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RECIST 1.1 criteria predict recurrence-free survival in advanced ovarian cancer submitted to neoadjuvant chemotherapy

Giorgio Bogani[a], Laura Matteucci[b], Stefano Tamberi[b], Antonino Ditto[a], Ilaria Sabatucci[a], Ferdinando Murgia[a,*], Valentina Arcangeli[c], Giuseppa Maltese[a], Giuseppe Comerci[d], Marco Stefanetti[e], Cristina Sonetto[a], Giuseppina Calareso[f], Alfonso Marchiano[f], Valentina Chiappa[a], Domenica Lorusso[a], Francesco Raspagliesi[a]

[a] Gynecologic Oncology, IRCCS National Cancer Institute, Milan, Italy
[b] Medical Oncology, Ospedale degli Infermi, Faenza, Italy
[c] Medical Oncology, Ospedale Infermi, Rimini, Italy
[d] Obstetrics and Gynecology, Ospedale S. Maria delle Croci, Ravenna, Italy
[e] Obstetrics and Gynecology, Ospedale Infermi, Rimini, Italy
[f] Department of Radiology, IRCCS National Cancer Institute, Milan, Italy

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ABSTRACT

Objective: Neoadjuvant chemotherapy plus interval debulking surgery is growing treatment strategy for advanced ovarian cancer patients with unresectable disease. Here, we aimed to assess predictors of surgical unresectability and survival of patients submitted to neoadjuvant chemotherapy plus interval debulking surgery.

Methods: Data of consecutive 193 patients undergoing neoadjuvant chemotherapy plus interval debulking surgery were retrospectively evaluated in four Italian oncologic centers. RECIST 1.1 guidelines were used to assess response to neoadjuvant chemotherapy. Survival outcomes were evaluated using Kaplan-Meier and Cox proportional hazard models.

Results: Overall, 155 (80.3%) and 38 (19.7%) patients had optimal and non-optimal cytoreduction at the time of interval debulking surgery. Via multivariate analysis, age (OR: 2.87 (95%CI: 1.29, 6.36) per 10-year increase) and radiological response to neoadjuvant chemotherapy (OR: 48.1 (95%CI: 6.33, 365.3)) impact on the inability to perform a complete cytoreduction. Patients having complete or partial response experienced a significant better disease-free survival than patients having stable or progressive disease at radiological examination (median disease-free survival 16.8 vs. 11.0 months; HR: 0.42 (95%CI: 0.09, 0.78); p = .001). Radiological response did not predict for overall survival (p = .719).

Conclusions: RECIST1.1 response criteria might be helpful to predict surgical resectability and disease-free survival of advanced stage ovarian cancer patients undergoing neoadjuvant chemotherapy plus interval debulking surgery.

Introduction

Ovarian cancer is one the most common gynecological malignancies in developed countries. In 2019, an estimated 22,500 new cases of ovarian cancer will be diagnosed in the United States and 13,900 women will die from the disease [1]. Primary debulking surgery followed by platinum-based adjuvant chemotherapy represents the mainstay of treatment for women affected by advanced stage (IIIC and IV) ovarian cancer [2]. The goal of primary debulking surgery should be to achieve complete tumor resection with no macroscopic residual disease. In fact, a robust evidence suggested that residual disease at primary debulking surgery is one the most important modifiable factors influencing survival outcomes [2,3]. However, growing evidence supports that neoadjuvant chemotherapy followed by interval debulking surgery could be an alternative treatment modality for unresectable disease or for patients' who could poorly tolerate potential surgery-related morbidity [4–6]. The aim of surgical procedure even at interval debulking surgery is to remove all gross abdominal disease [2,3]. Ideally, patients undergoing interval debulking surgery are more likely to have complete cytoreduction, with no residual disease, at the end of the procedure [5–7]. Compared to

* Corresponding author.
E-mail address: ferdinando.murgia@istitutotumori.mi.it (F. Murgia).

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primary debulking surgery, interval debulking surgery is related to lower surgical complexity and lower postoperative morbidity [7]. However, although interval debulking surgery is generally less technically demanding than primary surgery, there are some cases in which optimal (residual disease < 1 cm) and complete (no macroscopic residual disease) cytoreduction is not achieved [4–6]. Therefore, these patients not only gain no benefit from surgery, but also are at risk of developing surgery-related morbidity. In the present study we sought to identify predictors of surgical unresectability of patients submitted to neoadjuvant chemotherapy plus interval debulking surgery. As secondary endpoint we aimed to evaluate outcomes of ovarian cancer patients having not optimal cytoreduction at the time of interval debulking surgery.

Materials and methods

Data of consecutive patients with newly diagnosed invasive epithelial ovarian, primary peritoneal and Fallopian tube cancer undergoing neoadjuvant chemotherapy plus interval debulking surgery, in four Italian referral centers between 2000 and 2015, were prospectively collected. The Institutional Review Board (IRB) of all included centers approved this study. All the patients signed written consent for data collection for research purpose. Patients who did not consent to use their clinical information for research purposes were excluded. The computerized surgical database, containing data on every surgical procedure performed for patients enrolled into the study is of research quality and has been updated by trained residents and nurses. Individual records were screened in order to identify baseline patients' and diseases' characteristics. Staging system and architectural grade were reported in accord to the International Federation of Obstetrics and Gynecologists (FIGO) statements released in 2009 [8]. The World Health Organization (WHO) taxonomy was used in order to classify histological subtypes [8]. The database was retrospectively queried in order to identify the amount of residual disease at the time of interval debulking surgery.

Inclusion criteria were: (1) histologically-proven invasive epithelial ovarian, primary peritoneal and Fallopian tube cancer; (2) presence of gross unresectable intra-abdominal disease (FIGO stage IIIC-IV) at primary surgical exploration; (3) treatment with neoadjuvant chemotherapy plus interval debulking surgery. Exclusion criteria were: (1) consent withdrawn; (2) final diagnosis of borderline ovarian tumor; (3) recurrent disease (4) presence of synchronous solid cancer (within 5 years); (5) performance status not allowing surgical treatment (execution of exclusive chemotherapy). Primary endpoint measure was to evaluate predictors of unsuccessful surgical attempt at interval debulking surgery. As secondary endpoint measure we aimed to report survival outcomes of patients having non-optimal cytoreductive procedures.

In all four included centers, primary debulking surgery followed by adjuvant therapy was the standard of care, over the whole study period while, the choice to have neoadjuvant chemotherapy plus interval debulking surgery was reserved to patients with FIGO stage IIIC-IV unresectable disease or for patients judged to be unfit to have PDS. Preoperative medical evaluations were performed according to the American Society of Anesthesiologists (ASA) score and the Eastern Cooperative Oncology Group (ECOG) scale of performance status [9]. Medical comorbidities were recorded as well and graded per the Charlson comorbidity index [10].

Data regarding neoadjuvant chemotherapy regimens are reported elsewhere [8]. Generally, patients received 3 or 4 cycles of neoadjuvant chemotherapy [8]. Before having interval debulking surgery, patients were evaluated by clinical and radiological examinations. CA125 levels were monitored as well during neoadjuvant chemotherapy administration. Radiological response to neoadjuvant chemotherapy was evaluated retrospectively using the Response Evaluation Criteria In Solid Tumors guideline version 1.1 (RECIST 1.1) [11].

Basically, target lesion response was defined as reported below:

Complete response

Disappearance of all non-nodal target lesions. Additionally, any suspected lymph nodes assigned as target lesions must have a reduction in short axis to <10 mm.

Partial response

At least a 30% decrease in the sum of diameters of all lesions compared to baseline.

Progressive disease

At least 20% increase in the sum of diameters of all measured target lesions, compared to the smallest sum of diameters of all target lesions recorded at or after baseline (the sum must demonstrate an absolute increase > 5 mm)

Stable disease

Neither sufficient shrinkage to quantify for partial response or complete response nor an increase in lesions which would qualify for progressive disease.

Unknown

Lesions have been assessed using a different radiological method than at baseline.

Surgical plan were aimed to remove all macroscopic disease and included the execution of hysterectomy with the removal of adnexal structures, omentectomy, and peritonectomy and visceral resections when involved by the tumor. Generally, primary cytoreductive surgery was aborted in case of extensive involvement of the bowel (conditioning multiple, more than three, bowel resections or more than two/three resection necessary in order to reach complete cytoreductive surgery), extensive involvement/retraction of the mesentery and porta hepatis nodes involvement. Presence of disease located in the upper abdomen, on the celiac trunk as well as the presence of intra-parenchymal (e.g., hepatic) or extra-abdominal disease (stage IV) were not an absolute contraindication to cytoreduction. Generally, systemic retroperitoneal staging was omitted. Resection of bulky nodes was systematically part of cytoreduction procedures; residual disease was classified as: no residual disease (residual disease 0); less than 1 cm (residual disease <1.0 cm) and more than 1 cm (residual disease >1) [2]. These information are reported consistently on the operative notes.

Adjuvant regimen consisted in platinum-based chemotherapy with or without antiangiogenetic agent (i.e., bevacizumab) depending on the study periods. Follow-up evaluations were scheduled every 4 months for the first 2 years after surgery, every 6 months between 2- and 5-year after surgery and annually thereafter. Survival data were extrapolated from a dedicated database prospectively up-dated on a regular basis in each centre. Rigorous efforts, including telephonic interviews, were done to improve quality of follow-up data. Duration of follow-up was counted from date of surgery to date of death or last follow-up.

Statistical analysis

Predicting variables were evaluated for their association with non-optimal cytoreduction based on fitting univariate logistic

regression model. A multivariate model was applied using stepwise and backward selection methods to all variables with a p value <.20. Correlations were estimated using odds ratio (OR) and corresponding 95% confidence intervals (CIs). OR and 95%CI were calculated when appropriate. Length of follow-up was calculated from time of first cycle of neoadjuvant chemotherapy to time of death or last follow-up. Survival outcomes were evaluated with both Kaplan-Meier and Cox models. Disease-free and overall survivals were estimated using the Kaplan-Meier method. Hazard ratio (HR) and 95% CI were calculated for each comparison. Univariate and multivariate analyses were performed when appropriate, using Cox proportional hazard model. All covariates with a p value <.20, based on univariate analyses were included in the multivariate model. All p values were two-sided; p values <.05 were considered statistically significant. Analyses were performed using the Prism Graph Pad (GraphPad Software, San Diego, CA) version 6.0 for Microsoft SPSS (SPSS Statistics. International Business Machines Corporation IBM. 2013. Armonk, USA) version 20.0 for Mac.

Results

Over the study period, 196 consecutive patients affected by advanced stage ovarian cancer had neoadjuvant chemotherapy plus interval debulking surgery due to the presence of unresectable disease. Three patients did not consent to use their clinical information for research purposes and they were excluded, thus leaving 193 patients for the analysis. Mean population age was 57.8 (10.3) years. Overall, 163 (84.5%) and 30 (15.5%) patients were diagnosed with FIGO stage IIIC and IV ovarian cancer. The mean (SD) follow-up for the entire cohort of patients was 37.0 (27.4) months.

Overall, 155 (80.3%) and 38 (19.7%) patients had optimal and non-optimal cytoreduction at the time of interval debulking surgery. Fig. 1 shows the flow of patients thorough the study design. Baseline characteristics of patients achieving optimal and non-optimal cytoreduction are reported in Table 1. As expected patients achieving optimal cytoreduction experienced better disease-free (HR: 0.63 (95%CI: 0.37, 0.88); p = .010) and overall (HR: 0.60 (95%CI: 0.32, 0.94); p = .050) survival outcomes than patients having non-optimal cytoreduction (Fig. 2).

Considering factors predicting non-optimal cytoreduction we observed that, via univariate analysis, radiological response to neoadjuvant (assessed by RECIST1.1 criteria) and time interval (>4 weeks) between the end of neoadjuvant chemotherapy and interval debulking surgery, predicted an ineffective surgical attempt. Additionally, increasing age was slightly associated with non-optimal cytoreduction. Via multivariate analysis, age (OR: 2.87 (95%CI: 1.29, 6.36) per 10-year increase) and radiological response to neoadjuvant chemotherapy (OR: 48.1 (95%CI: 6.33, 365.3)) impact on the inability to perform a complete cytoreduction. Table 2 reports univariate and multivariate analyses.

Fig. 3 displays survival curves on the basis of radiological responses to neoadjuvant chemotherapy. We observed that radiological response to neoadjuvant chemotherapy influence disease-free survival (p = .056). In particular, comparing patients having complete response or partial response to patients having

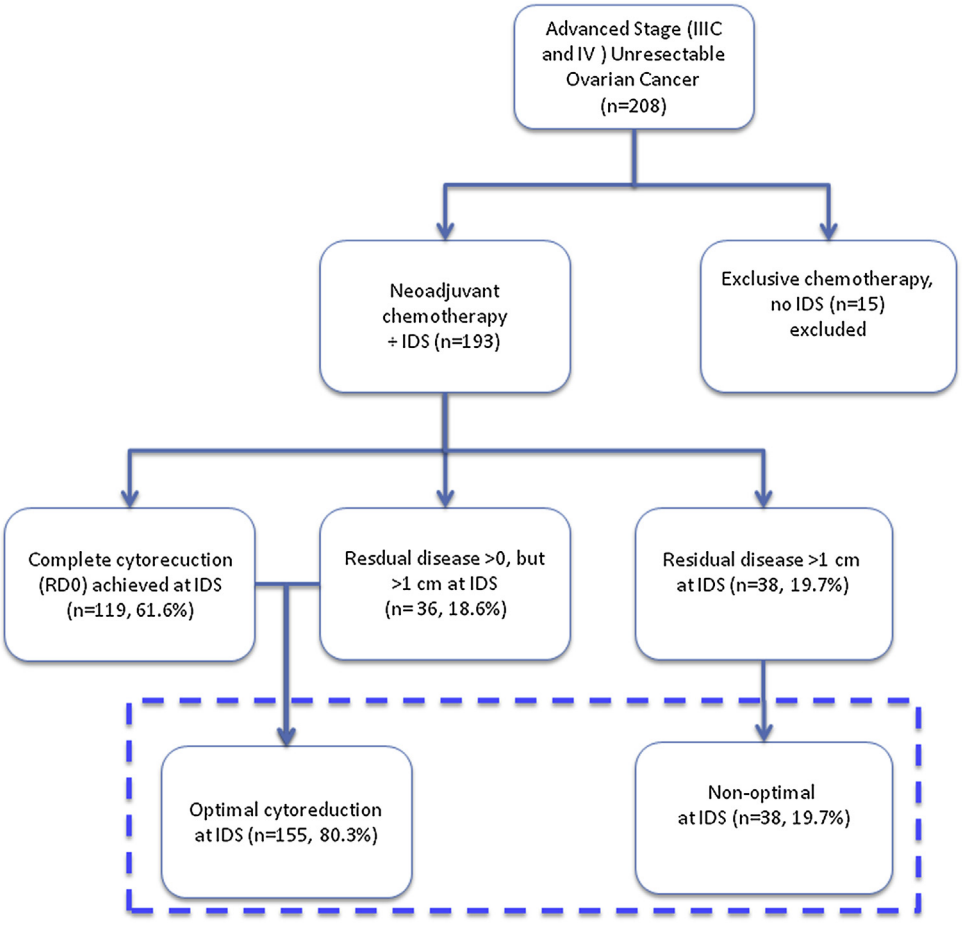

Fig. 1. Study design.

Table 1
Baseline patients characteristics.

Characteristics	Optimal cytoreduction (RD<1 cm) n = 155, 80.3%	Non-optimal cytoreduction (RD>1 cm) n = 38,19.7%	P value
Age, yrs, mean (SD)	57.5 (10.2)	59.9 (10.1)	0.165
BMI, Kg/mq, mean (SD)	24.5 (4.1)	24.9 (4.3)	0.724
FIGO Stage	131 (84.5%)	32 (84.2%)	1.00
IIIC	24 (15.5%)	6 (15.8%)	
IV			
BRCA germline mutation	13 (8.3%)	1 (2.6%)	0.310
CA125 at baseline, median (IQR)	865.0 (275, 1857)	993.0 (336, 2088)	0.65
Histology	128 (82.6%)	30 (78.9%)	0.639
High-grade serous	27 (17.4%)	8 (21.1%)	
Others			
Cycles of NACT, mean (SD)	3.9 (1.1)	4.0 (1.0)	0.342
CA125 levels post NACT, median (IQR)	26.0 (11, 64)	51.5 (28, 122.3)	0.002
Response to NACT (RECIST1.1)	23 (14.9%)	0 (0%)	0.009
Complete response	75 (48.3%)	11 (28.9%)	0.044
Partial response	1 (0.6%)	3 (7.9%)	0.024
Stable disease	2 (1.3%)	2 (5.2%)	0.174
Progressive disease	54 (34.9%)	22 (57.9%)	0.015
Unknown			
Time between last cycle of NACT and IDS, weeks, mean (SD)	4.3 (1.9)	4.4 (2.7)	0.165
Number of cycles following IDS, mean (SD)	2.6 (3.0)	3.8 (1.6)	<0.001
Bevacizumab maintenance	26 (16.7%)	2 (5.2%)	0.076
Follow-up, mo, mean (SD)	37.5 (29.4)	32.7 (26.4)	0.292

Abbreviations: BMIbody mass index; NACT, neoadjuvant chemotherapy; IDS, interval debulking surgery; FIGO, international Federation of Obstetrics and Gynecologists; RECIST 1.1; Response Evaluation Criteria In Solid Tumors guideline version 1.1 (RECIST 1.1) [11], mo, months; yrs, years; SD, standard deviation; IQR, interquartile range.

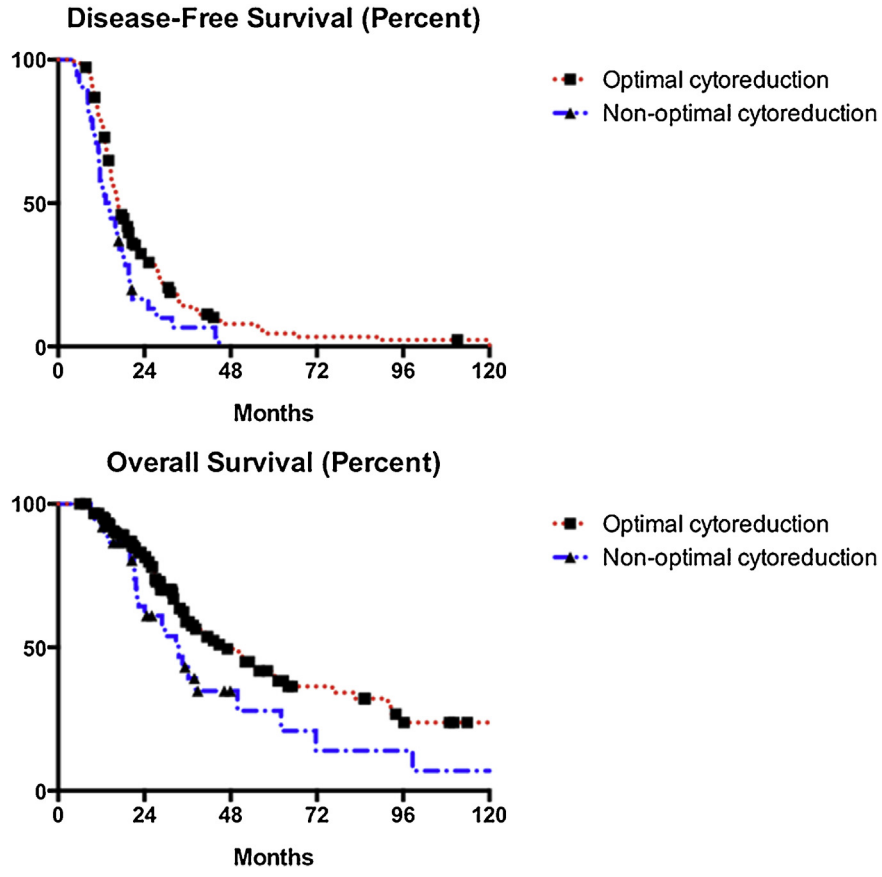

Fig. 2. Survival outcomes on the basis of residual disease.

stable or progressive disease we observed that the former group experienced a significant better disease-free survival than the latter one (median disease-free survival 16.8 vs. 11.0 months; HR: 0.42 (95%CI: 0.09, 0.78); p = .001) While, radiological response to neoadjuvant chemotherapy did not predict for overall survival (p = .719). This is also confirmed when focusing only on the group of patients non achieving optimal cytoreduction (n = 38) in which post-neoadjuvant chemotherapy radiological examination assessed by RECIST 1.1 criteria predicts disease-free survival (Table 3).

Table 2
Factors predicting non-optimal cytoreduction at interval debulking surgery.

Characteristics	Univariate (OR, (95%CI))	P value	Multivariate (OR, (95%CI))	P value
Age, yrs	**1.27 (0.89, 1.82)**	**0.184**	**2.87 (1.29, 6.36)**	**0.009**
BMI, Kg/mq	1.10 (0.65, 1.86)	0.710	–	–
ECOG performance status	Reference	0.306	–	–
0-1	2.11 (0.50, 8.87)			
2-3				
FIGO Stage	Reference	0.934	–	–
IIIC	0.96 (0.36, 2.53)			
IV				
BRCA mutation	Not estimable	0.999	–	–
CA125 at baseline	0.99 (0.98, 1.00)	0.359	–	–
Histology	0.98 (0.41, 2.53)	0.970		
High grade serous vs. others	Not estimable	0.999		
Low grade serous vs. others	1.36 (0.13, 13.4)	0.792		
Endometriod vs. others	1.01 (0.11, 9.33)	0.991		
Undifferentiated vs. others				
Cycles of NACT	1.07 (0.79, 1.46)	0.630	–	–
CA125 levels post NACT	0.99 (0.90, 1.09)	0.956	–	–
Change in CA125 levels	0.99 (0.97, 1.00)	0.353	–	–
Response to NACT (assessed by RECIST 1.1)	**Reference**	**0.001**	**Reference**	**<0.001**
Complete/partial response	**14.8 (3.11, 70.7)**		**48.1 (6.33, 365.3)**	
No response/ progressive disease				
Time between last cycle of NACT and IDS	**Reference**	**0.046**	**Reference**	**0.103**
<4 weeks	**0.48 (0.23, 0.98)**		**0.32 (0.85, 1.25)**	
4 weeks or more				

Abbreviations: BMI: body mass index; NACT, neoadjuvant chemotherapy; IDS, interval debulking surgery; ECOG, Eastern Cooperative Oncology Group; FIGO, international Federation of Obstetrics and Gynecologists; RECIST 1.1; Response Evaluation Criteria In Solid Tumors guideline version 1.1 (RECIST 1.1) [11], yrs, years; OR, odds ratio; 95%CI, 95% confidence interval.

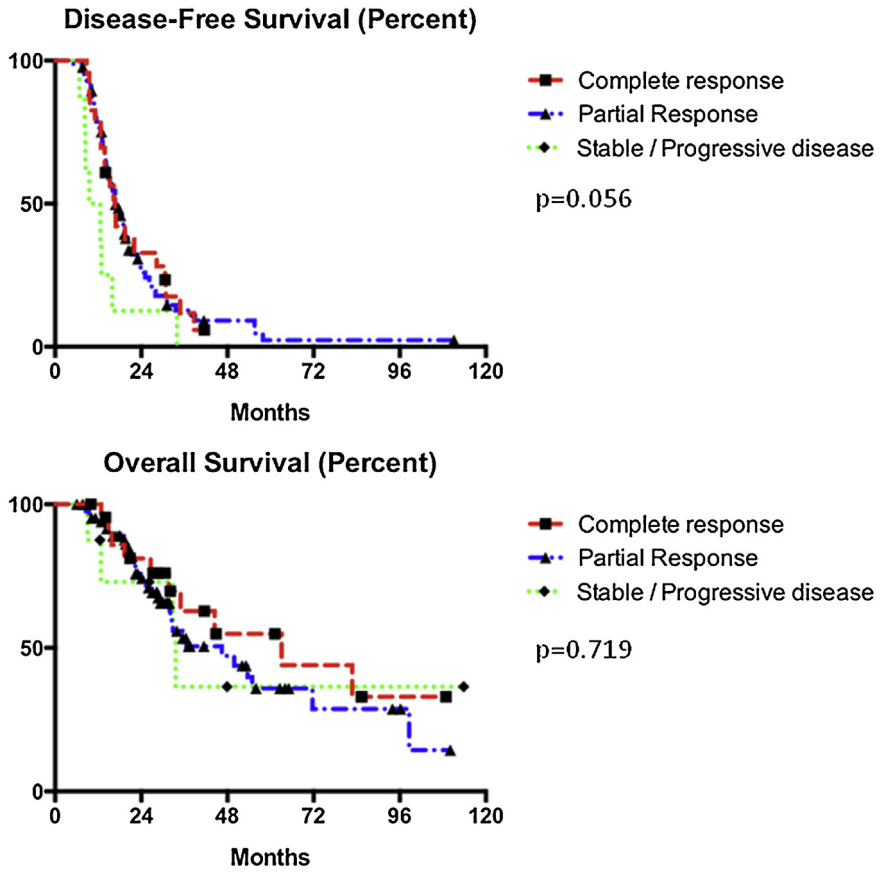

Fig. 3. Survival outcomes on the basis of response assessed by RECIST1.1.

Table 3
Factors predicting disease-free and overall survival for patients having non-optimal cytoreduction at interval debulking surgery.

	Factors predicting for disease-free survival		Factors predicting for overall survival	
Characteristics	(HR, (95%CI))	P value	(HR, (95%CI))	P value
Age, yrs	0.97 (0.69, 1.37)	0.902	0.99 (0.66, 1.49)	0.994
CA125 levels at baseline	0.99 (0.97, 1.01)	0.554	0.98 (0.96, 1.01)	0.240
Histology	1.73 (0.74, 4.06)	0.204	1.72 (0.50, 5.89)	0.385
High grade serous vs. others	Not estimable	0.999	Not estimable	0.999
Low grade serous vs. others	0.34 (0.00, 7.60)	0.221	0.04 (0.00, 317.5)	0.492
Endometriod vs. others	0.74 (0.10, 5.50)	0.772	0.04 (0.00, >999.9)	0.639
Undifferentiated vs. others				
FIGO Stage IV	0.40 (0.13, 1.18)	0.098	0.65 (0.21, 1.98)	0.458
Cycles of NACT	1.02 (0.74, 1.45)	0.894	1.33 (0.92, 1.93)	0.124
No response to NACT at imaging before IDS	**4.15 (1.17, 14.7)**	**0.028**	1.28 (0.35, 4.65)	0.698
CA125 levels after NACT	1.02 (0.81, 1.29)	0.835	0.90 (0.66, 1.31)	0.532
4+ weeks between NACT and IDS	0.52 (0.26, 1.30)	0.062	1.11 (0.95, 1.30)	0.175
Number of cycles of adjuvant chemotherapy post IDS	0.85 (0.66, 1.09)	0.208	1.04 (0.80, 1.36)	0.704
Bevacizumab maintenance	0.04 (0.00, 12.5)	0.278	0.04 (0.00, >999.9)	0.686

Abbreviations: BMI: body mass index; NACT, neoadjuvant chemotherapy; IDS, interval debulking surgery; ECOG, Eastern Cooperative Oncology Group; FIGO, international Federation of Obstetrics and Gynecologists; RECIST 1.1; Response Evaluation Criteria In Solid Tumors guideline version 1.1 (RECIST 1.1) [11], yrs, years; HR, hazard ratio; 95%CI, 95% confidence interval.

Discussion

In the present study we observed that advanced age and radiological response to neoadjuvant chemotherapy assessed by RECIST 1.1 criteria are the main factors predicting for non-optimal cytoreduction. Moreover, we observed that radiological response to neoadjuvant chemotherapy correlates with worse disease-free survival, but it does not impact on overall survival. In the recent years, accumulating evidence support the utilization of neoadjuvant chemotherapy plus interval debulking surgery an alternative treatment modality for patients with advance stage ovarian cancer [5–7]. Moreover, other investigators pointed out that neoadjuvant chemotherapy plus interval debulking surgery correlates with a lower morbidity rate than primary debulking surgery [7]. However, the potential biases related to low optimal cytoreduction rates in the primary surgery group did not allow to draw definitive conclusion on the real value of interval debulking surgery, thus primary debulking surgery should be considered the standard of care. The Trial on Radical Upfront Surgery in Advanced Ovarian Cancer (TRUST) will be clarify the role of IDS for advanced ovarian cancer [12]

However, the prevalence of neoadjuvant chemotherapy plus interval debulking surgery utilization is increasing worldwide [13]. A recent published study, using the National Cancer Database (NCDB), on 62,727 ovarian cancer patients evaluated different pattern of care (primary debulking surgery vs. interval debulking surgery). They observed that variables associated with increased likelihood of neoadjuvant chemotherapy use are: (i) age older than 50 years, (ii) severe comorbidities, (iii) FIGO stage IV disease, and (iv) high-grade ovarian cancer. Several predictors of response to neoadjuvant chemotherapy are still under investigation [14–17]. In the present paper, we evaluated factors predicting for an ineffective surgical attempts and factors influencing survival in patients receiving neoadjuvant chemotherapy followed by interval debulking surgery. Interestingly, we observed that radiological response by RECIST 1.1 criteria had an important role in predicting both surgical resectability and disease-free survival. patients undergoing interval debulking surgery. Other investigators evaluated the impact of radiological examination in predict response to neoadjuvant chemotherapy [14]. Vallius T et al., observed that ^{18}F-FDG-PET/CT was able to identify patients who would not respond to neoadjuvant chemotherapy [14]. Vallius et al., observed that change in median omental SUV max during neoadjuvant chemotherapy is associate with histopathological response to neoadjuvant chemotherapy. A SUV max decrease of less than 57% identified histopathological non-responders [14]. Other investigators suggested that CA125 and HE4 levels ranging might predict to complete cytoreduction at the time of interval debulking surgery [15–17]. In our study patients not achieving optimal cytoreduction had a slight, non significantly higher CA125 levels than patients achieving optimal cytoreduction but it did not impact surgical and oncologic outcomes (Table 1). Several features might be related to these discordant results, including: (i) surgical aggressiveness; (ii) patients selection to have interval debulking surgery instead of primary debulking surgery; (iii) different therapeutic strategies (including number of neoadjuvant chemotherapy cycles). Another group investigated the role of laparoscopy in evaluating surgical outcome after neoadjuvant chemotherapy with interesting results but, although minimally invasive, laparoscopy remains a surgical procedures requiring general anesthesia and not a preoperative evaluable tool and moreover no impact on prognosis has been reported for the laparoscopic respectability score [7].

Our results might have several implications in clinical practice: (i) The application of RECIST1.1 criteria would be useful in provide an accurate counselling for patients undergoing surgery. (ii) In our clinical practice IDS is performed via open surgery; while patients with poor radiological response might benefit from a primary evaluation of abdominal disease via minimally invasive surgery, thus reducing morbidity and length of hospital stay of ineffective laparotomies. (iii) In our research, response to RECIST1.1 criteria and older age were the only factor predicting response in ovarian cancer patients having neoadjuvant chemotherapy.

Additionally, other four points of the present paper deserve to be addressed: (i) since this is a retrospective analysis, it is possible that several confounding factors might influence the interpretation of our results. In fact, the retrospective evaluation of CT scan and the application of RECIST1.1 criteria did not provide a fair evaluation of response to treatments; (ii) according to the strict rules of RECIST1.1 criteria, several patients were classified with “unknown response”; these rules reduced the sample size and then the power of the study; but they provided a clear value of the type of response achieved, thus improving the value of our results; (iii) a team of expert gynecologic oncologists surgeons performed all operation, thus our results are not fully projectable in a setting lacking for surgical and oncologic skills. (iv) in our study RECIST1.1 criteria predicted disease-free but not overall survival. In fact, recent data underlined that no single variable is able to impact on overall survival of ovarian cancer patients [18]. As aforementioned, the inherent bias of the retrospective study design is the main

limitation of the present study. A prospective studies is needed to confirm our results. Moreover, the our study have a very broad time-frame. Obviously surgeons change, techniques evolve, and other confounders in this retrospective cohort might influence the interpretation of our findings. While, the large sample size and the multi-institutional study design are the main strengths of our investigation.

In conclusion our study investigated factors predicting for an ineffective surgical attempts in patients with advanced stage ovarian cancer undergoing neoadjuvant chemotherapy plus interval debulking surgery. At present interval debulking surgery should not be denied in patients having poor response to neoadjuvant chemotherapy at radiological examination but the application of RECIST1.1 criteria is helpful in predicting response to neoadjuvant chemotherapy, surgical results and disease-free survival. Further study are warranted in order to identify predictors of response to neoadjuvant chemotherapy, thus improving patients' care and avoiding unnecessary and potentially toxic surgical procedures in unresponsive patients.

Conflicts of interest

The authors report no conflict of interest. No funding sources supported this investigation. No funding sources supported this investigation.

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