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ORIGINAL RESEARCH

# Clinical Characteristics and Prognosis of Gastric Cancer Patients with *BRCA 1/2* Germline Mutations: Report of Ten Cases and a Literature Review



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**Background:** The prognosis of gastric cancer (GC) is poor with a median overall survival (OS) of less than 12 months in advanced-stage disease. The search for distinct genetic subgroups of GC patients and predictive biomarkers is ongoing. While *BRCA1* or *BRCA2* germline mutations (gBRCAm) have potential therapeutic implications in ovarian, breast and pancreatic cancers, their significance in GC patients has not been established.

**Patients and Methods:** A retrospective multi-center data analysis of GC patients with gBRCAm was conducted, detailing the clinical characteristics and disease course in this unique subset of patients.

**Results:** Ten GC patients with gBRCAm were identified, six of them with metastatic disease. The median OS of all ten GC patients was 47.5 (13–192) months. Median OS for patients diagnosed with operable disease was 55.5 (13–192) months and of the patients with metastatic disease (calculated from metastatic disease diagnosis) 32 (15–52) months with an exceptional 1-, 2- and 3-year survival rate of 100%, 83.3% and 50%, respectively.

**Conclusion:** These preliminary data suggest that gBRCAm in GC patients are associated with a favorable prognosis. Furthermore, gBRCAm might be a predictive biomarker to DNA-damaging agents response in GC patients, similarly to its established role in other malignancies. Further research is needed to confirm our findings.

**Keywords:** gastric cancer, *BRCA1*, *BRCA2*, DNA-damaging agents, PARP inhibitors

## Introduction

Gastric cancer (GC) is the fifth most frequently diagnosed malignancy worldwide and the third leading cause of cancer-related death.[1] The prognosis of GC remains poor with a median overall survival (OS) rate of less than a year in the advanced setting despite great efforts to find new therapeutic agents and biomarkers.[2]

*BRCA1* or *BRCA2* germline mutation (gBRCAm) carriers with breast, ovarian, prostate and pancreatic cancer demonstrate durable responses to DNA-damaging agents (platinum agents and PARP (Poly ADP-ribose polymerase) inhibitors).[3–7] Increased risk for GC in gBRCAm carriers has been previously suggested,[8,9] yet GC is not considered a part of the cancer spectrum in gBRCAm carriers. Targeted sequencing of gastric cancer samples detected *BRCA2* somatic mutations in 8% of the cases in a Chinese cohort, regardless of patients' personal or familial background of malignancies.[10] A similar number was reported in a different publication

reporting mutations in homologous recombination deficiency (HRD) genes (ATM, BRCA1, BRCA2) in 7.5% of 400 GC patients undergoing both somatic and germline next generation sequencing (NGS).[11] Figer et al detected the *6174delT BRCA2* Ashkenazi Jewish founder mutation in 5.7% of 35 GC patients of Ashkenazi origin. This prevalence is higher than the 1.16% expected prevalence rate of the mutation in the general Ashkenazi population.[12] Alexandrov et al identified a unique somatic molecular signature found in various tumors of gBRCAm carriers. Interestingly, this distinct molecular signature was found also in tumors not harboring a *BRCA1/2* mutation, suggesting that other mechanisms impairing DNA damage repair may exist.[13]

To the best of our knowledge, there are only a few reports describing the clinical course of GC patients harboring *BRCA1/2* germline or somatic mutations.[10,14] Chen et al report prolonged OS of 45 GC patients with *BRCA2* mutations compared to *BRCA2* wild type (WT) patients. The report does not specify whether patients had somatic or germline mutations, stages of GC diagnosis and treatments administrated.[10] Ichikawa et al recently described three gBRCAm carriers with GC; two patients with operable T4N+ tumors are alive 2 years after surgery and adjuvant treatment. The third patient is alive and continuing treatment 5 years after metastatic disease diagnosis.[14]

In order to evaluate further the role of gBRCAm as a prognostic and/or predictive factor in GC patients, we describe the characteristics and clinical course of a cohort of GC patients harboring these mutations.

## Patients and Methods

A retrospective review of databases from high-risk oncogenetic clinics in three hospitals – Sheba Medical Center, Rabin Medical Center and Hadassah Medical Center – was conducted in order to identify gBRCAm carriers with gastric adenocarcinomas. The first genetic registry was established in 1994, hence our data cover the period between 1994 until 2018. *BRCA 1/2* Jewish founder mutations testing was carried out by targeted genotyping as described by Bernstein et al.[15] In some cases, testing was done by single gene sanger sequencing or by next generation sequencing. Patients' demographics, family history, as well as histopathologic characteristics, treatments administrated and disease outcomes were obtained from medical records.

The research was approved by the local ethics committees of the three participating centers: Sheba Medical Center, Rabin Medical Center and Hadassah Medical Center. Patient data access complied with relevant data protection and privacy regulations.

## Results

We identified ten GC patients with a gBRCAm. Demographic and clinicopathological characteristics of these patients are described in Table 1 and summarized in Table 2. We did not identify any unique histopathological features in stage, location, grade and histology, neither could we identify differences between *BRCA1* and *BRCA2* carriers.

Four patients with early-stage disease underwent surgery and did not receive any adjuvant chemotherapy; one of them had recurrent metastatic disease (29 months after surgery). Two patients received adjuvant platinum-based treatment; one had recurrent metastatic disease (13 months after surgery).

Four patients had metastatic disease at first diagnosis. Among the total six patients with metastatic disease (including patients presenting with metastatic disease and patients with recurring metastatic disease after surgery), all but one were treated with DNA-damaging agents including platinum agents and/or PARP inhibitors. Treatments administrated to metastatic patients included also other chemotherapy agents, Trastuzumab, Ramucirumab and immunotherapy.

The median OS of all ten GC patients in our cohort was 47.5 (13–192) months. Median OS for patients diagnosed with operable disease was 55.5 (13–192) months. The six patients with metastatic disease had a median OS rate (calculated from metastatic disease diagnosis) of 32 (15–52) months. The 1-, 2- and 3-year survival rates with metastatic disease were 100%, 83.3% and 50%, respectively. Two patients were alive and continuing treatment with an OS of 28 and 36 months at data cutoff (Figure 1).

## Discussion

Although GC in gBRCAm carriers has been previously described, it is not considered a *BRCA*-associated malignancy.[6,8,9,12,14,16,17]

Identifying GC as a possible *BRCA* associated malignancy may have both therapeutic and diagnostic implications: *BRCA1/2* mutations may predict a better response to DNA-damaging agents. In addition, the possibility of screening and early detection of GC in *BRCA* carriers and their family members might be considered.

To our best knowledge, this is the largest detailed cohort of GC patients harboring a pathogenic gBRCAm. Data encompass patients' genetics, personal and familial history along with clinicopathological characteristics and

**Table 1** BRCA1/2 Germline Mutation Carriers with GC

| Case | Sex | Age at GC* | Ethnicity | BRCA Mutation | First Degree Relative with BRCA Associated Malignancy^ | First Degree Relative with GC | Personal History of Other Malignancy | Stage of GC at Diagnosis | Histological Type | Tumor Location | HER2 Status | Adjuvant Treatment | Recurrent Metastatic Disease (Months from Surgery) | DNA Damaging Agents for Metastatic Disease | OS (mos) | OS from Diagnosis of Metastatic Disease | Clinical Status |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 71 | Ashkenazi | *BRCA1* 185delAG | Yes | No | Colon, Ovary | IA | Unknown | Missing | Negative | No | No | NA | 192 | NA | DNED |
| 2 | F | 56 | Sepharadi | *BRCA2* 6024dupG | Yes | No | Breast | IIA | Unknown | Body | Unknown | Platinum based Chemoradiation | Yes (13) | Yes | 28 | 15 | DWD |
| 3 | F | 74 | Ashkenazi | *BRCA2* 6174delT | Yes | No | No | IB | Intestinal | Cardia | Positive | No | Yes (29) | No | 56 | 27 | DWD |
| 4 | M | 65 | Ashkenazi | *BRCA2* 6174delT | No | Yes | No | IV | Diffuse | Body | Negative | NA | NA | Yes | 43 | 43 | DWD |
| 5 | F | 56 | Yemenite | *BRCA2* 8765delAG | Yes | Yes | Breast-Bilateral | IV | Unknown | Body | Negative | NA | NA | Yes | 52 | 52 | DWD |
| 6 | M | 64 | Ashkenazi | *BRCA2* 6174delT | Yes | No | No | IV | Intestinal | GEJ | Negative | NA | NA | Yes | 36 | 36 | AWD |
| 7 | M | 63 | Yemenite | *BRCA2* 8765delAG | Yes | No | No | IA | Unknown | Body | Unknown | No | No | NA | 81 | NA | ANED |
| 8 | F | 52 | Ashkenazi | *BRCA2* 6174delT | No | No | No | IIA | Mixed | Antrum | Negative | Platinum based Chemotherapy | No | NA | 55 | NA | ANED |
| 9 | M | 69 | Ashkenazi | *BRCA1* 185delAG | No | No | No | IV | Unknown | Cardia | Negative | NA | NA | Yes | 28 | 28 | AWD |
| 10 | M | 68 | Ashkenazi | *BRCA1* 185delAG | Yes | No | No | IB | Unknown | GEJ | Unknown | No | No | NA | 13 | NA | ANED |

**Notes:** *Age at GC diagnosis. ^Breast, ovarian or pancreatic cancer.

**Abbreviations:** GC, gastric cancer; GEJ, gastroesophageal junction; NA, not applicable; OS, overall survival; mos, months; DNED, died no evidence of disease; DWD, dead with disease; AWD, alive with disease; ANED, alive no evidence of disease.

**Table 2** Demographic, Genetic and Clinicopathological Characteristics of BRCA1/2 Carriers with Gastric Cancer

| Characteristics | N=10 |
|---|---|
| Gender: Male | 5 |
| Female | 5 |
| Average age at GC diagnosis (range) | 63.8 (52–74) |
| Ethnicity: Jewish Ashkenazi | 7 |
| Other | 3 |
| Mutation: *BRCA1* 185delAG | 3 |
| *BRCA2* 6174delT | 4 |
| *BRCA2* 8765delAG | 2 |
| *BRCA2* 6024dupG | 1 |
| Personal history of malignancy | 3 |
| First degree relative with BRCA associated malignancy* | 7 |
| First degree relative with gastric cancer | 2 |
| Stage of GC at diagnosis- Operable | 6 |
| Metastatic | 4 |
| Total number of patients with metastatic GC** | 6 |
| Her2: Positive | 1 |
| Negative | 6 |
| DNA-damaging treatment for metastatic GC | 5 |

**Notes:** *Breast, ovary, pancreatic cancer. **Including patients presenting with metastatic GC or recurrence after operation.

most important – systemic treatments administrated and disease outcome.

Most of our patients had a *BRCA2* mutation. This is in concordance with previous reports of GC found mostly in *BRCA2* families.[8,9,12] Interestingly, only *BRCA2* somatic mutations were detected in consecutive NGS of GC specimens, with no *BRCA1* somatic mutations identified.[10]

All of the *BRCA1/2* mutations in this cohort are well known pathogenic germline mutations described previously.[15,18] Three are known founder or predominant Jewish mutations that are included in a targeted panel of 14 recurring Israeli *BRCA1/2* mutations test.[15] Most of the patients or families in our cohort were known to be gBRCAm carriers before GC diagnosis, with two patients, both *BRCA2* carriers, having a first degree relative with GC. Unfortunately, none of them were screened for GC and both were diagnosed with metastatic disease.

Most patients in our cohort had a first-degree member with a *BRCA* associated malignancy, suggesting the phenotype of these families is not different from the classical breast and ovarian syndrome and that GC might be a part of the syndrome.

Treatment with DNA-damaging agents (platinum and PARP inhibitors) in *BRCA1/2* associated cancers including breast, ovarian, pancreatic and prostate cancers has been proved to prolong progression-free survival, and the *BRCA1/2* mutation serves as a predictive biomarker to these agents.[3–7]

Despite great efforts to identify new treatments, the standard systemic treatment for advanced GC remains chemotherapy, adding Trastuzumab in HER2-positive patients. Median OS rate is less than a year in HER2 negative and up to 16 months in HER2-positive patients.-[2,19] Triple chemotherapy regimens increases the response rate, but median OS remains less than a year. The one- and two-year survival rate with triple chemotherapy is 40% and 18%, respectively.[20] Second-line chemotherapy achieves a median OS of about 4 months.[2] The addition of the biologic agent Ramucirumab to second-line chemotherapy extends median OS of pretreated GC patients by another 2 months.[21] Immunotherapy in GC patients gives hope for prolonged responses for a subset of patients, with the predictive biomarkers of High Microsatellite Instability (MSI-H) and possibly PDL-1 expression.[22–24] The addition of a PARP inhibitor to chemotherapy in metastatic GC patients was tested in the GOLD trial. The trial recruited metastatic GC patients and stratified them by the Ataxia-Telangiectasia (ATM) protein expression. The trial failed to prove benefit either

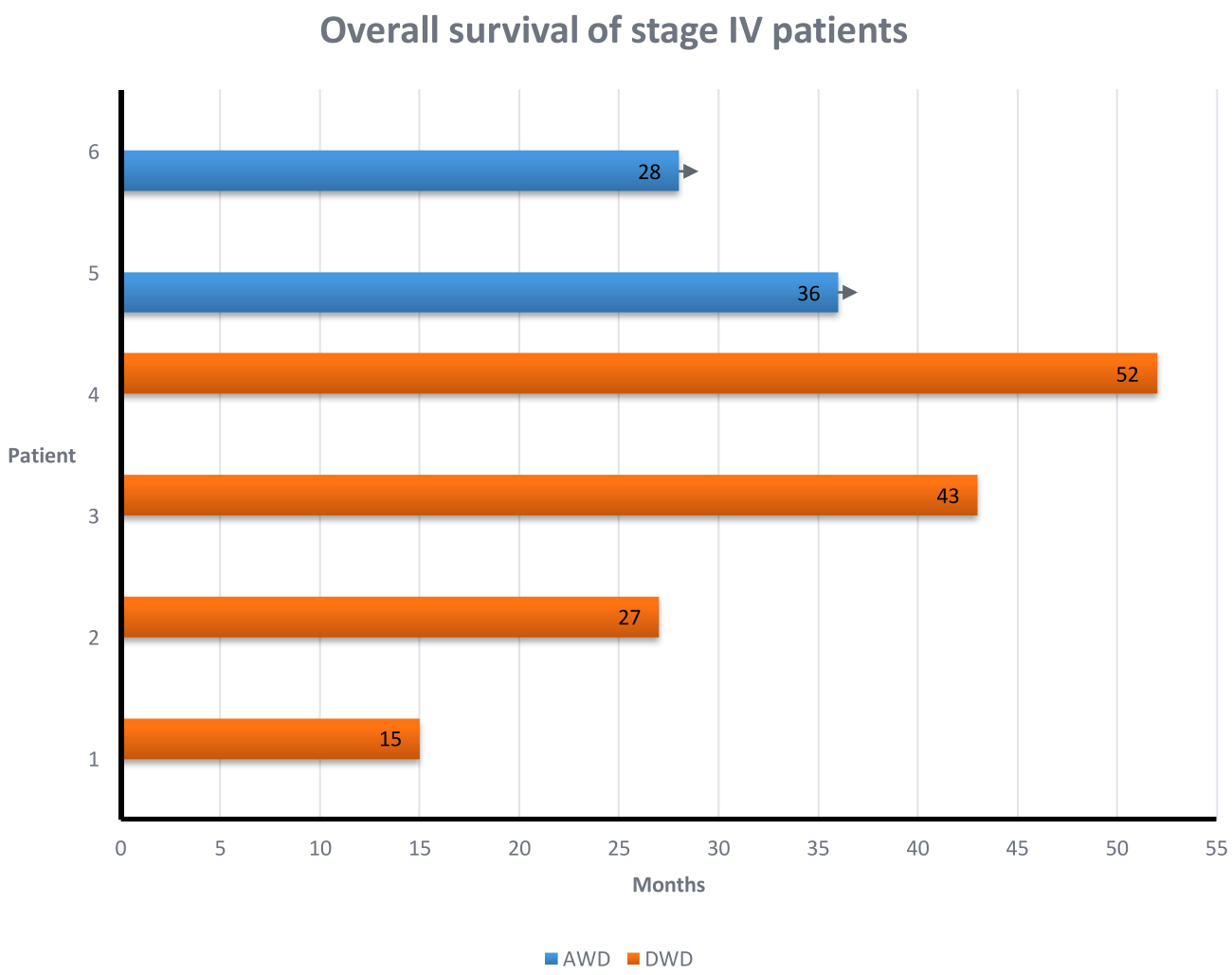


**Figure 1** Overall survival at data cutoff.
**Abbreviations:** DWD, dead with disease; AWD, alive with disease.

in unselected patients or in the ATM negative subgroup. The publication does not include data regarding germline or somatic BRCA mutations of the patients.[25] Several ongoing clinical trials are evaluating the effect of PARP inhibitors in GC (Table 3). In addition, various strategies to increase the efficacy of PARP inhibitors in GC are being investigated. Koutas et al found that c-MET inhibition increases the anti-tumor activity of PARP inhibitors in cell lines.[26]

The median OS of our metastatic GC patients was strikingly better than the reported OS of the general population of metastatic GC patients and is consistent with the few previous publications of better outcome of *BRCA1/2* carriers with GC.[2,10,14] This outcome is also superior to data from the Israeli cancer registry, that reports a median OS survival of 13.6 months for all-stage GC patients between the years 2000–2014.[27]

Our findings suggest that gBRCAm can be a predictive biomarker for response to DNA-damaging agents in GC patients.

Our study has several limitations that should be acknowledged: it is retrospective and includes a small number of patients. GC patients are not routinely tested for *BRCA1/2* mutations. Most patients are tested only for the common Jewish mutations and do not undergo full *BRCA1/2* sequencing. Patients in this cohort were treated according to the treating physicians' preferences hence diverse protocols were employed.

The strength of our study is the detailed information including genetic and family history along with

**Table 3** Clinical Trials with PARP Inhibitors in GC

| Trial | Phase | Treatment | Patient Population | Genomic Alteration | Primary End Point | Trial Status |
|---|---|---|---|---|---|---|
| NCT02033551 | 1 | Veliparib | Previously treated | BRCA mut | Safety | Completed |
| NCT01123876 | 1 | Veliparib + FOLFIRI | Previously treated | Non required | Safety | Completed |
| NCT03026881 | 1 | Fluzoparib + Apatinib + Paclitaxel | Previously treated | Non required | Safety | Unknown |
| MEDIOLA NCT02734004 | 1/2 | MEDI4736 + Olaparib | Previously treated | Non required | Safety, DCR, ORR | Active, not recruiting |
| NCT03008278 | 1/2 | Olaparib + Ramucirumab | Previously treated | Non required | Safety, ORR | Recruiting |
| NCT03008278 | 1/2 | Olaparib + Ramucirumab | Previously treated | Non required | ORR | Recruiting |
| NCT04209686 | 2 | Paclitaxel + Pembrolizumab + Olaparib | Previously treated | Non required | OS | Recruiting |
| LODESTAR NCT04171700 | 2 | Rucaparib | Previously treated | BRCA or deleterious HRR mut | ORR | Recruiting |
| NCT03427814 | 2 randomized | Pamiparib/ placebo | Previously treated and responded to first-line platinum | Non required | PFS | Active, not recruiting |
| NCT04550494 | 2 randomized | Pactiltaxel + Olaparib/placebo | Progressed following first line-therapy | Known ATM status | PFS | Completed |

**Abbreviations:** PARP, poly ADP-ribose polymerase; GC, gastric cancer; Mut, mutation; HRR, homologous recombination repair; ATM, ataxia telangiectasia; DCR, disease control rate; ORR, overall response rate; OS, overall survival; PFS, progression free survival.

clinicopathological information and, most importantly, treatment outcomes and long term follow up.

## Conclusions

This retrospective case series describes a specific subgroup of GC patients: gBRCAm carriers. We report a favorable course with a prolonged OS of metastatic GC patients harboring these germline mutations. Our findings buttress the significance of *BRCA1/2* germline mutations as a tumor agnostic biomarker.

Further research is needed to understand the incidence, disease characteristics and response to various treatments in gBRCAm carriers with GC.

## Ethics Approval

This research is in compliance with ethical standards. The research was approved by the local ethics (IRB) committees of the three participating centers: Sheba Medical Center (434-17 approved 24/7/2017), Rabin Medical Center (0161-17 approved 3/5/2017) and Hadassah Medical Center (0346-12 approved April 2013). A waver was given for informed consent since the study is a retrospective, medical file-based research.

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## Disclosure

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