OPEN ACCESS

Global Academic Journal of Medical Sciences

Available online at www.gajrc.com
DOI: https://doi.org/10.36348/gajms.2024.v06i04.007

ISSN: 2706-9036 (P)
ISSN: 2707-2533 (O)

Original Research Article

Comparison of Overall Survival, Progression Free Survival (PFS), Treatment Free Interval (TFI) between BRCA1 and BRCA2 Associated Epithelial Ovarian Cancer

Dr. Mst. Jakanta Faika[1*], Prof Jannatul Ferdous[2], Dr. Monowara Begum[3], Dr. Rowson Ara[4], Dr. Zakia Sultana[5], Dr. Tarana Tasnim[6], Dr. Tahurun Nesa[7], Dr. Sharmin Akter[8], Dr. Shohana Askari[9], Dr. Avijit Loha[10]

[1]Medical Officer, Department of Gynecological Oncology, Mugda Medical College Hospital, Dhaka, Bangladesh
[2]Professor Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka, Bangladesh
[3]Consultant, Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka, Bangladesh
[4]Medical Officer, Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka, Bangladesh
[5]Assistant Registrar, Department of Obstetrics and Gynaecology, Shaheed M. Mansur Ali Medical College Hospital, Sirajganj, Bangladesh.
[6]Medical Officer, Department of Obstetrics and Gynaecology, Mugda Medical College Hospital, Dhaka, Bangladesh
[7]Medical Officer, Department of Obstetrics and Gynaecology, Mugda Medical College Hospital, Dhaka, Bangladesh
[8]Assistant Registrar, Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka, Bangladesh
[9]Resident Surgeon, Department of Obstetrics and Gynaecology, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh
[10]Deputy Civil Surgeon, Mymensingh Civil Surgeon Office, Mymensingh, Bangladesh

***Corresponding Author**
Dr. Mst. Jakanta Faika
Medical Officer, Department of Gynecological Oncology, Mugda Medical College Hospital, Dhaka, Bangladesh

Article History
Received: 05.07.2024
Accepted: 12.08.2024
Published: 14.08.2024

Abstract: ***Background:*** The eighth most frequent gynecologic cancer in the world is ovarian cancer. Due to its advanced state at diagnosis, it is the worst gynecological cancer. The high mortality rate is largely due to the tendency to early spreading in the abdominal cavity, and most ovarian cancers being diagnosed at advanced stages (FIGO stage III & IV). Despite a high response rate to platinum-based chemotherapy, the overall survival (OS) remains poor with a 5-year overall survival of only 30–40%. ***Objective:*** The aim of this study is to Compare the Overall Survival, Progression Free Survival (PFS), Treatment Free Interval (TFI), Platinum Sensitive Recurrence (PSR) & Platinum resistant Recurrence (PRR) in patients with BRCA mutation and without BRCA mutation. ***Methods:*** The longitudinal cohort study was conducted in the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU) & NICRH Dhaka. A total 30 women with histopathologically confirmed advanced stage (FIGO stage III & IV) serous epithelial ovarian cancer were included in the study. Participants were divided into two groups: patients with BRCA1 associated epithelial ovarian cancer and those patients with BRCA2 associated epithelial ovarian cancer. The questionnaire was pretested, corrected and finalized. Data were collected by face-to-face interview and analyzed by appropriate computer based programmed software Statistical Package for the Social Sciences (SPSS), version 24. ***Results:*** In this study, maximum study subjects 17 (80.9%) were in ≤45 years age group in

BRCA1 associated EOC group and 6 (66.6%) were in >45 years age group in unexposed group. Mean age of the study subjects was 42.3±3.5 and 30.23±4.4 years in BRCA1 associated EOC and BRCA2 associated EOC group respectively. Majority of the patients 17 (80.9%) and 18 (85.7%) 6 (66.6%) were literate and 4 (19.1%) and 3 (33.3%) were illiterate in BRCA1 associated EOC and BRCA2 associated EOC group respectively. About 9 (42.9%) respondent of BRCA1 associated EOC group and 6 (66.6%) of BRCA2 associated EOC group had family history of breast / ovarian cancer. ***Conclusion:*** For epithelial ovarian cancer patients who received chemotherapy, we confirmed survival benefit for BRCA1 and BRCA2 germline pathogenic variant carriers. This may indicate higher sensitivity to chemotherapy, both in first line treatment and in the recurrent setting. The observed benefit appears to be limited to a relatively short period after epithelial ovarian cancer diagnosis.

Keywords: Overall Survival, Progression Free Survival (PFS), Treatment Free Interval (TFI), Epithelial Ovarian Cancer.

INTRODUCTION

Ovarian cancer is thought to be among the deadliest neoplasms of all gynecologic cancers [1]. The American Cancer Society projects that there will be 14,180 ovarian cancer-related fatalities and 21,290 new instances of the disease in the United States in 2015 [2]. Roughly 90% of ovarian cancer cases are epithelial malignancies. The prognosis for most epithelial ovarian malignancies is poor because they are typically not detected until they are in an advanced stage [3]. Nevertheless, this malignancy responds to chemotherapy the best out of all gynecologic cancers. A number of patients experience full remissions after receiving both chemotherapy and surgery [4].

Despite the fact that first-line chemotherapy is effective in treating epithelial ovarian cancer, over half of these patients experience recurrence within two years of finishing treatment. Over 70% of patients with advanced malignancies (stage III/IV, for example) experience recurrence within five years, compared to 55% after two years [5]. After recurrence, the median overall survival (OS) is about two years. Because a full remission is difficult to achieve, post-recurrence therapy goals are different from those of first-line treatments. These objectives seek to increase OS while also enhancing QOL and symptom relief [6]. The primary treatment option for advanced or recurring ovarian malignancies is chemotherapy. The specific chemotherapy drugs that most influence a good prognosis are still unknown.

Oncology phase III clinical trials serve a number of functions, including (i) comparing novel medicines to established therapies, (ii) assessing the impact of new treatments on patient quality of life, (iii) identifying toxicity profiles, and (iv) assessing the financial impact of introducing new treatments. Although the number of available treatment alternatives has increased, OS has historically been considered a valid endpoint when choosing an effective treatment strategy for cancer patients. Instead of using OS as the primary endpoint, several clinical trials for second- or third-line treatments of ovarian cancer have been using progression-free survival (PFS).

It would be incorrect to conclude that a non-statistically significant OS outcome in a randomized trial is evidence for the lack of clinical utility of an investigative approach that has been shown to improve PFS. Significant improvements in PFS may not, however, translate into a similar improvement in OS. [7]. Thus, once the disease has advanced, it is crucial to comprehend the effects of therapy approaches. Post-progression therapies were found to have an impact on patient outcomes, and PPS was anticipated to function as a legitimate OS predictor, according to emerging evidence. PPS was found to be more strongly linked with OS than PFS in an analysis of phase III trials of first-line chemotherapy for advanced epithelial ovarian cancer, particularly in more recent studies [8].

Even though ovarian cancer patients respond well to first-line chemotherapy, the illness frequently progresses, and many require second- and third-line therapies. The exact effects of PPS in second- or third-line chemotherapy for this illness, however, are not well understood. We postulated that among patients with ovarian epithelial carcinoma receiving second- or third-line treatment, OS is a more suitable objective than PFS.

An inability to use the DNA repair mechanism homologous recombination to repair double-strand breaks is linked to BRCA insufficiency [9]. This could result in increased survival rates and

higher response rates to first-line platinum-based chemotherapy, which destroys double strands of DNA [10]. Although the published outcomes are inconsistent, some studies have found higher survival for BRCA-associated EOC patients than for sporadic patients [11]. The benefit of survival might only apply to BRCA2 gPV carriers [12] or to the first five to 10 years [13]. A small number of patients were included in a few trials that revealed greater response rates to platinum-based chemotherapy following recurrent EOC in BRCA gPV carriers than in patients with sporadic EOC [14]. Furthermore, the individual pathogenic variation and/or related gene may influence the sensitivity to platinum-based treatment. Overall, there is still no solid proof that patients with EOC who are also BRCA-associated have a better prognosis. Furthermore, even though BRCA1 and BRCA2 tumors may be distinct cancers, prognosis and survival following EOC for BRCA1 and BRCA2 were not examined independently in the majority of investigations.

METHODOLOGY

The longitudinal cohort study was conducted in the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU) & NICRH Dhaka. A total 30 women with histopathologically confirmed advanced stage (FIGO stage III & IV) serous epithelial ovarian cancer were included in the study. Participants were divided into two groups: patients with BRCA1 associated epithelial ovarian cancer and those patients with BRCA2 associated epithelial ovarian cancer. Patients who matched the inclusion and exclusion criteria were approached for participation in the study. Patients who were not willing to give consent were excluded. Purposive sampling was done according to the availability of the patients who fulfilled the selection criteria. Face to face interview was done to collect data with a semi-structured questionnaire. After collection, the data were checked and cleaned, followed by editing, compiling, coding, and categorizing according to the objectives and variable to detect errors and to maintain consistency, relevancy and quality control. Statistical evaluation of the results used to be obtained via the use of a window-based computer software program devised with Statistical Packages for Social Sciences (SPSS-24).

RESULTS

Table I: Distribution of the patients according to age (n = 30)

Age (years)	BRCA1 associated EOC (n=21)	BRCA2 associated EOC (n=9)
≤45	17 (80.9)	3 (33.3)
>45	4 (19.1)	6 (66.6)
Mean ± SD	**42.3±3.5**	**30.23±4.4**

Table I shows that, maximum study subjects 17 (80.9%) were in ≤45 years age group in BRCA1 associated EOC group and 6 (66.6) were in >45 years age group in unexposed group. Mean age of the study subjects was 42.3±3.5 and 30.23±4.4 years in BRCA1 associated EOC and BRCA2 associated EOC group respectively.

Table II: Distribution of the patients according to educational status (n = 30)

Education	BRCA1 associated EOC (n=21)	BRCA2 associated EOC (n=9)
Illiterate	4 (19.1)	3 (33.3)
Literate	17 (80.9)	6 (66.6)

Table II shows that, majority of the patients 17 (80.9%) and 6 (66.6) were literate and 4 (19.1%) and 3 (33.3) were illiterate in BRCA1 associated EOC and BRCA2 associated EOC group respectively

Table III: Distribution of the patients according to family history of breast / ovarian cancer (n = 30)

Family history of breast / ovarian cancer	BRCA1 associated EOC (n=21)	BRCA2 associated EOC (n=9)
Yes	9 (42.9)	6 (66.6)
No	12 (57.1)	3 (33.3)

Table III shows that, 9 (42.9%) respondent of BRCA1 associated EOC group and 6 (66.6) of BRCA2 associated EOC group had family history of breast / ovarian cancer.

Table IV: Distribution of the patients according to Primary Debulking Surgery (n = 30)

Primary Debulking Surgery	BRCA1 associated EOC (n=21)	BRCA2 associated EOC (n=9)
Yes	9 (42.9)	6(66.6)
No	12 (57.1)	3 (33.3)

Table IV shows that, majority respondents of BRCA2 associated EOC group 6 (66.6) underwent Primary Debulking Surgery as primary treatment modality, whereas 12 (57.1) BRCA1 associated EOC group did not receive Primary Debulking Surgery.

Table V: Distribution of the patients according to Neoadjuvant Chemotherapy and Interval Debulking Surgery (n = 30)

Neoadjuvant Chemotherapy and Interval Debulking Surgery	BRCA1 associated EOC (n=21)	BRCA2 associated EOC (n=9)
Yes	12 (57.1)	3 (33.3)
No	9 (42.9)	6(66.6)

Table V shows that, majority respondents of BRCA1 associated EOC group 12 (57.1%) received neo adjuvant chemotherapy and interval debulking surgery, whereas 3 (33.3) respondents of BRCA2 associated EOC group received Neoadjuvant chemotherapy and interval debulking surgery.

Table VI: Distribution of the patients according to status of recurrence of disease after treatment (n = 30)

Status of recurrence	BRCA1 associated EOC (n=21)	BRCA2 associated EOC (n=9)
Yes	5 (23.8)	3 (33.3)
No	16 (76.2)	6(66.6)

Table VI shows that, 5 (23.8%) respondent of BRCA1 associated EOC group and 3 (33.3) of BRCA2 associated EOC group showed recurrence of disease. Though disease recurrence was less in BRCA1 associated EOC group.

Table VIII: Distribution of the patients according to types of recurrence (n = 30)

Types of recurrence	BRCA1 associated EOC (n=21)	BRCA2 associated EOC (n=9)
Platinum Sensitive	4 (19.0)	3(33.3)
Platinum Resistant	1 (4.8)	1(11.1)
No	16 (76.2)	5(55.5)

Table VIII shows that, 4 (19.0%) respondents of BRCA1 associated EOC group and 3(33.3) of BRCA2 associated EOC group showed platinum sensitive recurrence and 1 (4.8%) respondents of Exposed group and 1(11.1) of Unexposed group showed platinum resistant recurrence.

Table IX: Distribution of the patients according to Time of recurrence, Progression free survival and Treatment free interval (n = 30)

Types of recurrence	BRCA1 associated EOC (n=21)	BRCA2 associated EOC (n=9)
Time of recurrence (months)	11.34±2.63	9.33±3.34
Progression free survival (months)	13.35±2.24	11.18±2.54
Treatment free interval (months)	11.17±2.16	9.24±2.07

Table IX shows that, Mean time of recurrence for BRCA1 associated EOC group and for BRCA2 associated EOC group was 11.34±2.63 and 9.33±3.34 months respectively. Mean progression free survival for BRCA1 associated EOC group and for BRCA2 associated EOC group was 13.35±2.24 and 11.18±2.54 months respectively. Mean treatment free interval (TFI) for BRCA1 associated EOC group and for BRCA2 associated EOC group was 11.17±2.16 and 9.24±2.07 months respectively.

Table X: Distribution of the patients according to one-year overall survival (n = 42)

One-year overall survival	BRCA1 associated EOC (n=21)	BRCA2 associated EOC (n=9)
Present	19 (90.5)	6(66.6)
Absent	2 (9.5)	3(33.3)

Table X shows that, One-year overall survival for BRCA1 associated EOC group was more 19 (90.5%) and for BRCA2 associated EOC group was 6 (66.6)

DISCUSSION

One of the most prevalent forms of cancer in women is ovarian cancer, which also happens to be the leading cause of death from gynecological cancer and one of the most common causes of deadly cancer in women overall. Most patients come with advanced-stage disease since the symptoms are generally ambiguous, making early detection difficult [15]. Surgery and chemotherapy are typically used in the treatment of ovarian cancer. It is commonly known that hereditary mutations in BRCA1 and BRCA2 increase the risk of ovarian cancer. Despite the widespread belief that germline BRCA mutations cause between 5.0% and 10.0% of ovarian cancer cases, new research indicates that this number is likely underestimated. In line with the age-specific penetrance of BRCA1 versus BRCA2 carriers, BRCA1 carriers had epithelial ovarian cancer (EOC) at an earlier age than BRCA2 carriers.

The cross-sectional observational study was conducted in the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. A total 30 women with histopathologically confirmed early stage (FIGO stage III & IV) serous epithelial ovarian cancer were included in the study.

In this study, maximum study subjects 17 (80.9%) were in ≤45 years age group in BRCA1 associated EOC group and 6 (66.6) were in >45 years age group in unexposed group. Mean age of the study subjects was 42.3±3.5 and 30.23±4.4 years in BRCA1 associated EOC and BRCA2 associated EOC group respectively. Another study shows the risk of ovarian cancer increases in women who have ovulated more over their lifetime. This includes those who have never had children, those who begin ovulation at a younger age or reach menopause at an older age [16]. Ovarian cancer is most commonly diagnosed after menopause [17]. In this present study it was observed that age belonged to ≤45 years was significantly ($p<0.05$) more common in BRCA1 & 2 mutation group between two groups, however educational status was almost alike between two groups, no statistical significant difference was observed between two groups. Neff *et al.,* (2017) study found convincing evidence of an age discrepancy for onset of disease between BRCA1/2, with BRCA1 patients having an increased risk after age 40 and BRCA2 patients after age 50 years, which is comparable with the current study [10]. National Comprehensive Cancer Network (NCCN) and Society of Gynecologic Oncology (SGO) recommend consideration of salpingo-oophorectomy (RRSO) following completion of childbearing and after 35 years in women with known BRCA mutation. This is based on the relative increase in risk of a gynecologic malignancy in a BRCA1 carrier after 40 years. Kim *et al.,* 2019 study observed that 60.8% patients belonged to age ≥50 years in BRCA mutation and 75.3% in BRCA non mutated group ($p>0.05$), which is higher age ranged with the current study [18]. Similarly, Shi *et al.,* (2018) study also higher age ranged ages at diagnosis between pathogenic mutation carriers and non-carriers. Shi *et al.,* (2018) study showed there were no significant ($p>0.05$) differences in mean ages at diagnosis between pathogenic mutation and non-mutation group. The higher age ranged obtained by the above authors maybe due to geographical variations, racial, ethnic differences and genetic causes may have significant influence on their study subjects.

Majority of the patients 17 (80.9%) and 6 (6.66) were literate and 4 (19.1%) and 3 (3.33%) were illiterate in BRCA1 associated EOC and BRCA2 associated EOC group respectively. Alberg *et al.,* (2016) study findings suggested that ovarian cancer risk may be inversely associated with socioeconomic status, higher levels of education were inversely associated with ovarian cancer risk and individuals with the highest income level had a non-significantly lower risk than did those with the lowest income level.

In this present study, about 9 (42.9%) respondent of BRCA1 associated EOC group and 6 (66.6%) of BRCA2 associated EOC group had family history of breast / ovarian cancer. In another study it was observed that 36.36% respondent of Exposed group and 25% of Unexposed group showed positive family history of breast and ovarian cancer. Positive family history of breast/ovarian cancer was significantly ($p=0.031$) associated with BRCA1 & BRCA 2 mutation group. Shi *et al.,* (2018) study reported that patients who had family or personal history of Hereditary Breast and Ovarian Cancer (HBOC) related tumors had a significantly ($p<0.001$) increased rate of pathogenic gBRCA1/2 mutations, which support with the present study. In last decade, recommendations for BRCA testing and genetic counseling have further expanded to any individual who is diagnosed with an invasive ovarian cancer, even in the absence of a family history (Society of Gynecologic Oncology, 2015 and National Comprehensive Cancer Network, 2017) [17, 18]. On the others hand, according to Bolton *et al.,* 2012 cases from BRCA 1/BRCA 2 non-mutated families could carry germline mutations in genes in the same

pathway as BRCA1/BRCA2 or in different pathways that produce similar clinical features [19].

In this study, majority respondents of BRCA2 associated EOC group 6 (66.6) underwent Primary Debulking Surgery as primary treatment modality, whereas 12 (57.1%) BRCA1 associated EOC group did not receive Primary Debulking Surgery. Majority respondents of BRCA1 associated EOC group 12 (57.1%) received neo adjuvant chemotherapy and interval debulking surgery, whereas 3 (33.3) respondents of BRCA2 associated EOC group received Neoadjuvant chemotherapy and interval debulking surgery. Shi *et al.,* (2018) study obtained that the effect of gBRCA1/2 mutations might be superior on the initial response to chemotherapy, particularly in those with incomplete cytoreduction, leading to a better survival. Majority respondents of Unexposed group (75%) received Primary Debulking Surgery whether majority respondents of exposed group (54.55%) received Neo adjuvant chemotherapy and interval debulking surgery. Significant difference was not found between groups regarding type of treatment. Kim *et al.,* (2019) study observed that nearly two third (62.7%) patients received primary debulking surgery (PDS) in BRCA mutation and 61.0% in BRCA non-mutation type, which also not significant (p=0.378) between two groups in terms type of treatment. In contrary to Shi *et al.,* (2018) study findings, Hyman stated that there was no correlation between the BRCA mutation status and the rate of optimal debulking surgery [2], which might be affected by various ethnics and different sample size. Narod, (2016) study mentioned that survival is maximized when residual disease is minimized after complete cytoreduction and chemotherapy [20]. Moreover, Ren *et al.,* 2015 found that neoadjuvant chemotherapy was independently associated with OS, which was consistent with previous retrospective study [21]. Petrillo *et al.,* (2017) reported that in the subgroup of BRCA1/BRCA2 non-mutation carriers, patients with neoadjuvant chemotherapy had a worse PFS than those with primary debulking surgery, but no significant difference was found in BRCA1/BRCA2 mutation carriers, nor in the estimation of OS [22].

About 5 (23.8%) respondent of BRCA1 associated EOC group and 3(3.33) of BRCA2 associated EOC group showed recurrence of disease. Though disease recurrence was less in BRCA1 associated EOC group. About 4 (19.0%) respondents of BRCA1 associated EOC group and 3 (33.3) of BRCA2 associated EOC group showed platinum sensitive recurrence and 1 (4.8%) respondents of BRCA1 associated EOC group and 1 (11.1) of BRCA2 associated EOC group showed platinum resistant recurrence. Regarding the status of recurrence of disease after treatment in another study it was observed that majority respondents of both groups did not show any recurrence of disease. In this study, 18.18% respondent of Exposed group type and 25% of Unexposed group showed platinum sensitive recurrence. It was observed that there was no significant difference between two groups in terms of types of recurrence (p=0.231). This study suggest that women are routinely referred for genetic counseling and genetic testing either during or soon after their primary systemic therapy is completed so that this information is available in a timely fashion for inclusion in decisions about subsequent treatment strategies in the event of a relapse (Pal *et al.,* 2007). Kim *et al.,* (2019) study observed that the proportions of platinum-sensitive recurrence (PSR) were 80.6% and. 63.8% in BRCA1 & BRCA2 mutation group and BRCA 1 & BRCA 2 non mutation group respectively and showed not significant (p=0.099) between two groups [8].

Mean time of recurrence for BRCA1 associated EOC group and for BRCA2 associated EOC group was 11.34±2.63 and 9.33±3.34 months respectively. Mean progression free survival for BRCA1 associated EOC group and for BRCA2 associated EOC group was 13.35±2.24 and 11.18±2.54 months respectively. Mean treatment free interval (TFI) for BRCA1 associated EOC group and for BRCA2 associated EOC group was 11.17±2.16 and 9.24±2.07 months respectively. One-year overall survival for BRCA1 associated EOC group was more 19 (90.5%) and for BRCA2 associated EOC group was 6 (66.6). In another study, Mean time of recurrence for Exposed group and for Unexposed group was 10.34±2.73 and 8.33±3.44 months respectively. Independent sample t test showed the difference was not statistically significant (p=0.556). In this current study it was observed that Mean progression free survival for Exposed group and for Unexposed group was 12.35±2.23 and 10.18±2.56 months respectively. Independent sample t test showed the difference was statistically significant (p=0.030). Kim *et al.,* (2019) obtained in their study that patients in the BRCA mutation group had significantly (p<0.001) longer (median, 21.7 vs. 15.4 months) progression-free survival (PFS) than those in the non-mutated BRCA group. Mean treatment free interval (TFI) for Exposed group and for Unexposed group was 12.17±2.18 and 10.24±2.09 months respectively. Independent sample t test showed the difference was statistically significant (p=0.013). Kim *et al.,* (2019) study showed that the median treatment free interval was longer in the patients with BRCA mutations (12.3 months vs. 9.0 months, P=0.002), which support with the present study [8].

CONCLUSION

In conclusion, survival benefit for BRCA1/2-associated EOC patients treated with mainly platinum-based chemotherapy. This may indicate higher sensitivity to chemotherapy, both in the first line and in the recurrent setting. The observed benefit appears to be limited to a relatively short period after EOC diagnosis.

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