How do differences in inclusion criteria in emulation studies impact the outcome of overall survival?

– Emulating an ovarian cancer clinical trial in Norwegian registries

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BACKGROUND

Ovarian cancer (OVC) is a major healthcare problem worldwide. Globally, ovarian cancer is the seventh most common cancer in women, and the eighth most common cause of cancer death. A gradually more dynamic policy landscape in the United States and Europe have created a fertile ground for the use of real-world data (RWD) to improve current methods of clinical evidence generation. One of the potential uses of RWD is in evaluating the feasibility of a clinical trial. However, RWD can also be used to study the impact of individual inclusion criteria to tailor a RCT that is feasible and/or relevant for real life clinical practice.

OBJECTIVES

The aim of the study was to determine the impact of varying clinical trial inclusion criteria from a 2nd line ovarian cancer trial in an emulation using real world data. The number of patients that could be included as well as their survival was reported.

METHODS

This study is a retrospective registry-based study of patients with advanced (FIGO stage 3-4) high-grade serous ovarian cancer in Norway. We emulated the inclusion and exclusion criteria of a phase I, 2nd line ovarian cancer vaccine (NCT03839524). Patients with ovarian cancer in 2015-2021 were included in the study population. Data came from the Cancer Registry of Norway and the Norwegian Patient Registry containing hospital data. The flowchart showing what the inclusion criteria applied were and their impact in terms of how many percent were removed and how many patients were left is shown in **figure 1**.

A separate key inclusion criterion was that the patients should have used platinum drugs in combination with taxanes in 5 or 6 courses during first line treatment. We emulated different ways of relaxing this assumption. We allowed platinum to be used alone or in combination with another chemotherapy drug and we allowed for varying ranges of treatment courses given (any number, of courses 3-7 courses, 4-7 courses as well as the original 5-6 courses). The proportion who died within the end of follow up (31st of December) was calculated for each of these combinations as well as the number of patients that fulfilled all the inclusion and exclusion criteria.

CONCLUSION

Different implementations of clinical trial inclusion criteria related to first line treatment in ovarian cancer led to varying number of patients included and differences in overall survival. RWD can be useful when assessing the impact of potential inclusion criteria during the planning of RCTs, both to assess the number of patients that can be included but also how key features such as survival changes. Results such as ours can also be useful to understand how real world populations differ from RCT populations when doing HTA assessments, since it can highlight which clinical choices are done and how it affects population size and outcomes.

RESULTS

There were 3350 ovarian cancer patients in Norway in 2015-2021. In **figure 1** we see how the application of inclusion criteria removes a total of 84% of patients leaving only 542 persons. In **figure 2** we show the impact of varying the first line treatment on number of patients and their survival. Green squares is patients receiving any platinum treatment both alone and in combinations, red circles show patients receiving platinum drugs in combination with any other chemotherapy and blue triangles show platinum drugs used in combination with taxanes. Symbols marked with 3 follow the original inclusion criteria of 5 or 6 courses and we see that there are fewer patients, around 300 for all platinum and platinum combinations, down to 112 for platinum+taxane combination. Platinum+taxane treated patients have a slightly lower survival (44-47% dead before the end of study, vs 38-42% in the other groups) and covers a smaller proportion of the real population of ovarian cancer patients. In total only 3.3% of all ovarian cancer patients would have been included using the strictest set of inclusion criteria.

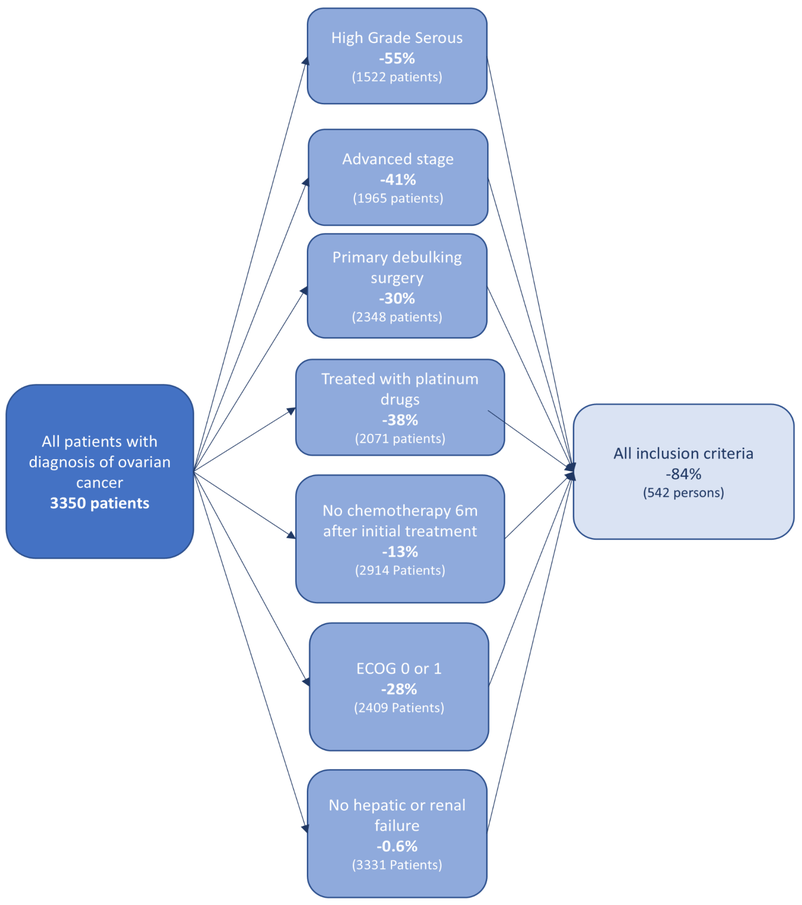

Figure 1: *Inclusion criteria and the percentage that do not fulfil each criteria as well as the number of patients that fit the criteria.*

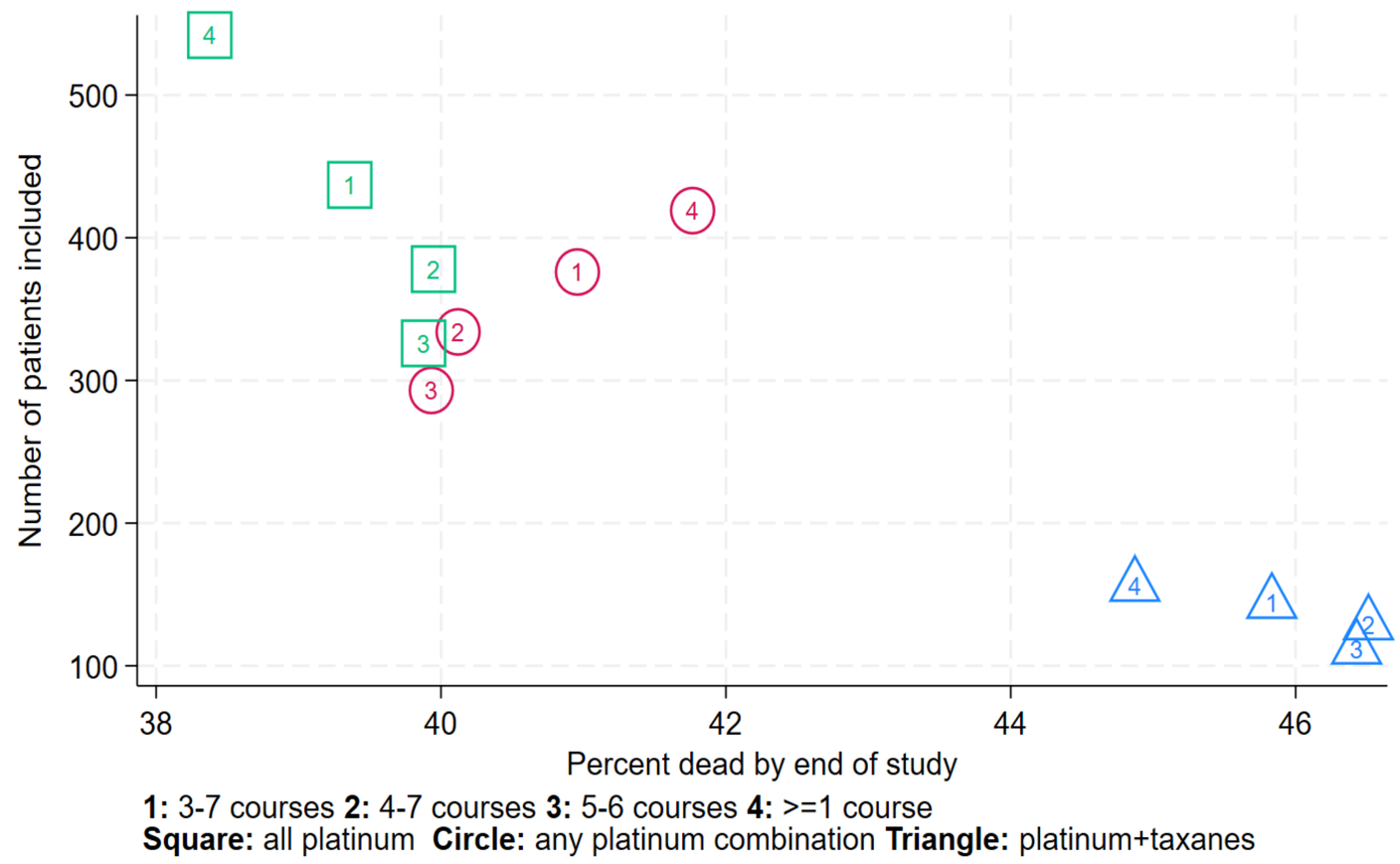

Figure 2: *Groups of patients fitting different types of 1st line treatment (squares, circles and triangles) and the number of courses of these treatments (numbers) Y-axis shows number of patients, X-axis the percent dead by the end of the study period (31st December 2021).*

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