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### ► To cite this version:

Pierre Blanchard, Anne Aupérin, Jean-Pierre Pignon. Are Individual patient data meta-analyses still needed today in oncology? A discussion focused on Head & Neck oncology. *Acta Oncologica*, 2019, 18th Acta Oncologica symposium: BiGART2019 - Biology-Guided Adaptive Radiotherapy - Aarhus, Denmark - May 22-24, 2019, 58 (10), pp.1333-1336. 10.1080/0284186X.2019.1649458 . hal-03144150

**HAL Id: hal-03144150**

**<https://hal.science/hal-03144150v1>**

Submitted on 17 Feb 2021

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## **Are Individual patient data meta-analyses still needed today in oncology? A discussion focused on Head & Neck oncology**

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**Keywords:** head and neck cancers; radiotherapy; chemotherapy; meta-analysis; biostatistics

### **Word count:**

- Abstract:
- Manuscript:

**Acknowledgement:** Jean Bourhis, Benjamin Lacas, Stefan Michiels, all investigators, statisticians and steering committee members involved in the meta-analyses

## **Introduction**

Head and neck cancers are a leading cause of cancer incidence and mortality, with over 800 000 new cases and 400 000 deaths estimated in 2018 by GLOBOCAN[1]. Over the years, a wide range of randomized controlled trials have been conducted to define the best treatment strategies for each disease site and tumor stage. These trials have evaluated the role of chemotherapy, altered fractionated radiotherapy, targeted therapy or radioprotectants. To help define treatment guidelines, individual patient data meta-analyses were conducted by collaborative groups led by the meta-analysis unit at Gustave Roussy Cancer Center, launched in 1994 by Jean Bourhis and Jean-Pierre Pignon. They have focused on the role of chemotherapy[2,3] or altered fractionation radiotherapy[4] in locally advanced head and neck squamous cell cancers (HNSCC), amifostine[5], and chemotherapy in nasopharyngeal cancer (NPC)[6]. Additional works have studied surrogate endpoints for HNSCC[7] and NPC[8], network meta-analyses for HNSCC[9] and NPC[10]; but also the impact of missing data on trial characteristics[11] or the use of alternative relative efficacy metrics such as the restricted mean survival time difference[12].

The aim of this article is to focus on the relevance of meta-analyses today and tomorrow in a world where patients' and tumors' genomic profiling and tailored treatment could become the rule. We will concentrate on individual patient data meta-analyses, which is the gold standard for collecting and synthesizing evidence[13]. The medical literature is currently flooded with meta-analyses based on published data. A quick search on Pubmed performed on December 28<sup>th</sup> 2018 using the keywords "head neck cancer" and the built-in filter "meta-analysis" retrieved 2080 references, with more than 250 new "meta-analyses" performed each year since 2014. A minority of these is synthesizing comparative data prospectively collected, and only a handful is based on individual patient data.

### **What is the process of an individual patient data meta-analysis?**

One who wants to perform an individual patient data (IPD) meta-analysis has to follow a process that involves the following steps[13]:

1. Defining the clinical question
2. Perform a trial search based on published (literature databases, conference proceedings) and unpublished (clinical trials registries) data
3. Write a protocol that summarizes the question, available data, statistical analysis plan, publication policy, approved by a steering committee and submitted to a meta-analysis registry (<https://www.crd.york.ac.uk/prospero/>)
4. Contact trial teams and collect (ideally updated) individual patient data

5. Perform a quality check (randomization, follow-up, balance of patients' characteristics) for each trial and then a re-analysis that will be validated by the meta-analysis team and the trial's investigator or statistician
6. Perform the meta-analysis, discuss the results at an internal investigators meeting and then present and publish the results, following the PRISMA-IPD guidelines (Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data)[14]

Steps 4-6 are specific to IPD meta-analyses. In meta-analyses based on published data, quality can only be checked by reading the article and using one of many quality assessment tools, such as the Cochrane's risk of bias tool[15]. Then the meta-analysis is performed only based on published data, sometimes requiring extracting information (from survival curves for instance[16]) when it is not provided in details. Endpoints cannot be standardized, nor can data be updated. However even in published data meta-analyses, investigators should write a protocol and have a pre-specified analysis plan, and they should try to contact directly investigators when relevant information cannot be found in the articles. The superiority of IPD meta-analyses resides in the ability to check the quality of data/trials and keep only high quality ones, to obtain updated data, obtain feedback from trialists regarding their own data and the overall interpretation of the meta-analysis, perform analyses based on standardized endpoints and to perform robust secondary analyses according to patient characteristics.

### **Why meta-analyses are still needed – estimating “true” treatment effects and conducting secondary analyses**

There is a debate surrounding the clinical usefulness of meta-analyses today. Indeed, with the advent of precision medicine, treatment strategies could end up being defined based on patient and tumor molecular and genetic characteristics rather than classical clinical and pathological grouping. Recently immunotherapy drugs have been approved based on molecular classifications independently of tumor location. Organ defined meta-analyses could then become irrelevant. Besides, defining patient subgroups based on molecular characteristics, as is done for many solid cancers, would end up in very small groups of patients for which randomized trial could be not feasible, or even not ethical if early stage trials show important treatment efficacy. Last, the pace of clinical research has sped up lately, and competition between products has increased. Meta-analyses are by nature performed after the trials, and meta-analyses could become irrelevant if clinical research in the field has in between moved to a different therapeutic area. This is the case currently in HNSCC with the shift from targeted therapies and in particular anti-EGFR therapy field to

immunotherapy. Would, for example, an anti-EGFR meta-analysis still be of interest to clinicians today? We believe so, and will try to demonstrate this point in the following paragraphs.

With the currently accepted significance level of 5%, there is a risk that one in twenty trials could be positive just by chance, even if the treatment tested has no real clinical activity. Trials replication increases the reliability of the results. It is known that smaller or single center trials overestimate treatment efficacy[17,18]. They are more frequently published when positive and are hence at higher risk of being false positive[19]. Pooling data of all trials, published or not, would then reduce this risk and improve the validity of treatment effect estimates. As an example, the synergistic effect of cetuximab given concurrently with radiotherapy for the treatment of locally advanced head and neck cancers has been demonstrated in a randomized trial[20], with an absolute overall survival benefit that was of similar magnitude as the one estimated for radiotherapy-cisplatin in the IPD meta-analyses[2]. In this trial there was no added toxicity of concurrent cetuximab compared to radiotherapy alone. This trial was immediately criticized for not comparing radiotherapy-cetuximab with the standard of care at the time of publication, radiotherapy with concurrent cisplatin, although it was argued by the authors that when the trial was designed radiotherapy alone was the standard of care. In the following years, retrospective reports have been published suggesting that the addition of cetuximab to radiotherapy did increase toxicity[21] and that efficacy could be inferior to radiotherapy with concurrent cisplatin[22], and most prospective trials of EGFR inhibitors in combination with radiotherapy for head and neck cancers turned out to be negative. And two trials showed no difference between radiotherapy plus cetuximab and radiotherapy plus cisplatin, but one was underpowered[23] and the other one had a factorial design that also randomized induction chemotherapy[24], hence introducing an interaction. It was just recently that two large randomized trials were published[25,26], that compared radiotherapy plus cisplatin to radiotherapy plus cetuximab in p16 positive oropharyngeal cancer patients and showed that radiotherapy plus cetuximab was associated with similar acute and late toxicity and lower overall survival than radiotherapy plus cisplatin, again with an absolute difference that is similar to that of radiotherapy plus cisplatin compared to radiotherapy alone in the IPD meta-analyses[2]. Retrospectively, it appears that the effect of radiotherapy plus cetuximab might have been overestimated by the initial randomized trial. Again, replication is key, and the more trials there are, the closer we will be to the true value of a treatment effect.

The same is even truer for secondary endpoints. Indeed, the analysis of secondary endpoints, such as locoregional control, distant control or cause-specific mortality is frequently underpowered in individual trials. And it is very difficult to perform subgroup analyses with a reasonable power outside the frame of a meta-analysis. Therefore, even when the standard of care is known, there is an

interest to perform an individual patient data meta-analysis. The goal here would be to allow a more reliable estimation of treatment effect and to evaluate other efficacy and toxicity endpoints. IPD meta-analyses enable to update follow-up and provide long-term efficacy and toxicity data compared to individual trials. Such databases allow also performing subgroup analyses that could then lead to the development of additional trials. Indeed, meta-analyses inform our clinical decisions of the day, form the foundation of clinical practice guidelines[27] and allow us to develop future research questions[28]. As an example, the Lung-ART trial (NCT00410683) was designed following the PORT meta-analysis[29]. Last, meta-analyses nowadays allow collecting and analyzing biomarker data to study their prognostic and predictive value[30].

### **Barriers to the performance of individual patient data meta-analyses and potential solutions**

Although they are widely regarded as providing level I evidence, it is becoming increasingly difficult to perform IPD meta-analyses. Below we summarize the main barriers and potential solutions

1. *Competition between meta-analysis groups and research duplication.* As said above, many meta-analyses based on published data are performed, often multiple on the same topic, and readers can feel overloaded with meta-analyses. In head and neck cancers specifically, meta-analyses on published data are published earlier than the IPD one because IPD MA take much longer to be finalized. Education of the public needed, as all meta-analyses do not provide the same level of evidence and that the variability in the meta-analysis process and data collected could provide contradictory findings.
2. *Reluctance to provide data of individual trials.* Running a randomized trial is hard work, and investigators want, as can be understood, to publish their trial prior to providing data to the meta-analysis. Sometimes investigators just don't want to share the data, and it usually takes time to convince them, usually with the help of the steering committee and by showing them the progress of the meta-analysis and the data gathered to this point. In either case this can incur delay in data collection for the meta-analysis, sometimes by years.
3. *Administrative barriers to share data.* The regulations surrounding data sharing are getting increasingly complex, even at the cooperative group level, and can delay if not prevent data sharing. Indeed pharmaceutical companies have in the past told us that the wording of informed consent prevented them to share individual patient data with our group.
4. *Data sharing policies for industry funded trials.* Many trials are now funded by industry, and that can pose specific problems in terms of trial conduct and data sharing, although

most of them advocate for transparency and data sharing[31]. For example, the follow-up will be stopped early in negative trials, precluding any data collection for long term events, either for toxicity or efficacy. Most of the time, the trial database is not provided and only a remote access to the trial database is available, which increases the time to collect and analyze the data, especially in the framework of a meta-analysis where the simultaneous analysis of multiple datasets is required[32]. It can also be difficult to identify the right point of contact for a trial, and data sharing policies vary from company to company. In some cases companies can see the meta-analysis as a threat to their market share and prefer not to provide individual patient data.

5. *Pace of clinical research and competition between products.* It takes time to perform an IPD meta-analysis, and once the project is launched, the field may have moved into another direction. This is the case for our current EGFR-inhibitors meta-analysis (CRD42017056939). Indeed, the field is now mostly evaluating immunotherapeutic agents. However, the meta-analysis might provide insights into the efficacy and toxicity of anti-EGFR and help define patient populations that could benefit from them.

Potential solutions include education of the public and medical community regarding quality of biomedical research and evidence, discussion with funding bodies over research waste, the requirement to post meta-analysis protocols on registries such as Prospero, the maintenance of strong links between cooperative groups through active and diverse steering committee and investigator meetings and the association with advocacy groups to promote reduced barriers to data sharing when performed for meta-analytic purposes. Novel methods, such as network meta-analyses or the implementation of older ideas, such as prospective meta-analyses[33], need to be employed to deal with the pace of clinical development. With respect to pharmaceutical companies, they should also be included early on when a meta-analysis intends to investigate patented drugs, and advocacy groups could help facilitate data sharing agreements.

### **Precision medicine and the future of meta-analyses**

Many believe that in the near future cancers will be treated based on each tumor's molecular profile rather than using as today the location of the tumor and its clinical and pathological characteristics. Although it is currently estimated that the percentage of patients with cancer estimated to benefit from genome-targeted therapy was around 5% in 2018[34], it seems clear that the trend is towards the development of biomarker informed therapies. However meta-analyses could clearly adapt to this new definition of diseases, by performing meta-analyses on biomarker defined population rather than on a specific tumor site, and the meta-analytic process would remain relevant. Our group has

already performed biomarker meta-analyses, in lung [30] and head and neck[35] cancers, and intends to keep exploring this research area.

### **Conclusion**

We have described the process of conducting an individual patient data meta-analysis. IPD meta-analyses are still of major relevance today, but there are barriers to their implementation. We as a field need to overcome these barriers, agree to share data, and perform these meta-analyses for our patients and the scientific community.



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