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Hyperthermic intraperitoneal chemotherapy (HIPEC) after primary debulking surgery in advanced epithelial ovarian cancer: Is BRCA mutational status making the difference?

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ABSTRACT

Introduction: The role of a molecular pattern predictive of hyperthermic intraperitoneal chemotherapy (HIPEC) efficacy in advanced ovarian cancer (AOC) patients has been poorly investigated. We aimed to assess the effect of HIPEC after primary debulking surgery (PDS) in AOC according to patient's Breast Cancer Gene (BRCA) mutational status.

Methods: This is a retrospective, single center, case-control study. Data on AOC patients receiving HIPEC at the end of PDS as previously enrolled in a phase II monocentric trial (HIPEC group), were retrieved and matched for clinical and surgical characteristics with a group of cases who underwent PDS without receiving HIPEC between 01/2010 and 01/2015 (No HIPEC group). Patients with International Federation of Gynecology and Obstetrics (FIGO) stage ≥IIIB disease, aged between 18 and 70 years, with a laparoscopic Predictive Index value (PIV) ≤8 and residual disease ≤2.5 mm were included.

Results: 70 patients were included. With the except of age ($p = 0.012$), the populations were balanced for the main characteristics. At a median follow-up of 48 months, no differences in Progression Free Survival (PFS) ($p = 0.968$) and Overall Survival (OS) ($p = 0.789$) were recorded. Survival analysis according to HIPEC administration and BRCA mutational status showed an improved PFS ($p = 0.011$) and OS ($p = 0.003$) in BRCA mutated compared to wild-type patients when HIPEC was not administered, whilst they were superimposable in case of HIPEC administration ($p = 0.857$ vs $p = 0.372$; respectively). No differences in terms of neither intra-operative ($p = 1.0$) nor early post-operative complications ($p = 0.920$) were detected.

Conclusions: Our results show that HIPEC in AOC may be a promising treatment in BRCA wild-type patients, as it seems to balance their decreased chemosensitivity compared to mutation carriers.

1. Introduction

Ovarian cancer accounts to nearly 4% of new cancer diagnosis worldwide and is the most lethal among all gynecological malignancies, being the overall survival (OS) rate between 30 and 40% across the globe [1]. Cytoreduction to no gross residual disease (NGR) either in the upfront or interval setting in combination with platinum-taxane based chemotherapy represent the gold standard of treatment in case of advanced stage disease [2]. In the last few years, the use of hyperthermic intraperitoneal chemotherapy (HIPEC) as an additional treatment in advanced ovarian cancer (AOC) patients has progressively gained more interest, as it appears to be an attractive way to target microscopic peritoneal tumor deposits at the end of cytoreductive surgery [3]. In addition to that, hyperthermia appears to increase the sensitivity of tumor cells to platinum agents [4].

Recently, this therapeutic tool has been demonstrated to be an effective treatment strategy in improving ovarian cancer patient survival in the Interval Debulking Surgery (IDS) setting [5] without

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increasing *peri* and post-operative morbidity [6], whilst in other scenarios its efficacy has yet to be demonstrated with high quality data.

In the personalized medicine era where precision and translational medicine are in continuous development in order to tailor cancer treatment according to patient's and disease's characteristics [7], the role of a specific genetic pattern which may be predictive of HIPEC efficacy [8] is still quite poorly investigated with heterogeneous and controversial data [9,10].

For this reason, with this study we aimed to retrospectively investigate the effect of HIPEC after primary debulking surgery (PDS) in AOC in relation to patient's Breast Cancer Gene (BRCA) mutational status.

2. Materials and methods

This a retrospective, single center, case-control study. After obtaining Institutional Review Board (IRB) approval (Number DIPUSVSP-27–07–20,111, date 27/07/2020) we retrospectively retrieved data on AOC patients previously enrolled (between February 2015 and February 2016) in a phase II monocentric open label non-randomized trial published by our institution in 2018 [11]. The aim of the above-mentioned study was to explore the feasibility and efficacy of HIPEC together with PDS followed by first line therapy with Bevacizumab, as per trial design. This prospective trial included patient's aged ≥18 but < 70-year-old, deemed completely resectable at time of PDS according to a laparoscopic score ≤ 8[12], with an Eastern Cooperative Oncology Group (ECOG) performance status [13] <2, International Federation of Gynecology and Obstetrics (FIGO) stage ≥ to IIIB [14], cytoreduction to at least ≤ 2.5 mm disease achieved at the end of surgery, normal cardiac, hepatic, respiratory and bone marrow functions.

In the present study, patients who took part at the randomized trial and therefore received HIPEC after PDS were classified as "HIPEC group". Of note, BRCA mutational status was unknown in 5 cases participating to the prospective trial [11], therefore those patients were excluded from the present analysis.

For comparative purposes, data on women in the HIPEC group were matched for clinical characteristics with another group of consecutive cases who underwent PDS in our institution without receiving HIPEC between January 2010 and January 2015. Patients who did not receive HIPEC were named as "No HIPEC group".

Clinico-pathological data including BRCA mutational status, as well as number of cycles and adjuvant chemotherapy regimen +/- Bevacizumab administration were retrieved from institutional electronic database (RedCap® - Research Electronic Data Capture) for every case.

All operations were performed by a dedicated gynecologic oncology surgical team with the primary intent of achieving no gross residual disease (NGR).

As per our institution policy, every attempt of cytoreduction was preceded by a diagnostic laparoscopy to assess the intra-abdominal tumor load. Decision to go ahead with primary debulking surgery was therefore made in relation to intraoperative Predictive Index Value (PIV) according to Fagotti et al. [12].

In the HIPEC group, straight after completion of cytoreduction, intra-abdominal drains were positioned in the four abdominal quadrants. HIPEC perfusion was performed with closed technique with cisplatin 75 mg/m2 at the temperature of 41.5 C for 60 min.

Histological diagnosis was performed by dedicated gynecological oncology pathologists in every case.

For patients operated before 2014, stage and architectural grade were reclassified according to the 2014 FIGO classification [14].

Intraoperative complications were classified according to Common Terminology Criteria for Adverse Events (CTCAE) scale [15], where present.

Type and grade of early postoperative complications (within 30 days from surgery) were collected and classified according to Memorial Sloan Kettering Cancer Center (MSKCC) grading system [16] for all patients.

Progression free survival (PFS) was calculated from the date of surgery to date of first recurrence diagnosis, death or last follow up (FUP).

OS was calculated from the date of surgery to the last FUP or death.

2.1. Statistical analysis

Statistical analysis was performed using R-Studio 0.98.1091 software. Standard descriptive statistics were used to evaluate the distribution of factors and chi-square test or Fisher's exact test or Mann-Whitney U test were used to compare differences in their distribution between No HIPEC and HIPEC cases.

A propensity score-matching analysis was used to simulate the effect of randomization between groups. A 1:1 nearest-neighbor method was used to match No HIPEC patients versus HIPEC patients.

Clinical outcomes included OS and PFS. We employed Kaplan-Meier analyses to assess OS and PFS and the log-rank test to compare survival curves. All p-values < 0.05 were considered significant.

3. Results

Overall, 70 patients were included in the case-matched analysis. Among them, 35 (50%) underwent PDS plus HIPEC as part of the prospective protocol (HIPEC group) and were compared to an equal group of women who were submitted to surgery only (no HIPEC group). With the except of age, no significant differences in preoperative patient's and postoperative disease's characteristics were found between the two groups (Table 1). Indeed, women receiving HIPEC had a median age of one year older than patients not having HIPEC.

Overall, in our series, most of the patients presented with good performance status, being the ECOG=0 [13] in the vast majority of the cases (91.4%) and with advanced stage disease.

Regarding surgical characteristics, complete cytoreduction was achieved in most of the cases (90%) with a median PIV [12] of 4 among all population. In the no HIPEC group, 4 (11.4%) patients had an intraoperative PIV [12] score = 10. Indeed, 3 (8.6%) patients appeared to have miliary disease on small bowel loops and mesentery whilst in 1

Table 1
Patient's and disease's characteristics.

Characteristics	All	No HIPEC *	HIPEC*	p-value
# cases	70 (100)	35 (100)	35 (100)	
Age, years median (min-max)	51 (26–77)	50 (26–77)	51 (32–70)	0.012
BMI**, kg/mq median (min-max)	23 (17–37)	22 (17–37)	23 (18–23)	0.303
ECOG [13]				1
0	64 (91.4)	32 (91.4)	32 (91.4)	
1	6 (8.6)	3 (8.6)	3 (8.6)	
FIGO stage [14]				0.828
IIIA2	1 (1.4)	1 (2.9)	0 (0)	
IIIB	6 (8.6)	2 (5.7)	4 (11.4)	
IIIC	54 (77.1)	27 (77.2)	27 (77.2)	
IV	9 (12.9)	5 (14.2)	4 (11.4)	
LPS PI [12]	4 (0–10)	4 (0–10)	4 (0–8)	0.689
Residual tumor				0.106
No gross	63 (90)	29 (82.9)	34 (97.1)	
< 2.5 mm	7 (10)	6 (17.1)	1 (2.9)	
Mutational status				0.874
wild type	38 (54.3)	18 (51.4)	20 (57.1)	
BRCA1	27 (38.6)	14 (40.0)	13 (37.2)	
BRCA2	5 (7.1)	3 (8.6)	2 (5.7)	
# chemotherapy cycles, median (min-max)	6 (4–6)	6 (4–6)	6 (5–6)	1
Becavizumab	50 (71.4)	21 (60.0)	29 (82.9)	0.063
Bevacizumab maintenance	46 (65.7)	18 (51.4)	28 (80.0)	0.022
# cycles, median (min-max)	16 (4–22)	18 (6–22)	16 (4–22)	0.589

* Hyperthermic intraperitoneal chemotherapy;
** Body mass index.

(2.8%) case the gall bladder was involved with carcinosis. Despite disease distribution, NGR was achieved in 2 cases while < 2.5 mm of residual tumor was left in the remaining 2 patients.

Most of the included patients were found not to have BRCA mutation in their genetic pattern (54.3%) whilst among women carrying BRCA mutation, BRCA 1 mutation was the most frequently detected (38.6%).

Eventually, no differences neither in terms of number of adjuvant chemotherapy cycles nor Bevacizumab addiction were found between the two groups ($p = 1$ vs $p = 0.063$, respectively).

Table 2 describes intraoperative and early postoperative complication rate between the analyzed populations. Indeed, no significant differences were detected between the two populations neither in terms of intraoperative ($p = 1.0$), nor regarding early postoperative complications ($p = 0.920$).

Among patients who experienced severe (G3-G4) early postoperative complications, 4 and 1 patients belonged to the HIPEC and no HIPEC group, respectively. Specifically, in the HIPEC group 1 pleural effusions, 1 pelvic collection, 1 pneumothorax all requiring drainage and 1 anastomotic leak surgically treated were recorded. In the no HIPEC group, 1 patient suffered from a postoperative sepsis due to a pelvic collection.

At a median FUP time of 48 months (range, 15–143), 61 (87.1%) patients recurred and 32 (45.7%) died in the whole population. No differences in terms of both PFS ($p = 0.968$) and OS ($p = 0.789$) were recorded between the two groups. The 5-year PFS was 21.2% (95%CI 0.093–0.364) in the no-HIPEC group and 12.0% (95% CI 0.038–0.252) in the HIPEC group, with a median PFS of 22.2 months (95% confidence level (CL) 17.4–26.3) and 26.7 months (95% CL 21.5–32.8), respectively. The 5-year OS was 65.9% (95% CI 0.468–0.796) in the no-HIPEC group and 58.9% (95% CI 0.407–0.733) in the HIPEC group (Fig 1).

Subgroup analysis of population survival in relation to HIPEC administration and BRCA mutational status is depicted in Fig. 2. Our results showed a significant difference in both PFS ($p = 0.041$) and OS ($p = 0.021$) in favor of BRCA mutated patients. Specifically, a significant survival improvement in both PFS and OS was detected in BRCA mutated compared to BRCA wild-type patients when HIPEC was not administered ($p = 0.011$ vs $p = 0.003$; respectively) whilst they appeared to be superimposable in case of HIPEC administration ($p = 0.857$ vs $p = 0.372$; respectively) (Fig 2). Median PFS of patients non receiving HIPEC was 19.4 months (95% CL 13.6–22.5 in BRCA wild-type and 38.0 months (95% CL 17.1–70.8) in BRCA mutated patients whilst median PFS of women submitted to HIPEC treatment was 26.6 months (95% CL 14.6–32.8) in BRCA wild-type and 26.7 months (95% CL 15.8–35.3) in BRCA-mutated patients, respectively. Median OS was reached only in the No HIPEC BRCA wild-type subset of patients (62 months, 95%CL 39.9–85.9).

Table 2
Intraoperative and early post-operative complications.

	All (n= 70)	No HIPEC* (n= 35)	HIPEC* (n= 35)	p-value
Intra-operative complications[15]				1
No	53 (75.7)	26 (74.2)	27 (77.2)	
Yes	16 (22.6)	8 (22.8)	8 (22.8)	
Early post-operative complications [16]				0.920
No	53 (75.7)	28 (80.0)	25 (71.4)	
G1	2 (2.9)	2 (5.7)	0 (0)	
G2	4 (5.7)	3 (8.6)	6 (17.1)	
G3	8 (11.4)	1 (2.9)	3 (8.6)	
G4	2 (2.9)	0 (0)	1 (2.9)	

* Hyperthermic intraperitoneal chemotherapy.

4. Discussion

In the last few decades, the interest in HIPEC and AOC is gaining more and more attention due to the increasing amount of evidence demonstrating a survival advantage of patients receiving HIPEC in selected treatment settings [5], without compromising morbidity and recovery after surgery [5,6].

In our experience, BRCA mutated patients appear to have a longer survival compared to BRCA wild-type patients when HIPEC is not administered but, interestingly, this prognostic difference disappears in case of treatment with HIPEC at time of PDS in the same subgroup of patients. Alongside with that, we did not demonstrate an overall survival improvement of women receiving HIPEC at the time of primary surgery regardless their mutational status.

Nowadays, the more favorable outcome of ovarian cancer patients carrying BRCA mutation compared to non-carriers is well-known and has been demonstrated with high quality data [17], as BRCA mutated women seem to present a superior response to platinum-based chemotherapy. In fact, a large-pooled analysis of data from 26 observational studies including approximately 3800 AOC patients, showed that having a germline mutation of BRCA1 or BRCA2 genes was associated with improved 5-year overall survival with respect to non-mutated cases (36% for noncarriers, 44% for BRCA1 carriers, and 52% for BRCA2 carriers) [18].

Moreover, it is now worldwide accepted that the use of poly(ADP-ribose) polymerase (PARP) inhibitors in BRCA mutated patients is able to further provide significant survival advantage both as a maintenance therapy in relapsed OC and as first line treatment after adjuvant chemotherapy [19,20].

Analyzing the available evidence, we can speculate that in a subgroup of patients who, due to their genetic features, are supposed to be more sensitive to platinum agents the benefit of a loco-regional platinum-based treatment (HIPEC) should be even greater.

Interestingly, this aspect has been so far poorly investigated in gynecologic oncology literature with heterogenous studies and controversial results. One of the largest series published in 2014 by Safra et al. [21], aimed to retrospectively assess survival of 27 patients with recurrent ovarian cancer (ROC) receiving cytoreduction plus HIPEC, comparing them to 84 ROC patients receiving second line chemotherapy only. Indeed, a more than doubled PFS (15 months vs 6 months, $p < 0.001$) and significantly increased OS (79% vs. 45%, $p= 0.016$) was demonstrated in the surgery plus HIPEC with respect to the chemotherapy group, which appeared to be more evident in BRCA mutation carriers compared to non-carriers (20.9 vs. 12.6 months, $p = 0.048$).

Despite its promising results, in our opinion the main limitation of this study lies in its population diversity (both first and second recurrences were included) and mostly in the fact that in view of the recent DESKTOP III trial [22] results, it may be nowadays considered inappropriate gaining information on survival outcomes of ROC who did receive surgery compared to with ROC patients treated with chemotherapy only.

Alongside with that, data coming from a recent restrospective study comparing HIPEC, dose-dense (DD) and intraperitoneal (IP) chemotherapy [23] showed a PFS gain in patients treated with HIPEC (34.9 months) and IP (34.0 months) chemotherapy , compared to the DD chemotherapy group (27.6 months) ($p= 0.005$). Interestingly, a positive correlation of BRCA mutational status and OS was detected at multivariate analysis ($p < 0.0001$), despite data did not show a significant difference in OS among the three groups ($p = 0.136$).

In contrast with the results provided by the above mentioned studies [21,23], we did not find a survival difference in relation to HIPEC administration in the whole population neither in terms of PFS nor OS ($p = 0.968$ vs $p = 0.789$; respectively) (Fig. 1). However, if we do separate our patients into subgroups according to their BRCA mutational status, it seems that HIPEC treatment itself may play a role in balancing the chemosensitivity of two populations who have an intrinsic different

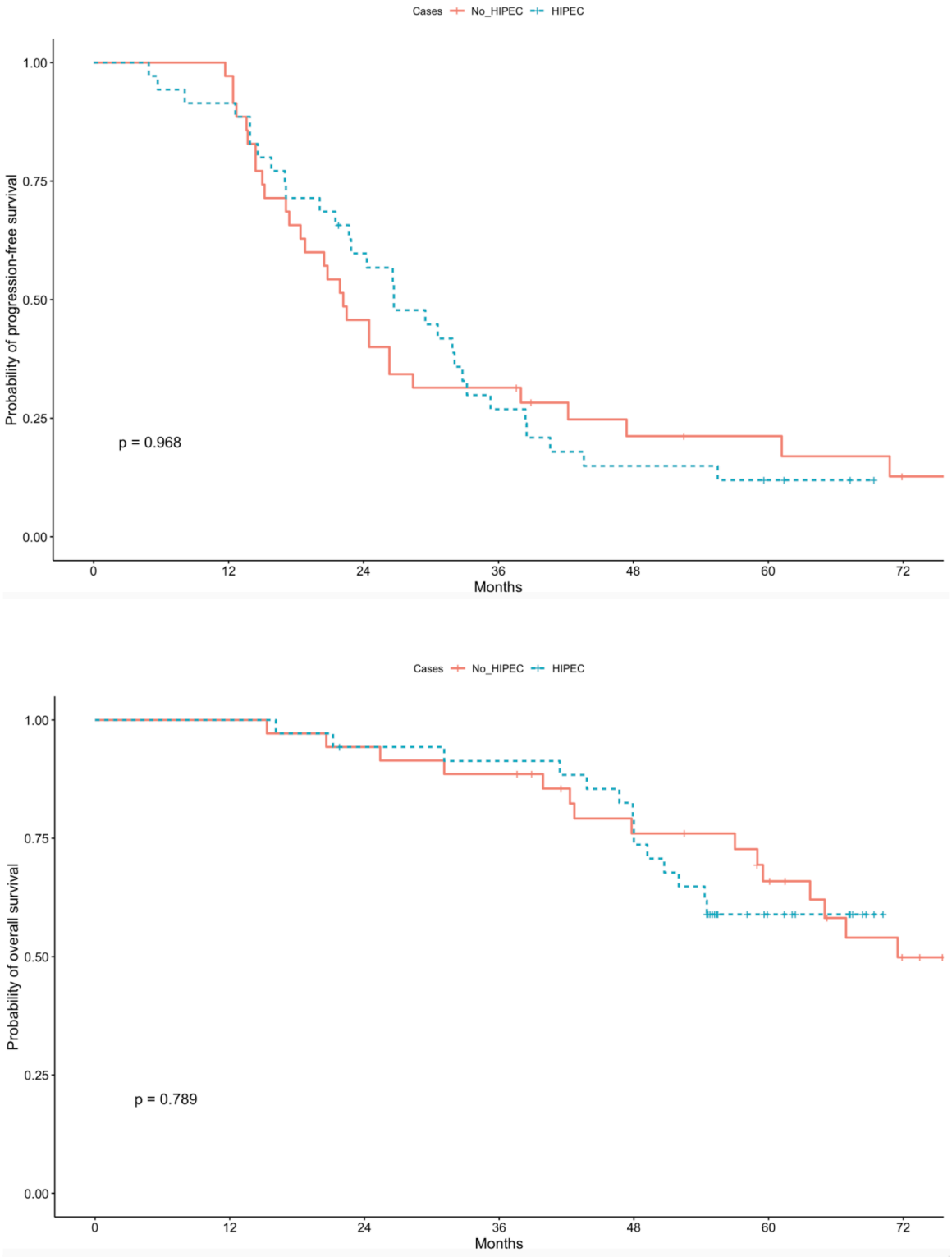

Fig. 1. Survival analysis of the entire population.

response to platinum agents and subsequently different survival outcomes, which is in line with available literature data [18].

We can therefore speculate that the subset of patients who may benefit the most from HIPEC administration are women not carrying BRCA mutation. In fact, the addition of HIPEC seems to make their prognosis superimposable to the already more favorable one of mutated patients, thus balancing the prognostic difference created by BRCA mutational status itself, without increasing intraoperative and postoperative morbidity rate ($p = 1.0$ vs $p = 0.920$; respectively).

The main limitations of our study are the retrospective nature of no-HIPEC group data collection and the small sample size, as per the intrinsic nature of the examined treatment which so far is not open to a large number of patients. In addition, despite cases were matched on several variables, the presence of selection bias cannot be excluded. On the other hand, some important elements are conferring strength to the results of our study. Indeed, the main features of the analyzed

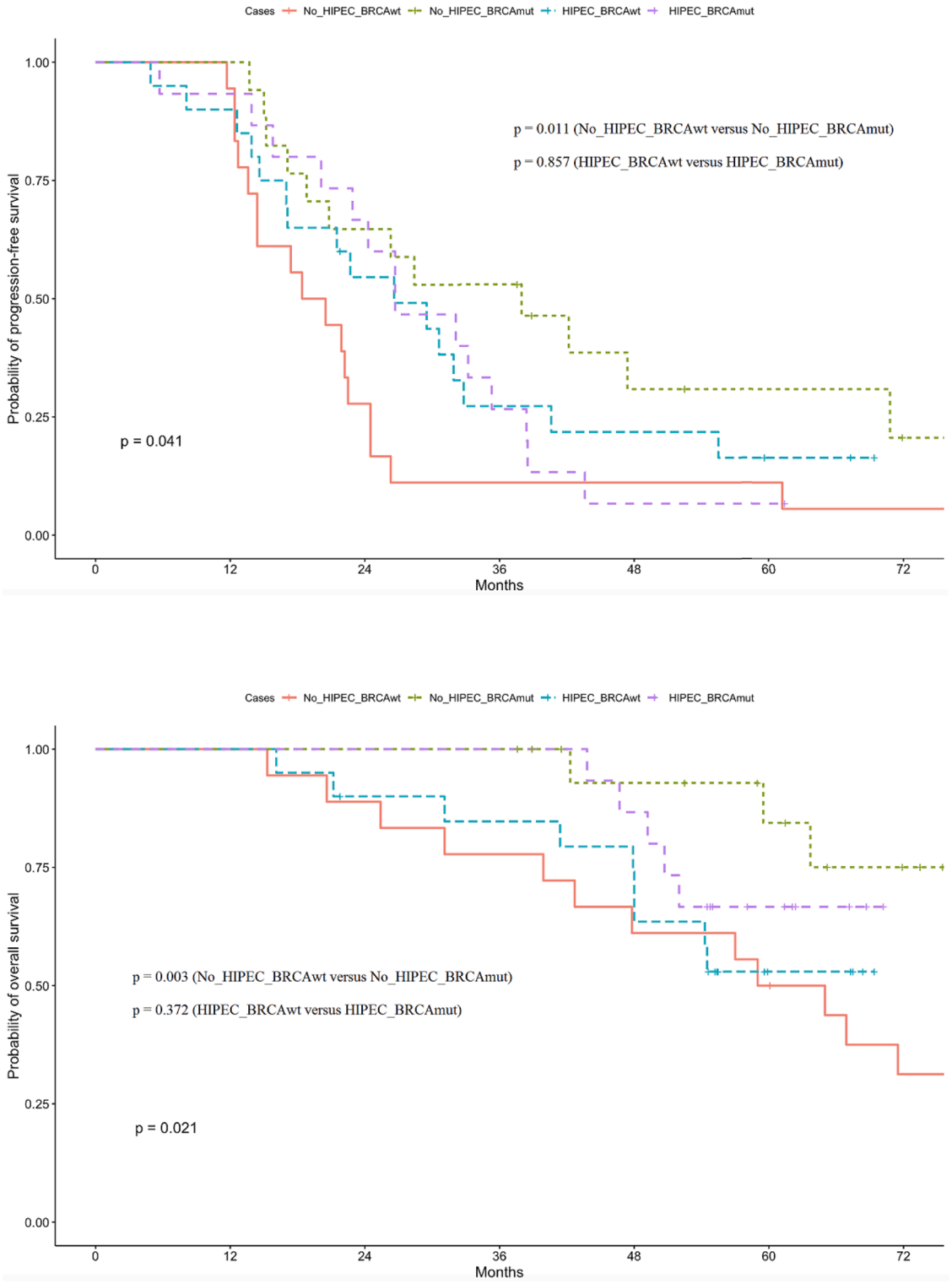

Fig. 2. Survival analysis in relation to HIPEC and BRCA mutational status.

population appear to be homogeneous (only primary diagnosis cases were included). Also, all patients have been treated in the same referral center by the same qualified surgical team with a uniform selection method to perform PDS. Eventually, the feasibility and safety of HIPEC in the examined group of patients have been previously demonstrated by our institution [11].

5. Conclusion

In conclusion, data on efficacy of HIPEC in relation to BRCA mutational status in AOC are overall lacking and requiring further development. Our results show that HIPEC in AOC may be a promising treatment especially for BRCA non-mutated patients, as it seems to minimize the effect of their less favorable prognosis with respect to BRCA mutation carriers. Prospective results of on the efficacy of HIPEC

after PDS and high-quality data regarding patient's survival in relation to their mutational status are awaited to keep working on personalized treatment strategies.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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CRediT authorship contribution statement

Valentina Ghirardi: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Francesca De Felice:** Formal analysis, Writing – review & editing. **Marco D'Indinosante:** Data curation, Writing – review & editing. **Federica Bernardini:** Data curation, Writing – review & editing. **Maria Teresa Giudice:** Data curation, Writing – review & editing. **Anna Fagotti:** Methodology, Supervision, Writing – original draft, Writing – review & editing. **Giovanni Scambia:** Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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