The Egyptian Journal of Hospital Medicine (October 2024) Vol. 97, Page 4593-4598

Challenges in Applying RECIST 1.1 in Advanced Ovarian Cancer

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ABSTRACT

Background: It is essential to evaluate tumor burden by measuring its response or progression using established standards like RECIST 1.1, which is applicable to various organs., however its application in ovarian cancer (OC) are more challenging.

Objective: To assess application of RECIST 1.1 criteria in advanced stage ovarian cancer (AOC) patients receiving NACT.

Methods: This retrospective study had been performed on 100 female patients with pathologically confirmed AOC (FIGO stages III and stage IV) who had debulking surgery after receiving NACT, aged from 37 to 80 years old. Each patient underwent follow up CECT scans to evaluated tumor response to NACT prior to interval debulking surgery by RECIST 1.1 after selection of target lesions and non-target lesions.

Results: There was a high percentage of ascites, peritoneal and omental involvement, which are considered by RECIST 1.1 to be non-measurable lesions. Non-target lesions were prevalent in a significant percentage of cases with advanced stage OC in contrast to target lesions, which were less than non-target lesions.

Conclusions: Application of RECIST 1.1 to assess response to neoadjuvant-chemotherapy (NAC) in patient with advanced stage ovarian cancer relies mainly on non-target lesion.

Keywords: Response assessment, Advanced stage ovarian cancer, RECIST 1.1 NAC, Interval debulking.

INTRODUCTION

Ovarian cancer (OC) is the 5th most common cause of cancer-related death and the deadliest gynecologic malignancy in women globally. Most of cases discovered at an advanced stage, when the cancer has spread and metastases have spread widely throughout the abdomen cavity, because early-stage disease typically exhibits no symptoms. This is a main reason why this disease has such a high death rate. The tumor's stage, grade, and histological subtype all affect the prognosis and responsiveness to treatment [(1)].

Patients with AOC are managed with primary-debulking surgery to accomplish total tumor removal with no macroscopic disease left behind followed by NAC. If complete cytoreduction is not achievable patients receive NAC first followed by interval-debulking [(2)]. Imaging is crucial in evaluating response of tumor to anti-cancer treatments as it gives an objective measurement of tumor burden, which aids in determining if treatment should be stopped, continued or modified [(3)].

Response evaluation criteria in solid tumors (RECIST 1.1) are now the reference standard for assessing therapeutic response in solid tumors, they are widely used and approved by many institutes [(4)].

RECIST criteria were designed to offer an objective, unbiased, and reliable way to measure tumor burden [(5)]. This criterion depends on an anatomical measurement of tumor burden using unidirectional changes in size to describe the outcome of treatment. Four categories are present to describe response (calculated by adding the diameters of measurable lesions): complete response (CR), partial response (PR), stable disease and progressive disease [(6)].

This study aimed to assess application of RECIST 1.1 criteria in advanced stage ovarian cancer (AOC) patients receiving NACT.

PATIENTS AND METHODS

This study is a retrospective study involved 100 female cases with age ranging from 37 to 80 years old, with pathologically confirmed advanced ovarian cancer (FIGOIII and IV) who had interval-debulking surgery after receiving NACT.

The inclusion criteria were: Female patients with FIGO stage III and IV who had advanced OC confirmed by histopathology, NAC treatment was scheduled in conjunction with interval debulking surgery, and available CECT at baseline and after chemotherapy. Criteria for exclusion involved patients with a history of oophorectomy, hysterectomy, or salpingo oophorectomy, recurrent disease, no measurable lesions at the initial CECT, poor performance status that precludes surgery, and no available surgical details.

Data regarding age, pathologic type and grade of ovarian cancer were obtained from medical-records. Patients received from three to nine cycles. Preoperative and basal follow-up CECT were acquired. By comparing baseline and preoperative follow-up scans using RECIST1.1, the radiological response to NACT was ascertained retrospectively by surgical data.

MDCT scans of abdomen and pelvis obtained from dome of the diaphragm to symphysis-pubis by sixty-four multi-detector systems (Philips-Brilliance, USA). Intravenous low osmolar nonionic contrast medium (100 ml) was given to all patients by a

Received: 10/09/2024
Accepted: 11/11/2024

computed injector with rate of 4 ml/second. Data acquired in Porto-venous phase with 5 mm slice thickness, and then multiplanar reconstruction in axial, coronal and sagittal planes were obtained. The CT scan acquisition parameters was as follow: 200 MA/S, 120 KVP, 512X512 matrix, 1.172 pitch, 64 X 0.625 mm section collimation, 5 mm slice thickness, section reconstruction interval of 1.4 mm, rotation time 0.75 sec, and table speed 15.4 mm/rotation.

Target and non-target lesion selection in baseline CECT was done according to criteria of RECIST 1.1. Five measurable lesions were selected, maximum two/organ, were selected as target lesions. Each lesion's longest diameter was measured on axial images then the sum of the longest diameters was calculated and recorded as the baseline sum of diameters. Other lesions were recorded as non-target lesions, whether they were measurable not selected as target lesion or true non-measurable. In follow up CECT scans the longest diameter of all target lesions were again measured and sum of longest diameters were calculated. Additionally, every non-target lesion was assessed and contrasted with the baseline images. If there were new lesions, they were reported.

RECIST1.1 criteria were used to retrospectively assess the radiological response to neo-adjuvant chemotherapy. The target lesion response was classified either: ***Complete response (CR):*** Disappearance of all non-nodal target lesions. Additionally, any suspected lymph nodes selected as target lesions must have a short axis to less than ten mm. ***Partial response (PR):*** A reduction of 30% in target lesions total diameter relative to the baseline. ***Progressive disease (PD)***: is defined as a 20% increase in the sum of all measured target lesion diameters at baseline (the sum must exhibit an increase > 5 mm). ***Stable disease (SD):*** Neither an increase in lesions that would indicate progressing disease nor enough shrinkage to measure for a partial or full response [(7)]. As there is no measurement required for non-target lesions, they had different response categories: **CR:** Disappearance of all non-target lesions and level of tumor marker returned to normal. Every LN must have a short axis less than ten mm, ***Non-CR/Non-PD*:** at least one non-target lesion still present, along with the level of tumor marker above normal, ***PD:*** Unequivocal progression of pre-existing non-target lesions. Progress also includes the emergence of one or more new lesions [(8)].

Following the identification of the proper response for target and non-target lesions, the overall response can be calculated as shown in **(Table 1)**.

Table (1): Assessment of overall response with RECIST 1.1 [(9)]**:**

Overall Response	Target Lesion	Non-target Lesion	New Lesions
CR	CR	CR	No
PR	CR	Non-CR or non-PD	No
PR	PR	Non-PD	No
SD	SD	Non-PD	No
PD	PD	Any	Possible
PD	Any	PD	Possible
PD	Any	Any	Yes

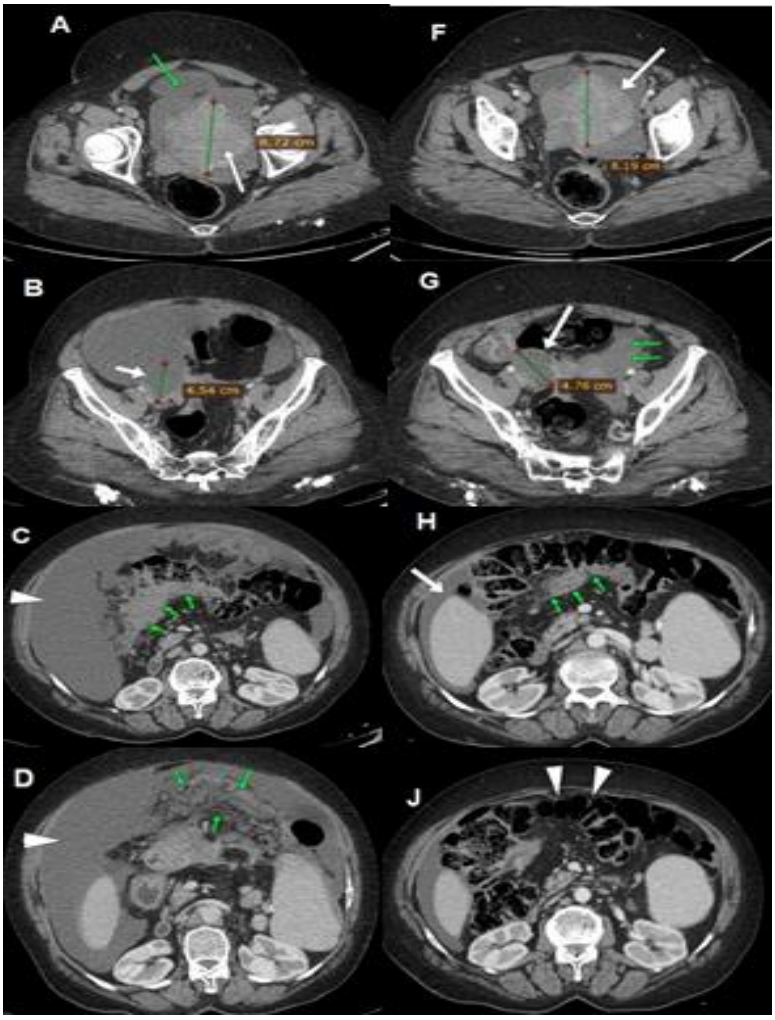

Figure (1): Stable disease response in 63 years old female high grade ovarian serous carcinoma. Baseline (A, B, C and D) and follow up after 6 cycles of NACT (F, G, H and J) CECT scans of abdomen and pelvis shows left adnexal mass, which show minimal decrease in size in FU (white arrow in A and F). Right adnexal mass with increased size in FU (white arrow in B and G) with -3% change from baseline, target lesion response is SD. Ascites (Arrow head in C white arrow in H) and mesenteric mass (Green arrow in C and H) show regression in FU scans while omental cake (green arrow in D) totally resolved (arrow head in J), thus non-target lesion response is Non-CR/ Non-PD. Overall response is SD.

Ethical approval:

The work had been performed following approval from the Ethics Committee of Mansoura University Hospitals, Mansoura, Egypt (approval code: MD.20.01.277). Signed consent was provided by each participant to use his information, at the entry to the hospital. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis: SPSS software was used to analyze the data (SPSS Inc., PASW statistics for windows version 25, Chicago). Data were presented as frequency and percentage. Monte Carlo tests were used to compare qualitative data between groups as appropriate. P value <0.05 was considered significant.

RESULTS

Our inclusion criteria were met by 100 consecutive cases with advanced stage OC receiving NACT and did IDS during study period. The response to NACT was evaluated by RECIST 1.1 criteria. The results are shown in the **(Table 2)**. 55% of patients had PR and 31% had stable disease.

Table (2): RECIST1.1 radiological response among study group

RECIST 1.1 response assessment category	Patients (n=100)
Complete response (CR)	5(5.0)
Partial response (PR)	55(55.0)
Stable disease (SD)	31 (31.0)
Progressive disease (PD)	9 (9.0)

Data are expressed as number (percentage).

Adnexal masses were the most prevalent target lesion, occurring in 93 patients (93%) followed by peritoneal deposits in 42 patients (42%), omental deposits in 35 patients (35%), LN involvement (short axis>1.5 cm) in 21 patients (21%), and parenchymal metastases, which were the least common at 10%. Ascites was the most prevalent non-target lesion in 88 patients (88%) followed by peritoneal (73%), omental infiltrations (68%), pleural effusion (32%), LN involvement (24%) and parenchymal metastasis representing only 4%. Two patients (2%) have new lesions, which included ascites, omental deposits, and LN involvement as shown in **(Table 3)**.

Table (3): Types of selected lesions among study group

Target lesion	N	%	Non-target lesion	N	%
Adnexal mass			**Ascites**		
• Absent	7	7.0	• Present	88	88.0
• Unilateral	40	40.0	• Absent	12	12.0
• Bilateral	53	53.0	**Pleural effusion**		
Omental			• Present	32	32.0
• Present	35	35.0	• Absent	68	68.0
• Absent	65	65.0	**Omental**		
Peritoneal	42		• Present	68	68.0
• Present	58	42.0	• Absent	32	32.0
• Absent		58.0	**Peritoneal**		
Lymphadenopathy	21		• Present	73	73.0
• Present	79	21.0	• Absent	27	27.0
• Absent		79.0	**Lymphadenopathy**	24	24.0
Parenchymal metastasis	10		• Present	76	79.0
• Present	5	10.0	• Absent		
• HFL	2	5.0.	**Parenchymal metastasis**		
• SFL	1	2.0	• Present	4	4.0
• Both	2	1.0	• HFL	3	3.0
• SRG		2.0	• SFL	0	0.0
			• Both	1	1.0
			• SRG	0	0.0
			New lesions		
			• Present	2	2.0
			• LN	1	1.0
			• Omental deposit and Ascites	1	1.0

The distribution of lesions among patients reveals that the most common number of lesions was 3 in 35 patients, as per RECIST 1.1 guidelines. On the other hand, 39 patients had 3 nontarget lesions **(Figs. 2 and 3)**.

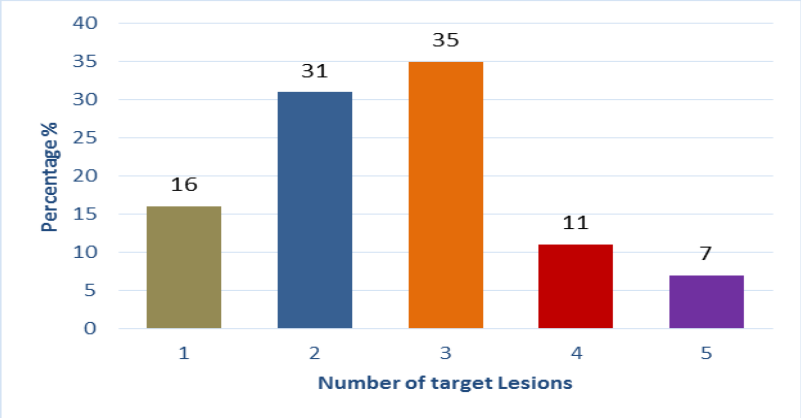

Fig. (2): Number of selected target lesions among study group.

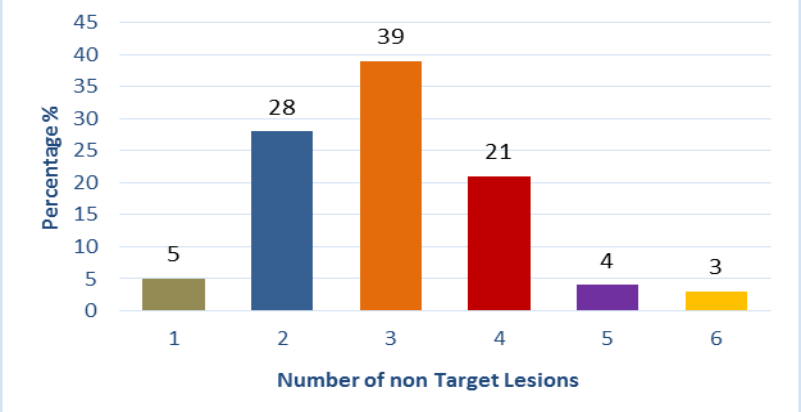

Fig. (3): Number of non-target lesions among study group.

The degree of completeness of the cytoreduction achieved at IDS was significantly correlated with the RECIST 1.1 responses **(Table 4)**. All patients (5) who had CR had complete cytoreduction (100%). Complete cytoreduction was achieved in 48 (88.3%) of PR, 20(65.5%) of SD and 6 (66.7%) of PD.

Table (4): RECIST response in association with cytoreduction

Cytoreduction	Complete response (N=5)	Partial response (N=55)	Stable disease (N=31)	Progressive disease (N=9)	Test of significance
Complete cytoreduction	5(100)	48(87.3)	20(64.5)	6(66.7)	**X^2 (MC)=7.89**
Incomplete cytoreduction	0	7(12.7)	11(35.5)	3(33.3)	**P=0.039***

*: Statistically significant, MC: Monte Carlo test. Data are expressed as number (percentage).

DISCUSSION

The present study assesses the RECIST1.1 response after neo-adjuvant chemotherapy in stage III and IV AOC patients. Based on our results, RECIST 1.1 can be used as good predictor for response to NACT and predictor of cytoreduction**.**

Ovarian cancer is a heterogeneous tumor diagnosed at an advanced stage in most of cases with significant morbimortality. Ovarian cancer typically spread via transcoelomic dissemination, with omental, peritoneal, and nodal metastases as well as development of ascites and pleural effusion, which considered by RECIST to be non-measurable [(5)].

Our study's statistical analysis revealed that target lesions were less than nontarget lesions. Prevalence of nontarget lesions in patients with AOC; 16% of patient had only one target lesion and the maximum number of target lesions (5 per patient) was present in only 7%. In contrast 68% of patients had 3 or more non-target lesions, and only 5% of patients had one non-target lesion**.** Because non-target lesion response assessment is a more subjective procedure as the size changes aren't calculated or measured in a quantitative manner as they are for target lesions, it is challenging to evaluate tumor response in ovarian cancer using RECIST 1.1 based on non-target lesions [(9)]. In addition, current study showed that there were high percentage of ascites, peritoneal and omental involvement (88%, 73% and 68%), which are considered by RECIST1.1 to be non-measurable lesions, making it difficult to assess tumor response precisely.

Similar findings were detected by another study, which found that two thirds or more of the scans showed ascites, bowel encasement, diaphragm involvement, and diffuse peritoneal thickening [(10)].

According to another study, the percentages were 81% ascites, 86% peritoneal thickening, and 78% omental cake [(11)].

A different study also revealed that 62.7% of patients had diffuse peritoneal thickening, 34.7% had more omentum involvement, 32% had pleural effusion and ascites, 29.3% had mesocolon metastases, and 12% had intraparenchymal liver metastases [(12)].

Also RECIST 1.1 criteria depends on CT images, which have limited sensitivity for very small lesions, as bowel or diffuse peritoneal nodules[(13)]. Additionally, it is challenging to evaluate poorly defined lesions using unidimensional criteria, and these lesions will also exhibit greater inter- and intrareader measurement differences [(14)].

Compared to existing literature, the current study's overall rate of complete cytoreduction following neo-adjuvant chemotherapy was 79%. According to recent studies, the overall rate of complete cytoreduction following NACT and IDS ranges from 30% to 60% [(15)].

79% of the participants in the current study experienced complete cytoreduction following NACT, which is greater than the rate reported in the literature. This could be attributable to smaller number of nonresponder (i.e. SD+ PD), surgeon factor, which plays a main role in the achievement of complete cytoreduction, and center facilities which were usually not considered in previous studies. Our findings demonstrated that the extent and completeness of cytoreduction during IDS can be predicted by the radiological response to NACT as measured by RECIST 1.1. A statistically significant correlation (p value of 0.039) was found between the achievement of complete cytoreduction and the RECIST 1.1 response. Rates of complete cytoreduction were 100% in CR, 80% in PR, 64.5% in SD and 66.7% in PD patients. Complete cytoreduction rates of 100% in CR, 95.8% in PR, 50% in SD, and 12.5% in PD categories were reported in prospective observational research [(16)].

Another study found 75% in CR, 55 in % PR, 42% in SD and 48% in PD patients [(17)]. Contrary to current results, one study reported that RECIST 1.1 criteria should serve as a perfect surrogate especially in patient with response category i.e. CR and PR, which ended up with complete cytoreduction, however, it is not a reliable criterion for complete cytoreduction in nonresponders [(16)].

The authors of a different study likewise came to the conclusion that the RECIST response should not be used to evaluate the chemotherapy response in advanced stages of ovarian cancer, their study showed 16% of patients in the SD or PD category achieved complete cytoreduction, while 40% of patients with CR or PR didn't. Thus, the function of RECIST criteria response assessment in AOC at the time of interval debulking surgeries is questionable [(17)].

CONCLUSION

Although current study supports the application of RECIST 1.1 in AOC despite the presence of large number of non-target lesions, yet further inter and intraobserver studies are recommended to validate its reproducibility.

Fund: Nil.
Conflict of Interest: Nil.

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