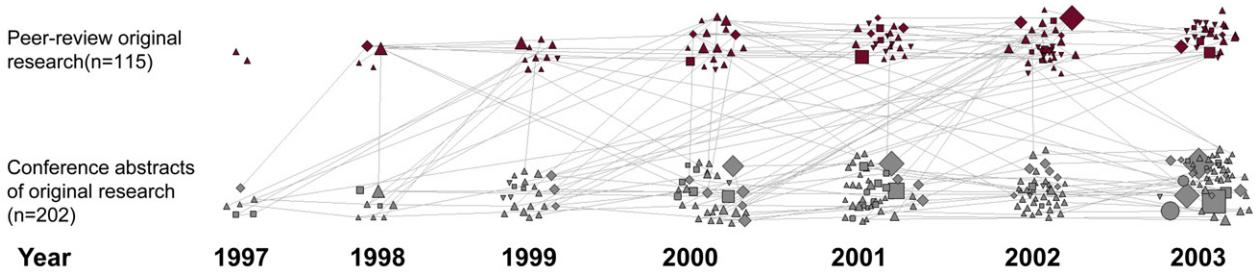


Fig. 4. Visualization of rituximab document network (1997–2003). In this figure, we represent the foundational relationships among documents. Gray lines represent two types of relationships: 1) Study clusters, or relationships within original research documents, and 2) Direct citations of original research by other documents. Horizontal, vertical, and up-sloping diagonal lines represent the different types of relationships within a study cluster. Horizontal lines within one document type (i.e., conference abstracts or peer-review publications) represent the appearance of different documents over time. Vertical and up-sloping diagonal lines represent progression from conference abstract to peer-review publication.

3. Discussion

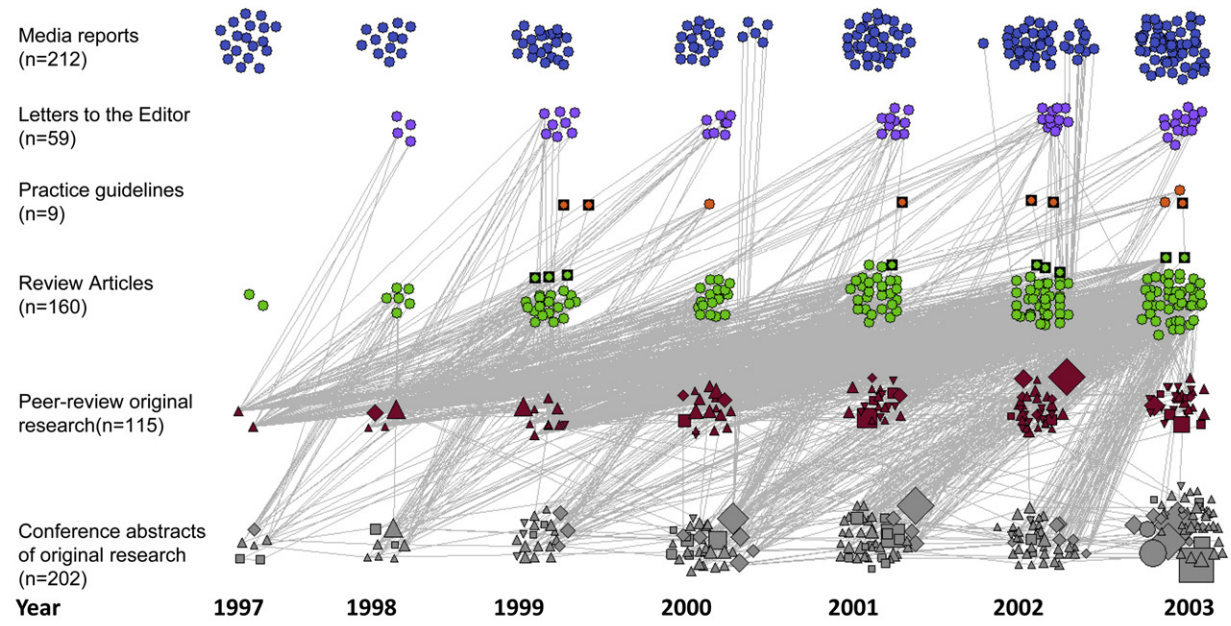
We identified 757 documents meeting our inclusion criteria with high inter-rater agreement. Of 757 documents, 317 (42%) were original research, representing 209 study clusters. Within the original research, most were small, uncontrolled studies, and <10% were RCTs. We identified



Estimate of Effect and Quality of Evidence (RCTs of Rituximab + Chemotherapy vs. Chemotherapy alone)

Mortality 2 studies total	No comparative studies			0.53 [0.36, 0.80] ⊕⊕⊕○ 1 study	0.67 [0.51, 0.90] ⊕⊕⊕○ 2 studies	0.70 [0.54, 0.92] ⊕⊕⊕○ 2 studies	0.70 [0.54, 0.92] ⊕⊕⊕○ 2 studies
Response 6 studies total				1.26 [1.08, 1.47] ⊕⊕⊕○ 1 study	1.35 [1.01, 1.81] ⊕⊕⊕○ 2 studies	1.14 [1.03, 1.25] ⊕⊕⊕○ 4 studies	1.24 [1.02, 1.52] ⊕⊕⊕○ 6 studies
Safety 1 study total				No studies reporting outcome	1.30 [0.75, 2.77] ⊕⊕⊕○ 1 study	0.60 [0.38, 0.96] ⊕⊕⊕○ 1 study	0.60 [0.38, 0.96] ⊕⊕⊕○ 1 study
Total new study clusters (RCT/non-RCT)	7 (1/6)	7 (0/7)	21 (3/18)	33 (2/31)	41 (2/39)	48 (3/45)	52 (4/48)

Fig. 5. Visualization of original research documents, study clusters, estimates of effect, and quality of evidence by outcome. Systematic review and bibliometric network analysis outputs. In these figures, we juxtapose the relationships between document types and original research, and the estimates of effect for original research data of patient-centered comparisons and outcomes. Each point represents one document. Gray = conference abstracts of original research; red = peer-review original research; green = review articles (green with black boxes = systematic reviews; all other represent narrative reviews); orange = practice guidelines (orange with black boxes = practice guidelines citing a systematic review); lavender = - letters to the editor or editorials; blue = media reports. For original research documents (gray or red), symbols represent study design: ◆ = randomized controlled trial; ▲ = case series; ▼ = case study; ■ = database study; ● = other. Symbol size represents number of enrolled patients. In this figure, we demonstrate the body of original research documents and study clusters from Fig. 4, juxtaposed against the cumulative meta-analysis estimate of effect and quality of evidence from Table 5. [a]This study appeared as a conference abstract and reported grade 3 or 4 adverse events in aggregate. [b]This study was the peer-review publication of the 2001 conference abstract. The estimate of effect represents the proportion of grade 3 or 4 infections. Authors did not report grade 3 or 4 adverse events in aggregate.



Estimate of Effect and Quality of Evidence (RCTs of Rituximab + Chemotherapy vs. Chemotherapy alone)

Mortality 2 studies total	No comparative studies	0.53 [0.36, 0.80] ⊕⊕⊕○ 1 study	0.67 [0.51, 0.90] ⊕⊕⊕○ 2 studies	0.70 [0.54, 0.92] ⊕⊕⊕○ 2 studies	0.70 [0.54, 0.92] ⊕⊕⊕○ 2 studies
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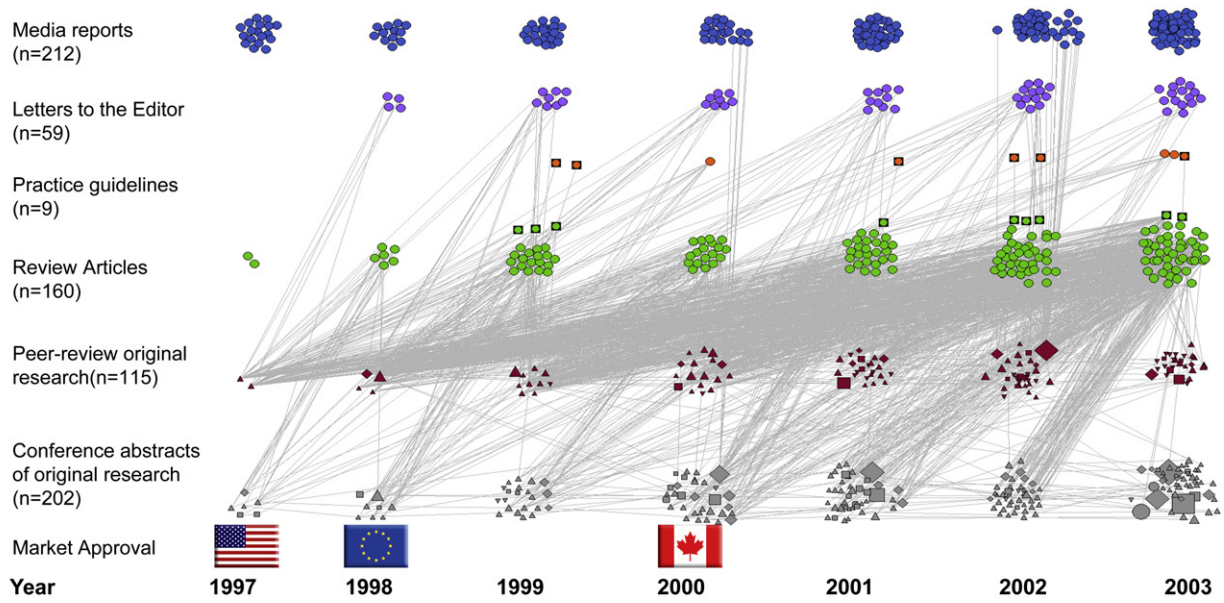
Fig. 6. Visualization of original research documents, study clusters, estimates of effect, and quality of evidence by outcome and citation relationships from review articles, practice guidelines, editorials, letters to the editor, and media reports to original research documents. In this figure, we display how original research documents are cited by review articles, practice guidelines, editorials, and media reports. Note how few original research documents were cited by media reports. In this figure, the cumulative meta-analysis estimate of effect and quality of evidence can be demonstrated from Table 5. [a]This study appeared as a conference abstract and reported grade 3 or 4 adverse events in aggregate. [b]This study was the peer-review publication of the 2001 conference abstract. The estimate of effect represents the proportion of grade 3 or 4 infections. Authors did not report grade 3 or 4 adverse events in aggregate.

many different combinations of rituximab interventions, and <4% reported data on our comparisons and outcomes of interest; of these, the overall quality of evidence was downgraded from high to moderate, primarily because of poor reporting. Of our four outcomes of interest, two study clusters reported mortality, six reported tumor response, and one reported adverse events; we found no information on quality of life. Because of inconsistent reporting, we made data assumptions to estimate effect sizes. By 2003, of 317 original research documents and 209 study clusters, only seven study clusters reported our comparisons of interest. Overall, only six study clusters, represented by 12 original research documents reported our outcomes of interest, and only one study was available in the peer-review literature [8].

Rituximab appeared to quickly become standard therapy (Table 4). Overall, there appears to be disjointed development of the evidentiary base moving to the next comparisons before definitive conclusions on the outcomes we chose to study could be drawn from the previous research. From the cumulative meta-analysis, effect estimates of the available RCT data favored rituximab; however, we had less confidence in the quality of data because of poor reporting. Thus, in contrast to the volume of original rituximab research, we found few traditional study designs (RCTs) or outputs (peer-review publications) that would be more likely to inform clinical or policy decisions.

We studied the 440 related documents and their representation of the original research evidence by visualization of the document network and empiric study of direct citation relationships. The most influential original research document was a 166-person case-series peer-review publication of single-agent rituximab, accounting for 7% of all citations. In this highly cited publication, the primary outcome measure was tumor response, 48% of all patients responded, and the median duration of follow-up was 11.8 months [13].

In our case study, reviews accounted for over 90% of all direct citations to original research data, and systematic reviews accounted for <6% of all reviews (Fig. 4). For every



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Mortality 2 studies total	No comparative studies			0.53 [0.36, 0.80] ⊕⊕⊕○ 1 study	0.67 [0.51, 0.90] ⊕⊕⊕○ 2 studies	0.70 [0.54, 0.92] ⊕⊕⊕○ 2 studies	0.70 [0.54, 0.92] ⊕⊕⊕○ 2 studies
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Total new study clusters (RCT/non-RCT)	7 (1/6)	7 (0/7)	21 (3/18)	33 (2/31)	41 (2/39)	48 (3/45)	52 (4/48)

Fig. 7. The systematic review and bibliometric network analysis: evidence in context.

review article, we identified 1.3 original research study clusters, representing only 30% more original research than synthesis, and much duplicate effort among review authors. For comparison, the ratio of review articles to original research in pathology, physiology, and cardiology in 2006 was 1:6, 1:6, and 1:7, respectively [16]. Thus, with the high numbers of review articles, there is a risk of over-representing the evidence and users misperceiving the volume, maturity, and definitiveness of original research evidence. From this analysis, it is unclear why the volume of review articles was high. Future research with this methodology may consider including funding sources or conflict of interest statements to better understand the high volume of review articles.

Finally, rituximab generated many media reports, accounting for 28% of all included documents (Fig. 4). Only 8% of 212 media reports cited any original research data, and of these, the 17 media reports cited three original RCT research documents representing two study clusters. The first cited document occurred in 2000, receiving attention from high-profile newspapers such as the New York Times [17]. Although the cited study was an RCT reporting mortality and response [11] (Table 5, Figs. 5 and 6), the authors reported no safety information, and it was a conference abstract of an interim analysis of an unblinded trial. Health service researchers or policy analysts could use data from the SeBriNA to brief decision makers about the potential risks and benefits of a policy decision based on the maturity, quantity, and quality of available scientific data.

Strengths of this case study include comprehensiveness and reproducibility of included documents, inclusion of gray literature, documented decision rules, and visual representation of the document network. In this case, visual inspection of the quantity of original research data and review documents may imply a strong evidence base for the new technology. In contrast, high-quality, relevant information was sparse and media reports initially highlighted less mature research data. We suggest that the document network is a helpful addition to existing evidence synthesis tools such as evidence tables because it juxtaposes evidence quantity against evidence quality.

Our study has limitations. For our case study, we included four outcomes that we presumed were important to patients, restricted our search to one conference, and made data assumptions about the number of patients allocated to each treatment group. Our case study reflects the challenges of

using conference abstract data to inform clinical and policy decisions, and offers possible suggestions to address poorly reported public data. Moreover, our case study may be typical of the only data available to decision makers, who need to interpret and synthesize the information to inform decisions about funding new health care technologies. Future research needs to examine the usefulness of other sources to address publication bias, such as trial registries and use of multiple sources of gray literature (e.g., multiple conferences).

Direct citation linkages between related documents and original research data describe relationships. However, evidence consumers need more information about the nature of these relationships, and we believe that content analysis is an important next step to contextualize the evidence. For example, of many media reports, few cited original research; we need more analysis to understand the focus of the media reports. Content analysis will facilitate better interpretation of the role of original research across document types.

Rituximab is widely regarded as an important treatment breakthrough for patients with NHL by the clinical community [18,19]. From our case study, evidence alone did not appear to support widespread uptake of rituximab into the different clinical trial regimens. Thus, other documents, such as regulatory approval submissions or policy decisions from different jurisdictions may further contextualize original research. Finally, other considerations such as patients' values and preferences, balance between benefits and harms, and resource use also inform recommendations [20].

4. Conclusions

We applied the SeBriNA methodology to early evidence for rituximab for NHL. Of 757 rituximab documents, RCTs of relevant comparisons and outcomes represented $<3\%$ of original research. In contrast, review articles, guidelines, editorials, and media reports outnumbered relevant original research. The SeBriNA facilitated the analysis, contextualization, and interpretation of these complex relationships. We need further research to understand the added value of content analysis and determine the utility, acceptability, and generalizability of this methodology to other health care questions.

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Author contributions: Study conception, design, data acquisition, and analysis (M.E.K.), interpretation of data (M.E.K., M.C.B.); drafting the article (M.E.K.), critical revisions for important intellectual content (M.C.B.); final approval of the version to be published (M.E.K., M.C.B.).

Appendix

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2012.03.008.

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