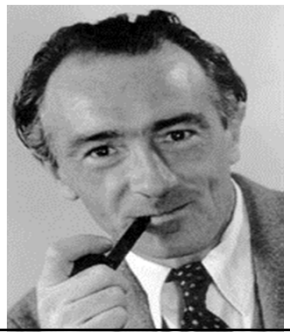
OVERVIEW OF COCHRANE METAANALYSIS AND PRISMA

DR KANHU CHARAN PATRO

Pronunciation	/kɒkrɪn/
Formation	1993; 25 years ago (as Cochrane Collaboration)
Type	International NPO
Purpose	Independent research into data about health care
Headquarters	London, England[1]
Region served	Worldwide
Official language	English
Leader	Mark Wilson (CEO)[2]
Volunteers	Over 37,000 (2015) [3]
Website	www.cochrane.org
Formerly called	Cochrane Collaboration

1. Cochrane, previously known as the **Cochrane Collaboration**, was founded in 1993 under the leadership of **Iain Chalmers**
2. It was developed in response to **Archie Cochrane's** call for up-to-date, systematic reviews of all relevant randomized controlled trials of health care

Archie Cochrane



MAVERICK STREAK

If you describe someone as a **maverick**, you mean that they are unconventional and independent, and do not think or behave in the same way as other people

VIGNETTE

The Remarkable Archie

Origins of the Cochrane Collaboration

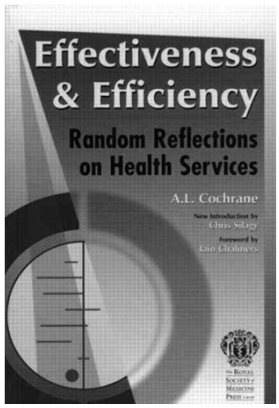
Warren Winkelstein, Jr

Most epidemiologists are familiar with the Cochrane Collaboration, which provides critical and systematic reviews of randomized trials relevant to medical practice and health policy. The Cochrane Collaboration has so far enlisted 15,000 volunteers worldwide in the preparation of these reviews.[1] Today, more people are familiar with the Cochrane Collaboration than with Cochrane himself. But the man is worth remembering—Archibald Leman Cochrane was one of the most colorful medical scientists of the 20th century.

Archie, as he was known, came from a wealthy family, thereby enjoying lifelong financial security. As a young man, he suffered from a sexual dysfunction for which he could not find treatment in the United Kingdom.[2] He underwent psychoanalysis in Germany. While there, he became fluent in German—and infuriated by the Nazis. When his Jewish analyst fled to Vienna and subsequently to Holland, Archie followed. On returning to England, he enlisted in the International Brigade to fight fascism in Spain. During World War II, he was held prisoner for 4 years.

Archibald Leman Cochrane

else. I date the real beginnings of my love of whiskey to this



In this seminal book, first published in 1972 by the Nuffield Provincial Hospitals Trust and issued in this imprint in 1999, he called for an international register of randomised controlled trials, and for explicit quality criteria for appraising published research, but neither goal was achieved in his lifetime.

Cochrane was pilloried by colleagues for appearing on television to promote abortion and to claim (rightly, at the time) that there was no evidence of benefit from routine cervical smears

All effective treatments must be free.

PLACARD

On returning to England, he enlisted in the International Brigade to fight fascism in Spain. During World War II, he was held prisoner for 4 years

After the war, Archie studied the chest diseases of mining populations in Wales, launching a series of remarkable surveys that reached more than 90% of their target populations. His studies of lung diseases and his papers on quality of health and medical care services are characterized by innovation and even audacity.

Cochrane retired to his home, Rhoose Farm House, in the Vale of Glamorgan, Wales, where he created a prizewinning garden, hung an impressive art collection, and entertained epidemiologists from around the world. He died in 1988 at the age of 79

Cochrane's raw moral courage, his indefatigable pursuit of the truth, and his irreverence towards the scientific establishment remain an inspiration to those of us whose research time is increasingly spent in petty correspondence with ethical committees, grant giving bodies, and journal editors

WHAT IS METAANALYSIS?

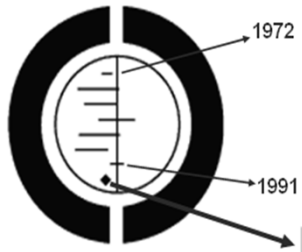
Conceptually, a **meta-analysis** uses a statistical approach to combine the results from multiple studies in an effort to increase power (over individual studies), improve estimates of the size of the effect and/or to resolve uncertainty when reports disagree

What is the difference between a systematic review and meta analysis?

1. **systematic review** answers a defined research question by collecting and summarizing all empirical evidence that fits pre-specified eligibility criteria.
2. A **meta-analysis** is the use of statistical methods to summarize the results of these studies.

Meta-analysis is a statistical technique for combining data from multiple studies on a particular topic. Compared to other study designs (such as randomized controlled trials or cohort studies), the **meta-analysis** comes in at the top of the 'levels of evidence' pyramid in evidence-based healthcare

THE COCHRANE LOGO



1972 First RCT

Prevention of prenatal death by antenatal corticosteroid therapy for fetal maturation

1991

Meta-analysis:
Steroïds lower death risk with 30-50%!!

THE COCHRANE COLLABORATION®

> Cochrane evidence is produced and disseminated by an amazing global network of volunteer collaborators bound together by a shared vision. Whether you're a health practitioner or policy maker, researcher, patient, or you're just interested in health; we invite you to join us today, and help us improve health decisions worldwide!
>
> *Cochrane CEO, Mark Wilson*

Our vision

Our vision is a world of improved health where decisions about health and health care are informed by high-quality, relevant and up-to-date synthesized research evidence.

Our mission

Our mission is to promote evidence-informed health decision-making by producing high-quality, relevant, accessible systematic reviews and other synthesized research evidence.

Our work is internationally recognized as the benchmark for high-quality information about the effectiveness of health care.

1. **Collaboration**
   by fostering global co-operation, teamwork, and open and transparent communication and decision-making.
2. **Building on the enthusiasm of individuals**
   by involving, supporting and training people of different skills and backgrounds.
3. **Avoiding duplication of effort**
   by good management, co-ordination and effective internal communications to maximize economy of effort.
4. **Minimizing bias**
   through a variety of approaches such as scientific rigour, ensuring broad participation, and avoiding conflicts of interest.
5. **Keeping up-to-date**
   by a commitment to ensure that Cochrane Reviews are maintained through identification and incorporation of new evidence.
6. **Striving for relevance**
   by promoting the assessment of health questions using outcomes that matter to people making choices in health and health care.
7. **Promoting access**
   by wide dissemination of our outputs, taking advantage of strategic alliances, and by promoting appropriate access models and delivery solutions to meet the needs of users worldwide.
8. **Ensuring quality**
   by applying advances in methodology, developing systems for quality improvement, and being open and responsive to criticism.
9. **Continuity**
   by ensuring that responsibility for reviews, editorial processes, and key functions is maintained and renewed.
10. **Enabling wide participation**
    in our work by reducing barriers to contributing and by encouraging diversity.

COCHRANE AND WIKI

THE COCHRANE COLLABORATION®

WIKIPEDIA
The Free Encyclopedia

COCHRANE AND WHO

THE COCHRANE COLLABORATION®

WHO

HEADQUARTER

Cochrane Collaboration

- group >28,000 volunteers
- >100 countries
- Review health care interventions tested in biomedical randomized controlled trials.[3]
- + more non-randomized, observational studies.
- systematic reviews published as "Cochrane Reviews"
- in the Cochrane Library.

Goals and Prinicples

The goal of the collaboration is to *help people make well informed decisions about health care by preparing, maintaining and ensuring the accessibility of systematic reviews of the effects of health care interventions.* The principles of the Cochrane Collaboration are:

- collaboration
- building on the enthusiasm of individuals
- avoiding duplication
- minimizing bias
- keeping up to date
- striving for relevance
- promoting access
- ensuring quality
- continuity
- enabling wide participation

Meta Analysis

- combines the results of several studies
- that address a set of related research hypotheses
- In its simplest form, this is normally by identification of a common measure of effect size,
- for which a weighted average might be the output of a meta-analyses.
- Here the weighting might be related to sample sizes within the individual studies.
- More generally there are other differences between the studies that need to be allowed for, but the general aim of a meta-analysis is to more powerfully estimate the true "effect size" as opposed to a smaller "effect size" derived in a single study under a given single set of assumptions and conditions.

Advantages of Meta Analysis

- Shows if the results are more varied than expected from sample diversity
- Derivation and statistical testing of overall factors / effect size parameters in related studies
- Generalization to the population of studies
- Ability to control for between-study variation
- Including moderators to explain variation
- Higher statistical power to detect an effect than in 'n=1 sized study sample'
- Deal with information overload: the high number of articles published each year.
- combines several studies ➡ less influenced by local findings than single studies will be.
- May show if a publication bias exists.

Steps in Meta Analysis

1. Formulation of the problem
2. Search of literature
3. Selection of studies ('incorporation criteria')
   - Based on quality criteria, e.g. the requirement of randomization and blinding in a clinical trial
   - Selection of specific studies on a well-specified subject, e.g. the treatment of breast cancer.
   - Decide whether unpublished studies are included to avoid publication bias
4. Decide which dependent variables or summary measures are allowed.
   - Differences (discrete data)
   - Means (continuous data)

THE COCHRANE COLLABORATION

Funding Cochrane

- £100 million over last 7 years
- >£150 million – $250 billion US Dollars over 20 years of its existence

Core and group income and expenditure 2010/11

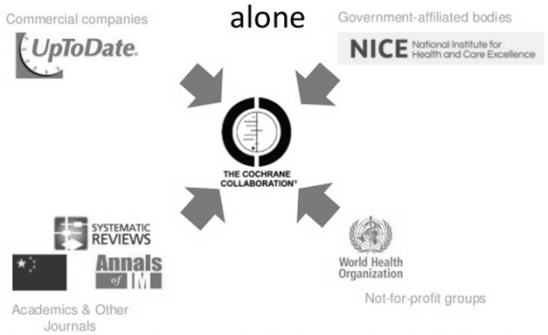
http://blog.tripdatabase.com/2013/04/a-critique-of-cochrane-collaboration.html#sthash.vicz56f0.dpuf

Want to get involved?

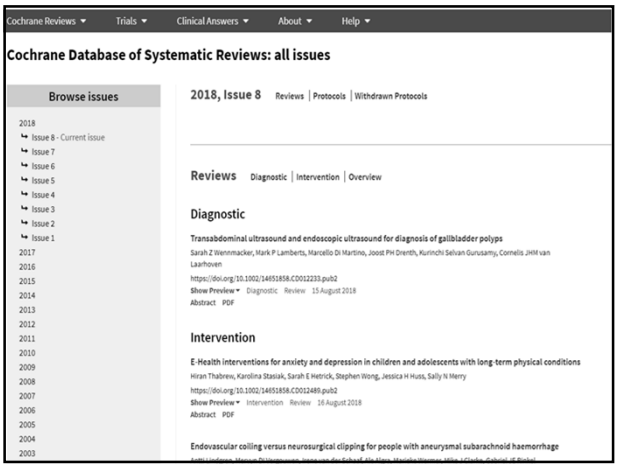
Visit: www.cochrane.org!

THE COCHRANE COLLABORATION®

Whilst unique, Cochrane is no longer alone



"Anyone who produces, or who finds a way to make Systematic Reviews more digestible and more relevant to the audience, is in competition with Cochrane"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2017
2016
2015
2014
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2012
2011
2010
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2008
2007
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2005
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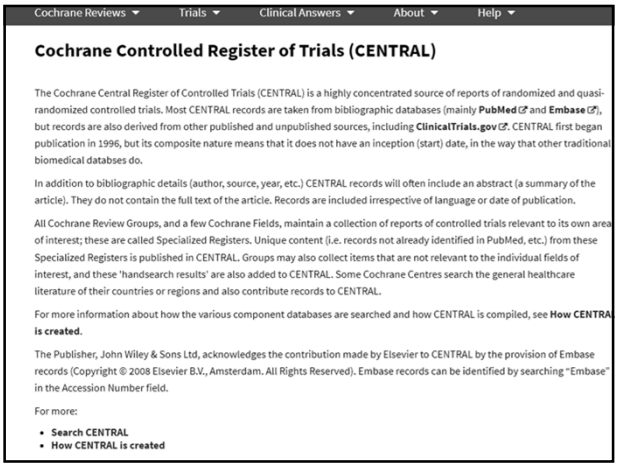
Diagnostic
Transabdominal ultrasound and endoscopic ultrasound for diagnosis of gallbladder polyps
Sarah Z Wennmacker, Mark P Lamberts, Marcello Di Martino, Joost PH Drenth, Kurinchi Selvan Gurusamy, Cornelis JHM van Laarhoven
https://doi.org/10.1002/14651858.CD012233.pub2
Show Preview Diagnostic Review 15 August 2018
Abstract PDF
Intervention
E-Health interventions for anxiety and depression in children and adolescents with long-term physical conditions
Hiran Thabrew, Karolina Stasiak, Sarah E Hetrick, Stephen Wong, Jessica H Huss, Sally N Merry
https://doi.org/10.1002/14651858.CD012489.pub2
Show Preview Intervention Review 16 August 2018
Abstract PDF
Endovascular coiling versus neurosurgical clipping for people with aneurysmal subarachnoid haemorrhage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Cochrane Controlled Register of Trials (CENTRAL)
The Cochrane Central Register of Controlled Trials (CENTRAL) is a highly concentrated source of reports of randomized and quasi-randomized controlled trials. Most CENTRAL records are taken from bibliographic databases (mainly PubMed and Embase), but records are also derived from other published and unpublished sources, including ClinicalTrials.gov. CENTRAL first began publication in 1996, but its composite nature means that it does not have an inception (start) date, in the way that other traditional biomedical databses do.
In addition to bibliographic details (author, source, year, etc.) CENTRAL records will often include an abstract (a summary of the article). They do not contain the full text of the article. Records are included irrespective of language or date of publication.
All Cochrane Review Groups, and a few Cochrane Fields, maintain a collection of reports of controlled trials relevant to its own area of interest; these are called Specialized Registers. Unique content (i.e. records not already identified in PubMed, etc.) from these Specialized Registers is published in CENTRAL. Groups may also collect items that are not relevant to the individual fields of interest, and these 'handsearch results' are also added to CENTRAL. Some Cochrane Centres search the general healthcare literature of their countries or regions and also contribute records to CENTRAL.
For more information about how the various component databases are searched and how CENTRAL is compiled, see How CENTRAL is created.
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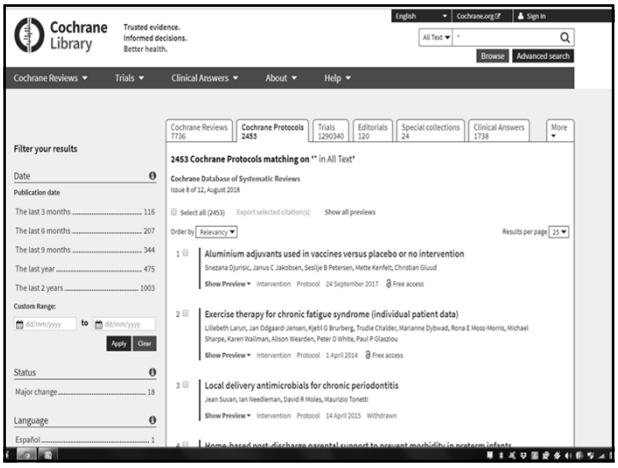
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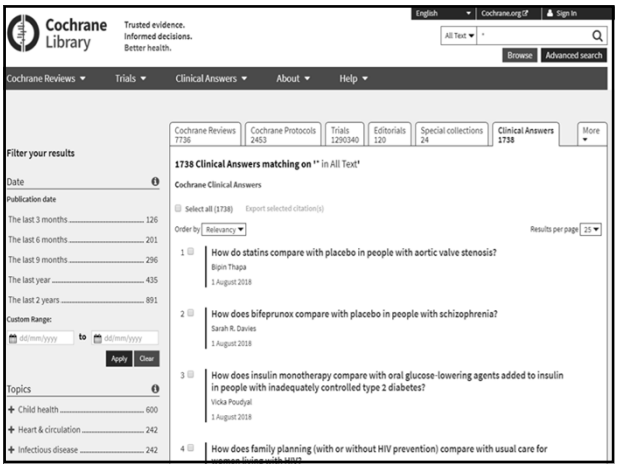
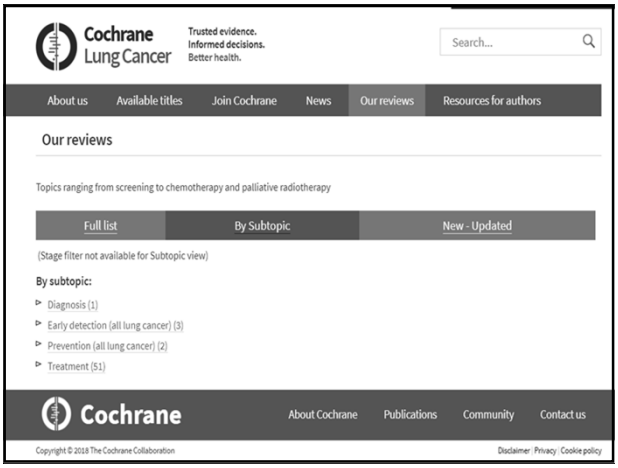
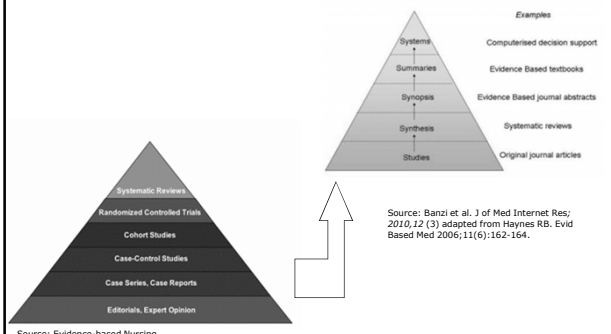
1 Aluminium adjuvants used in vaccines versus placebo or no intervention
Snezana Djurisic, Janus C Jakobsen, Sesilje B Petersen, Mette Kenfelt, Christian Gluud
Show Preview Intervention Protocol 24 September 2017 Free access
2 Exercise therapy for chronic fatigue syndrome (individual patient data)
Lillebeth Larun, Jan Odgaard-Jensen, Kjetil G Brurberg, Trudie Chalder, Marianne Dybwad, Rona E Moss-Morris, Michael Sharpe, Karen Wallman, Alison Wearden, Peter D White, Paul P Glasziou
Show Preview Intervention Protocol 1 April 2014 Free access
3 Local delivery antimicrobials for chronic periodontitis
Jean Suvan, Ian Needleman, David R Moles, Maurizio Tonetti
Show Preview Intervention Protocol 14 April 2015 Withdrawn





Large number of studies – need to synthesise & summarise



Source: Evidence-based Nursing
http://ebp.lib.uic.edu/nursing/node/12

Source: Banzi et al. J of Med Internet Res; *2010,12* (3) adapted from Haynes RB. Evid Based Med 2006;11(6):162-164.

39

Different types of reviews

- Narrative (overview)
- Systematic review
  - Meta-analysis

40

Narrative reviews (NR)

- Provide an overview of a particular topic
- Often cover a wide range of issues within a given topic
- Can be useful for understanding new concepts
- But there are problems associated with NR:
  - they are rarely comprehensive
  - they do not reveal many details about their methodology
  - they are highly susceptible to reviewers' bias
  - they seldom take into account differences in the quality of studies
  - they can often come to the wrong conclusion – careful interpretation needed

41

Example of NR

Systematic reviews (SR)

- SR is a scientific investigation that focuses on a specific question and uses explicit, prespecified scientific methods to identify, select, assess, and summarise the findings of similar but separate studies.
- It may include a quantitative synthesis (meta-analysis), depending on the available data

[Eden et al. Finding what works in health care: Standards for systematic reviews, Institute of Medicine, 2011]

43

Systematic reviews (2)

- The importance of SR is increasingly appreciated
  - Clinical practice guideline development
  - Clinical and policy decisions

BUT

- The quality of published SR is variable and often inadequate
  - In many cases we are unable to judge the quality of SR because the methodology is poorly reported or the SR is poorly conducted

44

Key characteristics of SR

- Focused well defined research question
- Clearly stated title and objectives
- Comprehensive strategy for identification of all relevant studies (published & unpublished)
- Explicit (and justified) predefined inclusion & exclusion criteria
- Critical appraisal of studies
- Clear analysis of the results of eligible studies
  - Quantitative (meta-analysis)
  - Qualitative
- Structured report

45

Cochrane SR

- Development of Cochrane SR is coordinated by the Cochrane Collaboration

The Cochrane Collaboration
Working together to provide the best evidence for health care

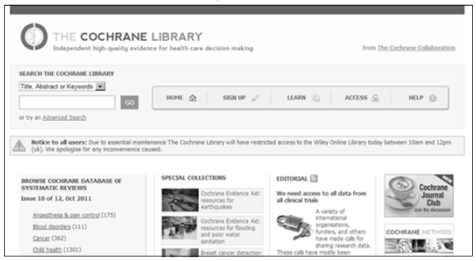
  - Established in 1993
  - International network of 28,000 from 100 countries
  - About 4,600 Cochrane reviews published
  - They are internationally recognised as a benchmark for high quality information about the effectiveness of healthcare

http://www.cochrane.org

46

Cochrane Library (CLIB)

- All Cochrane reviews published in CLIB
- Published by Wiley-Blackwell (indexed by PubMed, impact factor 6.1)
- Free access in the UK and many other countries

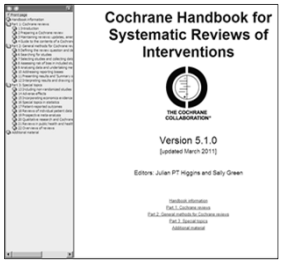


http://www.thecochranelibrary.com/

47

Methodology of Cochrane reviews

- Methodology robustly developed (continuous improvements)
- Handbook – free online access: http://www.cochrane.org/training/cochrane-handbook
- Good to follow even if doing "non-Cochrane" SR
- UK Cochrane Centre - training

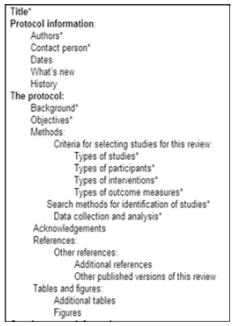


48

Process of conducting Cochrane SR

- PROTOCOL – important
  - Minimise potential bias in the review conduct:

    Reviews are retrospective, need to establish the methods in advance
  - Planning
  - Review team
  - Cochrane protocols are peer reviewed and published



49

Cochrane review conduct – key points

- Protocol
- Objectives
  - Focused well defined research question
  - Primary outcome (one)
  - Minimum number of secondary outcomes
  - Include adverse events (harms) if relevant
- Literature search
  - Comprehensive (electronic databases, grey literature, reference lists, personal communication, ..)
  - Useful to involve an information specialist in developing search strategies (consider ss peer review)
  - Keep detailed record of search methods and search results!

50

Cochrane review conduct – key points (2)

- Data collection and analysis
  - Selection of studies using predefined selection criteria
  - Independently done by more than one reviewer
  - Important to determine how to solve disagreements between reviewers
- Data extraction
  - Data extraction form (pilot – items, format, ..)
  - Independently done by more than one reviewer

51

Cochrane review conduct – key points (3)

- Assessment of risk of bias
  - Problems with the design and execution of individual studies of healthcare interventions raise questions about the validity of their findings
  - In clinical trials, biases can be broadly categorized as selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases that do not fit into these categories
  - Cochrane Collaboration developed the 'Risk of bias tool'
    7 specific domains:
    - sequence generation (selection bias)
    - allocation concealment (selection bias)
    - blinding of participants and personnel (performance bias)
    - blinding of outcome assessment (detection bias)
    - incomplete outcome data (attrition bias)
    - selective outcome reporting (reporting bias)
    - other potential sources of bias

52

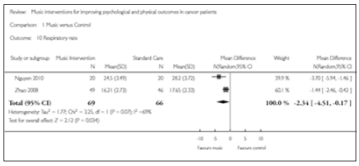
Cochrane review conduct – key points (4)

- Data synthesis
  - **Qualitative:** descriptive summary
  - **Quantitative - meta-analysis:** pooling data from a number of studies when there are
    - Minimal differences between studies
    - Outcome measured in the same way
    - Data are available

Study weight

Different statistical methods for pooling

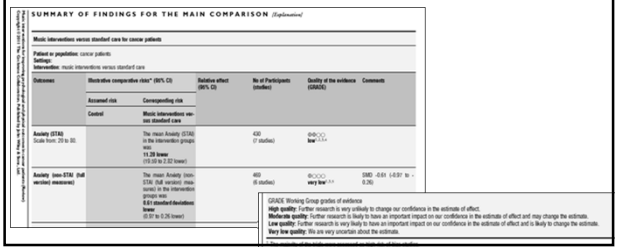
Subgroup analysis
Sensitivity analysis



53

Interpretation of results

- Clear statement of findings
- Authors conclusions should reflect findings
- Clear presentation is important
- Summary of findings tables
  - Key information in a quick and accessible format
  - Relating the quality of evidence to the outcomes


SUMMARY OF FINDINGS FOR THE MAIN COMPARISON (Explanations)

Music interventions versus standard care for cancer patients

Patient or population: cancer patients
Settings:
Intervention: music interventions versus standard care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Music interventions versus standard care				
Anxiety (STAI) Scale from: 20 to 80.		The mean Anxiety (STAI) in the intervention groups was 11.28 lower (19.09 to 2.52 lower)		430 (7 studies)	⊕⊕◯◯ low 1,2,3	
Anxiety (non-STAI (full version) measures)		The mean Anxiety (non-STAI (full version) measures) in the intervention groups was 0.61 standard deviations lower (0.97 to 0.26 lower)		403 (6 studies)	⊕◯◯◯ very low 2,3	SMD -0.61 (-0.97 to -0.26)

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Publishing SR

- Differences between publishing SR in the Cochrane Library and in a journal:
  - Cochrane has some specific rules (e.g. titles structure: a title cannot start with 'A' or 'The'; should not not include 'a systematic review of')
- Publishing in a journal: PRISMA Statement
  - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (2009)
  - 27-item checklist, flow diagram
  - PRISMA authors are also heavily involved in the Cochrane work, high compatibility of both guides

http://www.prisma-statement.org/

55

Poor reporting of systematic reviews

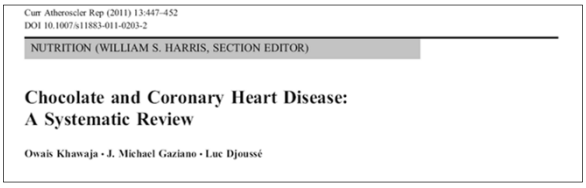
- Good reporting of primary studies is crucial for SR development

  BUT
- Reviews are not immune to the problems of poor reporting
  - Moher et al. assessed epidemiological and reporting characteristics and bias-related aspects of 300 systematic reviews (of which 125 were Cochrane reviews). The overall quality of reporting of key aspects of methodology was very inconsistent with particularly discouraging findings for non-Cochrane reviews.

[Moher; PLoS Medicine 2007]

56

Example of bad reporting


Curr Atheroscler Rep (2011) 13:447–452
DOI 10.1007/s11883-011-0203-2

NUTRITION (WILLIAM S. HARRIS, SECTION EDITOR)

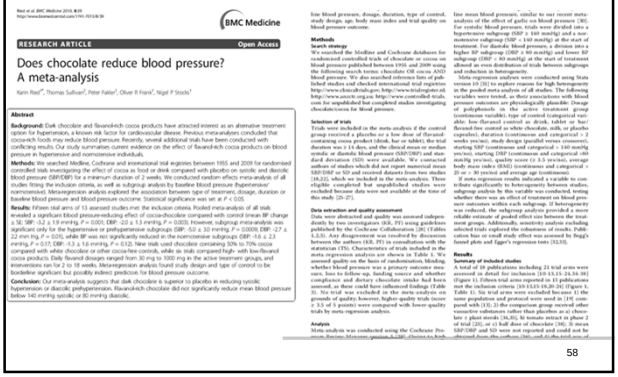
Chocolate and Coronary Heart Disease: A Systematic Review

Owais Khawaja · J. Michael Gaziano · Luc Djoussé

- Nowhere in the paper any mention of the review methodology!

57

Example of good reporting



BMC Medicine

RESEARCH ARTICLE Open Access

Does chocolate reduce blood pressure? A meta-analysis

Yarm Ried[*], Thomas Sullivan[†], Peter Fahler[†], Oliver R Frank[†], Nigel P Stocks[†]

Abstract

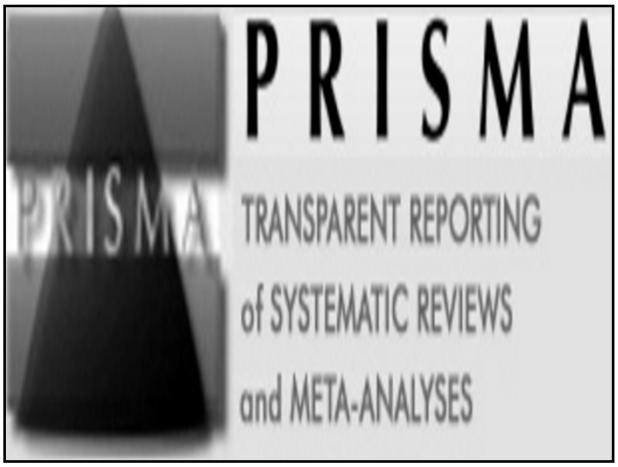
Background: Dark chocolate and flavanol-rich cocoa products have attracted interest as an alternative treatment option for hypertension, a known risk factor for cardiovascular disease. Previous meta-analyses concluded that cocoa-rich foods may reduce blood pressure. Recently, several additional trials have been conducted with conflicting results. Our study summarises current evidence on the effect of flavanol-rich cocoa products on blood pressure in hypertensive and normotensive individuals.

Methods: We searched Medline, Cochrane and international trial registries between 1955 and 2009 for randomised controlled trials investigating the effect of cocoa as food or drink compared with placebo on systolic and diastolic blood pressure (SBP/DBP) for a minimum duration of 2 weeks. We conducted random effects meta-analysis of all studies fitting the inclusion criteria, as well as subgroup analysis by baseline blood pressure (hypertensive/normotensive). Meta-regression analysis explored the association between type of treatment, dosage, duration or baseline blood pressure and blood pressure outcome. Statistical significance was set at $P < 0.05$.

Results: Fifteen trial arms of 13 assessed studies met the inclusion criteria. Pooled meta-analysis of all trials revealed a significant blood pressure-reducing effect of cocoa/chocolate compared with control (mean BP change ± SE: SBP: -3.2 ± 1.9 mmHg, $P = 0.001$; DBP: -2.0 ± 1.3 mmHg, $P = 0.003$). However, subgroup meta-analysis was significant only for the hypertensive or prehypertensive subgroups (SBP: -5.0 ± 3.0 mmHg $P = 0.0009$; DBP: -2.7 ± 2.2 mm Hg, $P = 0.03$), while BP was not significantly reduced in the normotensive subgroups (SBP: -1.6 ± 2.3 mmHg, $P = 0.17$; DBP: -1.3 ± 1.6 mmHg, $P = 0.12$). Nine trials used chocolate containing 30% to 70% cocoa compared with white chocolate or other cocoa-free controls, while six trials compared high- with low-flavanol cocoa products. Daily flavanol dosages ranged from 30 mg to 1000 mg in the active treatment groups, and interventions ran for 2 to 18 weeks. Meta-regression analysis found study design and type of control to be borderline significant but possibly indirect predictors for blood pressure outcome.

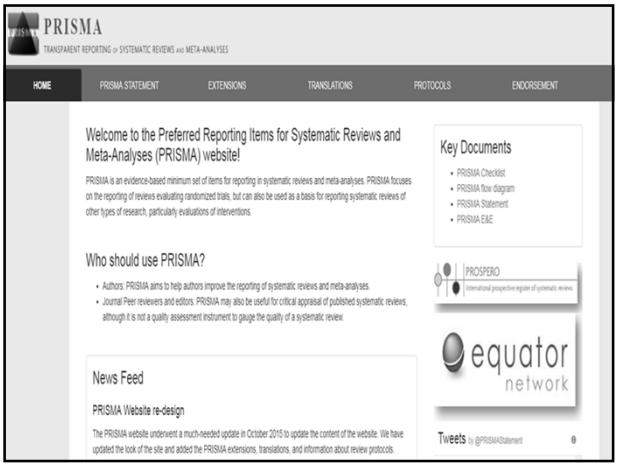
Conclusion: Our meta-analysis suggests that dark chocolate is superior to placebo in reducing systolic hypertension or diastolic prehypertension. Flavanol-rich chocolate did not significantly reduce mean blood pressure below 140 mmHg systolic or 80 mmHg diastolic.

58



PRISMA

TRANSPARENT REPORTING of SYSTEMATIC REVIEWS and META-ANALYSES



PRISMA

TRANSPARENT REPORTING OF SYSTEMATIC REVIEWS AND META-ANALYSES

HOME | PRISMA STATEMENT | EXTENSIONS | TRANSLATIONS | PROTOCOLS | ENDORSEMENT

Welcome to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) website!

PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. PRISMA focuses on the reporting of reviews evaluating randomized trials, but can also be used as a basis for reporting systematic reviews of other types of research, particularly evaluations of interventions.

Who should use PRISMA?

- Authors: PRISMA aims to help authors improve the reporting of systematic reviews and meta-analyses.
- Journal Peer reviewers and editors: PRISMA may also be useful for critical appraisal of published systematic reviews, although it is not a quality assessment instrument to gauge the quality of a systematic review.

News Feed

PRISMA Website re-design

The PRISMA website underwent a much-needed update in October 2015 to update the content of the website. We have updated the look of the site and added the PRISMA extensions, translations, and information about review protocols.

Key Documents

- PRISMA Checklist
- PRISMA flow diagram
- PRISMA Statement
- PRISMA E&E

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International prospective register of systematic reviews

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Cynthia Mulrow

Cynthia Mulrow, 2011

Born	23 May 1953 Edinburg, Texas
Residence	San Antonio, Texas
Nationality	American
Alma mater	Baylor College of Medicine (MD) Duke University School of Medicine London School of Hygiene & Tropical Medicine
Occupation	Physician, professor, researcher
Known for	Research on systematic reviews, research methodology, and chronic conditions

THE PRISMA DEVELOPMENT

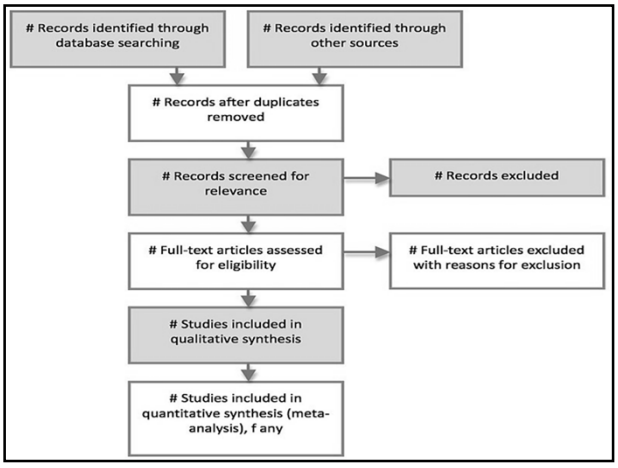
1. In 1987, Cynthia Mulrow examined for the first time the methodological quality of a sample of 50 review articles published in four leading medical journals between 1985 and 1986 She found that none met a set of eight explicit scientific criteria, and that the lack of quality assessment of primary studies was a major pitfall in these reviews
2. IN 1996, an international group of 30 clinical epidemiologists, clinicians, statisticians, editors, and researchers convened The Quality of Reporting of Meta-analyses (QUOROM) conference to address standards for improving the quality of reporting of meta-analyses of clinical randomized controlled trials
3. The conference resulted in the QUOROM, a checklist, and a flow diagram that described the preferred way to present the abstract, introduction, methods, results, and discussion sections of a report of a systematic review or a meta-analysis.
4. Eight of the original 18 items formed the basis of the QUOROM reporting. Evaluation of reporting was organized into headings and subheadings regarding searches, selection, validity assessment, data abstraction, study characteristics, and quantitative data synthesis.
5. In 2009, the QUOROM was updated to address several conceptual and practical advances in the science of systematic reviews, and was renamed PRISMA (Preferred Reporting Items of Systematic reviews and Meta-Analyses)
6. A three-day meeting was held in Ottawa, Canada, in June 2005 with 29 participants, including review authors, methodologists, clinicians, medical editors, and a consumer. The objective of the Ottawa meeting was to revise and expand the QUOROM checklist and flow diagram, as needed

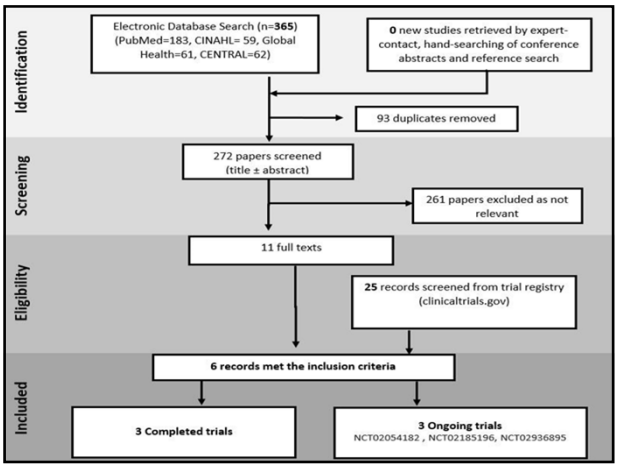
THE PRISMA IMPCAT

1. The use of checklists like PRISMA is likely to improve the reporting quality of a systematic review and provides substantial transparency in the selection process of papers in a systematic review.
2. The PRISMA Statement has been published in several journals.
3. Many journal's publishing health research refer to PRISMA in their Instructions to Authors and some require authors to adhere to them. The PRISMA Group advised that PRISMA should replace QUOROM for those journals that endorsed QUOROM in the past.
4. Recent surveys of leading medical journals evaluated the extent to which the PRISMA Statement has been incorporated into their Instructions to Authors.
5. In a sample of 146 journals publishing systematic reviews, the PRISMA Statement was referred to in the instructions to authors for 27% of journals; more often in general and internal medicine journals (50%) than in specialty medicine journals (25%).
6. These results showed that the uptake of PRISMA guidelines by journals is still inadequate although there has been some improvement over time.

PRISMA CHECKLIST

The checklist includes 27 items pertaining to the content of a systematic review and meta-analysis, which include the title, abstract, methods, results, discussion and funding.

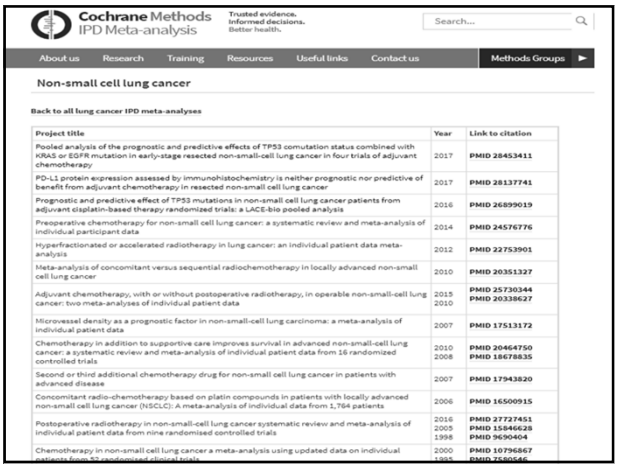




PRISMA explanation & elaboration paper

- Explanation and rationale for reporting of suggested information (items)
- Examples of good reporting
- Relevant data about how this information is reported presently

68



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Non-small cell lung cancer

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Project title	Year	Link to citation
Pooled analysis of the prognostic and predictive effects of TP53 comutation status combined with KRAS or EGFR mutation in early-stage resected non-small-cell lung cancer in four trials of adjuvant chemotherapy	2017	PMID 28453411
PD-L1 protein expression assessed by immunohistochemistry is neither prognostic nor predictive of benefit from adjuvant chemotherapy in resected non-small cell lung cancer	2017	PMID 28137741
Prognostic and predictive effect of TP53 mutations in non-small cell lung cancer patients from adjuvant cisplatin-based therapy randomized trials: a LACE-bio pooled analysis	2016	PMID 26899019
Preoperative chemotherapy for non-small cell lung cancer: a systematic review and meta-analysis of individual participant data	2014	PMID 24576776
Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis	2012	PMID 22753901
Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small cell lung cancer	2010	PMID 20351327
Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data	2015 2010	PMID 25730344 PMID 20338627
Microvessel density as a prognostic factor in non-small-cell lung carcinoma: a meta-analysis of individual patient data	2007	PMID 17513172
Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials	2010 2008	PMID 20464750 PMID 18678835
Second or third additional chemotherapy drug for non-small cell lung cancer in patients with advanced disease	2007	PMID 17943820
Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): A meta-analysis of individual data from 1,764 patients	2006	PMID 16500915
Postoperative radiotherapy in non-small-cell lung cancer systematic review and meta-analysis of individual patient data from nine randomised controlled trials	2016 2005 1998	PMID 27727451 PMID 15846628 PMID 9690404
Chemotherapy in non-small cell lung cancer a meta-analysis using updated data on individual patients from 52 randomised clinical trials	2000 1995	PMID 10796867 PMID 7569545

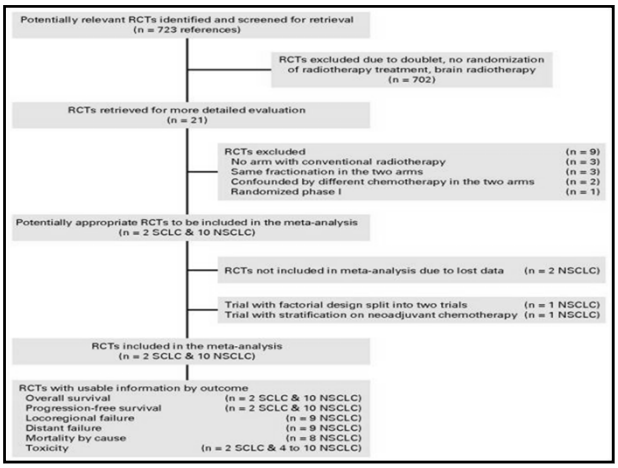
Hyperfractionated or Accelerated Radiotherapy in Lung Cancer: An Individual Patient Data Meta-Analysis

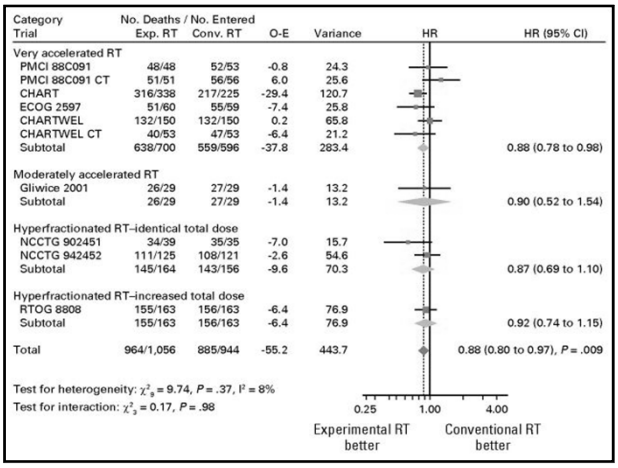
Audrey Mauguen/JCO/2012

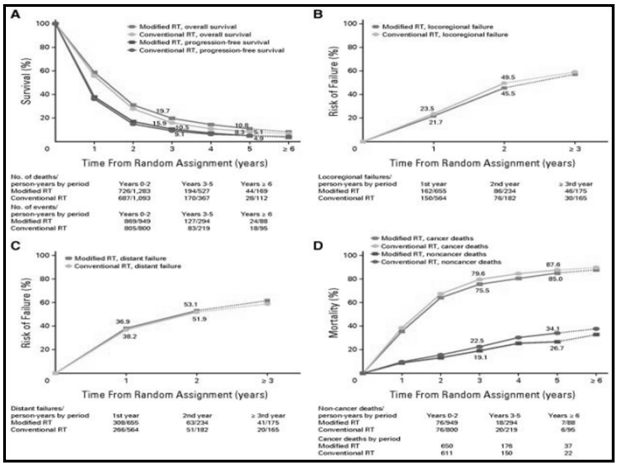
1. In lung cancer, randomized trials assessing hyperfractionated or accelerated radiotherapy seem to yield conflicting results regarding the effects on overall (OS) or progression-free survival (PFS).
2. The Meta-Analysis of Radiotherapy in Lung Cancer Collaborative Group decided to address the role of modified radiotherapy fractionation.

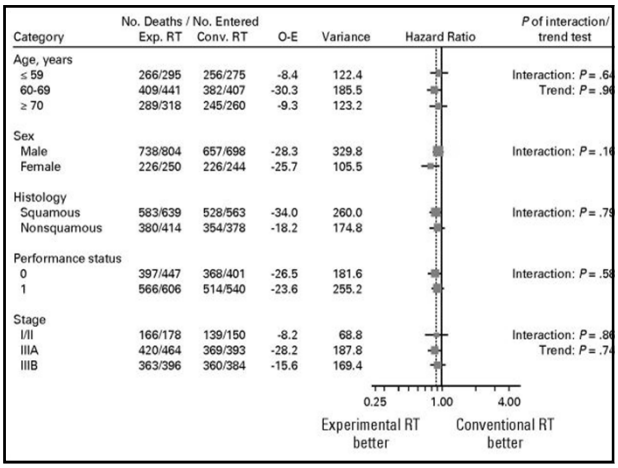
Material and Methods

- We performed an individual patient data meta-analysis in patients with nonmetastatic lung cancer, which included trials comparing modified radiotherapy with conventional radiotherapy.


Potentially relevant RCTs identified and screened for retrieval (n = 723 references)
RCTs excluded due to doublet, no randomization of radiotherapy treatment, brain radiotherapy (n = 702)
RCTs retrieved for more detailed evaluation (n = 21)
RCTs excluded (n = 9)
No arm with conventional radiotherapy (n = 3)
Same fractionation in the two arms (n = 3)
Confounded by different chemotherapy in the two arms (n = 2)
Randomized phase I (n = 1)
Potentially appropriate RCTs to be included in the meta-analysis (n = 2 SCLC & 10 NSCLC)
RCTs not included in meta-analysis due to lost data (n = 2 NSCLC)
Trial with factorial design split into two trials (n = 1 NSCLC)
Trial with stratification on neoadjuvant chemotherapy (n = 1 NSCLC)
RCTs included in the meta-analysis (n = 2 SCLC & 10 NSCLC)
RCTs with usable information by outcome
Overall survival (n = 2 SCLC & 10 NSCLC)
Progression-free survival (n = 2 SCLC & 10 NSCLC)
Locoregional failure (n = 9 NSCLC)
Distant failure (n = 9 NSCLC)
Mortality by cause (n = 8 NSCLC)
Toxicity (n = 2 SCLC & 4 to 10 NSCLC)


Category / Trial
No. Deaths / No. Entered Exp. RT
Conv. RT
O-E
Variance
HR
HR (95% CI)
Very accelerated RT
PMCI 88C091 48/48 52/53 -0.8 24.3
PMCI 88C091 CT 51/51 56/56 6.0 25.6
CHART 316/338 217/225 -29.4 120.7
ECOG 2597 51/60 55/59 -7.4 25.8
CHARTWEL 132/150 132/150 0.2 65.8
CHARTWEL CT 40/53 47/53 -6.4 21.2
Subtotal 638/700 559/596 -37.8 283.4 0.88 (0.78 to 0.98)
Moderately accelerated RT
Gliwice 2001 26/29 27/29 -1.4 13.2
Subtotal 26/29 27/29 -1.4 13.2 0.90 (0.52 to 1.54)
Hyperfractionated RT–identical total dose
NCCTG 902451 34/39 35/35 -7.0 15.7
NCCTG 942452 111/125 108/121 -2.6 54.6
Subtotal 145/164 143/156 -9.6 70.3 0.87 (0.69 to 1.10)
Hyperfractionated RT–increased total dose
RTOG 8808 155/163 156/163 -6.4 76.9
Subtotal 155/163 156/163 -6.4 76.9 0.92 (0.74 to 1.15)
Total 964/1,056 885/944 -55.2 443.7 0.88 (0.80 to 0.97), P = .009
Test for heterogeneity: $\chi^2_9 = 9.74$, P = .37, $I^2 = 8\%$
Test for interaction: $\chi^2_3 = 0.17$, P = .98
0.25
1.00
4.00
Experimental RT better
Conventional RT better


A
Survival (%)
Modified RT, overall survival
Conventional RT, overall survival
Modified RT, progression-free survival
Conventional RT, progression-free survival
Time From Random Assignment (years)
B
Risk of Failure (%)
Modified RT, locoregional failure
Conventional RT, locoregional failure
Time From Random Assignment (years)
C
Risk of Failure (%)
Modified RT, distant failure
Conventional RT, distant failure
Time From Random Assignment (years)
D
Mortality (%)
Modified RT, cancer deaths
Conventional RT, cancer deaths
Modified RT, noncancer deaths
Conventional RT, noncancer deaths
Time From Random Assignment (years)



Category	No. Deaths / No. Entered Exp. RT	Conv. RT	O-E	Variance	Hazard Ratio	*P* of interaction/ trend test
Age, years						
≤ 59	266/295	256/275	-8.4	122.4		Interaction: *P* = .64
60-69	409/441	382/407	-30.3	185.5		Trend: *P* = .90
≥ 70	289/318	245/260	-9.3	123.2		
Sex						
Male	738/804	657/698	-28.3	329.8		Interaction: *P* = .16
Female	226/250	226/244	-25.7	105.5		
Histology						
Squamous	583/639	528/563	-34.0	260.0		Interaction: *P* = .79
Nonsquamous	380/414	354/378	-18.2	174.8		
Performance status						
0	397/447	368/401	-26.5	181.6		Interaction: *P* = .58
1	566/606	514/540	-23.6	255.2		
Stage						
I/II	166/178	139/150	-8.2	68.8		Interaction: *P* = .86
IIIA	420/464	369/393	-28.2	187.8		Trend: *P* = .74
IIIB	363/396	360/384	-15.6	169.4		

RESULTS

1. **In non–small-cell lung cancer (NSCLC; 10 trials, 2,000 patients),**
2. **modified fractionation improved OS as compared with conventional schedules (hazard ratio [HR] = 0.88, 95% CI, 0.80 to 0.97; *P* = .009), resulting in an absolute benefit of 2.5% (8.3% to 10.8%) at 5 years.**
3. **No evidence of heterogeneity between trials was found. There was no evidence of a benefit on PFS (HR = 0.94; 95% CI, 0.86 to 1.03; *P* = .19).**
4. **Modified radiotherapy reduced deaths resulting from lung cancer (HR = 0.89; 95% CI, 0.81 to 0.98; *P* = .02), and there was a nonsignificant reduction of non–lung cancer deaths (HR = 0.87; 95% CI, 0.66 to 1.15; *P* = .33).**
5. **In small-cell lung cancer (SCLC; two trials, 685 patients), similar results were found: OS, HR = 0.87, 95% CI, 0.74 to 1.02, *P* = .08; PFS, HR = 0.88, 95% CI, 0.75 to 1.03, *P* = .11.**
6. **In both NSCLC and SCLC, the use of modified radiotherapy increased the risk of acute esophageal toxicity (odds ratio [OR] = 2.44 in NSCLC and OR = 2.41 in SCLC; *P* < .001) but did not have an impact on the risk of other acute toxicities.**

AUTHOR CONCLUSION

1. **Patients with nonmetastatic NSCLC derived a significant OS benefit from accelerated or hyperfractionated radiotherapy;**
2. **A similar but nonsignificant trend was observed for SCLC. As expected, there was increased acute esophageal toxicity.**

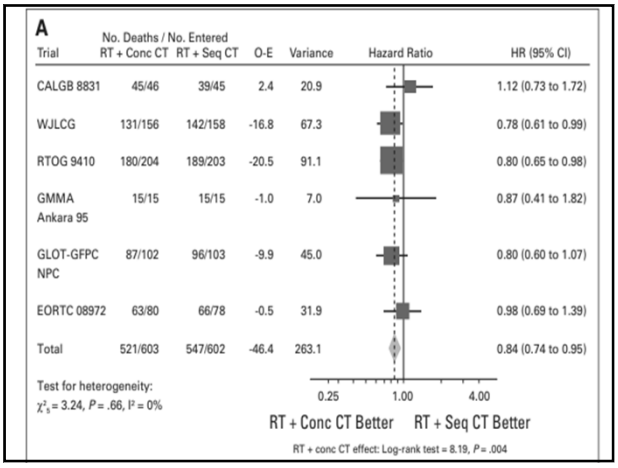
Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

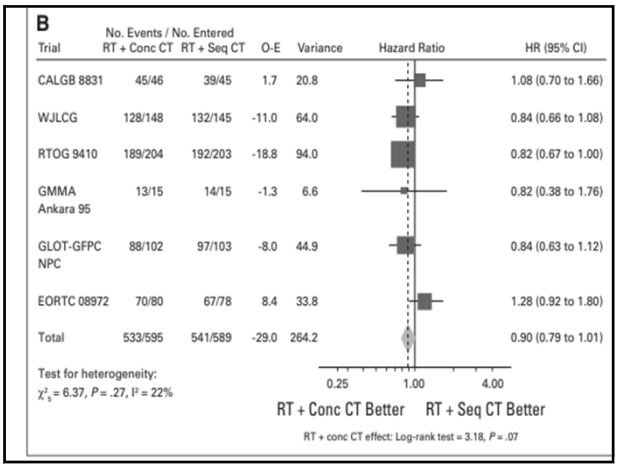
Anne Aupe´rin/JCO/2010

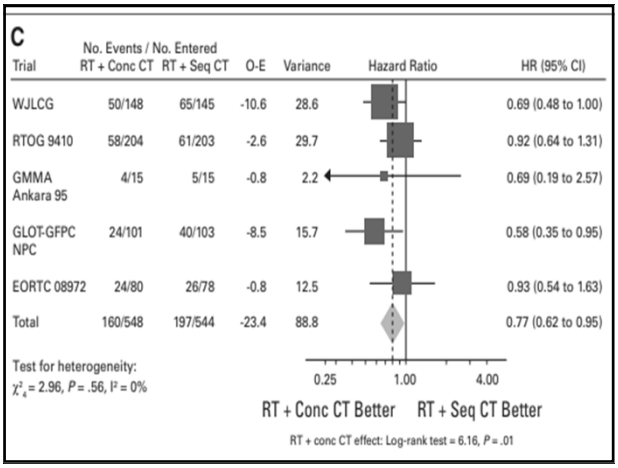
Table 1. Trial Characteristics

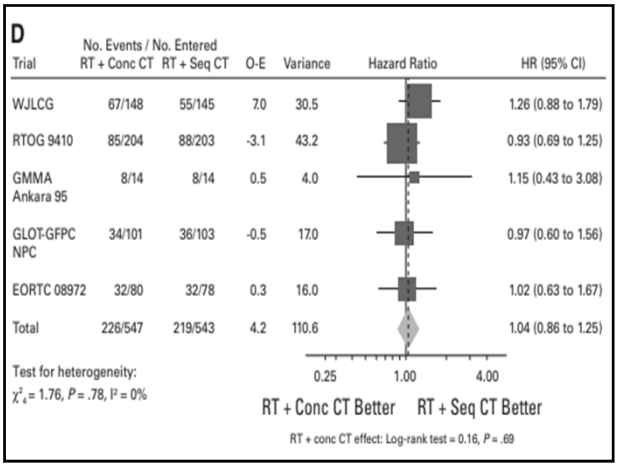
Trial	Accrual Period	No. of Randomly Assigned Patients	Patients Alive	Median Follow-Up (years)	Concomitant Chemoradiotherapy		Sequential Chemoradiotherapy	
					Chemotherapy	Radiotherapy	Chemotherapy	Radiotherapy
CALGB 8831[14•]	1988-1989	91	7	9.2	Cb 100 mg/m²/wk × 6 wk	Start on day 50 after induction CT: 60 Gy, 30 f, 6 wk, RT started in 80% of patients	Consolidation CT (start 3 wk after RT end): cisplatin 100 mg/m² day 1, Vb 5 mg/m² days 1, 15 for 4 cycles	Start on day 50 after induction CT: 60 Gy, 30 f, 6 wk, RT started in 78% of patients
WJLCG[15]	1992-1994	314	41	4.9	Cisplatin 80 mg/m² days 1, 29, Vd 3 mg/m² days 1, 8, 29, 36, Mi 8 mg/m² days 1,29	Start on day 2: 28 Gy 14 f, 10 days of rest, 28 Gy, 14 f, RT started in 100% of patients	Induction CT: cisplatin 80 mg/m² days 1, 29, Vd 3 mg/m² days 1, 8, 29, 36, Mi 8 mg/m² days 1,29	Start after CT completion: 56 Gy, 28 f, RT started in 98% of patients
RTOG 9410[16]	1994-1998	407	38	6.4	Cisplatin 100 mg/m² days 1, 29, Vb 5 mg/m² weekly × 5 wk	Start on day 1, 60 Gy, RT started in 99% of patients	Induction CT: cisplatin 100 mg/m² days 1, 29, Vb 5 mg/m² weekly × 5 wk	Start on day 50: 60 Gy, RT started in 90% of patients
GMMA Ankara 1995[17]	1995-1996	30	0		Cisplatin 6 mg/m² daily	Start on day 1: 36 Gy 12 f, 7 days of rest, 12.5 Gy 5 f, RT started in 100% of patients	Induction CT: cisplatin 40 mg/m², Et 200 mg/m², If 200 mg/m² days 1, 3, 5, 29, 31, 33	Start 3 wk after CT completion: 36 Gy 12 f, 7 d rest, 12.5 Gy 5 f, RT started in 100% of patients
GLOT-GFPC NPC 95-01[18]	1996-2000	205	22	8.0	Cisplatin 20 mg/m² days 1-5, 29-33, Et 50 mg/m² days 1-5, 29-33; consolidation CT: cisplatin 80 mg/m² days 78, 106, Vn 30 mg/m²/wk days 78-127	Start on day 1: 66 Gy, 33 f, 6.5 wk, RT started in 94% of patients	Induction CT: cisplatin 120 mg/m² days 1, 29, 57, Vn 30 mg/m²/wk days 1-78	Start after CT completion: 66 Gy, 33 f, 6.5 wk, RT started 64% of patients
EORTC 08972[20]	1999-2003	158	29	4.2	Cisplatin 6 mg/m² daily	Start on day 1: 66 Gy, 24 f, 32 days, RT started in 85% of patients	Induction CT: cisplatin 75 mg/m² days 2, 23, gemcitabine 1,250 mg/m² days 1, 8, 22, 29	Start on day 50: 66 Gy, 24 f, 32 days, RT started in 97% of patients

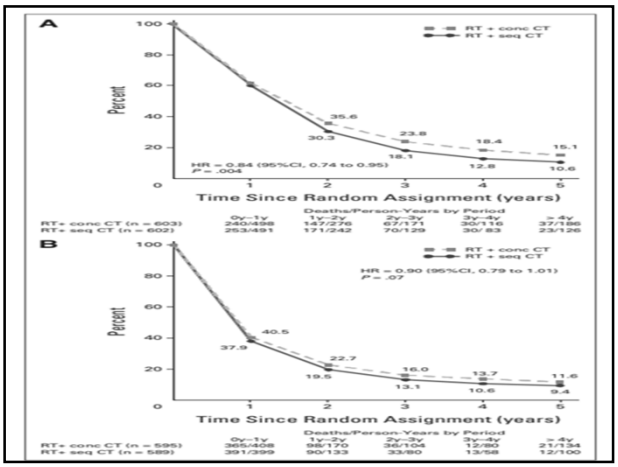
Abbreviations: CALGB, Cancer and Leukemia Group B; Cb, carboplatin; wk, week; CT, chemotherapy; f, fraction; RT, radiotherapy; Vb, vinblastine; WJLCG, West Japan Lung Cancer Group; Vd, vindesine; Mi, mitomycin; RTOG, Radiotherapy Oncology Group; GMMA, Gülhane Military Medicine Academy; Et, etoposide; If, ifosfamide; GLOT-GFPC NPC, Groupe Lyon-Saint-Etienne d'Oncologie Thoracique–Groupe Français Non Petites Cellules; Vn, vinorelbine; EORTC, European Organisation for Research and Treatment of Cancer.
•Induction chemotherapy in both arms: cisplatin 100 mg/m² days 1 and 29, Vb 5 mg/m² days 1, 8, 15, 22, and 29.




B
Trial
No. Events / No. Entered
RT + Conc CT
RT + Seq CT
O-E
Variance
Hazard Ratio
HR (95% CI)
CALGB 8831 45/46 39/45 1.7 20.8 1.08 (0.70 to 1.66)
WJLCG 128/148 132/145 -11.0 64.0 0.84 (0.66 to 1.08)
RTOG 9410 189/204 192/203 -18.8 94.0 0.82 (0.67 to 1.00)
GMMA Ankara 95 13/15 14/15 -1.3 6.6 0.82 (0.38 to 1.76)
GLOT-GFPC NPC 88/102 97/103 -8.0 44.9 0.84 (0.63 to 1.12)
EORTC 08972 70/80 67/78 8.4 33.8 1.28 (0.92 to 1.80)
Total 533/595 541/589 -29.0 264.2 0.90 (0.79 to 1.01)
Test for heterogeneity:
χ^2_5 = 6.37, P = .27, I² = 22%
0.25
1.00
4.00
RT + Conc CT Better
RT + Seq CT Better
RT + conc CT effect: Log-rank test = 3.18, P = .07


C
Trial
No. Events / No. Entered
RT + Conc CT
RT + Seq CT
O-E
Variance
Hazard Ratio
HR (95% CI)
WJLCG 50/148 65/145 -10.6 28.6 0.69 (0.48 to 1.00)
RTOG 9410 58/204 61/203 -2.6 29.7 0.92 (0.64 to 1.31)
GMMA Ankara 95 4/15 5/15 -0.8 2.2 0.69 (0.19 to 2.57)
GLOT-GFPC NPC 24/101 40/103 -8.5 15.7 0.58 (0.35 to 0.95)
EORTC 08972 24/80 26/78 -0.8 12.5 0.93 (0.54 to 1.63)
Total 160/548 197/544 -23.4 88.8 0.77 (0.62 to 0.95)
Test for heterogeneity:
χ^2_4 = 2.96, P = .56, I² = 0%
0.25
1.00
4.00
RT + Conc CT Better
RT + Seq CT Better
RT + conc CT effect: Log-rank test = 6.16, P = .01


D
Trial
No. Events / No. Entered
RT + Conc CT
RT + Seq CT
O-E
Variance
Hazard Ratio
HR (95% CI)
WJLCG 67/148 55/145 7.0 30.5 1.26 (0.88 to 1.79)
RTOG 9410 85/204 88/203 -3.1 43.2 0.93 (0.69 to 1.25)
GMMA Ankara 95 8/14 8/14 0.5 4.0 1.15 (0.43 to 3.08)
GLOT-GFPC NPC 34/101 36/103 -0.5 17.0 0.97 (0.60 to 1.56)
EORTC 08972 32/80 32/78 0.3 16.0 1.02 (0.63 to 1.67)
Total 226/547 219/543 4.2 110.6 1.04 (0.86 to 1.25)
Test for heterogeneity:
χ^2_4 = 1.76, P = .78, I² = 0%
0.25
1.00
4.00
RT + Conc CT Better
RT + Seq CT Better
RT + conc CT effect: Log-rank test = 0.16, P = .69



RESULTS

1. 7 eligible trials, data from six trials were received (1,205 patients, 92% of all randomly assigned patients).
2. Median follow-up was 6 years.
3. There was a significant benefit of concomitant radiochemotherapy on overall survival (HR, 0.84; 95% CI, 0.74 to 0.95; P .004), with an absolute benefit of 5.7% (from 18.1% to 23.8%) at 3 years and 4.5% at 5 years.
4. For progression-free survival, the HR was 0.90 (95% CI, 0.79 to 1.01; P=.07).
5. Concomitant treatment decreased locoregional progression (HR, 0.77; 95% CI, 0.62 to 0.95; P .01); its effect was not different from that of sequential treatment on distant progression (HR, 1.04; 95% CI, 0.86 to 1.25; P .69).
6. Concomitant radiochemotherapy increased acute esophageal toxicity (grade 3-4) from 4% to 18% with a relative risk of 4.9 (95% CI, 3.1 to 7.8; P .001).
7. There was no significant difference regarding acute pulmonary toxicity.

AUTHOR CONCLUSION

Concomitant radiochemotherapy, as compared with sequential radiochemotherapy, improved survival of patients with locally advanced NSCLC, primarily because of a better locoregional control, but at the cost of manageable increased acute esophageal toxicity

Cochrane Library

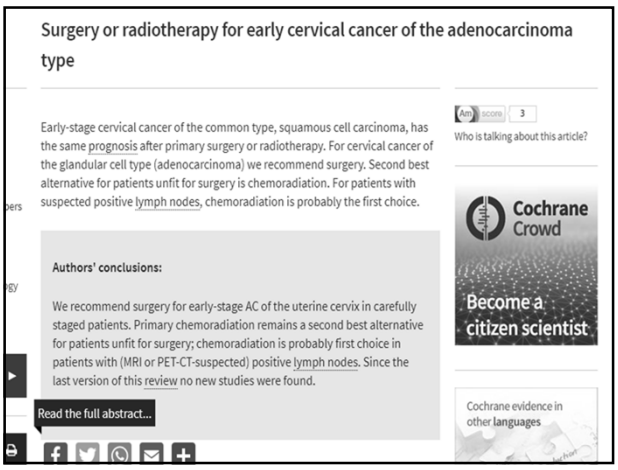
Cochrane Database of Systematic Reviews

Temozolomide for high grade glioma (Review)

Hart MG, Garside R, Rogers G, Stein K, Grant R

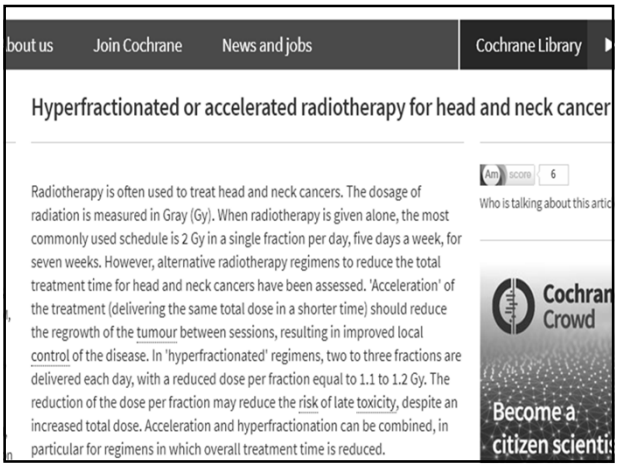
Authors conclusion

1. Temozolomide when given in both concomitant and adjuvant phases is an effective primary therapy in GBM compared to radiotherapy alone.
2. It prolongs survival and delays progression without impacting on QoL but it does increase early adverse events.
3. In recurrent GBM, temozolomide compared with standard chemotherapy improves time-to-progression (TTP) and may have benefits on QoL without increasing adverse events but it does not improve overall.
4. In the elderly, temozolomide alone appears comparable to radiotherapy in terms of OS and PFS but with a higher instance of adverse events



Author conclusion

- Analysis of a subgroup of one RCT showed that surgery for early cervical AC was better than radiotherapy.
- However, the majority of operated patients required adjuvant radiotherapy, which is associated with greater morbidity.
- Furthermore, the radiotherapy in this study was not optimal, and surgery was not compared to chemoradiation, which is currently recommended in most centres.
- Finally, modern imaging techniques (i.e. magnetic resonance imaging (MRI) and positive emission tomography - computed tomography (PET-CT) scanning) allow better selection of patients and node-negative patients can now be more easily identified for surgery, thereby reducing the risk of 'double trouble' caused by surgery and adjuvant radiotherapy.

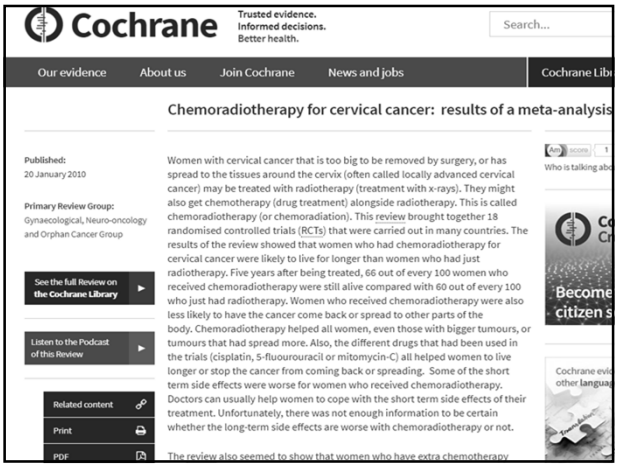


Author conclusion

- 15 trials with 6515 patients
- Median follow up was six years
- Mostly oropharynx and larynx
- There was a significant survival benefit with altered fractionation radiotherapy
- Corresponding to an absolute benefit of 3.4% at five years (hazard ratio (HR) 0.92, 95% CI 0.86 to 0.97; P = 0.003)

Author conclusion

- The benefit was significantly higher with hyperfractionated radiotherapy (8% at five years) than with accelerated radiotherapy (2% with accelerated fractionation .
- The benefit was significantly higher in the youngest patients (under 50 year old)
- There was a benefit in locoregional control in favour of altered fractionation versus conventional radiotherapy (6.4% at five years; P < 0.0001),



Author conclusion

- 18 trials were identified and 15 of these were eligible for inclusion in the main analysis.
- On the basis of 13 trials that compared chemoradiotherapy versus the same radiotherapy, there was a 6% improvement in 5-year survival with chemoradiotherapy (hazard ratio (HR) = 0.81, P < 0.001).
- A larger survival benefit was seen for the two further trials in which chemotherapy was administered after chemoradiotherapy.
- There was a significant survival benefit for both the group of trials that used platinum-based (HR = 0.83, P = 0.017) and non-platinum based (HR = 0.77, P= 0.009) chemoradiotherapy, but no evidence of a difference in the size of the benefit by radiotherapy or chemotherapy dose or scheduling was seen.
- Chemoradiotherapy also reduced local and distant recurrence and progression and improved disease-free survival (DFS).
- There was a suggestion of a difference in the size of the survival benefit with tumourstage, but not across other patient subgroups.
- Acute haematological and gastro-intestinal toxicity were increased with chemoradiotherapy, but datawere too sparse for an analysis of late toxicity.

Surgery versus stereotactic radiotherapy for people with single or solitary brain metastasis

20 August 2018

- There was no difference in progression-free survival in the study comparing surgery plus WBRT versus stereotactic radiosurgery plus WBRT
- there were no differences in quality of life

Interventions for the treatment of brain radionecrosis after radiotherapy or radiosurgery

Author conclusion

1. Bevacizumab showed radiological response which was associated with minimal improvement in cognition or symptom severity
2. Edaravone plus corticosteroids versus corticosteroids alone reported greater reduction in the surrounding oedema with combination treatment but no effect on the enhancing radionecrosis lesion.

Author conclusion

Edaravone, sold as under the brand names **Radicava** and **Radicut**, is an intravenous medication used to help with recovery following a stroke and to treat amyotrophic lateral sclerosis (ALS).

Primary cryotherapy for localised or locally advanced prostate cancer

Based on very low quality evidence, primary whole gland cryotherapy has uncertain effects on oncologic outcomes, QoL, and major adverse events compared to external beam radiotherapy

Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors

AUTHOR CONCLUSION

1. There is high-certainty evidence that HPV vaccines protect against cervical precancer in adolescent girls and young women aged 15 to 26.
2. The effect is higher for lesions associated with HPV16/18 than for lesions irrespective of HPV type.
3. The effect is greater in those who are negative for hrHPV or HPV16/18 DNA at enrolment than those unselected for HPV DNA status.
4. There is moderate-certainty evidence that HPV vaccines reduce CIN2+ in older women who are HPV16/18 negative, but not when they are unselected by HPV DNA status

Bisphosphonates in multiple myeloma: an updated network meta-analysis

Author conclusion

1. Use of bisphosphonates in participants with MM reduces pathological vertebral fractures, SREs and pain.
2. Bisphosphonates were associated with an increased risk of developing ONJ.
3. For every 1000 participants treated with bisphosphonates, about one patient will suffer from the ONJ.
4. We found no evidence of superiority of any specific aminobisphosphonate (zoledronate, pamidronate or ibandronate) or non-aminobisphosphonate (etidronate or clodronate) for any outcome.
5. zoledronate was found to be better than placebo and first-generation bisposphonate (etidronate) in pooled direct and indirect analyses for improving OS and other outcomes such as vertebral fractures.
6. Direct head-to-head trials of the second-generation bisphosphonates are needed to settle the issue if zoledronate is truly the most efficacious bisphosphonate currently used in practice

Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals

AUTHOR CONCLUSION

1. Nine studies comprising 338,467 individuals randomized to screening and 405,919 individuals to the control groups.
2. In the analyses based on indirect comparison of the two screening methods, the relative risk of dying from colorectal cancer was 0.85 (95% credibility interval 0.72 to 1.01, low quality evidence) for flexible sigmoidoscopy screening compared to FOBT.
3. There is high quality evidence that both flexible sigmoidoscopy and faecal occult blood testing reduce colorectal cancer mortality when applied as screening tools

Bisphosphonates and other bone agents for breast cancer

AUTHOR CONCLUSION

1. Included 44 RCTs involving 37,302 women.
2. For women with EBC, bisphosphonates reduce the risk of bone metastases and provide an overall survival benefit compared to placebo or no bisphosphonates
3. There is preliminary evidence suggestive that bisphosphonates provide an overall survival and disease-free survival benefit in postmenopausal women only when compared to placebo or no bisphosphonate
4. In women with ABC without clinically evident bone metastases, there was no evidence of an effect of bisphosphonates on bone metastases
5. Bisphosphonates did not significantly reduce the incidence of fractures when compared to placebo/no bisphosphonates

Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix

AUTHOR CONCLUSION

1. 17 published and two unpublished) including 4580 patients
2. Concomitant chemoradiation appears to improve overall survival and progression-free survival in locally advanced cervical cancer.
3. The review strongly suggests chemoradiation improves overall survival and progression free survival, whether or not platinum was used with absolute benefits of 10% and 13% respectively.
4. There was some evidence that the effect was greater in trials including a high proportion of stage I and II patients
5. Chemoradiation also showed significant benefit for local recurrence and a suggestion of a benefit for distant recurrence

Chemotherapy as an adjunct to radiotherapy in locally advanced nasopharyngeal carcinoma

AUTHOR CONCLUSION

1. Eight trials with 1753 patients were included. One trial with a 2 x 2 design was counted twice in the analysis.
2. The median follow up was six years
3. he pooled hazard ratio of death was 0.82 (95% confidence interval (CI) 0.71 to 0.95; P = 0.006) corresponding to an absolute survival benefit of 6% at five years from chemotherapy (from 56% to 62%)
4. Chemotherapy led to a small but significant benefit for overall survival and event-free survival. This benefit was essentially observed when chemotherapy was administered concomitantly with radiotherapy.
5. A significant interaction was observed between chemotherapy timings and overall survival (P = 0.005), explaining the heterogeneity observed in the treatment effect (P = 0.03) with the highest benefit from concomitant chemotherapy.

Early versus delayed postoperative radiotherapy for treatment of low-grade gliomas

AUTHOR CONCLUSION

1. one large, multi-institutional, prospective RCT, involving 311 participants
2. The median OS in the early radiotherapy group was 7.4 years, while the delayed radiotherapy group experienced a median overall survival of 7.2 years
3. People with LGG who undergo early radiotherapy showed an increase in time to progression compared with people who were observed and had radiotherapy at the time of progression
4. There was no significant difference in overall survival between people who had early versus delayed radiotherapy
5. People who underwent early radiation had better seizure control at one year than people who underwent delayed radiation
6. There were no cases of radiation-induced malignant transformation of LGG
7. However, it remains unclear whether there are differences in memory, executive function, cognitive function, or quality of life between the two groups since these measures were not evaluated.

The role of additional radiotherapy for primary central nervous system lymphoma

AUTHOR CONCLUSION

1. 556 potentially relevant studies only two met the inclusion criteria
2. In summary, the currently available evidence (one RCT) is not sufficient to conclude that WBR plus chemotherapy and chemotherapy alone have similar effects on overall survival in people with PCNSL.
3. The findings suggest that the addition of radiotherapy (WBR) to chemotherapy may increase progression-free survival, but may also increase the incidence of neurotoxicity compared to chemotherapy only (methotrexate monotherapy).
4. As the role of chemoradiotherapy in the treatment of PCNSL remains unclear, further prospective, randomised trials are needed before definitive conclusions can be drawn.

Adjuvant chemotherapy for advanced endometrial cancer

AUTHOR CONCLUSION

1. 4 multicentre RCTs involving 1269 women with primary FIGO stage III/IV endometrial cancer.
2. There is moderate quality evidence that chemotherapy increases survival time after primary surgery by approximately 25% relative to radiotherapy in stage III and IV endometrial cancer.
3. There is limited evidence that it is associated with more adverse effects.
4. There is some uncertainty as to whether triplet regimens offer similar survival benefits over doublet regimens in the long-term.
5. Further research is needed to determine which chemotherapy regimen(s) are the most effective and least toxic, and whether the addition of radiotherapy further improves outcomes.

Primary groin irradiation versus primary groin surgery for early vulvar cancer

AUTHOR CONCLUSION

1. No new RCTs were identified by the updated search. Out of twelve identified papers only one met the selection criteria.
2. Although primary radiotherapy for the groin results in less short term and long term morbidity compared with inguinal and femoral groin dissection, there is not enough evidence to prove that it is as effective regarding control of tumours in the groin.
3. In the only RCT, tumour recurrence and survival were both better in the surgery arm overall, although the irradiation dose may have been inadequate.
4. In daily practice this means that surgery is the first choice treatment for the groin lymph nodes in early vulvar cancer.
5. When the condition of the patient is such that the increased risk of morbidity with the use of surgery outweighs the chances of cure, then primary radiotherapy is a good alternative treatment

Hormonal therapy in advanced or recurrent endometrial cancer

AUTHOR CONCLUSION

1. Found six trials (542 participants) that met our inclusion criteria
2. From the available RCTs, we found insufficient evidence that hormonal treatment in any form, dose or as part of combination therapy improves the survival of patients with advanced or recurrent endometrial cancer.
3. However, a large number of patients would be needed to demonstrate an effect on survival in a RCT and none of the included trials in this review had a sufficient number of patients to demonstrate a significant difference.
4. In view of the absence of a proven survival advantage and the heterogeneity of patient populations, the decision to use any type of hormonal therapy should be individualised and with the intent to palliate the disease.
5. It is debatable whether outcomes such as quality of life, treatment response or palliative measures such as relieving symptoms should take preference over overall and progression-free survival as the major objectives of future trials.

GREEN TEA

Green tea (Camellia sinensis) for the prevention of cancer

WHAT IS GREEN TEA?

1. Tea is one of the most commonly consumed beverages worldwide.
2. Teas from the plant Camellia sinensis can be grouped into green, black and oolong tea.
3. Cross-culturally tea drinking habits vary.
4. Camellia sinensis contains the active ingredient polyphenol, which has a subgroup known as catechins.
5. Catechins are powerful antioxidants. It has been suggested that green tea polyphenol may inhibit cell proliferation
6. observational studies have suggested that green tea may have cancer-preventative effects

AUTHOR CONCLUSION

1. 51 studies with more than 1.6 million participants were included.
2. 27 of them were case-control studies, 23 cohort studies and one randomised controlled trial (RCT)
3. There is insufficient and conflicting evidence to give any firm recommendations regarding green tea consumption for cancer prevention.
4. The results of this review, including its trends of associations, need to be interpreted with caution and their generalisability is questionable, as the majority of included studies were carried out in Asia (n = 47) where the tea drinking culture is pronounced.
5. Desirable green tea intake is 3 to 5 cups per day (up to 1200 ml/day), providing a minimum of 250 mg/day catechins.
6. If not exceeding the daily recommended allowance, those who enjoy a cup of green tea should continue its consumption.
7. Drinking green tea appears to be safe at moderate, regular and habitual use.

Drugs for preventing lung cancer in healthy people

AUTHOR CONCLUSION

1. In the first version of this review four studies were included; in this review update, an additional five studies have been included.
2. There is no evidence for recommending supplements of vitamins A, C, E, selenium, either alone or in different combinations,
3. for the prevention of lung cancer and lung cancer mortality in healthy people.
4. There is some evidence that the use of beta-carotene supplements could be associated with a small increase in lung cancer incidence and mortality in smokers or persons exposed to asbestos.
5. single study that included 7627 women and found a higher risk of lung cancer incidence for those taking vitamin C but not for total cancer incidence, but that effect was not seen in males or when the results for males and females were pooled.

Concurrent chemoradiotherapy in non-small cell lung cancer

AUTHOR CONCLUSION

1. Nineteen randomised studies (2728 participants) of concurrent chemoradiotherapy versus radiotherapy alone were included.
2. Chemoradiotherapy significantly reduced overall risk of death (HR 0.71, 95% CI 0.64 to 0.80; I^2 0%; 1607 participants) and overall progression-free survival at any site (HR 0.69, 95% CI 0.58 to 0.81; I^2 45%; 1145 participants).
3. Incidence of acute oesophagitis, neutropenia and anaemia were significantly increased with concurrent chemoradiation.
4. Six trials (1024 patients) of concurrent versus sequential chemoradiation were included.
5. A significant benefit of concurrent treatment was shown in overall survival (HR 0.74, 95% CI 0.62 to 0.89; I^2 0%; 702 participants). This represented a 10% absolute survival benefit at 2 years.
6. More treatment-related deaths (4% vs 2%) were reported in the concurrent arm without statistical significance (RR 2.02, 95% CI 0.90 to 4.52; I^2 0%; 950 participants).
7. There was increased severe oesophagitis with concurrent treatment (RR 4.96, 95%CI 2.17 to 11.37; I^2 66%; 947 participants).

Antiepileptic drugs for preventing seizures in people with brain tumors

AUTHOR CONCLUSION

1. Main results

A. There was no difference between the treatment interventions and the control groups in preventing a first seizure in participants with brain tumors.

B. The risk of an adverse event was higher for those on antiepileptic drugs than for participants not on antiepileptic drugs (NNH 3; RR 6.10, 95% CI 1.10 to 34.63; P = 0.046).

1. Authors' conclusions

A. The evidence is neutral, neither for nor against seizure prophylaxis, in people with brain tumors. These conclusions apply only for the antiepileptic drugs phenytoin, phenobarbital, and divalproex sodium.

B. The decision to start an antiepileptic drug for seizure prophylaxis is ultimately guided by assessment of individual risk factors and careful discussion with patients.

Interventions for treating oral candidiasis for patients with cancer receiving treatment

AUTHOR CONCLUSION

1. Treatment of cancer is increasingly effective but is associated with short and long term side effects.
2. Oral and gastrointestinal side effects, including oral candidiasis, remain a major source of illness despite the use of a variety of agents to treat them
3. Ten trials involving 940 patients, satisfied the inclusion criteria and are included in this review. Drugs absorbed from the gastrointestinal (GI) tract were beneficial in eradication of oral candidiasis compared with drugs not absorbed from the GI tract (three trials: RR = 1.29, 95% confidence interval (CI) 1.09 to 1.52), however there was significant heterogeneity.
4. A drug absorbed from the GI tract, ketoconazole, was more beneficial than placebo in eradicating oral candidiasis (one trial: RR = 3.61, 95% CI 1.47 to 8.88).
5. Clotrimazole, at a higher dose of 50 mg was more effective than a lower 10 mg dose in eradicating oral candidiasis, when assessed mycologically (one trial: RR = 2.00, 95% CI 1.11 to 3.60).

Cochrane Central Register of Controlled Trials (CENTRAL)

1. **CENTRAL** is comprised of these Specialized **Registers**, relevant records retrieved from MEDLINE and EMBASE , and records retrieved through hand searching (planned manual searching of a journal or conference proceedings to identify all reports of randomised **controlled trials** and **controlled clinical trials**).
2. The Cochrane Central Register of Controlled Trials (CENTRAL) is a bibliographic database that provides a highly concentrated source of reports of randomized controlled trials. Records contain the list of authors, the title of the article, the source, volume, issue, page numbers, and, in many cases, a summary of the article (abstract). They do not contain the full text of the article.

Thank you