ruolo della metanalisi nella valutazione di efficacy and effectiveness

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to me, *knowledge* is about access and understanding. Action is then a choice (hopefully an informed one) for the individual.

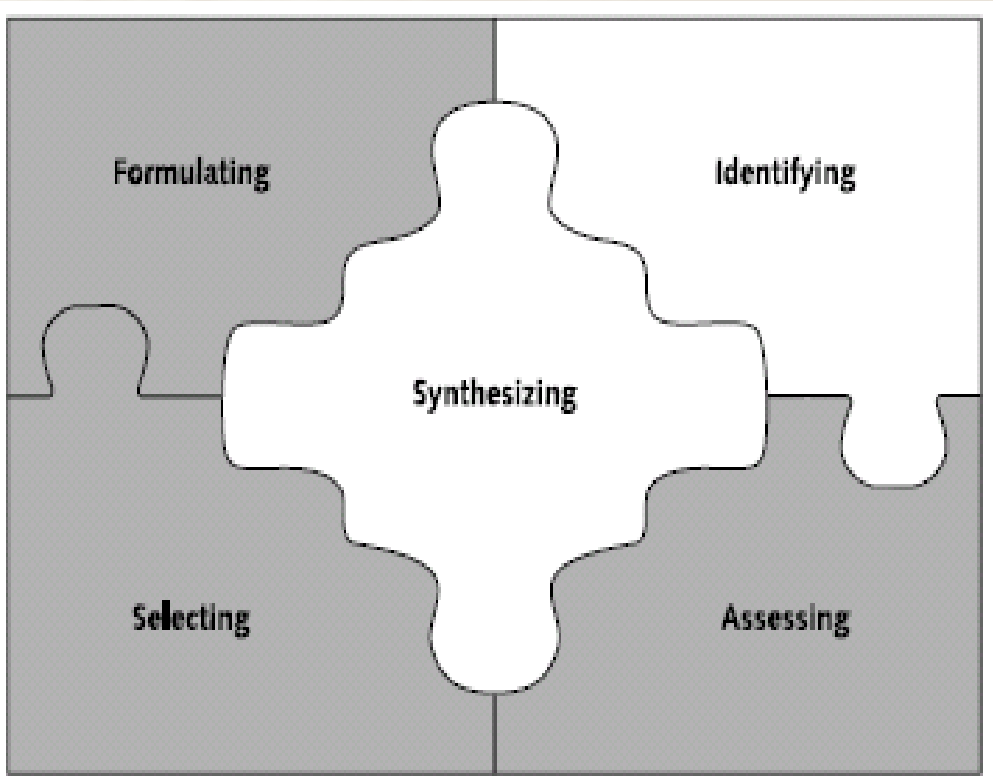
Chris Silagy, 1999

perché le RS

- L’accesso ai risultati della ricerca è non sistematico, spesso casuale;
- La quantità e la disponibilità di dati è enorme ed in aumento: migliaia di SCC pubblicate/anno
- La qualità della ricerca è variabile

“challenges” delle revisioni sistematiche

- formulazione del quesito
- identificazione e selezione degli studi rilevanti
- valutazione della generalizzabilità dei risultati ottenuti



P. Santaguida et al. *Ann Intern Med. 2005;142:1066-1072.*

I°: formulare il quesito

- Caratteristiche farmacologiche vs. effetto a lungo termine
  - Panel di esperti e pazienti per mettere a fuoco il problema clinico (es. tiazolinidinedioni nel diabete tipo II)
- Obbiettivi terapeutici del trattamento
  - Effetto su sintomi vs meccanismi:
    - influenza sull'intervallo temporale della rilevazione dell'outcome
    - eterogeneità di effetti
- Popolazione in studio
  - Sottogruppi, farmacogenetica… (es: polimorfismi inducono effetti diversi tra antiipertensivi,… verifica di effetti legati alla razza)
- Confronti diretti ed indiretti

II°selezionare gli studi

- Unpublished data
- Disegno consistente con gli obiettivi terapeutici
  - Schedule, confronti, piano statistico…
- Inclusione degli studi osservazionali
  - Outcomes non valutati dagli RCs
  - Quantificare la dimensione del bias generato dalla selezione dei pts valutati negli RCTs
    - es. risposta sostenuta con interferone nelle epatiti: 30% nei trial, 13% in studi di outcome

III° verificare la generalizzabilità

le domande sull'effetto di un intervento

Funziona in condizioni controllate (RCT)?

Funziona in condizioni 'reali''?

Contribuisce ad un più efficiente uso delle risorse?

distinguere i trials di effectiveness da quelli di efficacy

1 popolazione rappresentata

2 ristrettezza dei criteri di eleggibilità

3 outcomes

4 durata dello studio

5 rilevanza degli interventi a confronto

5 valutazione degli eventi avversi

6 dimensione campionaria ‘tarata’ sulle differenze minime attese dal punto di vista dei pazienti

7 analisi per intention-to-treat

AHRQ Publication April 2006

esempi di differenze - BMJ 2008;337

	Highly explanatory attitude (NASCET[7])	Highly pragmatic attitude (Thomas et al[8])
Question	Among patients with symptomatic 70-99% stenosis of carotid artery can carotid endarterectomy plus best medical therapy reduce outcomes of major stroke or death over next two years compared with best medical therapy alone?	Does a short course of acupuncture delivered by a qualified acupuncturist reduce pain in patients with persistent non-specific low-back pain?
Setting	Volunteer academic and specialist hospitals with multidisciplinary neurological-neurosurgical teams and high procedure volumes with low mortality in US and Canada	General practice and private acupuncture clinics in UK
Participants	Symptomatic patients stratified for carotid stenosis severity, with primary interest in severe carotid stenosis (high risk) group, who were thought to be most likely to respond to endarterectomy. Exclusions included mental incompetence and another illness likely to cause death within 5 years. Patients also were temporarily ineligible if they had any of seven transient medical conditions (eg, uncontrolled hypertension or diabetes)	Anyone aged 18-65 with non-specific low back pain of 4-52 weeks' duration who were judged to be suitable by their general practitioner. There were some exclusion criteria, eg those with spinal disease
Intervention	Endarterectomy had to be carried out (rather than stenting or some other operation), but the surgeon was given leeway in how it was performed. Surgeons had to be approved by an expert panel, and were restricted to those who had performed at least 50 carotid endarterectomies in the past 24 months with a postoperative complication rate (stroke or death within 30 days) of less than 6%. Centre compliance with the study protocol was monitored, with the chief investigator visiting in the case of deficiencies	Acupuncturists determined the content and number of treatments according to patients' needs
Outcomes	The primary outcome was time to ipsilateral stroke, the outcome most likely to be affected by carotid endarterectomy. Secondary outcomes: all strokes, major strokes, and mortality	Primary outcome was bodily pain as measured by SF-36. Secondary outcomes included use of pain killers and patient satisfaction
Relevance to practice	Indirect—patients and clinicians are highly selected and it isn't clear how widely applicable the results are	Direct—general practitioners and patients can immediately use the trial results in their decision making

limiti degli studi di efficacy

- Popolazioni trascurate
- Impiego di comparatori impropri
- (Ab)uso di parametri surrogati
- Insufficiente potenza per valutare la sicurezza

fattori qualificanti degli studi pragmatici

- Selezione di interventi da confrontare che siano rilevanti clinicamente
- Inclusione di diverse popolazioni di partecipanti, da setting di pratica clinica eterogenei
- Recupero dei dati relativi ad un ampio range di health outcomes, senza limitarsi a valutare quelli richiesti dagli enti regolatori

- La pubblicazione dei trial pragmatici è legata allo sviluppo della ricerca indipendente

rilevanza degli endpoints

Bohlius J et al.: Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of RCTs

Lancet 2009; 373: 1532-42

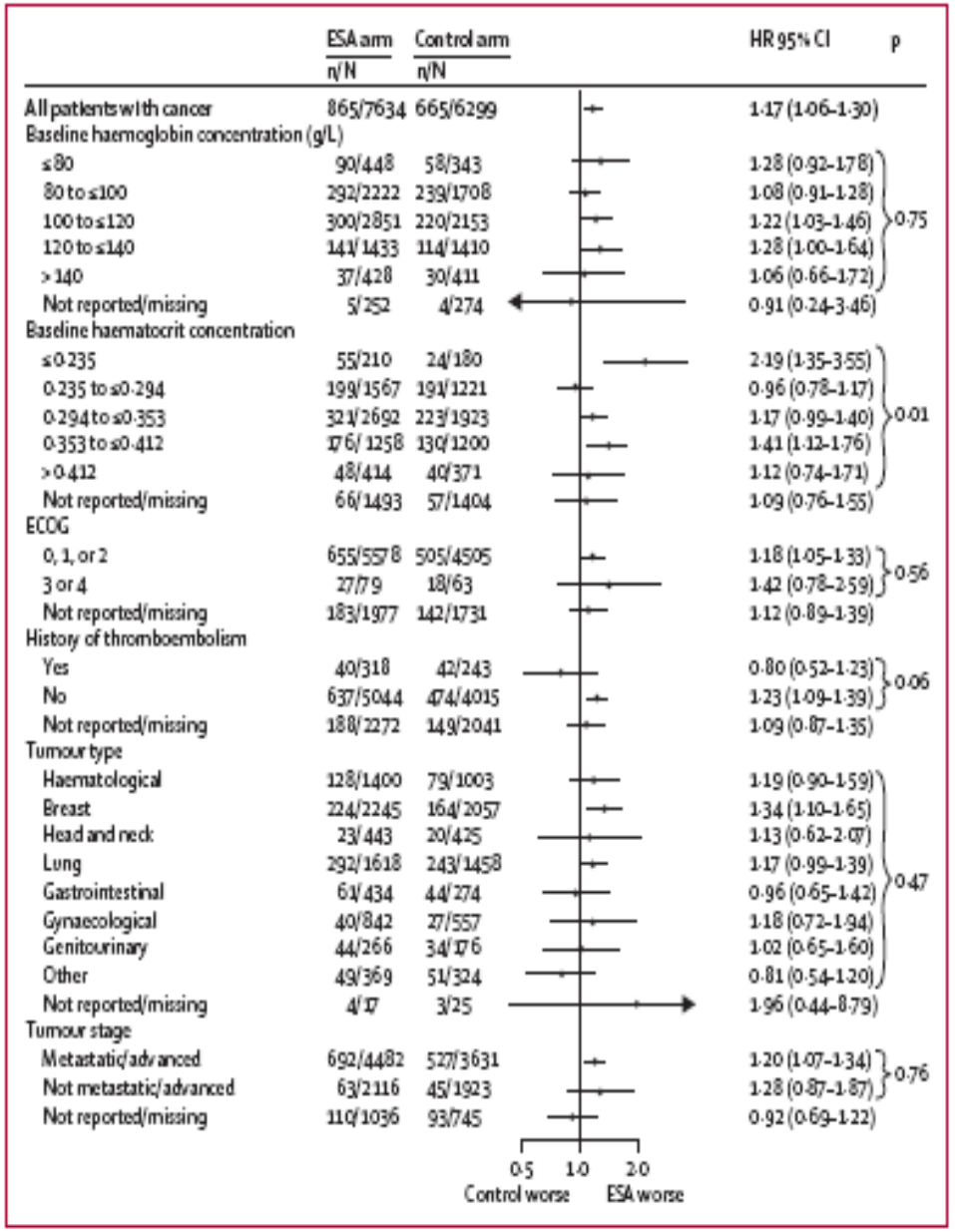
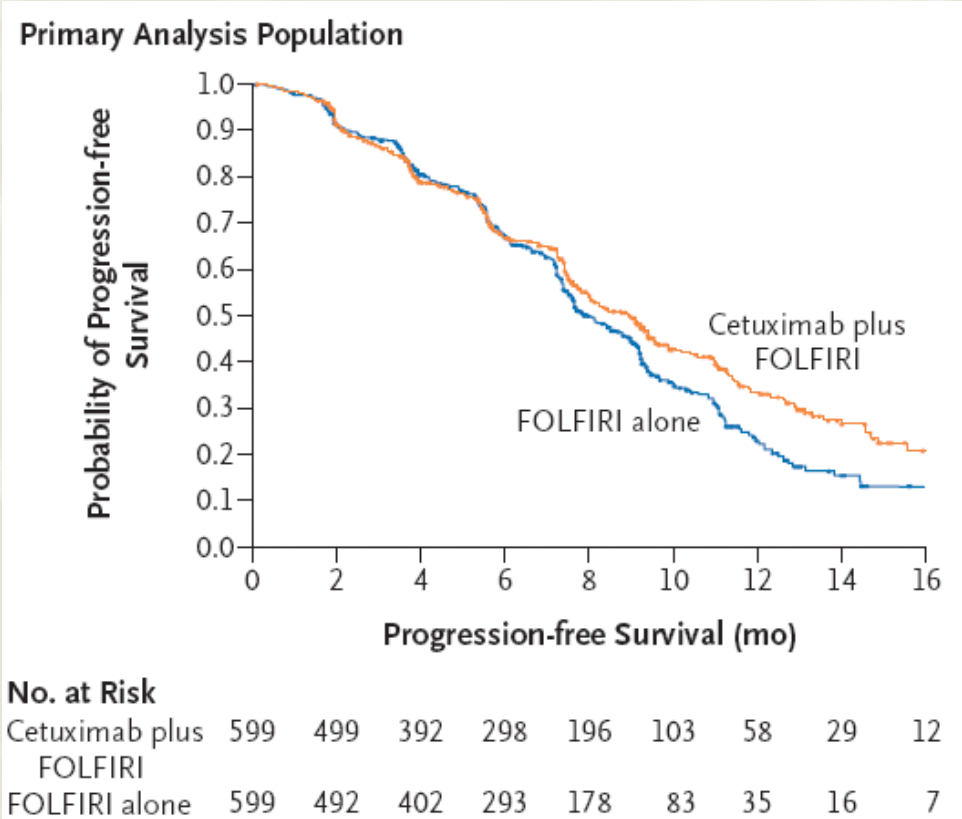


Figure 5: Mortality in all patients with cancer during active study periods, stratified by patient characteristics

autorizzazioni e RS

Crystal study



Tappenden, P., R. Jones, et al. (2007). "Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer." Health Technol Assess 11(12): 1-128, iii-iv.

The evidence .... suggests that cetuximab plus irinotecan has some clinical activity. While it is difficult to suggest whether cetuximab represents value for money, indirect comparisons suggest that the incremental cost-utility of cetuximab plus irinotecan is unlikely to be better than pound 30,000 per QALY gained.

GRADE - metodologia

- Definire il problema
- Definire l’importanza relativa degli outcome
- Ricercare le prove di effetti
- Valutare la qualità delle prove per ciascuno degli outcome
- Riassumere e valutare la qualità globale delle prove
- Fare un bilancio dei benefici e degli eventi avversi

- **Definire la forza della raccomandazione**

- Implementazione e verifica

GRADE in oncologia

Purpose
In the area of anticancer drugs, the legitimate search for effective interventions can be jeopardized by the strong pressure for accelerated approval, which may hinder the full assessment of their benefit-risk profile. We aimed to produce drug-specific recommendations using an explicit approach that separates the judgments on quality of evidence from the judgment about strength of recommendations.

Materials and Methods
We used the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system to develop recommendations for the use of specific anticancer drugs/regimens; 12 clinical questions relevant to adjuvant treatment of breast (three), colorectal (four) and lung (five) cancer have been assessed by multidisciplinary panels supported by a group of methodologists.

Results
For nine of 12 questions, recommendations were produced (one strong and six weak in favor and one weak and one strong against the index treatment); for the remaining three questions no specific course of action could be recommended. The perceived benefits to risk balance of the treatment was the most important and statistically significant ($P < .01$) predictor of panels' recommendations and of their strength, whereas panelists' personal (age, sex) and professional (specialty) characteristics were not statistically associated.

Conclusion
Because the GRADE system sets out an explicit process going from evaluation of the quality of evidence and benefit-risk profile to the judgment of the strength of recommendations, in this experience, it proved very useful to combine methodologic rigor with the interdisciplinary participation that is important in the definition of evidence based clinical policies.

J Clin Oncol 26:1033-1039. © 2008 by American Society of Clinical Oncology

key points

- L’efficacia degli interventi sanitari può essere intesa come efficacy o effectiveness. Nello stesso trial tali caratteristiche possono coesistere, sono complementari ed occorre trovare il corretto bilanciamento.

- Fondamentale il ruolo delle RS per un critical appraisal di questi studi e per definire i “pts unmet needs” dalle evidenze disponibili