Contributions of meta-analyses based on individual patient data to therapeutic progress in colorectal cancer

Abstract  Meta-analysis is the statistical process of combining information from several studies addressing the same question. Meta-analyses based on individual patient data are far more reliable and informative than those based on summary statistics obtained from the trialists or extracted from the published literature. Meta-analysis of randomized clinical trials may contribute to therapeutic progress through (1) establishing efficacy benefits beyond a reasonable doubt, (2) identifying sources of heterogeneity between trials, (3) studying subsets reliably, (4) confirming differences in toxicity profiles, (5) evaluating the cost-effectiveness of experimental therapies, (6) assessing surrogate endpoints, and (7) addressing ancillary questions. All of these potential contributions are illustrated with examples in early and advanced colorectal cancer.

Key words  Meta-analysis · Colorectal cancer

Principles and types of meta-analysis

Meta-analysis (also called “overview”) is the statistical process of combining information from several studies addressing the same question.1 In the development of an experimental therapy, several clinical trials are typically conducted to compare the new therapy against some other therapy considered standard for the condition under study. In such a situation, clinicians informally compare and/or combine the results coming from these various trials.2 Meta-analysis is a systematic and quantitative approach to this very combination process, and as such, it is an essential tool for evidence-based medicine.3

A clear distinction must be made between different types of meta-analysis. The first type of meta-analysis, which is the most frequently adopted but also the least informative and least reliable, uses data extracted from the published reports of trials, such as the value of a test statistic or its associated P value, the proportions of events in each treatment group, and the survival estimates read off the published curves in each treatment group at some meaningful time point. Such meta-analyses are often severely flawed.4,5 One of the main drawbacks of meta-analyses of published trials is the possible presence of publication bias, whereby clinical trials that happen to show a large (or significant) treatment benefit tend to be published faster than the others. Also, the published statistical analyses may be subject to exclusion bias through the exclusion of some patients (e.g., those considered inevaluable or insufficiently treated), and this too can lead to a biased estimate of treatment effect. Finally, the data available in the publications may be inadequate to perform meaningful calculations. If the outcome of interest is survival, for instance, published survival curves do not provide sufficient information, in general, for the meta-analysis to be possible without strong, unwarranted, and untestable assumptions about censoring. All in all, meta-analyses based on results published in the medical literature should be regarded as first steps towards more reliable types of meta-analyses such as those described later in this article.6

The second type of meta-analysis uses summary data, such as the number of events of interest and the number of patients treated in each treatment group, obtained from the principal investigators of all trials, whether published or unpublished. In this way publication bias and exclusion bias can both be avoided. Moreover, simple but unbiased summary statistics can be obtained even for outcomes that are time-related (e.g., the hazard ratio calculated from a life table analysis, or the absolute number of deaths per treatment arm).7 Such a meta-analysis also requires that the principal investigators of all trials be contacted, which takes time but ensures the relevance of the questions addressed...
by the meta-analysis, and the interpretation of its results. Such an approach was adopted in the mid-1980s to show that adjuvant therapy of colorectal cancer provided a small but definite benefit in terms of overall survival: overall, patients randomized to receive adjuvant 5-fluorouracil-based chemotherapy for at least 1 year tended to have a longer survival than patients randomized to no such treatment (17 trials, 6791 randomized patients, survival odds ratio, 0.83; \( P = 0.03 \)).\(^8\) That early meta-analysis also suggested that adjuvant radiotherapy might result in a small survival benefit, but the main conclusion of the meta-analysis was that convincing evidence of the benefit of adjuvant therapies was lacking, and that larger trials should be conducted for reliable conclusions to be reached.

The third type of meta-analysis, and the only one that will be discussed in the remainder of this article, uses individual patient data obtained from the principal investigators of all trials, whether published or unpublished. The data required on each patient typically include the patient and center identification; the date of randomization; and relevant prognostic factors and outcome data, such as response to treatment, time to disease progression, and time to death.\(^9\) Obtaining individual patient data is a long and difficult process that can take several years.\(^10\) However, many important advantages ensue: the latest follow-up can be included on all patients; the quality of individual patient data can be controlled and questions raised in case of doubt (for instance, if the randomization sequence appears suspicious); and more detailed analyses can be performed if individual patient data are available (e.g., subgroup analyses and prognostic factor analyses).

Meta-analysis of randomized clinical trials may contribute in many ways to therapeutic progress, and the purpose of this article is to illustrate various uses of meta-analysis in the context of colorectal cancer.\(^11\) The following sections will examine in turn different contributions of meta-analysis towards:

1. Establishing efficacy benefits beyond a reasonable doubt
2. Identifying sources of heterogeneity between trials
3. Studying subsets reliably
4. Confirming differences in toxicity profiles
5. Evaluating the cost-effectiveness of experimental therapies
6. Assessing surrogate endpoints
7. Addressing ancillary questions

### Establishing efficacy benefits beyond a reasonable doubt

Today, meta-analysis is commonly used in the health sciences, especially to combine the results of randomized clinical trials, in which interest focuses on the difference in outcome between a group of patients receiving some experimental therapy and a group of patients receiving the best available standard therapy. The difference expected between these randomized groups is typically small. The detection of small, but medically worthwhile treatment effects, requires as many observations as possible, and therefore the combination of all trials addressing the same question has a better chance of being conclusive than any of the trials taken in isolation. Due to the larger sample size, a meta-analysis yields a more powerful statistical test and an increased precision of the treatment effect under consideration. In addition, individual trials may be subject to various sources of bias, and a meta-analysis may then provide a less biased picture of the true treatment effect by looking at the totality of the information, rather than at some selected subset of it.

Successive meta-analyses were conducted by the Meta-Analysis Group In Cancer (MAGIC) in advanced colorectal cancer to confirm the benefits, in terms of response rate, of various experimental treatments as compared with bolus administration of 5-fluorouracil, which, at the time, was the standard treatment for patients with advanced colorectal tumors (Table 1). Taking these four meta-analyses together, there was approximately a doubling of the response rate in the experimental arms as compared with the control arms.\(^12\)\(^-\)\(^20\)

Taking these four meta-analyses together, it could further be shown that the survival of patients with liver metastases confined to the liver was improved by the experimental treatments (22 trials, 1458 patients, hazard ratio [HR], 0.88; \( P = 0.037 \)).\(^21\) In contrast, a meta-analysis of trials investigating the benefit of interferon-\(\alpha\) showed that this drug in association with 5-fluorouracil produced a lower response rate than did 5-fluorouracil modulated with leucovorin (18% vs 23%; 7 trials, 1488 patients; \( P = 0.042 \)).\(^22\) When added to 5-fluorouracil modulated by leucovorin, interferon-\(\alpha\) produced no additional benefit in terms of response rate (24% vs 25%; 12 trials, 1766 patients; \( P = 0.80 \)).\(^22\)

In the adjuvant setting, several meta-analyses based on individual patient data have been conducted in early

<table>
<thead>
<tr>
<th>Experimental treatment</th>
<th>Number of Trials</th>
<th>Number of Patients</th>
<th>Response rates</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modulation of 5-fluorouracil by leucovorin(^12)</td>
<td>9</td>
<td>1381</td>
<td>23%</td>
<td>11%</td>
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<tr>
<td>Modulation of 5-fluorouracil by methotrexate(^15)</td>
<td>8</td>
<td>1178</td>
<td>19%</td>
<td>10%</td>
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<td>Continuous infusion of 5-fluorouracil(^16)</td>
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<td>1219</td>
<td>22%</td>
<td>14%</td>
</tr>
<tr>
<td>Hepatic arterial infusion of 5-fluorouracil(^17)</td>
<td>7</td>
<td>654</td>
<td>41%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Table 1. Successive meta-analyses showing improvements in response rate with experimental 5-fluorouracil-based treatments for advanced colorectal cancer