Meta-analysis: Critical appraisal

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Format

- What is the role of systematic reviews and meta-analysis in radiation oncology?
- Where do you find good quality systematic reviews and meta-analysis?
- How do you critically appraise a systematic review and meta-analysis?

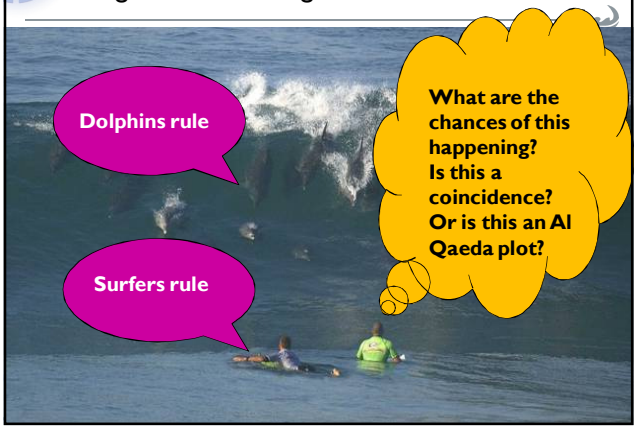
The bottom line

- What do radiation oncologists and patients need?
  - Reliable and up to date evidence of the efficacy and safety of interventions
- What kind of evidence is required?
  - Evidence that is internally valid (the truth)
  - Evidence that is externally valid (applicable to you)
  - Evidence that is comprehensive (takes account of all studies and not only those that are easily available)
  - Evidence that is up to date (takes account of the latest research)
  - Evidence that provides estimates of how effective or harmful the intervention is (is the difference in interventions clinically and statistically important?)

Getting the evidence right: Wha

Getting the evidence right: Strange bedfellows

Getting the evidence right: the effects of chance



Threats to Internal Validity

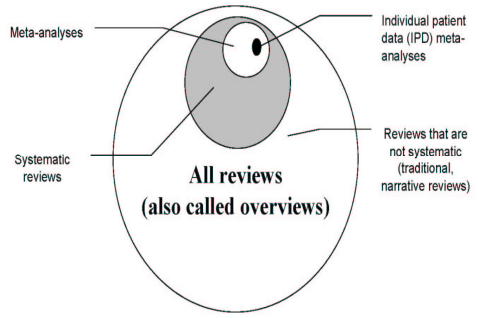
- Any factor or process that tends to deviate the results or conclusions of a trial systematically away from the truth
- Deviation in results can occur due to systematic (bias) or random errors (chance)
- Random errors reduce with increase in sample size; detected by p values
- Bias can result in overestimates or underestimates of the results of a trial (cannot be detected by p values)
- Bias can occur due to voluntary or involuntary reasons (not the same as fraud)

Not all evidence is equally convincing: **Levels of Evidence**

Level	Intervention	Prognosis	Diagnosis	Etiology
Least biased I	Systematic Review of level II studies	Systematic Review of Level II studies	Systematic Review of Level II studies	Systematic Review of Level II studies
II	RCT	Inception cohort study	Cross sectional study among consecutive patients	Prospective cohort study
III	•Non-randomized controlled clinical trial •Controlled before and after study •Cohort study •Case control study	•Untreated controls in an RCT •Retrospectively assembled cohort study	•Cross sectional study among non-consecutive patients •Case control study	•Retrospective cohort study •Case control study
Most biased IV	Case series	Case series	Case series Cohort of patients at different stages of disease	Cross sectional study

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

- The application of scientific strategies that limit bias to the systematic assembly, critical appraisal, and synthesis of all relevant studies on a specific topic
- Many (not all) systematic reviews use meta analysis to synthesize data
- Meta-analysis is the statistical technique used to combine the results of several independent studies that are similar in the methods, populations studied, interventions and outcomes



Narrative Review	Systematic Review
No Methods section;not reproducible	Clearly described protocol with detailed methods
Limited searching for trials (often limited to Medline);leads to 'publication bias'	Comprehensive searching for published and unpublished trials with no language restrictions
Include different study designs,often do not evaluate validity	Mostly include only RCTs or next best study design;evaluates validity
Over-reliance on p values	Estimates size of effect with confidence intervals (precision)
Uses 'vote counting';each trial given same weight	Differentially weights trials so that larger trials with more information and precise results are given more weight
Descriptive	Meta-analysis pools results of similar trials;provides a 'tower of power'
Subjective;Biased	Objective (two or more authors who independently undertake review)

Problems with traditional reviews

- Lag behind and often vary significantly from continuously updated or cumulative meta-analysis (Lau et al 1992)

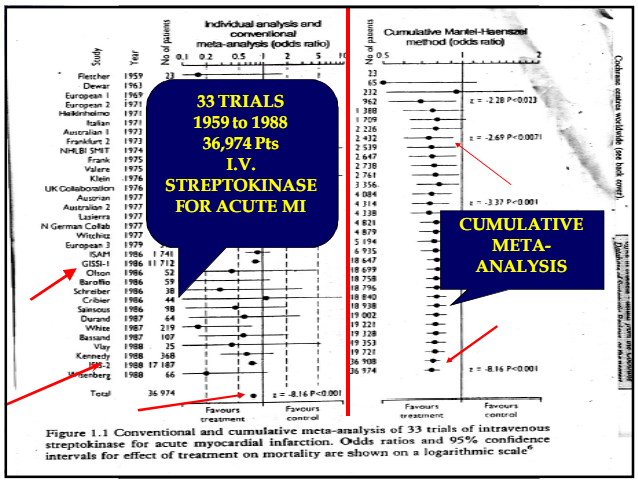
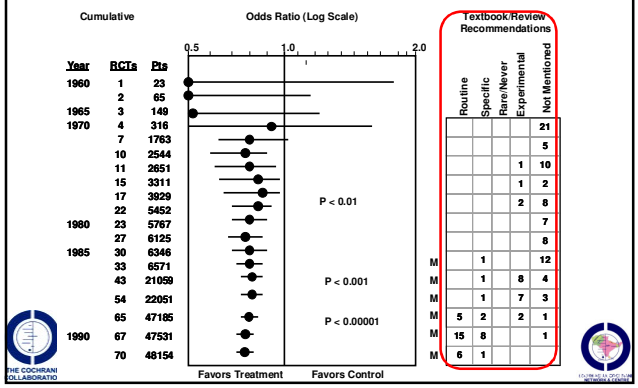


Figure 1.1 Conventional and cumulative meta-analysis of 33 trials of intravenous streptokinase for acute myocardial infarction. Odds ratios and 95% confidence intervals for effect of treatment on mortality are shown on a logarithmic scale[6]

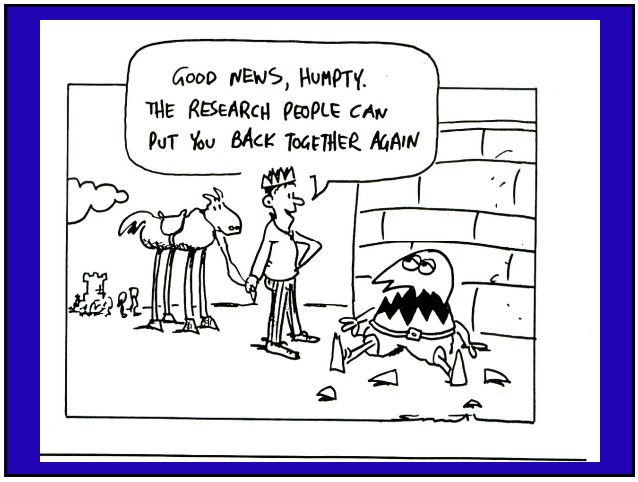
Thrombolysis for Acute MI



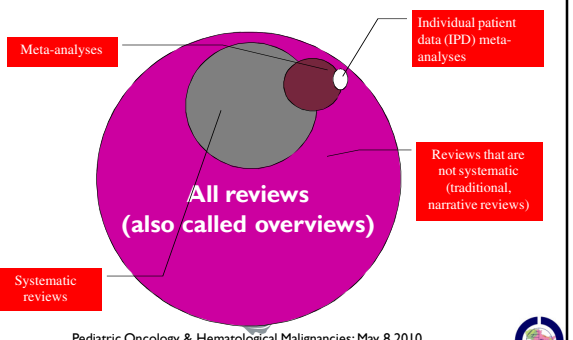
Criticisms of systematic reviews

"Exercise in mega silliness" (Eysenck 1978)

"Adding apples and oranges can render the exercise fruitless" (Eysenck 1995)



In practice, not all meta-analyses are conducted as part of systematic reviews



When can meta-analyses mislead?

- When a meta-analysis is done outside of a systematic review
- When poor quality studies are included or when quality issues are ignored
- When inadequate attention is given to heterogeneity
  - Indiscriminate data aggregation can lead to inaccurate conclusions
- When reporting biases are a problem
  - Publication bias
  - Time lag bias
  - Duplicate publication bias
  - Language bias
  - Outcome reporting bias
  - Citation bias

Egger M et al. Uses and abuses of meta-analysis. Clinical Medicine 2001;1:478-84

Where can we find good quality systematic reviews ?

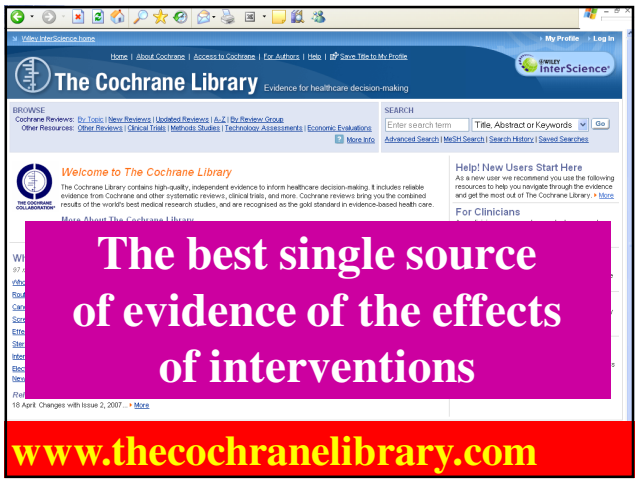
www.cochrane.org

THE COCHRANE COLLABORATION

Preparing, maintaining and disseminating systematic reviews of the effects of health care

What does the Cochrane Collaboration have to offer?

- Largest organization in the world devoted to producing, disseminating and maintaining systematic reviews (SRs) of the effects of interventions
- Also involved in producing SRs of the accuracy of diagnostic tests
- >22,000 volunteers who share common principles (www.cochrane.org)
- Main output is *The Cochrane Library*



The Cochrane Library is a collection of Evidence-Based Medicine databases:

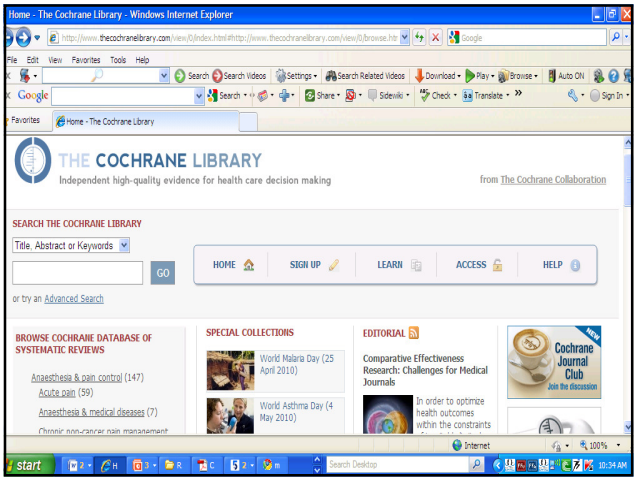
Database	Issue 3 2009
The Cochrane Database of Systematic Reviews (CDSR; Cochrane Reviews)	5821
The Cochrane Database of Reviews of Effects (DARE; Other Reviews)	10,894
The Cochrane Central Register of Controlled Trials (CENTRAL; Clinical Trials)	5,86,829
The Cochrane Methodology Register (CMR; Methods Studies)	11,837
Health Technology Assessment Database (HTA; Technology Assessments)	7947
NHS Economic Evaluation Database (NHSEED; Economic Evaluations)	26,917
About the Cochrane Collaboration	94

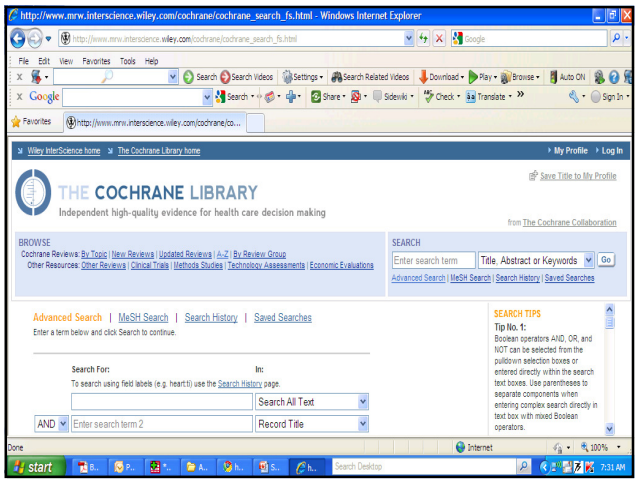
Are Cochrane Systematic Reviews different from other systematic reviews?

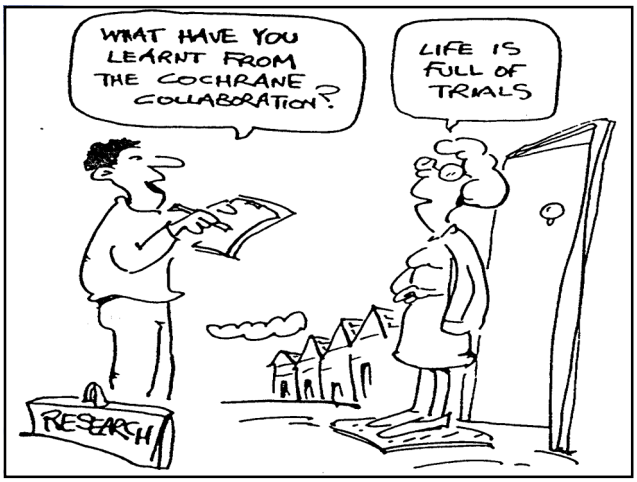
- Only about 20% of reviews published each year are Cochrane Systematic Reviews
- Cochrane Systematic Reviews emphasize methodological rigour
  - Found to be of better quality, more up to date, & less biased in methods and interpretation than non-Cochrane systematic reviews
  - Free of conflicted sources of funding
- Used to inform practice guidelines of the WHO, many policy making bodies world-wide; have changed health practices too

Jadad et al. Methodology and reports of systematic reviews and meta-analyses: a comparison of Cochrane reviews with articles published in paper-based journals. JAMA 1998;280:278-280.

Moher D, et al. Epidemiology and reporting characteristics of systematic reviews. PLoS Med 2007; 4(3): e78. doi:10.1371/journal. pmed.0040078`

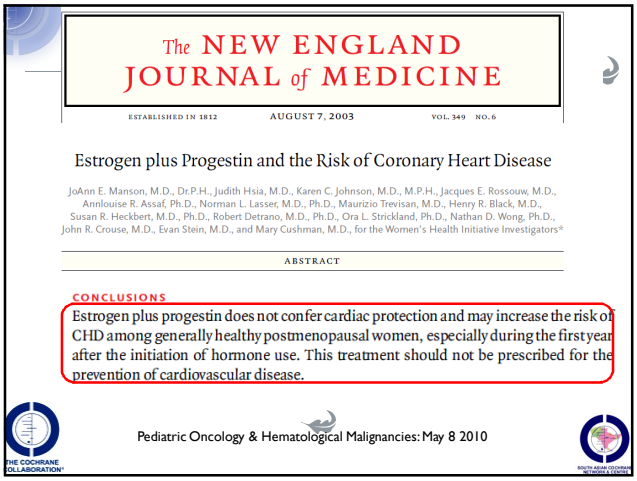






Why cant we use evidence from observational studies for evaluating the effects of interventions?

- Hormone replacement therapy for post-menopausal women provides an instructive example
- For a decade, organizations recommended that clinicians encourage postmenopausal women to use hormone replacement therapy believing this would reduce cardiovascular risks
- Because the data came from observational studies with inconsistent results, the evidence for a reduction in cardiovascular risk was of very low quality



Farquhar C, Marjoribanks J, Lethaby A, Suckling JA, Lamberts Q. Long term hormone therapy for peri-menopausal and postmenopausal women. *Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD004143*

- **Objectives**
  - To assess the effect of long-term HT on mortality, cardiovascular outcomes, cancer, gallbladder disease, cognition, fractures and quality of life.
- **Selection criteria**
  - Randomised double-blind trials of HT versus placebo, taken for at least one year by peri-menopausal or postmenopausal women.
  - HT included oestrogens, with or without progestogens, via oral, trans-dermal, subcutaneous or trans-nasal routes.

Farquhar C, Marjoribanks J, Lethaby A, Suckling JA, Lamberts Q. Long term hormone therapy for peri-menopausal and postmenopausal women. *Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD004143*

- **Main results**
- Nineteen trials involving 41,904 women were included.
- **In relatively healthy women,** combined continuous HT **significantly increased the risk of venous thrombo-embolism or coronary event** (after one year's use**), stroke** (after three years),
- **Among women aged over 65** who were relatively healthy (i.e. generally fit, without overt disease) and taking continuous combined HT, there **was a statistically significant increase in the incidence of dementia.**

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Farquhar C, Marjoribanks J, Lethaby A, Suckling JA, Lamberts Q. Long term hormone therapy for peri-menopausal and postmenopausal women. *Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD004143*

- **Authors' conclusions**
  - **HT is not indicated for the routine management of chronic disease.** We need more evidence on the safety of HT for menopausal symptom control, though short-term use appears to be relatively safe for healthy younger women

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The Cochrane Library

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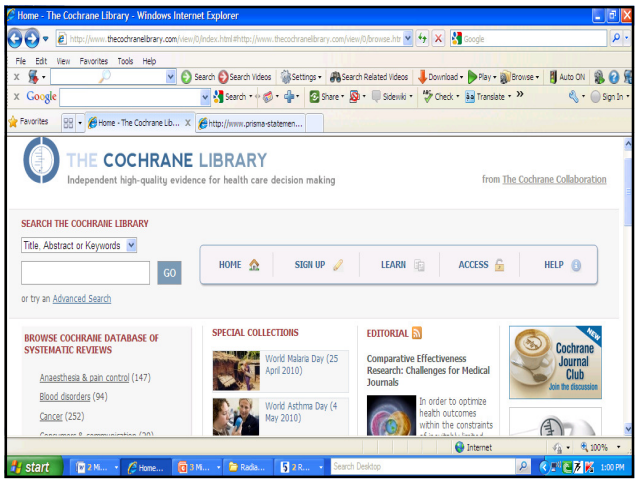
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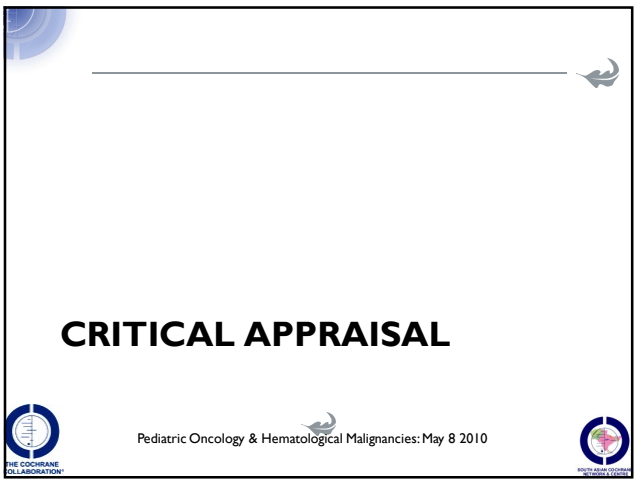
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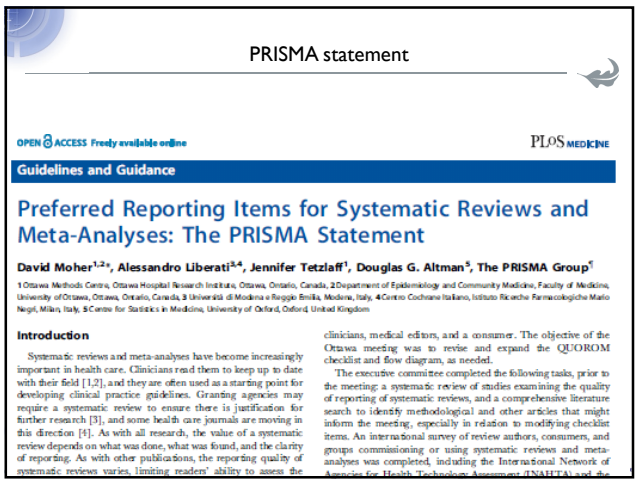
http://www.equator-network.org/

http://www.equator-network.org/resource-centre/library-of-health-research-reporting/

PRISMA statement



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PLoS MEDICINE

Guidelines and Guidance

Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

David Moher[1,2*], Alessandro Liberati[3,4], Jennifer Tetzlaff[1], Douglas G. Altman[5], The PRISMA Group[¶]

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Introduction

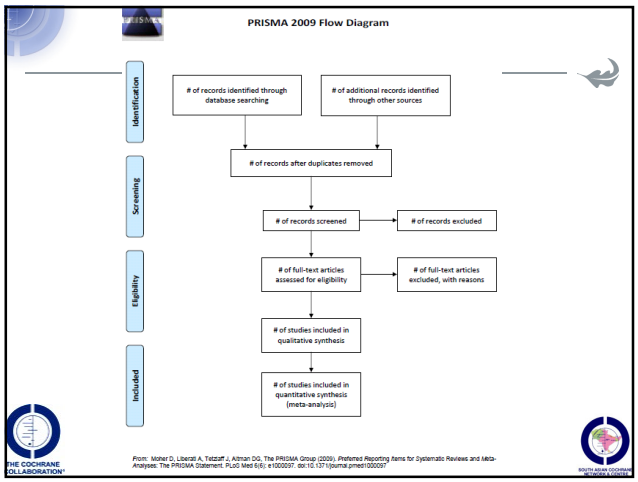
Systematic reviews and meta-analyses have become increasingly important in health care. Clinicians read them to keep up to date with their field [1,2], and they are often used as a starting point for developing clinical practice guidelines. Granting agencies may require a systematic review to ensure there is justification for further research [3], and some health care journals are moving in this direction [4]. As with all research, the value of a systematic review depends on what was done, what was found, and the clarity of reporting. As with other publications, the reporting quality of systematic reviews varies, limiting readers' ability to assess the

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 executive committee completed the following tasks, prior to the meeting: a systematic review of studies examining the quality of reporting of systematic reviews, and a comprehensive literature search to identify methodological and other articles that might inform the meeting, especially in relation to modifying checklist items. An international survey of review authors, consumers, and groups commissioning or using systematic reviews and meta-analyses was completed, including the International Network of Agencies for Health Technology Assessment (INAHTA) and the

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	



What to look for in a systematic review?

- A clearly defined, explicit question
- Comprehensive and systematic search for studies
- Explicit, reproducible strategy for screening and including or excluding studies (inclusion/exclusion criteria)
- Assessment of quality of primary studies
- Explicit, reproducible data extraction
- Appropriate analysis and reporting of results
  - Exploration of heterogeneity, publication bias, sensitivity analyses, sub-group analyses etc.
- Discussion should consider limitations and strength of evidence
  - evidence of no effect vs. no evidence of effect
- Interpretation supported by data
- Implications for patient care and future research

[Intervention Review]

Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix

John A Green[1], John J Kirwan[2], Jayne Tierney[3], Claire L Vale[3], Paul R Symonds[4], Lydia L Fresco[5], Chris Williams[6], Mandy Collingwood[7]

[1]Clatterbridge Centre for Oncology, Clatterbridge Hospital, Merseyside, UK. [2]Gynaecology Department, Liverpool Women's Hospital, Liverpool, UK. [3]Meta-analysis Group, MRC Clinical Trials Unit, London, UK. [4]Department of Oncology, Leicester Royal Infirmary, Leicester, UK. [5]Nottingham City Hospital, Nottingham, UK. [6]Cochrane Gynaecological Cancer Review Group, Royal United Hospital, Bath, UK. [7]Radiotherapy Department, Churchill Hospital, Oxford, UK

Contact address: John Green, Department of Clinical Health Psychology, St Mary's Hospital, Clarence Wing, Praed Street, London, W2 1NY, UK. john.green@nhs.net.

Editorial group: Cochrane Gynaecological Cancer Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 1, 2010.
Review content assessed as up-to-date: 22 May 2005.

Citation: Green JA, Kirwan JJ, Tierney J, Vale CL, Symonds PR, Fresco LL, Williams C, Collingwood M. Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD002225. DOI: 10.1002/14651858.CD002225.pub2.

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Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix

- **Objectives**
- This systematic review aims to compare the effectiveness of concomitant chemotherapy and radiation therapy with radiotherapy in the treatment of locally advanced carcinoma of the cervix.

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Architecture of a focused question: a 4-part review question

P - Who is the patient or what problem is being addressed?

I - What is the intervention or exposure?

C – What is the comparison group?

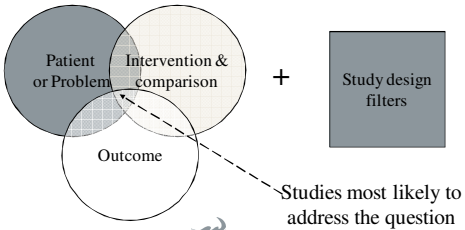
O - What is the outcome or endpoint?

+ study design

Richardson et al. The well-built clinical question: a key to evidence-based decisions. ACP Journal Club 1995;A-12
Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. Ann Intern Med 1997;127:380-7

How a focused question helps in searching for studies

PICO + STUDY DESIGN FILTER



Methods

- **Criteria for considering studies for this review**
- **Types of studies**
- The review was restricted to:
  - RCTs in cancer of the uterine cervix
  - Trials accruing patients from January 1980
- **Types of participants**
- Patients with locally advanced cancer of the uterine cervix (FIGO stage IB-IVA).

Methods

- **Types of interventions**
- **Inclusion criteria were:**
- • Trials comparing concomitant cytotoxic chemotherapy plus radiotherapy (with or without surgery)* with radiotherapy (with or without surgery)* alone
- • In the experimental arm, further adjuvant chemotherapy in addition to concomitant chemotherapy was an allowable option
- *For the purposes of this review, hydroxyurea was considered an inactive agent and therefore allowable with local treatment

Methods

- **Types of interventions**
- **Exclusion criteria were:**
- Trials that used radiosensitisers or radioprotectors in the experimental arm
- A radiosensitiser is defined as a drug that has no cytotoxic activity at the dose and schedule employed, but when combined with ionising radiation produces increased cell killing.
- • A radiation protector is a drug which when given with ionising radiation reduces the effect of that radiation.

Methods

- **Types of outcome measures**
- Survival and progression-free survival were considered the primary end points,while rates of local and distant recurrence were analysed as secondary endpoints.
- We collected and analysed additional data on the type and severity of acute and late toxicity.

Searching for trials

- **Electronic searches**
- The Cochrane Gynaecological Cancer Collaborative Review Group's specialised register of trials
- MEDLINE (date of last search May 2004)
- CancerLit (date of last search 2003. NB Cancerlit is no longer updated)
- The Cochrane Central Register of Controlled Trials CENTRAL (2004, Issue 2)
- LILACS (date of last search June 2004)

Searching for trials

- **Electronic searches**
- The following trial registers were searched for open and closed trials:
- Physicians Data Query Protocols (Open and Closed Protocols)
- (date of last search June 2004)
- United Kingdom Co-ordinating Committee on Cancer Research
- (UKCCCR) Register of Cancer Trials (Open and Closed Protocols) (date of last search June 2004)
- MetaRegister (June 2004)
- For MEDLINE search strategy see Appendix 1.

Searching for trials

- **Searching other resources**
- The references lists of all published trial reports and review articles were searched for further trial reports.

Concomitant chemoradiotherapy versus radiation: Survival by type of Chemotherapy

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	O-E	Variance	Weight	Peto Odds Ratio Exp[(O-E) / V], Fixed, 99% CI
1.1.1 Platinum chemotherapy								
Whitney 1999	79	177	108	191	-13.38	44.45	15.9%	0.74 [0.50, 1.09]
Onishi 1999	10	18	8	15	0.63	1.87	0.7%	1.40 [0.21, 9.21]
Tseng 1997	23	60	22	62	3.7	11.25	4.0%	1.39 [0.64, 2.99]
Eifel 2004	59	194	102	195	-30.7	41.82	15.0%	0.48 [0.32, 0.71]
Peters 2000	21	127	36	116	-8.93	13.26	4.8%	0.51 [0.25, 1.03]
Keys 1999	27	183	49	186	-10.99	17.84	6.4%	0.54 [0.29, 0.99]
Rose 1999	116	349	89	177	-23.38	45.77	16.4%	0.60 [0.41, 0.88]
Pearcey 2002	49	127	52	126	-3.29	25.7	9.2%	0.88 [0.53, 1.46]
Leborgne 2000	42	75	39	78	2.61	15.02	5.4%	1.19 [0.61, 2.31]
Subtotal (95% CI)		**1310**		**1146**			**77.8%**	**0.68 [0.60, 0.78]**
Total events	426		505					
Heterogeneity: Chi² = 21.28, df = 8 (P = 0.006); I² = 62%								
Test for overall effect: Z = 5.68 (P < 0.00001)								
1.1.2 Non-platinum chemotherapy								
Lorvidhaya 2003	68	238	98	450	-15.61	32.33	11.6%	0.62 [0.39, 0.97]
Hernandez 1991	21	36	6	18	3.62	5.18	1.9%	2.01 [0.65, 6.24]
Wong 1999	21	110	34	110	-3.93	12.41	4.4%	0.73 [0.35, 1.51]
Roberts 2000	20	78	30	82	-4.8	12	4.3%	0.67 [0.32, 1.41]
Subtotal (95% CI)		**462**		**660**			**22.2%**	**0.72 [0.56, 0.92]**
Total events	130		168					
Heterogeneity: Chi² = 6.30, df = 3 (P = 0.10); I² = 52%								
Test for overall effect: Z = 2.63 (P = 0.008)								
Total (95% CI)		**1772**		**1806**			**100.0%**	**0.69 [0.61, 0.77]**
Total events	556		673					
Heterogeneity: Chi² = 27.71, df = 12 (P = 0.006); I² = 57%								
Test for overall effect: Z = 6.25 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%								

Peto Odds Ratio Exp[(O-E) / V], Fixed, 99% CI

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

Concomitant chemoradiotherapy versus radiation: Survival by scheduling of chemotherapy

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	O-E	Variance	Weight	Peto Odds Ratio Exp[(O-E) / V], Fixed, 99% CI
1.2.1 Concomitant CT								
Whitney 1999	79	177	108	191	-13.38	44.45	15.9%	0.74 [0.50, 1.09]
Hernandez 1991	21	36	6	18	3.62	5.18	1.9%	2.01 [0.65, 6.24]
Onishi 1999	10	18	8	15	0.63	1.87	0.7%	1.40 [0.21, 9.21]
Tseng 1997	23	60	22	62	3.7	11.25	4.0%	1.39 [0.64, 2.99]
Eifel 2004	59	194	102	195	-30.7	41.82	15.0%	0.48 [0.32, 0.71]
Pearcey 2002	49	127	52	126	-3.29	25.7	9.2%	0.88 [0.53, 1.46]
Rose 1999	116	349	89	177	-23.38	45.77	16.4%	0.60 [0.41, 0.88]
Keys 1999	27	183	49	186	-10.99	17.84	6.4%	0.54 [0.29, 0.99]
Roberts 2000	20	78	30	82	-4.8	12	4.3%	0.67 [0.32, 1.41]
Leborgne 2000	42	75	39	78	2.61	15.02	5.4%	1.19 [0.61, 2.31]
Subtotal (95% CI)		**1297**		**1130**			**79.2%**	**0.71 [0.62, 0.81]**
Total events	446		505					
Heterogeneity: Chi² = 25.90, df = 9 (P = 0.002); I² = 65%								
Test for overall effect: Z = 5.11 (P < 0.00001)								
1.2.2 Concomitant and sequential								
Lorvidhaya 2003	68	238	98	450	-15.61	32.33	11.6%	0.62 [0.39, 0.97]
Wong 1999	21	110	34	110	-3.93	12.41	4.4%	0.73 [0.35, 1.51]
Peters 2000	21	127	36	116	-8.93	13.26	4.8%	0.51 [0.25, 1.03]
Subtotal (95% CI)		**475**		**676**			**20.8%**	**0.61 [0.47, 0.79]**
Total events	110		168					
Heterogeneity: Chi² = 0.82, df = 2 (P = 0.66); I² = 0%								
Test for overall effect: Z = 3.74 (P = 0.0002)								
Total (95% CI)		**1772**		**1806**			**100.0%**	**0.69 [0.61, 0.77]**
Total events	556		673					
Heterogeneity: Chi² = 27.71, df = 12 (P = 0.006); I² = 57%								
Test for overall effect: Z = 6.25 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.99, df = 1 (P = 0.32), I² = 0%								

Peto Odds Ratio Exp[(O-E) / V], Fixed, 99% CI

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

Concomitant chemoradiotherapy versus radiation: Survival by hydroxyurea as control

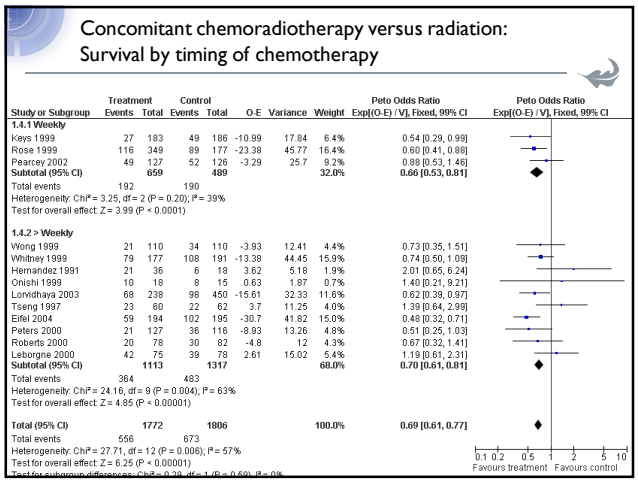
Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	O-E	Variance	Weight	Peto Odds Ratio Exp[(O-E) / V], Fixed, 99% CI
1.3.1 No hydroxyurea on control								
Wong 1999	21	110	34	110	-3.93	12.41	4.4%	0.73 [0.35, 1.51]
Hernandez 1991	21	36	6	18	3.62	5.18	1.9%	2.01 [0.65, 6.24]
Onishi 1999	10	18	8	15	0.63	1.87	0.7%	1.40 [0.21, 9.21]
Lorvidhaya 2003	68	238	98	450	-15.61	32.33	11.6%	0.62 [0.39, 0.97]
Tseng 1997	23	60	22	62	3.7	11.25	4.0%	1.39 [0.64, 2.99]
Eifel 2004	59	194	102	195	-30.7	41.82	15.0%	0.48 [0.32, 0.71]
Peters 2000	21	127	36	116	-8.93	13.26	4.8%	0.51 [0.25, 1.03]
Pearcey 2002	49	127	52	126	-3.29	25.7	9.2%	0.88 [0.53, 1.46]
Keys 1999	27	183	49	186	-10.99	17.84	6.4%	0.54 [0.29, 0.99]
Roberts 2000	20	78	30	82	-4.8	12	4.3%	0.67 [0.32, 1.41]
Leborgne 2000	42	75	39	78	2.61	15.02	5.4%	1.19 [0.61, 2.31]
Subtotal (95% CI)		**1246**		**1438**			**67.7%**	**0.70 [0.61, 0.81]**
Total events	361		476					
Heterogeneity: Chi² = 26.57, df = 10 (P = 0.003); I² = 62%								
Test for overall effect: Z = 4.93 (P < 0.00001)								
1.3.2 Hydroxyurea on control								
Whitney 1999	79	177	108	191	-13.38	44.45	15.9%	0.74 [0.50, 1.09]
Rose 1999	116	349	89	177	-23.38	45.77	16.4%	0.60 [0.41, 0.88]
Subtotal (95% CI)		**526**		**368**			**32.3%**	**0.67 [0.54, 0.82]**
Total events	195		197					
Heterogeneity: Chi² = 0.99, df = 1 (P = 0.32); I² = 0%								
Test for overall effect: Z = 3.87 (P = 0.0001)								
Total (95% CI)		**1772**		**1806**			**100.0%**	**0.69 [0.61, 0.77]**
Total events	556		673					
Heterogeneity: Chi² = 27.71, df = 12 (P = 0.006); I² = 57%								
Test for overall effect: Z = 6.25 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.70), I² = 0%								

Peto Odds Ratio Exp[(O-E) / V], Fixed, 99% CI

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

Concomitant chemoradiotherapy versus radiation: Survival by timing of chemotherapy



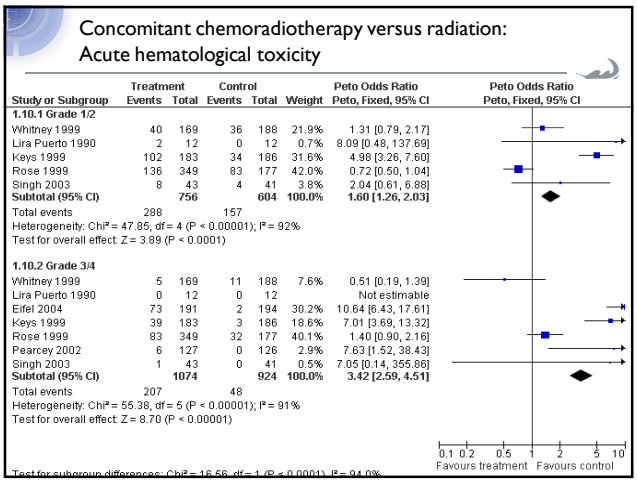
Study or Subgroup	Treatment Events	Total	Control Events	Total	O-E	Variance	Weight	Peto Odds Ratio Exp[(O-E) / V], Fixed, 99% CI
1.4.1 Weekly								
Keys 1999	27	183	49	186	-10.99	17.84	6.4%	0.54 [0.29, 0.99]
Rose 1999	116	349	89	177	-23.38	45.77	16.4%	0.60 [0.41, 0.88]
Pearcey 2002	49	127	52	126	-3.29	25.7	9.2%	0.88 [0.53, 1.46]
Subtotal (95% CI)		**659**		**489**			**32.0%**	**0.66 [0.53, 0.81]**
Total events	192		190					
Heterogeneity: Chi² = 3.25, df = 2 (P = 0.20); I² = 39%								
Test for overall effect: Z = 3.99 (P < 0.0001)								
1.4.2 > Weekly								
Wong 1999	21	110	34	110	-3.93	12.41	4.4%	0.73 [0.35, 1.51]
Whitney 1999	79	177	108	191	-13.38	44.45	15.9%	0.74 [0.50, 1.09]
Hernandez 1991	21	36	6	18	3.62	5.18	1.9%	2.01 [0.65, 6.24]
Onishi 1999	10	18	8	15	0.63	1.87	0.7%	1.40 [0.21, 9.21]
Lorvidhaya 2003	68	238	98	450	-15.61	32.33	11.6%	0.62 [0.39, 0.97]
Tseng 1997	23	60	22	62	3.7	11.25	4.0%	1.39 [0.64, 2.99]
Eifel 2004	59	194	102	195	-30.7	41.82	15.0%	0.48 [0.32, 0.71]
Peters 2000	21	127	36	116	-8.93	13.26	4.8%	0.51 [0.25, 1.03]
Roberts 2000	20	78	30	82	-4.8	12	4.3%	0.67 [0.32, 1.41]
Leborgne 2000	42	75	39	78	2.61	15.02	5.4%	1.19 [0.61, 2.31]
Subtotal (95% CI)		**1113**		**1317**			**68.0%**	**0.70 [0.61, 0.81]**
Total events	364		483					
Heterogeneity: Chi² = 24.16, df = 9 (P = 0.004); I² = 63%								
Test for overall effect: Z = 4.85 (P < 0.00001)								
Total (95% CI)		**1772**		**1806**			**100.0%**	**0.69 [0.61, 0.77]**
Total events	556		673					
Heterogeneity: Chi² = 27.71, df = 12 (P = 0.006); I² = 57%								
Test for overall effect: Z = 6.25 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%								

Peto Odds Ratio Exp[(O-E) / V], Fixed, 99% CI

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

Concomitant chemoradiotherapy versus radiation: Acute hematological toxicity



Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.10.1 Grade 1/2						
Whitney 1999	40	169	36	188	21.9%	1.31 [0.79, 2.17]
Lira Puerto 1990	2	12	0	12	0.7%	8.09 [0.48, 137.69]
Keys 1999	102	183	34	186	31.6%	4.98 [3.26, 7.60]
Rose 1999	136	349	83	177	42.0%	0.72 [0.50, 1.04]
Singh 2003	8	43	4	41	3.8%	2.04 [0.61, 6.88]
Subtotal (95% CI)		**756**		**604**	**100.0%**	**1.60 [1.26, 2.03]**
Total events	288		157			
Heterogeneity: Chi² = 47.85, df = 4 (P < 0.00001); I² = 92%						
Test for overall effect: Z = 3.89 (P < 0.0001)						
1.10.2 Grade 3/4						
Whitney 1999	5	169	11	188	7.6%	0.51 [0.19, 1.39]
Lira Puerto 1990	0	12	0	12		Not estimable
Eifel 2004	73	191	2	194	30.2%	10.64 [6.43, 17.61]
Keys 1999	39	183	3	186	18.6%	7.01 [3.69, 13.32]
Rose 1999	83	349	32	177	40.1%	1.40 [0.90, 2.16]
Pearcey 2002	6	127	0	126	2.9%	7.63 [1.52, 38.43]
Singh 2003	1	43	0	41	0.5%	7.05 [0.14, 355.86]
Subtotal (95% CI)		**1074**		**924**	**100.0%**	**3.42 [2.59, 4.51]**
Total events	207		48			
Heterogeneity: Chi² = 55.38, df = 5 (P < 0.00001); I² = 91%						
Test for overall effect: Z = 8.70 (P < 0.00001)						
Test for subgroup differences: Chi² = 16.56, df = 1 (P < 0.0001), I² = 94.0%						

Peto Odds Ratio Peto, Fixed, 95% CI

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

Conclusisons

based on the data analysed, a potential absolute survival benefit of 12% is attributable to the use of chemoradiotherapy, a figure which could not have been appreciated from the individual phase II or III trial data. Despite the above limitations, we believe that the weight of evidence favours the use of chemoradiotherapy and, because the results are derived from trials of different populations, using different treatment regimens and supportive care facilities, they are potentially generalisable. Application to the developing world requires the regimen to be cheap, and simple to administer, and we suggest that weekly cisplatin may fit these criteria.

Pediatric Oncology & Hematological Malignancies: May 8 2010

[Intervention Review]

Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis

Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC)[1]

[1]See list of members in acknowledgements section, UK

Contact address: Claire L Vale, Meta-analysis Group, MRC Clinical Trials Unit, 222 Euston Road, London, NW1 2DA, UK. cv@ctu.mrc.ac.uk. Hidden.

Editorial group: Cochrane Gynaecological Cancer Group.
Publication status and date: New, published in Issue 1, 2010.
Review content assessed as up-to-date: 22 October 2009.

Citation: Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD008285. DOI: 10.1002/14651858.CD008285.

ABSTRACT

Background

After a 1999 National Cancer Institute (NCI) clinical alert was issued, chemoradiotherapy has become widely used in treating women with cervical cancer. Two subsequent systematic reviews found that interpretation of the benefits was complicated and some important clinical questions were unanswered.

Objectives

We initiated a meta-analysis seeking updated individual patient data (IPD) from all randomised controlled trials (RCTs) to assess the effect of chemoradiotherapy on all outcomes. We pre-specified analyses to investigate whether the effect of chemoradiotherapy differed by trial or patient characteristics.

Search strategy

We supplemented MEDLINE, LILACS and CANCERLIT searches with information from trial registers, by handsearching relevant meeting proceedings and by discussion with relevant trialists and organisations. Searches were updated until October 2009.

Selection criteria

Both published and unpublished trials were eligible for inclusion provided the patients had been randomised between radiotherapy (with or without surgery) versus concomitant chemoradiotherapy (with or without surgery); that the method of randomisation precluded prior knowledge of the treatment to be assigned; and that the trial had completed patient recruitment before the date of the final analyses.

Data collection and analysis

We carried out a quantitative meta-analysis using updated information from individual patients from all available RCTs. We sought data from all patients randomised in all eligible trials. We obtained updated information on survival, recurrence and date of last follow up. To avoid potential bias, we requested information for all randomised patients, including those who had been excluded from the investigators' original analyses.

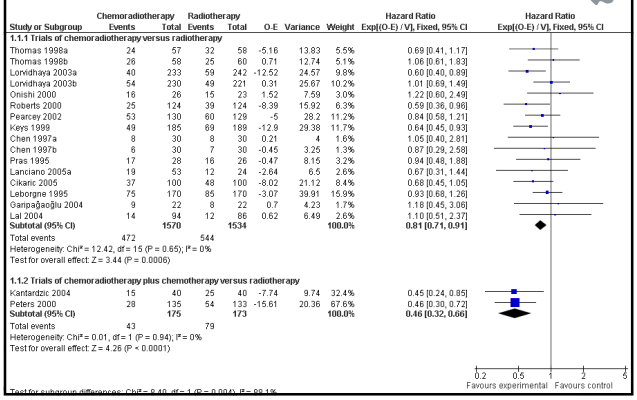
Pediatric Oncology & Hematological Malignancies: May 8 2010

Main results

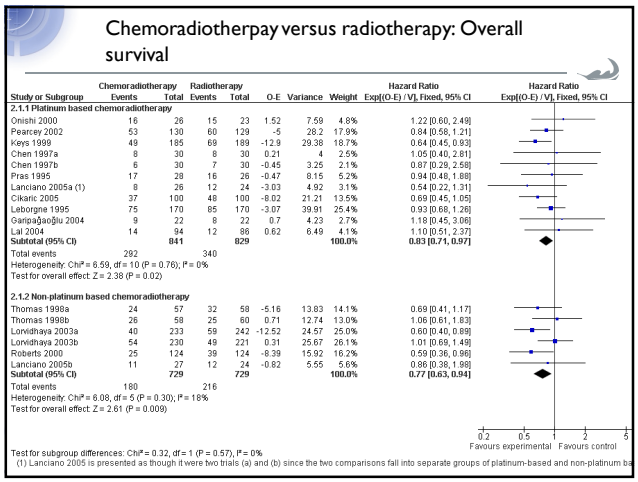
Eighteen trials were identified and 15 of these were eligible for inclusion in the main analysis. On the basis of 13 trials that compared chemoradiotherapy versus the same radiotherapy, there was a 6% improvement in 5-year survival with chemoradiotherapy (hazard ratio (HR) = 0.81, P < 0.001). A larger 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 tumour stage, but not across other patient subgroups. Acute haematological and gastro-intestinal toxicity were increased with chemoradiotherapy, but data were too sparse for an analysis of late toxicity.

Pediatric Oncology & Hematological Malignancies: May 8 2010

Chemoradiotherapy plus chemotherapy versus radiotherapy: Outcome overall survival



Chemoradiotherpay versus radiotherapy: Overall survival



Study or Subgroup	Chemoradiotherapy Events	Total	Radiotherapy Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
2.1.1 Platinum based chemoradiotherapy								
Onishi 2000	16	26	15	23	1.52	7.59	4.8%	1.22 [0.60, 2.49]
Pearcey 2002	53	130	60	129	-5	28.2	17.9%	0.84 [0.56, 1.21]
Keys 1999	49	185	69	189	-12.9	29.38	18.7%	0.64 [0.45, 0.93]
Chen 1997a	8	30	8	30	0.21	4	2.5%	1.05 [0.40, 2.81]
Chen 1997b	6	30	7	30	-0.45	3.25	2.1%	0.87 [0.29, 2.58]
Pras 1995	17	28	16	26	-0.47	8.15	5.2%	0.94 [0.48, 1.88]
Lanciano 2005a (1)	8	26	12	24	-3.03	4.92	3.1%	0.54 [0.22, 1.31]
Cikaric 2005	37	100	48	100	-8.02	21.21	13.5%	0.69 [0.45, 1.05]
Leborgne 1995	75	170	85	170	-3.07	39.91	25.4%	0.93 [0.68, 1.26]
Garipağaoğlu 2004	9	22	8	22	0.7	4.23	2.7%	1.18 [0.45, 3.06]
Lal 2004	14	94	12	86	0.62	6.49	4.1%	1.10 [0.51, 2.37]
Subtotal (95% CI)		**841**		**829**			**100.0%**	**0.83 [0.71, 0.97]**
Total events	292		340					
Heterogeneity: Chi² = 6.59, df = 10 (P = 0.76); I² = 0%								
Test for overall effect: Z = 2.38 (P = 0.02)								
2.1.2 Non-platinum based chemoradiotherapy								
Thomas 1998a	24	57	32	58	-5.16	13.83	14.1%	0.69 [0.41, 1.17]
Thomas 1998b	26	58	25	60	0.71	12.74	13.0%	1.06 [0.61, 1.83]
Lorvidhaya 2003a	40	233	59	242	-12.52	24.57	25.0%	0.60 [0.40, 0.89]
Lorvidhaya 2003b	54	230	49	221	0.31	25.67	26.1%	1.01 [0.69, 1.49]
Roberts 2000	25	124	39	124	-8.39	15.92	16.2%	0.59 [0.36, 0.96]
Lanciano 2005b	11	27	12	24	-0.82	5.55	5.6%	0.86 [0.38, 1.96]
Subtotal (95% CI)		**729**		**729**			**100.0%**	**0.77 [0.63, 0.94]**
Total events	180		216					
Heterogeneity: Chi² = 6.08, df = 5 (P = 0.30); I² = 18%								
Test for overall effect: Z = 2.61 (P = 0.009)								

Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI

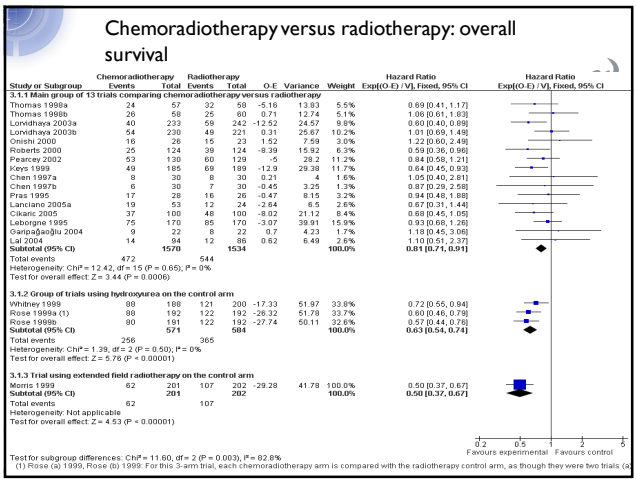
0.2 0.5 1 2 5

Favours experimental Favours control

Test for subgroup differences: Chi² = 0.32, df = 1 (P = 0.57), I² = 0%

(1) Lanciano 2005 is presented as though it were two trials (a) and (b) since the two comparisons fall into separate groups of platinum-based and non-platinum ba

Chemoradiotherapy versus radiotherapy: overall survival



Study or Subgroup	Chemoradiotherapy Events	Total	Radiotherapy Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
3.1.1 Main group of 13 trials comparing chemoradiotherapy versus radiotherapy								
Thomas 1998a	24	57	32	58	-5.16	13.83	5.5%	0.69 [0.41, 1.17]
Thomas 1998b	26	58	25	60	0.71	12.74	5.1%	1.06 [0.61, 1.83]
Lorvidhaya 2003a	40	233	59	242	-12.52	24.57	9.8%	0.60 [0.40, 0.89]
Lorvidhaya 2003b	54	230	49	221	0.31	25.67	10.2%	1.01 [0.69, 1.49]
Onishi 2000	16	26	15	23	1.52	7.59	3.0%	1.22 [0.60, 2.49]
Roberts 2000	25	124	39	124	-8.39	15.92	6.3%	0.59 [0.36, 0.96]
Pearcey 2002	53	130	60	129	-5	28.2	11.2%	0.84 [0.58, 1.21]
Keys 1999	49	185	69	189	-12.9	29.38	11.7%	0.64 [0.45, 0.93]
Chen 1997a	8	30	8	30	0.21	4	1.6%	1.05 [0.40, 2.81]
Chen 1997b	6	30	7	30	-0.45	3.25	1.3%	0.87 [0.29, 2.58]
Pras 1995	17	28	16	26	-0.47	8.15	3.2%	0.94 [0.48, 1.88]
Lanciano 2005a	19	53	12	24	-2.64	6.5	2.6%	0.67 [0.31, 1.44]
Cikaric 2005	37	100	48	100	-8.02	21.12	8.4%	0.68 [0.45, 1.05]
Leborgne 1995	75	170	85	170	-3.07	39.91	15.9%	0.93 [0.68, 1.26]
Garipağaoğlu 2004	9	22	8	22	0.7	4.23	1.7%	1.18 [0.45, 3.06]
Lal 2004	14	94	12	86	0.62	6.49	2.6%	1.10 [0.51, 2.37]
Subtotal (95% CI)		**1570**		**1534**			**100.0%**	**0.81 [0.71, 0.91]**
Total events	472		544					
Heterogeneity: Chi² = 12.42, df = 15 (P = 0.65); I² = 0%								
Test for overall effect: Z = 3.44 (P = 0.0006)								
3.1.2 Group of trials using hydroxyurea on the control arm								
Whitney 1999	88	188	121	200	-17.33	51.97	33.8%	0.72 [0.55, 0.94]
Rose 1999a (1)	98	192	122	192	-26.32	51.78	33.7%	0.60 [0.46, 0.79]
Rose 1999b	80	191	122	192	-27.74	50.11	32.6%	0.57 [0.44, 0.76]
Subtotal (95% CI)		**571**		**584**			**100.0%**	**0.63 [0.54, 0.74]**
Total events	266		365					
Heterogeneity: Chi² = 1.39, df = 2 (P = 0.50); I² = 0%								
Test for overall effect: Z = 5.76 (P < 0.00001)								
3.1.3 Trial using extended field radiotherapy on the control arm								
Morris 1999	62	201	107	202	-29.28	41.78	100.0%	0.50 [0.37, 0.67]
Subtotal (95% CI)		**201**		**202**			**100.0%**	**0.50 [0.37, 0.67]**
Total events	62		107					
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.53 (P < 0.00001)								

Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI

0.2 0.5 1 2 5

Favours experimental Favours control

Test for subgroup differences: Chi² = 11.60, df = 2 (P = 0.003), I² = 82.8%

(1) Rose (a) 1999, Rose (b) 1999: For this 3-arm trial, each chemoradiotherapy arm is compared with the radiotherapy control arm, as though they were two trials (a

Authors' conclusions

These results endorse the recommendations of the NCI alert, but also demonstrate their applicability to all women and a benefit of non-platinum based chemoradiotherapy. Furthermore, although these results suggest an additional benefit from adjuvant chemotherapy this requires testing in RCTs.

PLAIN LANGUAGE SUMMARY

Chemoradiotherapy for cervical cancer: results of a meta-analysis

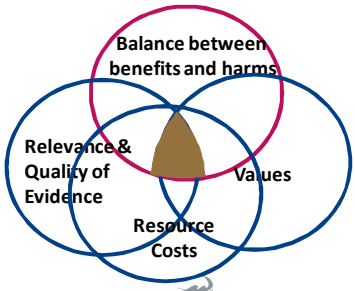
Women with cervical cancer that is too big to be removed by surgery, or has spread to the tissues around the cervix (often called locally advanced cervical cancer) may be treated with radiotherapy (treatment with x-rays). They might also get chemotherapy (drug treatment) alongside radiotherapy. This is called chemoradiotherapy (or chemoradiation). This review brought together 18 randomised controlled trials (RCTs) that were carried out in many countries. The results of the review showed that women who had chemoradiotherapy for cervical cancer were likely to live for longer than women who had just radiotherapy. Five years after being treated, 66 out of every 100 women who received chemoradiotherapy were still alive compared with 60 out of every 100 who just had radiotherapy. Women who received chemoradiotherapy were also less likely to have the cancer come back or spread to other parts of the body. Chemoradiotherapy helped all women, even those with bigger tumours, or tumours that had spread more. Also, the different drugs that had been used in the trials (cisplatin, 5-fluoururacil or mitomycin-C) all helped women to live longer or stop the cancer from coming back or spreading. Some of the short term side effects were worse for women who received chemoradiotherapy. Doctors can usually help women to cope with the short term side effects of their treatment. Unfortunately, there was not enough information to be certain whether the long-term side effects are worse with chemoradiotherapy or not.

The review also seemed to show that women who have extra chemotherapy (after they have had chemoradiotherapy) live longer than those who just have chemoradiotherapy. However, the researchers are less certain about these results and suggest that new RCTs are needed to find out whether giving extra chemotherapy is better for women with cervical cancer, or not.

Pediatric Oncology & Hematological Malignancies: May 8 2010

Factors that influence translation of evidence to policy recommendations

Evidence does not automatically transform into guidelines or practice



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Growth of contributors in India

	2000	2002	2003	2004	2005	2006	2007	2009
	← BC			AC →				
Authors	11	15	20	31	42	80	78	248
Editors	2	1	2	5	5	5	5	7
Others	2	15	18	28	19	35	43	284
Total	**19**	**31**	**40**	**64**	**76**	**120**	**126**	**413**

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