Reviewer's report

Title: Risk of stroke in patients with ovarian cancer: a nationwide population-based study

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Reviewer: Wolfgang Grisold

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Risk of stroke in patients with ovarian cancer: a nationwide population-based study:

This is an epidemiologically based paper, demonstrating that patients with ovarian cancer have a higher risk to suffer from stroke. 2 cohorts of app 8000 patients are compared, and age, hypertension, diabetes mellitus and „chemotherapy“ seem to increase the precipitating factors which could be identified. Chemotherapy is suggested, that platinum drugs in particular increase the risk to suffer from stroke.

It is an incredibly large sample, which in effect turns out that the risk of stroke for patients with ovary cancer is increased by 1,38. The risk factors as age, hypertension and diabetes are expected, and it seems surprising, that they are prominent in the ovary-cancer group.

It is the study of a large cohort, and although basic informations can be compared, no detail to either stroke type, nor coagulation can be given. This may be of importance, as the issue of stroke type has been discussed extensively in literature, as well as coagulations disorders. The assumption of a disarray in coagulation disorders is carried forward through many years, although the precise type of coagulation disorder, except some types of leukemia has never been defined. D-dimer seems to be changed in some series, but this is not specific.

Chemotherapy and stroke is also an interesting issue. The authors at one point speak of chemotherapy (in general), then on „platinum based“ drugs. This is also referred to in the tables. It may be worthwhile to explore this further, as the assumption of an increased stroke risk is based on case observations and small series, and would definitely need confirmation in large series. The question appears, whether any other chemotherapies have been used at all.

In summary, looking at the time perspective of this study, this is an analysis of the appearance of stroke, after diagnosis and treatment in a given, defined disease. It differs from other approaches, where stroke at presentation, during treatment and possibly to specific cancer mechanisms have been made. It also differs from the retrospective study by Graus et al, who were able to examine the pathological results. This study was from one center, and based on the
pathological endpoint.

Despite the shortcomings, which may be important to follow, this is an interesting observation. The paper should be overworked, some parts of the discussions shortened to the facts appearing in the study, and also the role of chemotherapy explained, as well as possible metastatic sequelae to the brain.

Some comments:

Survival of cancer stroke patients: This does not only depend on stroke, but also on cancer.

Ref.: 6, 7. Interesting, but paper 7 raises the point, if also CNS malignancies as metastasis or leptomeningeal disease were observed. Could it theoretically be, that this were added as stroke?

Discussion: The stroke risk is estimated: „Our data revealed a 1.49-fold increased risk of 206 developing ischemic stroke among patients with ovarian cancer“. In the introduction it is 1,38. What is right?

„Thromboembolism might contribute to cancer-related stroke, due to its high incidence in cancer patients.“ This is a very general statement. It could be made, if the stroke types were available.

„In addition, the presence of disseminated intravascular coagulation in patients with ovarian cancer may indicate a hypercoagulative status“- There is no indication in the results, that this might have been the case.

„One direct evidence for the hypercoagulative state is the frequently overexpressed tissue factor in ovarian cancer tissue, which could activate the extrinsic coagulation cascade and cause thrombolic events in ovarian cancer patients [14].“- was this measured in the cohort?

Line 220-228: are in the same line and must be clearly stated as suggestions, and possible explanations. This study does not explain these phenomena.

„Our study showed that ovarian cancer patients receiving chemotherapy, particularly platinum-based regimens, might have an additionally increased stroke risk. This effect was insignificant in non-platinum–based regimens. In prior studies, chemotherapy
associated increased stroke was observed in patients with head-and-neck cancer.

Comments on chemotherapy- see above.

„diabetes mellitus, and chemotherapy treatment

„following a diagnosis of ovarian cancer“ possibly platinum drugs should be added here. „Chemotherapy“ alone is too unspecific.

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.