Presence of brain metastases in patients with ovarian cancer: a place for BRCA1/2 gene testing?

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Abstract
Ovarian cancer represents the fourth most common female cancer, with the presence of brain metastases being rare (<2%) among these patients. This percentage, although, has risen in the last decades, possibly due to the improved anticancer therapies that result in better survival of these patients. A literature review that was conducted revealed several cases of ovarian cancer patients with brain metastasis being positive for BRCA1/2 gene mutations. In ovarian cancer, BRCA1/2 mutations are associated with different survivals and diseases—free survival, while the development of brain metastases has been thought to represent a different biological phenotype of the disease. Therefore, in this report, we discuss the basis of the hypothesis that ovarian cancer patients with brain metastases should be screened for BRCA1/2 gene mutations.

Editorial
Ovarian cancer is the fourth most common female malignancy in the Western world, with more than 22,000 new cases estimated to be diagnosed in 2013 in the US1.

The mutations of the BRCA1 and BRCA2 (Figure 1) genes are the strongest known genetic risk factors for both breast and epithelial ovarian cancer (EOC) and are found in 6%–15% of women with EOC2. The BRCA1 gene is involved in DNA repair, cell-cycle checkpoint control, chromatin remodelling, transcriptional regulation and mitogenesis, while the BRCA2 has an important role in homologous recombination4. The clinical characteristics of BRCA1/2 mutant ovarian cancer patients differ from those of non-mutants. Patients affected are more likely to be younger at diagnosis, have a personal history of other malignancies (i.e. breast) and a strong family history of breast/ovarian cancer. Moreover, a BRCA1-related ovarian cancer is more likely to be of serous histology3, higher grade6 and advanced stage3, while less data are available for BRCA2-related disease, mainly due to the lower prevalence.

The brain is considered a protected area due to the presence of the blood–brain barrier, and the process of tumour metastasis in this site requires a series of events that may involve abnormal expression of many different genes. Cerebral metastases secondary to ovarian cancer have been reported to be infrequent, and are observed in 0.5%–12% in various patient series7-9. This increase might be attributed to the induction of platinum-containing chemotherapy agents in the past 25 years, which improved survival after treatment of ovarian cancer10,11. The observation of a higher incidence of brain metastases in autopsies12,13 compared with clinical studies or registry records might also suggest that most cases of brain metastases may be subclinical14. While no clear relationship to known prognostic factors of ovarian cancer and the development of brain metastases is found yet, and the molecular mechanism has not been described, it has been suggested that this rare behaviour of ovarian cancer could be a distinct biological phenotype6,15,16.

A closer analysis of the available published articles reveals some useful evidence on a possible association between brain metastases and presence of BRCA1/2 gene mutations. Koul et al.17 reported two BRCA1-positive epithelial ovarian tumours with metastases to the central nervous system. Subsequently, Gourley et al.18, in a prospective study of a Scottish population with EOC or primary peritoneal cancer and germline BRCA1/2 mutations, identified one patient with brain metastases...
within the BRCA1/2 patient group. Faluyi et al.\textsuperscript{14}, in a study involving ovarian cancer patients with previous early breast cancer, reported that, among the five patients with brain metastases, two were found to carry a BRCA1 mutation, two were not tested for both BRCA1 and BRCA2 genes while one had a normal BRCA1 gene but did not complete BRCA2 testing. Furthermore, Sekine et al.\textsuperscript{16}, investigating the incidence of brain metastases in BRCA1-related ovarian cancers, reported that four of seven cases with brain metastases secondary to ovarian cancer were BRCA1-related. Finally, Root and Armaghany\textsuperscript{19} reported a case of a BRCA2-positive ovarian cancer patient who developed a solitary brain metastasis 3 years after being diagnosed with papillary cystadenocarcinoma (Table 1).

Recent studies have shown that mutations of the BRCA1/2 genes in patients with ovarian cancer have significant implications in the disease characteristics, cumulatively described by some authors as 'BRCaness'. Specifically, BRCA1/2 mutation status affects platinum sensitivity\textsuperscript{20,21}, progression-free survival\textsuperscript{21,22} and overall survival\textsuperscript{21–24} of ovarian cancer patients, apart from the previously described clinical characteristics. Recently, a multicentre study involving 3879 patients concluded that those with a germ-line mutation in BRCA1 or BRCA2 genes had improved 5-year overall survival, with BRCA2 carriers having the best prognosis\textsuperscript{25}. This improved survival of BRCA1/2 carriers has been alleged to be related to the intrinsic biological differences, the response to therapeutic agents or both\textsuperscript{25}. On the other hand, in addition to the differences in stage, grade and histology, BRCA1/2 carriers could have differences in other aspects of the disease. Gourley et al.\textsuperscript{18}, based on the results of their study, suggested that the finding of increased visceral metastases within the BRCA1/2 carrier group suggests that this might be a phenomenon related to the BRCA1/2 mutations themselves, rather than secondary to improved survival in BRCA1/2-associated cancers themselves\textsuperscript{21}.

As a result, it is not unreasonable to presume that BRCA1/2-associated ovarian cancer relates to more than just platinum sensitivity. The findings from the study by Gourley et al.\textsuperscript{18}, as well as the evidence coming from published studies that suggest a possible high incidence of BRCA1/2 mutations in patients with ovarian cancer and brain metastases, imply that BRCA1/2-associated ovarian cancer is a discrete clinical entity, with a behaviour that differs from most sporadic ovarian cancers. The association of BRCA1/2 mutations and brain metastases must be investigated in large patient series, in order to provide solid information on the prognosis, treatment and surveillance of such patients. With only the one-third of BRCA1/2 carriers with ovarian cancer being initially fit to receive genetic testing\textsuperscript{26}, it is obvious that BRCA1/2 mutation analysis might have to be considered for patients during the course of ovarian cancer, even if it is initially held in terms of a research protocol. This will not only identify patients suitable for targeted personalised therapies, but will also contribute to successful and informative genetic counselling of patients and their families.

### References