The prognostic value of residual disease after neoadjuvant chemotherapy in advanced ovarian cancer

Gynecologic Oncology 153 (2019) 445–451

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review Article

The prognostic value of residual disease after neoadjuvant chemotherapy in advanced ovarian cancer; A systematic review

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HIGHLIGHTS

- No macroscopic residual disease ensures the most favorable survival after neoadjuvant chemotherapy
- Optimal ICS seems to improve survival when compared to suboptimal ICS
- A cut-off in the amount of residual disease may be prognostically relevant, but it should not set goals for surgical outcomes

ARTICLE INFO

Article history:
Received 16 December 2018
Received in revised form 18 February 2019
Accepted 19 February 2019
Available online 27 February 2019

Keywords:
Neoadjuvant chemotherapy
Interval cytoreductive surgery
Outcome of surgery
Overall survival

ABSTRACT

Introduction. The ability to minimize residual disease during primary cytoreductive surgery is the strongest predictor for improved overall survival in advanced ovarian cancer. But while the probability to achieve a macroscopic complete resection increases if surgery is preceded by neoadjuvant chemotherapy (NACT), survival rates after NACT are similar to those observed after primary surgery. This may suggest that the prognostic effect of residual disease is altered after NACT. More specifically, randomized data suggest that there is no difference between optimal (0.1–1 cm) and suboptimal (>1 cm) cytoreductive surgery after NACT. Therefore, the aim of the current review is to establish the prognostic effect of the amount of residual disease after interval cytoreductive surgery (ICS) on overall survival.

Methods. Potential articles for inclusion in the current review were systematically searched through Medline, Embase and Cochrane in September 2017. Median overall survival (mOS) was summarized by the outcome of ICS per study. In addition, mOS was summarized for all studies together stratified by the outcome of ICS, based on the principle of a weighted average.

Results. In total, 3677 unique manuscripts were individually screened on title and abstract, which resulted in 11 individual studies that comprised a total of 2178 patients. MOS was 41 months for patients with no residual disease (range 33–54 months), 27 months for patients with 0.1–1 cm of residual disease (range 19–38 months) and 21 months with >1 cm of residual disease (range 14–27 months). Six studies showed significant differences between optimal and suboptimal ICS, while five studies showed no differences.

Conclusion. The summary of the currently available literature showed that after NACT, patients with optimal cytoreductive surgery experience lengthened survival compared to patients with suboptimal cytoreductive surgery. Patients with no macroscopic residual disease have, however, the most favorable survival outcomes, similar to what is seen after primary cytoreductive surgery.

Contents

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https://doi.org/10.1016/j.ygyno.2019.02.019
0090-8258/

1. Introduction

The vast majority of epithelial ovarian cancer patients is diagnosed with advanced stage disease, which is associated with poor clinical outcome [1,2]. Standard therapy comprises a combination of platinum-based chemotherapy and cytoreductive surgery. Patients survival strongly depends on the sensitivity to first-line chemotherapy and the ability to minimize residual disease during primary cytoreductive surgery (PCS), where patients with no macroscopic residual disease have the best prognosis [3,4].

Traditionally, patients underwent PCS followed by six cycles of adjuvant chemotherapy. Initial disease burden is a limiting factor in achieving an optimal surgical result. Neoadjuvant chemotherapy (NACT) was introduced to diminish intra-abdominal tumor load and, hence, increase the likelihood towards successful interval cytoreductive surgery (ICS). Two landmark randomized clinical trials (RCTs) compared clinical outcomes between PCS and NACT-ICS in International Federation of Gynecology and Obstetrics (FIGO) IIIC and IV patients, and showed similar survival rates between both groups [5,6], with reduced morbidity after NACT-ICS [7,8]. The percentage of patients with ≤1 cm of residual disease, however, was higher in the NACT-ICS group. The higher probability towards successful surgery after NACT was confirmed in the meta-analysis by Kang et al. [9]. The discrepancy between improved surgical outcome after NACT without improvement in long-term outcome raises the question why the prognostic value of surgical outcome differs for patients who receive PCS versus those that receive NACT-ICS.

A recent study by Meyer et al. showed that survival after PCS and NACT-ICS was similar in case of complete cytoreductive surgery (i.e. no macroscopic residual disease), while survival of PCS patients was significantly better after optimal cytoreductive surgery (0.1–1 cm of residual disease) when compared to NACT-ICS patients [10]. This suggests that any macroscopic residual disease after NACT is an unfavorable prognostic factor for survival. Moreover, randomized data suggest that there is no difference in survival between optimal (0.1–1 cm) and suboptimal (>1 cm) cytoreductive surgery after NACT [5]. The aim of the current review is therefore to establish the prognostic effect of the amount of residual disease after NACT-ICS on overall survival, in order to support clinical decision making for patients who benefit from ICS after NACT. More specifically, we aim to investigate if survival differences are present between suboptimal and optimal cytoreductive surgery.

2. Methods

The definition of residual disease after surgery has evolved over time. Successful cytoreductive surgery was previously defined as tumor residuals ≤2 cm, while nowadays it is defined as no macroscopic residual disease [4,11–13]. As our review aims to define the prognostic effect of residual disease in the current platinum-based era, we focused on studies that adopted current definitions for residual disease and categorized patients into complete (i.e. no macroscopic residual disease), optimal (i.e. largest diameter 0.1–1 cm) and suboptimal (i.e. largest diameter > 1 cm of residual disease) surgery. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) tool was used to ensure transparent reporting and is added to our supplementary material (S1) [14,15]. Moreover, the protocol for the current review is registered in the international prospective register of systematic reviews (PROSPERO) with the following registration number CRD42018083656 and can be accessed through the following website https://www.crd.york.ac.uk/PROSPERO/.

2.1. Search

Potential articles for inclusion in the current study were systematically searched through Medline, Embase and Cochrane (Cochrane Database of Systematic Reviews (CDSR) and Central) databases at September 2017. The systematic search is provided in the supplementary material for the Medline search (S2). After merging the results of the three searches, all records were individually screened on title and abstract by two authors (MT and OvdH). Discrepancies were discussed and resolved by consensus, resulting in either in- or exclusion for full text screen.

2.2. Inclusion and exclusion criteria

Study inclusion criteria were as follows: 1) primary epithelial ovarian, fallopian tube, or peritoneal carcinoma, 2) patients treated with NACT-ICS, 3) FIGO stages IIB to IV, 4) residual disease categorized as complete (i.e. no macroscopic residual disease), optimal (i.e. largest diameter 0.1–1 cm) and suboptimal (i.e. largest diameter > 1 cm) and 5) overall survival (OS) outcomes reported by the before mentioned categories of residual disease in patients that underwent NACT-ICS.

2.3. Data extraction

In case of multiple publications based on the same study cohort, the most relevant study (according to our inclusion criteria) was included. We extracted the following information for each eligible study; study design, year of publication, number of patients, % FIGO IIIC and IV patients, chemotherapy protocols, residual disease, median overall survival (mOS), 5-year survival rates, and hazard ratio's (HR) between complete, optimal and suboptimal cytoreductive surgery. Median survival and five-year survival rates were estimated from Kaplan-Meier curves if they were not mentioned in the text. In case data were unavailable in the manuscript or supplementary files, we contacted the corresponding author of the study for additional data.

2.4. Statistical analysis

mOS of patients from all studies was summarized based on the principle of a weighted average, where the number of patients of the study was leading in the weight of the analysis. Moreover, in most cox-regression analyses complete cytoreductive was selected as reference category. Since we were predominantly interested in the differences between optimal and suboptimal cytoreductive surgery, HR's were recalculated with suboptimal surgery as new reference category. This was based on the following formula: $((1/HR_{suboptimal\ vs.\ complete}) * HR_{optimal\ vs.\ complete}) = HR_{optimal\ vs.\ suboptimal}$. Confidence intervals could not be calculated, so statistical significance could not be determined.

2.5. Quality appraisal

Both reviewers (MT and OvdH) performed an independent assessment of the quality of all included studies. Retrospective cohort studies were assessed by the Newcastle Ottawa Scale (NOS) and RCTs were assessed by the Cochrane Risk of Bias Assessment tool [16,17]. Discrepancies were discussed and resolved by consensus.

3. Results

In total, 3677 unique manuscripts were individually screened on title and abstract. Hereafter, we selected 83 studies for a full-text review, and 11 studies were eventually identified as eligible and were included in the present study (Fig. 1) [5,6,18–26]. We included two RCTs, and nine observational studies. Included patient numbers ranged from 61 to 460, and resulted in a total of 2178 included patients.

3.1. Quality appraisal of retrospective studies

Based on the NOS scale, the quality of included retrospective cohort studies was high. The risk of selection bias was low in all studies, as consecutive patients were included in all studies. Comparability between groups differed among studies, and only two studies adjusted their survival analyses for both age and FIGO stage, being important prognostic factors for overall survival [22,26]. The assessment of outcome and length of follow-up was adequate in all studies, although only two of them reported on the loss to follow-up and whether it was equal between groups [18,20]. Overall 7 out of 9 studies had a score of 7 or higher, and two studies had an overall score of 6 (S3).

3.2. Quality appraisal of randomized studies

Based on the Cochrane Risk of Bias Tool, the quality of the two included RCTs was good. Both studies had a high risk of performance bias; as both patients and physicians were obviously aware of the chosen treatment (PCS or NACT-ICS) and blinding was impossible in both studies. This risk, however, did not influence the research question for this review as we only included patients of the NACT-ICS group. Risks of biases were scored as low (S4, S5).

3.3. Study populations

Study characteristics are summarized in Table 1. The vast majority of studies consisted of patients that were treated by either PCS or NACT-ICS, while two studies only included NACT-ICS patients. The percentages of included NACT-ICS patients ranged from 20% to 67%. All studies included FIGO IIIC and IV patients, and the percentages of FIGO IV patients ranged from 21% to 39%. Standard chemotherapeutic protocols consisted of a combination of carboplatin and paclitaxel. A total of 73% to 100% of patient populations was treated with this combination. Intraperitoneal chemotherapy was rarely used, but one study reported that 28% of their NACT-ICS patients received intraperitoneal chemotherapy, which was associated with improved survival in this study [23].

3.4. Survival outcomes after NACT stratified by the amount of residual disease

mOS was summarized for all studies in Fig. 2 and Table 2. Patients with no macroscopic residual disease had the most favorable survival in all studies. mOS after complete cytoreduction ranged from 33 to 54 months, and based on all studies the weighted average was 41 months. mOS of patients with an optimal cytoreduction ranged from 19 to 38 months, and mOS of patients with a suboptimal result ranged from 14 months to 27 months. The weighted average of mOS was 27 months for patients with 0.1–1 cm of residual disease and 21 months with >1 cm of residual disease.

Six studies showed significant, or likely significant, differences between optimal and suboptimal cytoreductive surgery

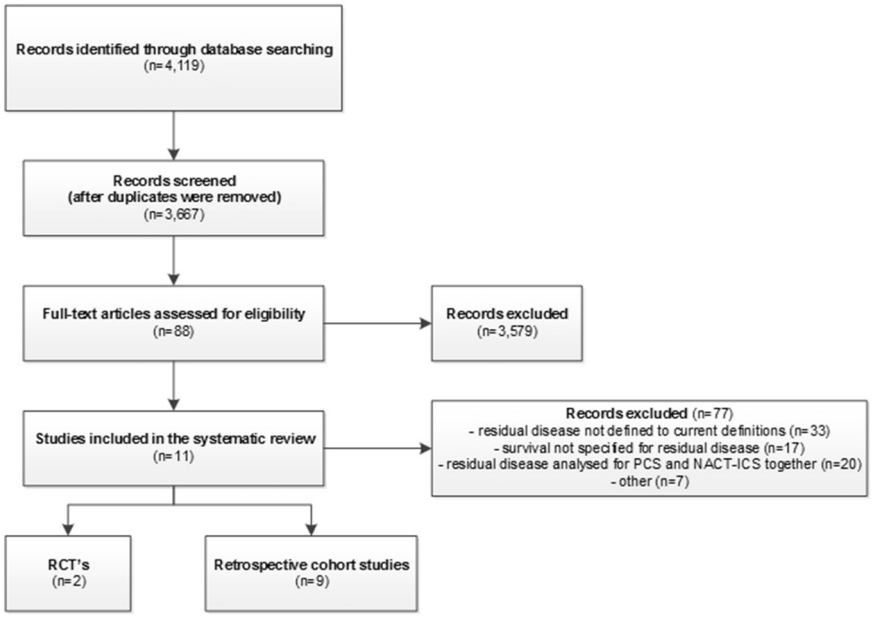

Fig. 1. Systematic search of the current review.

Table 1
Study characteristics of included studies in the current review.

Author	Country	Study period	N	N NACT-IDS (%)	FIGO IIIC (%)	FIGO IV (%)	Chemotherapy protocol
Bian [18]	China	2005–2010	339	114 (33.6)	88 (77.2)	26 (22.8)	Carboplatin-paclitaxel (71.1%) and cisplatin-paclitaxel (28.9%)
Colombo [19]	France	1990–2005	203	61 (30.0)	39 (63.9)	22 (36.1)	Platinum-paclitaxel (63.9%), Platinum-cyclophosphamide (31.2%), other (4.9%)
Fagö-Olsen [20]	Denmark	2005–2011	1677	335 (20.0)	206 (61.5)	129 (38.5)	Standard regimen was carboplatin-paclitaxel, no data on patient numbers were available in the Danish Cancer Registry
Iwase [21]	Japan	2000–2008	124	124 (100)	77 (62.1)	41 (33.1)	Carboplatin-paclitaxel (62.9%), ifosfamide-epirubicin-cisplatin (34.7%), other (2.4%)
Kehoe [6]	International	2004–2010	552	201 (36.4)[a]	149 (74.1)	52 (25.9)	Carboplatin-paclitaxel (76%), platinum only (23%), other (1%)
Markauskas [22]	Denmark	2007–2012	332	167 (50.2)	111 (66.5)	56 (33.5)	Standard regimen was carboplatin-paclitaxel, no data on patient numbers were provided
May [23]	Canada	2004–2011	303	161 (53.1)	129 (80.1)	32 (19.9)	Chemotherapeutic agents not mentioned, 44 (27.7%) intraperitoneal chemotherapy
Muraji [24]	Japan	2001–2010	124	124 (100)	86 (69.4)	38 (30.6)	Carboplatin-paclitaxel (100%)
Rosen [25]	Canada	2001–2011	326	143 (43.9)	113 (79.0)	30 (21.0)	Carboplatin-paclitaxel (100%), 1 (0.7%) intraperitoneal chemotherapy
Rutten [26]	Netherlands	1998–2010	689	462 (67.1)	334 (72.3)	128 (27.7)	Carboplatin-paclitaxel (96%), platinum only (2%), other (2%)
Vergote [5]	International	1998–2006	670	292 (43.6)[a]	253 (75.7)[b]	81 (24.3)[b]	Platinum-taxane (88%), platinum only (6%), other (6%)

[a] Patients that did not undergo debulking surgery, or had an unknown amount of residual disease were excluded in this table.
[b] FIGO stage was not stratified in patients with known residual disease; this represents the stage distribution in the 334 patients that were randomized to NACT-ICS.

[6,19,20,22,24,26], while five studies showed no differences [5,18,21,23,25]. Two studies directly compared survival between optimal and suboptimal outcomes after ICS and both found no significant differences between patients with 0.1–1 cm and > 1 cm of residual disease [18,25]. Other studies did not compare suboptimal and optimal outcomes, but chose patients with no macroscopic residual disease as reference category. Based on the effect of the recalculated hazard ratios (without confidence intervals), two additional studies probably found no differences between suboptimal and optimal surgery ($HR_{optimal}$ 1.10 and 1.01 compared to suboptimal ICS, Table 2) [5,23]. Other studies probably found survival differences between suboptimal and optimal surgery, with recalculated HRs ranging from 0.37 to 0.58 [22,24,26]. Two of the latter studies adjusted their survival models for age and FIGO stage with similar results [22,26]. For the remaining studies, HRs could not be recalculated due to missing data in the original manuscript [6,18–21].

4. Discussion

In the current systematic review, we aimed to establish the prognostic effect of residual disease after NACT in advanced stage ovarian cancer patients. More specifically, we were interested if patients with ≤1 cm of residual disease had a survival benefit over patients with >1 cm of residual disease. The included studies showed variable results, although mOS seems to be lengthened by optimal cytoreduction compared to suboptimal cytoreduction. Nevertheless, it is clear that complete cytoreductive surgery results in the most favorable survival outcomes.

In an era of evidence-based medicine, it is remarkable that the therapeutic effect of surgical cytoreduction has never been studied in a RCT. The importance of cytoreduction to no macroscopic residual disease, however, has become widely accepted despite the lack of robust evidence from RCT's. The landmark studies of Griffiths et al. and Hoskins et al., who showed that improved survival outcomes were obtained after minimizing the amount of residual disease, contributed to the key role of cytoreduction in the primary treatment of ovarian cancer patients [4,13,27–29]. Again, in the current review of the literature, patients who underwent a complete cytoreductive surgery had the most favorable prognosis.

It is suggested that initial disease burden at diagnosis may be a more powerful determinant in the survival of ovarian cancer patients than the amount of residual disease after cytoreductive surgery [30–32]. This may be a reason to abandon radical surgical procedures such as diaphragmatic surgery and upper-abdominal organ resections, since extensive surgery may induce more severe morbidity and perhaps even mortality [7,8]. A large retrospective analysis of the GOG-182 study investigated the independent prognostic effect of disease scores in FIGO III and IV patients with no residual disease after cytoreductive surgery. This study confirmed that a high disease score at diagnosis, compared to patients with a low disease score at diagnosis, resulted in impaired survival, although both groups had no residual disease after surgical cytoreduction. The authors concluded that the amount of residual disease alone does not undo the survival impact of initial disease burden [31]. Another analysis of the same study population, however, showed that in patients with a high disease score, survival improved if complete cytoreduction was reached when compared to optimal surgical results

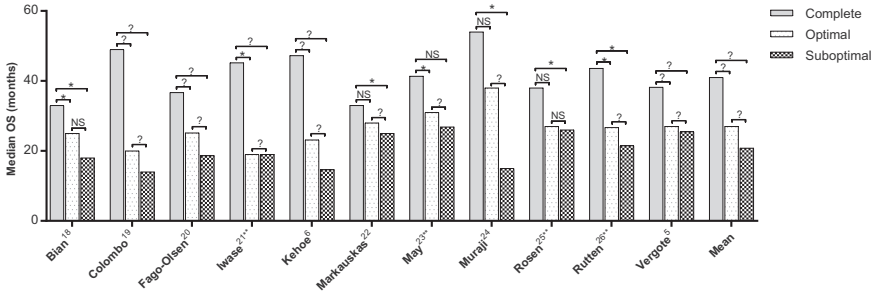

Fig. 2. Median overall survival of all studies included in the systematic review stratified by outcome of cytoreductive surgery. * $P < 0.05$, NS non-significant, ? significance not mentioned in the paper, ** Median overall survival based on Kaplan-Meier curve.

Table 2
Median overall survival and hazard ratios by outcome of cytoreductive surgery.

	Median overall survival (months)			Hazard ratio		
	Complete	Optimal	Suboptimal	Complete	Optimal	Suboptimal
Bian **[18]**	33	25	18	–	–	–
Colombo [19]	49	20	14	–	–	–
Fagö-Olsen [20]	37	25	19	–	–	–
Iwase **[21]**[a]	45	19	19	–	–	–
Kehoe [6]	47	23	15	–	–	–
Markauskas [22]	33	28	25	0.53	0.48	Reference
May **[23]**[a]	41	31	27	0.70	1.10	Reference
Muraji [24]	54	38	15	0.26	0.37	Reference
Rosen **[25]**[a]	38	27	26	0.56	0.79	Reference
Rutten [26]	44	27	22	0.32	0.58	Reference
Vergote **[5]**[b]	38	27	26	0.65	1.01	Reference
Mean	41	27	21			

Bold studies showed significant, or likely significant differences between optimal and suboptimal cytoreductive surgery.
[a] Median overall survival based on Kaplan-Meier curve
[b] Hazard ratio from univariable model, all others multivariable.

[33]. So, although extent of the disease at diagnosis is an important prognostic factor for overall survival, it is not a valid argument to limit the efforts of achieving a complete surgical result.

Other studies have questioned whether the outcome of surgical cytoreduction primarily reflects surgical skills or tumor biology [30,32,34]. A systematic review summarized the existing data of the relationship between biomarkers (such as protein expression, gene expression, copy-number alterations) and surgical outcomes [35]. There are some indications that tumor infiltrating lymphocytes, and specific gene profiles can predict surgical outcome [35–37]. The authors of the review, however, observed that the vast majority of studies used univariable statistical analysis, and if multivariable analysis was applied, most associations disappeared when incorporating confounders such as FIGO stage and histological subtype into their model. Moreover, even homogenous studies, consisting of advanced stage high-grade serous ovarian cancers, were unable to accurately predict surgical outcome [38]. So, although extensive disease and the possible interaction with tumor biology play a prognostic role in survival outcomes, it is not a definite predictor for successful surgery [35,39]. This finding is confirmed in studies that showed improved outcomes improve if surgery was executed by expert gynecologic-oncologists in high-volume hospitals [40,41]. Moreover, hospitals that incorporated systematic performance of radical upper abdominal surgery into their institutions obtained even better surgical- and survival outcomes [42–46]. This suggests that surgical skill can partly compensate for initial disease burden and it pleads for radical aggressive surgery in advanced ovarian cancer, although surgical morbidity should be incorporated in treatment decisions.

Earlier studies established that if complete cytoreductive surgery cannot be obtained, patients with ≤1 cm of residual disease had a favorable prognosis over patients with >1 cm of residual disease after PCS [47–50]. In the current study, we showed that the prognostic effect of optimal over suboptimal surgery is variable between the included studies after NACT. Based on the weighted average analysis, patients with an optimal surgical result experienced a median survival advantage of six months over suboptimal debulked patients. Although this finding suggests that optimal ICS may be a surgical goal, we propose that surgical resection of all residual lesions should be pursued to establish the most optimal prognosis, especially as there is no convincing evidence that optimal cytoreductive surgery actually establishes an independent improvement for overall survival.

One of the possible explanations for the variable results may be the lack of initial surgical effort in patients with >1 cm of residual disease, for example because gynecologists estimated that successful surgery was not feasible. It is likely that patients with no real effort to cytoreductive surgery experience decreased survival. The prognostic effect of initial effort has been demonstrated in randomized studies concerning second-look cytoreductive surgery (SCS). The study by van der Burg et al. randomized patients to SCS or no SCS after initial suboptimal PCS and three courses of subsequent chemotherapy. They found that the performance of SCS resulted in a median overall survival advantage of six months when compared to no SCS [51]. The consecutive randomized study of Rose, however, showed that SCS does not lengthen survival [52]. The main difference between the studies was the amount of residual disease present after the initial attempt to cytoreductive surgery (>5 cm residual disease in 77% versus 43% of all patients), and reflects the initial attempt towards no residual disease [51,52]. It is unfortunately unknown if the selected studies in the current review included patients with an inadequate effort to cytoreductive surgery.

Another possible explanation may be that the amount of residual disease has been interpreted variably between studies. The amount of residual disease is hampered by its subjective character, and it has been shown that gynecologists easily underestimate the amount of residual disease [53–55]. In particular, chemotherapy-induced fibrosis may increase the variability, since lesions that appear to be benign may still contain vital tumor elements [22,56]. This results in insufficient surgery, and leads to an overestimation of patients who are successfully operated after NACT. The study of May et al. showed that intraperitoneal chemotherapy, most profound in case of no macroscopic residual disease, can improve overall survival when compared to standard intravenous chemotherapy [23]. This is in accordance to the recently published randomized study on the beneficial effect of hyperthermic intraperitoneal chemotherapy after NACT in the Netherland [57]. The addition of intraoperative chemotherapy may eliminate microscopic disease, and therefore improve survival.

In most other tumor types, such as colorectal or breast cancer, the success of surgery is based on radical or irradical resections. From a biological point of view, radicality as prognostic factor seems to be more argumentative than the amount of residual disease as it is currently defined for ovarian cancer. An optimal surgical result, defined as ≤1 cm of residual disease in maximum diameter, comprises a variety of patients with possible differences in survival outcomes. An example is that patients with peritonitis carcinomatosis, and hence hundreds of minimal tumor spots, are categorized in the same group as patients with one spot of half a centimeter after surgical cytoreduction. The tumor volume of residual disease is therefore highly variable and the current definition may not represent true prognostic effects.

Following the recognition that an increasing amount of residual disease limits survival, it seems reasonable that a cut-off in the amount of macroscopic residual disease for the entire population may be prognostically relevant, but it should not set goals for surgical outcomes in advanced ovarian cancer. The aim should be to remove as much of the tumor as possible. In order to adjust survival models for possible confounders, macroscopic residual disease (yes or no), response to NACT,

surgical aggressiveness, initial disease burden, and tumor volume could be integrated into these models to predict survival outcomes more accurately. These aspects should therefore be incorporated in future studies to compare outcomes more easily.

The observation that survival outcomes after complete cytoreductive surgery are comparable between PCS and NACT-ICS, while they are different between optimal PCS and NACT-ICS, may be related to induced platinum resistance after NACT [10]. It is possible that an interruption in chemotherapy administration may give the remaining, still vital, tumor cells the chance to protect themselves against subsequent adjuvant platinum-based chemotherapy. The administration of six cycles of NACT followed by cytoreductive surgery with no subsequent post-operative chemotherapy, comparable to gastro-intestinal and breast cancer, might be one of the options to increase chemotherapy dose before surgery and to avoid an additional delay in chemotherapy administration.

There are a number of limitations in the current summary of the literature. Some studies were rather small, especially in their numbers of optimal and suboptimal cytoreductive surgeries, which limits their influence in the mOS rates for all studies combined. Moreover the natural selection for either PCS or NACT-ICS inherently influences survival, as the number of patients who were included in the studies and underwent NACT ranged between 20% and 67%. And finally, the surgical skills of gynecologists-oncologist plays a prominent factor in achieving the best surgical result, and this varies between studies which makes the comparison more complex.

Despite these limitations, we showed that patients with no residual disease after ICS experience the most favorable survival compared to patients with macroscopic residual disease. The additional prognostic effect of optimal versus suboptimal cytoreductive surgery probably lengthens survival but macroscopic residual disease of any diameter should not be the goal for cytoreductive surgery. Future prospective studies should include initial disease burden and extent of surgery to establish the prognostic effect of surgical outcome.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.02.019.

Funding

This work was supported by Dutch Cancer Society [IKNL2014-6838].

Conflicts of interest

None.

Author contributions

Study design/concepts: MT, OH, GS, KV, MA, RK
Data acquisition: MT, OH
Quality control of data and algorithms: MT, OH
Data analysis and interpretation: MT, OH, GS, KV, MA, RK.
Manuscript preparation: MT, OH
Manuscript editing and review: MT, OH, GS, KV, MA, RK.

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