



Pathological response of ovarian cancer to neoadjuvant chemotherapy

Alexandr O. Ivantsov

N.N. Petrov Institute of Oncology, Leningradskaya 68, St.-Petersburg 197758, Russia

Correspondence to: Alexandr O. Ivantsov. N.N. Petrov Institute of Oncology, Pesochny-2, 197758 St.-Petersburg, Russia. Email: shurikov@mail.ru.

Abstract: There is only a few of studies devoted to evaluation of pathologic response of ovarian cancer (OC) to neoadjuvant chemotherapy (NACT). Pathologic complete responses (pCR), which are characterized by the lack of viable tumor cells in surgical specimens, are rarely observed in ovarian carcinomas. Multiple reports demonstrate that pCR is associated with evidently improved disease outcomes. Recommendations of the International Collaboration on Cancer Reporting suggest to use recently developed Chemotherapy Response Scoring (CRS) system, which is based on the pathological analysis of surgically removed omental masses. CRS3 (complete or near-complete response) is characterized by the lack of residual tumor cells in the omentum or presence of tumor foci up to 2 mm maximum size. It is observed after NACT in approximately 30–40% patients with high-grade serous ovarian cancer (HGSOC) and is reproducibly associated with the improvement of the disease prognosis.

Keywords: Neoadjuvant chemotherapy (NACT); ovarian cancer (OC); pathologic response

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Use of neoadjuvant therapy for cancer treatment may have several purposes. First, it is aimed to reduce tumor burden and thus to permit less extensive surgical intervention. Secondly, neoadjuvant therapy is believed to be an *in vivo* test for evaluation of tumor sensitivity to a given drug scheme, which helps to adjust further treatment options. Thirdly, neoadjuvant therapy can be utilized for the trials of novel anticancer agents as it deals with chemo-naïve malignancies and provides an opportunity to investigate surgically excised drug-exposed tumor material.

Most of concepts devoted to the use of neoadjuvant chemotherapy (NACT) were developed in the framework of breast cancer (BC) studies (1,2). One of the goals of applying NACT for BC treatment is to save the cosmetic appearance of breast by utilizing organ-preserving surgery. While applying for BC, particularly its triple-negative subtype, NACT relatively often results in pathologic complete response (pCR), which is associated with low probability of tumor relapse and justifies abstinence from adjuvant therapy. Furthermore, the results of BC NACT trials are considered by regulatory bodies for the

registration of novel cytotoxic and targeted agents (3).

The application of NACT for the treatment of ovarian cancer (OC) is different from the one in BC in many respects. Overall, there is limited diversity with regard to treatment schemes: use of the doublet consisting of carboplatin and paclitaxel is currently the only widely accepted scheme, with little or no variation observed between different clinics (*Table 1*). NACT remains the treatment of choice mainly for those patients, who technically cannot be subjected to complete primary surgical debulking, either due to extensive disease spread or because of high risk of serious perioperative complications (18). pCR of OC to NACT are very rare; not surprisingly, unlike in case of BC, most of OC patients relapse even after complete surgical debulking (*Table 1*).

The response to primary therapy largely depends on OC histological type. High-grade serous OC (HGSOC) are characterized by a relatively high sensitivity to carboplatin-paclitaxel therapy, while other OC entities have limited responsiveness to this regimen. Earlier NACT studies involved OC patients of different histological types, with

Table 1 Pathologic response to neoadjuvant therapy in ovarian cancer patients

Study	Pathologic response criteria	Main findings
Le <i>et al.</i> (4); 62 OC patients [serous histology: 49 (79%)]; 3 cycles of carboplatin-paclitaxel; optimal surgical debulking (<2 cm) in 46 (74%) patients	Composite score considering the extent of (I) tumor necrosis, (II) fibrosis, (III) macrophage infiltration and (IV) tumor inflammation. These characteristics were assessed using 3 grades: 0 (none/minimal), 1 (moderate), and 2 (extensive)	Prolonged OS in patients with the response score >0 (73.2 months) vs. women with no response (38.9 months), P=0.014
Le <i>et al.</i> (5); 66 OC patients [serous histology: 58 (88%)], mainly stage IIIC (n=57) or IV (n=8), 3 cycles of carboplatin-paclitaxel, optimal surgical debulking (<1 cm) in 36 (55%) patients	Omental response using the criteria of Sassen <i>et al.</i> (6)	Patients with omental chemotherapy effects (n=8, 12%) had significantly longer OS as compared to non-responders (84.5 vs. 31.2 months, P=0.005)
Sassen <i>et al.</i> (6); 49 OC patients [serous histology: 46 (94%)]; stage IIIC (n=35) or IV (n=14); 3 cycles of carboplatin-paclitaxel (n=26) or carboplatin alone (n=23); all with optimal surgical debulking (<1 cm)	The study considered presence of (I) fibrosis, (II) necrosis, (III) inflammatory cell infiltrates, (IV) foamy macrophages, (V) isolated psammoma bodies, (VI) hemosiderin, (VII) giant cells of foreign-body type, (VIII) enlarged (giant) tumor cells, and (IX) pattern of tumor infiltration. The characteristics I-VIII are graded as 0/1 (absent or minimally present), 2 (focal occurrence), or 3 (wide-spread occurrence). The tumor extent was graded as 1 (macroscopic large tumor masses), 2 (multiple small tumor foci), or 3 (scattered solitary tumor cells or complete absence of residual tumor)	The pattern and extent of residual tumor infiltration was the only criterion associated with overall survival (lack of residual tumor or scattered solitary tumor cells: n=9, OS =45.3 months; the remaining cases (n=40): OS =26.2 months; P=0.006). pCR in 2 (4%) patients. Other regressive changes, taken alone or in combination, did not correlate with prognosis
Miller <i>et al.</i> (7); 18 OC patients; stage IIIC or IV; 3 or 6 cycles of carboplatin-paclitaxel	–	pCR in 2/18 (11%) patients
Ferron <i>et al.</i> (8); 58 OC patients [serous histology: 42 (72%)]; stage IIIC (n=49) or IV (n=9); 3–6 cycles of platinum-paclitaxel; all with complete surgical debulking	Group 1: pathologic complete response, i.e., no detectable residual disease in peritoneum or lymph nodes. Group 2: persistent residual disease, but with histological signs of response to chemotherapy: low-to-moderate mitotic index, necrosis >50% and fibrosis >50%. Group 3: persistence of at least one site with “active” cells defined as high mitotic index or necrosis <50%	Three-year event-free survival in groups 1 (n=8), 2 (n=14) and 3 (n=36) was 63%, 12% and 19%, respectively (P=0.02). Only pCR (n=8, 14%) was associated with the improved disease outcome. The degree of tumor cell viability is not a reliable marker
Samrao <i>et al.</i> (9); 67 OC patients; carboplatin-paclitaxel (3–4 cycles)	Four tumor characteristics were scored: fibrosis [1+ (mild), 2+ (moderate), 3+ (severe)]; necrosis [0, 1+ (1–50%), 2+ (>50%)]; percent of residual tumor [1+ (<5%), 2+ (5–50%), 3+ (>50%)]; inflammation [1+ (mild), 2+ (extensive)]	Patients with severe fibrosis (n=27, 40%) had longer relapse-free survival (20 months) as compared to women with moderate or mild fibrosis (12 months), P=0.03; similar association was observed for overall survival (51 vs. 32 months, P=0.02)
Muraji <i>et al.</i> (10); 124 OC patients, whose disease did not progress during NACT [serous histology: 87 (70.2%)]; stage IIIC (n=86) or IV (n=38); 3–4 cycles of carboplatin-paclitaxel; complete surgical debulking in 61 (49.2%) patients	4-tier system assessing the presence of viable tumor cells as well as the degree of necrosis, fibrosis and inflammation: Grade 0 (lack of response). Grade 1 (mild response): more than a third tumor cells remain viable. Grade 2 (marked response): degenerative changes in more than two thirds cancer cells. Grade 3 (complete response): lack of tumor cells in surgical specimens	Poor pathologic response (grades 0 or 1) was associated with reduced PFS and OS. pCR in 12 (9.7%) patients

Table 1 (continued)

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Study	Pathologic response criteria	Main findings
Petrillo <i>et al.</i> (11); 322 OC patients [serous histology: 264 (82%)]; stage IIIC (n=251) or IV (n=72); 3–6 cycles of platinum-based doublets (carboplatin-paclitaxel or carboplatin plus pegylated liposomal doxorubicin, n=271) or carboplatin alone (n=51); complete surgical debulking in 236 (73%) patients	Complete pathologic response: no residual neoplastic cells in surgical specimens. Microscopic disease: maximal diameter of tumor foci \leq 3 mm. Macroscopic disease: presence of tumor foci >3 mm	Median PFS was 36 months in patients with pCR (n=21, 6.5%), 16 months in women with residual microscopic disease (n=104, 32.3%) and 13 months in subjects with macroscopic disease (n=197, 61.2%), P=0.001. Median OS was 72, 38 and 29 months, respectively (P=0.018). Only pCR retained prognostic significance when patients with complete tumor resection were considered
Böhm <i>et al.</i> (12); 133 HGSOE patients: 62 and 71 in the training and validation sets, respectively; mainly stage IIIC (n=100) or IV (n=32); 3–6 cycles of carboplatin-paclitaxel (n=126) or carboplatin alone (n=6)	Chemotherapy response scores (CRS): CRS1: no or minimal tumor response. Mainly viable tumor with no or minimal regression-associated fibroinflammatory changes, limited to a few foci. CRS2: appreciable tumor response amid viable tumor that is readily identifiable. Tumor is regularly distributed, ranging from multifocal or diffuse regression-associated fibroinflammatory changes with viable tumor in sheets, streaks, or nodules to extensive regression-associated fibroinflammatory changes with multifocal residual tumor. CRS3: complete or near-complete response with no residual tumor or minimal irregularly scattered tumor foci seen as individual cells, cell groups, or nodules up to 2 mm maximum size. Mainly regression-associated fibroinflammatory changes or, in rare cases no or very little residual tumor in the complete absence of any inflammatory response. It is advisable to record whether there is no residual tumor or whether there is microscopic residual tumor present	Omental CRS3 in 30% and 27% of patients included in training and validation sets, respectively; longer PFS in CRS3 vs. CRS1/2 patients (18 vs. 12 months, P<0.001). CRS3 was associated with the probability of achieving complete surgical resection and platinum sensitivity
Coghlan <i>et al.</i> (13); 71 HGSOE patients; stage IIIC (n=51) or IV (n=20); carboplatin-paclitaxel [3–4 cycles (n=56) or other number of cycles]; complete surgical debulking in 39 (55%) patients	See Böhm <i>et al.</i> (12)	Omental CRS3 in 23 (32%) of patients; longer PFS in CRS3 vs. CRS1/2 patients (26 vs. 16 months, P=0.003)
Lee <i>et al.</i> (14); 110 HGSOE patients; stage IIIC (n=47) or IV (n=63); 3–4 (n=97) or more cycles of carboplatin-taxane; optimal surgical debulking (<1 cm) in 52 (47%) patients	See Böhm <i>et al.</i> (12)	Omental CRS3 in 47 (42.7%) of patients; longer PFS in CRS3 vs. CRS1/2 patients (18.6 vs. 14.5 months, P=0.016). CRS3 was associated with the probability of achieving complete surgical resection and platinum sensitivity
Singh <i>et al.</i> (15); 103 HGSOE patients; stage IIIC or IV; carboplatin-paclitaxel (3–6 cycles); complete surgical debulking in 25 (24%) patients	See Böhm <i>et al.</i> (12)	Omental CRS3 in 42 (41%) of patients; longer PFS in CRS3 vs. CRS1/2 patients (18 vs. 16 months, P=0.004); however, this association was not significant after controlling for debulking status

Table 1 (continued)

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Study	Pathologic response criteria	Main findings
Ditzel <i>et al.</i> (16); 68 HGSOC patients (omental specimens: 65 patients; adnexal specimens: 59 patients; both omental and adnexal specimens: 56 patients); mainly stage IIIC (n=15) or IV (n=45); carboplatin-paclitaxel [3–4 cycles (n=55) or other number of cycles (n=13)]; complete surgical debulking in 35 (51%) patients	See Böhm <i>et al.</i> (12)	Omental CRS3 in 27 (42%) of patients; longer PFS in CRS3 vs. CRS1/2 patients (18.9 vs. 10.9 months, P=0.02). No association between mitotic index in omental tumor samples and PFS or OS. Interobserver variability in CRS assessment is mainly related to the assessment of residual microscopic tumor volume (below or above 2 mm)
Gorodnova <i>et al.</i> (17); 74 HGSOC patients with BRCA1 germ-line mutation; mainly stage IIIC (n=42) or IV (n=29); NACT consisting of carboplatin-paclitaxel (n=22), cisplatin-cyclophosphamide (n=24), cisplatin-cyclophosphamide-doxorubicin (n=10), single-agent cisplatin (n=6) or cisplatin-mitomycin (n=12); complete surgical debulking in 49 (66%) patients	See Böhm <i>et al.</i> (12)	pCR in 2/12 (17%) patients receiving cisplatin plus mitomycin C, but in none of women treated by standard NACT regimens

CRS, chemotherapy response score; HGSOC, high-grade serous ovarian cancer; NACT, neoadjuvant chemotherapy; OC, ovarian cancer; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival

HGSOC constituting the majority but not all OC cases included (4,5,8,10). Recent investigations focus on the analysis HGSOC, which allows more balanced interstudy comparison (12–16).

There is a limited number of studies devoted to the analysis of OC pathologic response to NACT. Some of these reports attempted to evaluate the rates of pCR; while ranging from 0% to 4–14%, pCR demonstrated clear association with improved outcome (6–8,10,11,17). Recently accepted Chemotherapy Response Scoring (CRS, see below) system pools together complete and near-complete pathological responses (12). Although it is advised by the inventors of CRS to mention instances of complete pathological responses, subsequent confirmatory CRS studies did not specifically address this issue. Another difficulty in the assessing the true rate of pCR lies in the extent of the pathological analysis. OC surgery usually involves high amount of excised material; by definition, as more sites are subjected to morphological evaluation, as there are more chances to find small residual tumor cell clusters even in cases with exhaustive gross response. It is difficult to specify minimal extent of the required pathological analysis, but it is self-explanatory that the diagnosis of pCR has to be based on a very thorough

examination of all resected tissues. Given the rarity of pCR in OC after NACT, there are no appropriate clinical studies assessing further treatment options for these patients. In theory, abstinence from consequent adjuvant therapy can be considered for women with reliably established pCR; indeed, OC has little propensity to distant metastases, therefore lack of viable tumor cells in the sites of surgery may be considered as a surrogate for cure. It is necessary to keep in mind, that the currently used microscopic analysis of surgical material has some sensitivity limit. It remains to be established, whether instances of morphologically detected pCR will hold true upon the use of modern mutation-based methods for detection of single tumor cells.

While the majority of studies assessing pCR in HGSOC after NACT involved unselected patients exposed to paclitaxel and carboplatin doublet, there is a clinical study comparing the efficacy of distinct NACT schemes in BRCA1-driven OC patients (17). Although cancers arising in BRCA1 germ-line mutation carriers are characterized by increased sensitivity of the gross tumor mass to conventional chemotherapy (19), no pCR has been recorded in women receiving carboplatin plus paclitaxel, cisplatin plus cyclophosphamide, cisplatin plus cyclophosphamide plus doxorubicin or single-agent cisplatin. However, 2/12

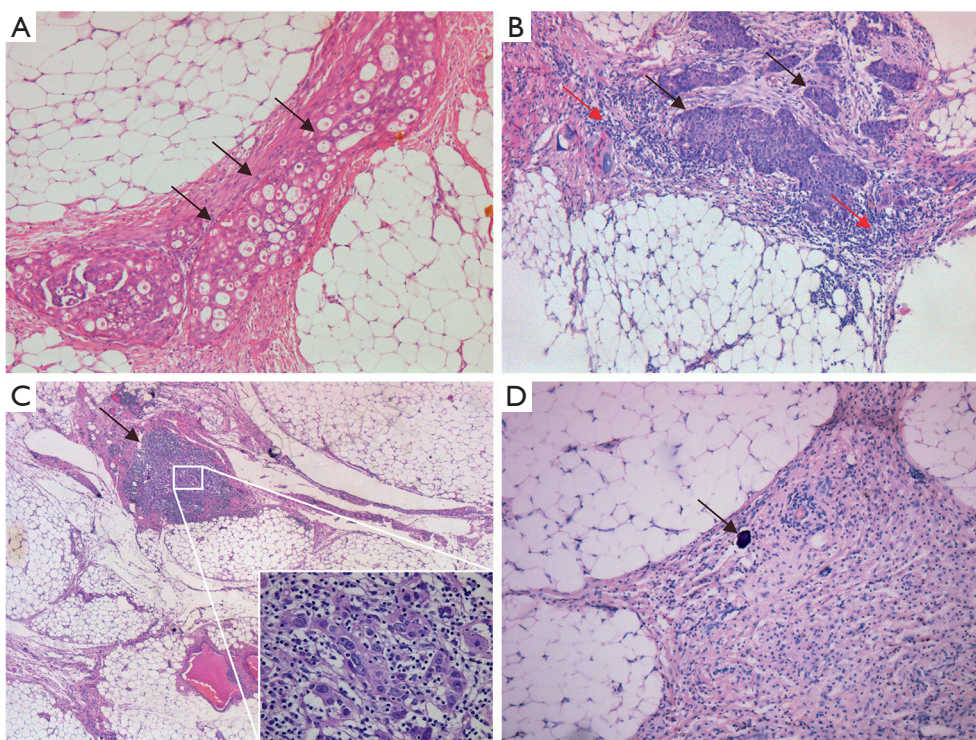


Figure 1 Pathological response in omentum according to Böhm *et al.* (12). (A) CRS1: fields of tumor cells (black arrows) and minimal fibroinflammatory changes (H&E, ×100); (B) CRS2: fields of tumor cells (black arrows) and prominent inflammatory infiltration (red arrows) (H&E, ×100); (C) CRS3: tumor focus with the size below 2 mm (black arrow) (H&E, ×50 and ×400); (D) complete histopathological regress: no viable tumor cells; single psammoma body (black arrow) (H&E, ×100).

(17%) BRCA1-mutated OC demonstrated pCR to the combination of cisplatin and mitomycin C (17).

The analysis of non-pCR responses to NACT involves relatively complicated grading systems. Overall, they consider the size and visual appearance of tumor foci as well as the degree of response-associated inflammatory, fibrotic and necrotic changes. Some studies suggested that evident post-NACT morphological changes are associated with improved disease outcomes (4,5,9,10), while Ferron *et al.* (8) and Petrillo *et al.* (11) stated that only pCR is of real prognostic value. Some standardization of the assessment of pathological response score is attributed to the recent work of Böhm *et al.* (12) who suggested a 3-tier score assessing the status of omental tumor dissemination (*Figure 1*). CRS1 (no or minimal tumor response) describes post-NACT carcinomas with high prevalence of viable tumor cells with no or minimal regression-associated fibroinflammatory changes. CRS2 (appreciable tumor response amid viable tumor) corresponds to situations, where viable tumor foci can be readily identified among regression-associated

fibroinflammatory changes. CRS3 (complete or near-complete response) is manifested either by the lack of residual tumor cells or presence of tumor foci up to 2 mm maximum size. According to the report of Böhm *et al.* (12) and some confirmatory studies, omental CRS3 is observed in approximately 30–40% HGSOc patients treated by NACT. Omental CRS3 is reproducibly associated with the improvement of the disease prognosis, while the differences in outcomes between women with CRS1 and CRS2 are minimal (12–16). Chemotherapy Response Scoring is included in the recommendations of the International Collaboration on Cancer Reporting (20) and there is an internet site facilitating appropriate training of pathologists (21).

Although the assessment of pathologic response after NACT is intuitively appealing, there are no clear guidelines which suggest clinical actions towards poor responders. Therefore, it is difficult to articulate, how the post-NACT morphological analysis affects the management of a given patient. Interestingly, recent study offered additional

cytotoxic agent (capecitabine) to BC patients, who failed to achieve pCR upon NACT; this attempt to cope with NACT-resistant residual tumor clones resulted in improved disease outcomes (22). In contrast to this experimental approach, the composition of NACT and adjuvant therapy in OC patients is usually identical, irrespective of the degree of pathologic response. It is recommended to evaluate the clinical utility of OC pathologic response assessment in prospective randomized NACT trials (23).

The treatment of advanced OC was long considered to be a more or less linear process, where NACT is provided in order to convert non-resectable disease into an operable condition, surgery is aimed to further reduce the gross tumor bulk, and, in ideal situation, to achieve complete tumor resection, and the adjuvant therapy is administered for the sake of elimination of residual invisible tumor cells. Given that the majority of HGSOC rapidly shrink in response to first cycles of NACT, one would expect that this strategy is likely to result in the cure of these highly chemosensitive tumors. In contrast to these assumptions, very most HGSOC threatened by NACT, surgery and adjuvant therapy relapse within a year after the completion of adjuvant therapy. Recent study of Sokolenko *et al.* (24) provides an explanation for these counterintuitive outcomes.

Sokolenko *et al.* (24) analysed a group of BRCA1-mutated HGSOC, which were treated by platinum-based NACT. BRCA1-driven tumors are characterized by the somatic loss of the remaining BRCA1 allele, which results in tumor-selective BRCA1 deficiency and is accompanied by pronounced vulnerability of cancer cells to platinum drugs (19). As expected, the majority (17/23, 74%) of treatment-naïve HGSOC exhibited loss-of-heterozygosity (LOH) in BRCA1 locus. However, when the authors analysed tumor specimens obtained after NACT, 11 (65%) out of 17 initially LOH-positive HGSOC demonstrated the restoration of BRCA1 heterozygosity. The subsequent molecular analysis reliably revealed that the gain of BRCA1 function in the residual tumor is attributed not to the second mutation in BRCA1 gene, but to the rapid selection of pre-existing BRCA1 proficient cells. This observation has a number of far-reaching outcomes, especially if we consider that even sporadic HGSOC often develop via somatic loss of BRCA1 function.

First of all, it demonstrates that long-term management of cancer disease is not a linear process. In fact, it may take just a few weeks for an initially chemosensitive tumor mass to become repopulated by drug-resistant tumor clones.

If post-NACT BRCA1-driven tumors no longer have a molecular target for platinum therapy, it is hard to expect that the continuation of the same therapy in the adjuvant setting will reduce the risk of relapse. Furthermore, the described findings call to reconsider the mission of pathological response assessment. If we believe, that the tumor shrinkage occurs in a more or less continuous way, the evaluation of tumor morphology at the end of NACT will indeed provide a valuable snapshot of the response to the therapy. However, if we assume that the post-NACT cancer mass consists of highly selected population of malignant cells, who succeeded to adapt to continuous exposure of cytotoxic drugs, their mere presence in the surgically removed tissues is likely to be a fatal sign, irrespectively of the visual appearance of tumor clones. The latter supposition is well compatible with the data of Sokolenko *et al.* (24), who observed perfectly viable cancer cells in post-NACT tissues despite excellent gross response to the therapy.

Overall, the fact of low pCR rate in OC is a clear indicator of limited long-term efficacy of existing systemic treatment options for advanced OC. Early-stage clinical trials involving novel drugs are usually performed on heavily pretreated OC patients, who are lacking standard therapeutic opportunities. Pathological and molecular findings demonstrate, that the tumor mass may critically change its biological properties during the treatment, due to selective pressure of anticancer therapy. Therefore, data obtained on heavily pretreated cancer patients cannot be extrapolated to the earlier lines of therapeutic intervention. Neoadjuvant drug trials, aimed at the increase of pCR rates, may facilitate the evaluation of novel drug schemes for OC treatment.

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Footnote

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