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Only complete tumour resection after neoadjuvant chemotherapy offers benefit over suboptimal debulking in advanced ovarian cancer

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ABSTRACT

Objective: The aim of this study was to compare surgical results and survival outcome of advanced ovarian cancer patients who were treated with primary versus interval debulking surgery.
Study design: In this retrospective study stage III and IV ovarian cancer patients who received debulking surgery from 2006 to 2015 were included. Surgical results were described as complete, optimal or suboptimal debulking and chi-square test was used to assess significant differences. Overall survival was measured using Kaplan-Meier curves, the log-rank test and uni- and multivariable Cox regression analyses.
Results: Of 146 patients included in the study, 55 patients were treated with primary debulking surgery (PDS) followed by adjuvant chemotherapy and 91 patients received neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS). Complete or optimal debulking (0–10 mm of residual disease) was achieved in 76.4% (n = 42) of the PDS group and in 79.1% (n = 72) of the IDS group. Overall median survival was 38 months for PDS and 31 months for IDS, which was not significantly different (p = 0.181). In the IDS group, a significant difference was found in OS between complete and optimal resection (p = 0.013). Besides that, no difference in survival outcome was found in the IDS group between patients with optimal or suboptimal debulking (median survival were 20 and 19 months respectively).
Conclusion: Complete debulking surgery is of utmost importance, both in case of PDS and IDS. Achieving optimal interval debulking of 1–10 mm residual disease did not show any survival benefit over suboptimal interval debulking.

Introduction

Ovarian cancer is the sixth most common invasive cancer diagnosed in Ireland. Each year, approximately 360 Irish women are diagnosed with this disease. The mortality rate is still quite high (10.5 deaths per 100.000 per year) and the five-year net survival in the period 2008–2012 was 33.5%, which has increased only little since 1999 (30.0%) [1,2,3].

The high mortality rates are mainly due to the late detection of the disease, since early stage ovarian carcinoma is asymptomatic and late stage disease presents with non-specific complaints like abdominal distention, bloated feeling, abdominal pain, and/or constipation [4]. Another explanation for the high death rates is that ovarian cancer affects mostly elderly women, who may not be fit for extensive debulking surgery; as a result they often receive palliative chemotherapy only [5].

Currently, the surgical treatment of advanced-stage epithelial ovarian cancer (EOC) is highly debated among gynaecology – oncology specialists. Surgery combined with chemotherapy is the mainstay of treatment and can be applied in two different approaches: primary debulking surgery (PDS) and neo-adjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS). Appropriate selection of patients into either of the treatment

Abbreviations: CA-125, cancer antigen 125; CT, computer tomography; EOC, epithelial ovarian cancer; FIGO, International Federation of Gynaecology and Obstetrics; HR, hazard ratio; IDS, interval debulking surgery; IQR, interquartile range; NACT, neoadjuvant chemotherapy; OS, overall survival; PDS, primary debulking surgery; RCT, randomised controlled trial.

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pathways is usually challenging and a shift towards NAC with subsequently IDS is taking place over the years [6]. A number of researchers have published patient data regarding surgical outcome and survival in order to find out which approach is superior [7–18]. According to two randomised controlled trials [8,17], no difference in survival was found between primary and interval debulking, however the post-operative complications and morbidity rates were lower after interval debulking. While the likelihood of complete resection to no macroscopic disease, which is the most important prognostic factor [19], was higher in interval debulking group, the best survival outcome was found in patients who were primarily debulked to no macroscopic disease [8].

We conducted this study to evaluate surgical results and survival outcome of primary versus interval debulking surgery in a specialised gynaecologic oncology unit in Ireland.

Materials and methods

Data from all stage III and IV ovarian cancer patients treated in gynaecologic oncology unit, Mater Misericordiae University Hospital, Ireland between January 2006 and August 2015 were collected and analysed retrospectively. The normal practice in the unit is that the individual patient's care plan is decided at a weekly multidisciplinary team meeting. The decision on primary versus interval debulking is based on a preoperative assessment of the tumour's resectability, taking into account patient specific characteristics such as age and performance status, radiological findings such as omental caking, presence of ascites, tumour involvement in the liver, diaphragm or spleen, pleural effusion, and pathological tumour specifics like the type, grade and aggressiveness of the tissue. Mostly, patients were selected for IDS in case of upper abdomen disease (involvement of liver, spleen or diaphragm) or distant metastases (including pleural effusion). On occasion IDS was preferred to avoid the risk of stoma when extensive intestinal resection was required, and retain quality of life.

Only patients with epithelial tumours were included. Patients who received debulking surgery for symptom control, had their surgery elsewhere, or whose surgical notes could not be found were excluded. All debulking surgeries were performed by specialist gynaecological oncologists.

We used the hospital electronic database to generate the data, which include patient's age and performance status, serum CA-125 at diagnosis, tumour localisations on computer tomography (CT), FIGO stage, recommendations from multidisciplinary team meeting, type of debulking surgery, intra-operative findings, postoperative complications, type of chemotherapy, and post treatment follow-up data. Patients were followed from the moment of surgery until death occurred.

Statistical analysis

Variables were collected for the two patient groups (PDS and IDS). In order to identify differences at baseline, p-values were calculated for the categorical variables using the chi-square test and for continuous variables using the independent samples *t*-test. We performed descriptive crosstabs analyses and the chi-square test in order to calculate differences between the surgical results of primary and interval debulking. Outcome measures, which we used for surgical results, were defined as 'complete' when the tumour was resected to no macroscopic disease, as 'optimal' when the largest tumour remnant was less than 10 mm in diameter and 'suboptimal' when a tumour remnant larger than 10 mm in diameter was left behind. We used the Kaplan-Meier method to calculate overall survival (OS) for our population. As a start point for OS the date of diagnosis was used. If this was not registered, the date of first visit to the gynaecology unit was used. OS was measured to the date of death, whatever the cause. When patients were still alive, the date of file assessment was noted (5th November 2015). The log-rank test was used to evaluate significance. Furthermore we used uni- and multivariable cox regression models to analyse overall survival. $P < 0.05$ was used as a cut-off for significant. All statistical analyses were performed using STATA/SE.

Results

Fig. 1 shows the patients selection procedure. We included one-hundred-forty-six patients in our analyses. Fifty-five of these patients (37.7%) received PDS with adjuvant chemotherapy afterwards. The remaining ninety-one patients (62.3%) underwent IDS after receiving NAC. Patient characteristics at baseline are listed in Table 1. Patients in the IDS group were significantly older than patients in the PDS group (62 vs 57 years, P = 0.017). No significant differences were found with respect to performance status, FIGO stage, radiological tumour localisation and serum CA-125 at entry. The mean length of follow up was 32 months (range 0–155 months).

Graph 1 shows the results of the debulking surgery. Complete resection to no macroscopic disease was achieved in 58.9% (n = 86) of the total population, 49.1% (n = 27) of the PDS group and 64.8% (n = 59) of the IDS group (p = 0.061). At least optimal cytoreduction (0–10 mm of residual disease) was achieved in 78.1% (n = 114) of the total population, 76.4% (n = 42) of the PDS group and 79.1% (n = 72) of the IDS group (p = 0.965). Suboptimal debulking (residual disease $\geq$ 10 mm) was achieved in 21.9% (n = 32) of the total population, 23.6% in PDS (n = 13) and 20.9% in IDS (n = 19) (p = 0.697).

Postoperative complications occurred in 11 patients (20.4%) who were treated with PDS and in 10 of the IDS patients (11.9%) (p = 0.134), which mainly consisted our of haemorrhage, infection or postoperative neurologic complaints (data not shown).

Overall survival

Median OS for the total population was 37 months (95% CI 29–45), and 38 (95% CI 31–58) and 31 months (95% CI 24–45) for PDS and IDS respectively, which was not significantly different (P = 0.181). This is illustrated in Fig. 2. Three and five year OS for the total population were 51.7% and 25.6%. Figs. 2–4 show the overall survival curves in relation to the moment of surgery and surgical result.

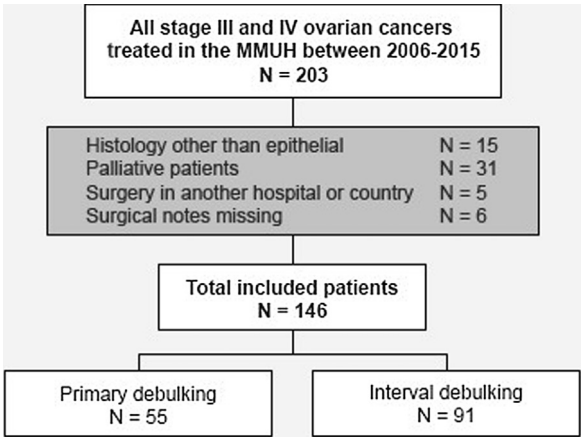
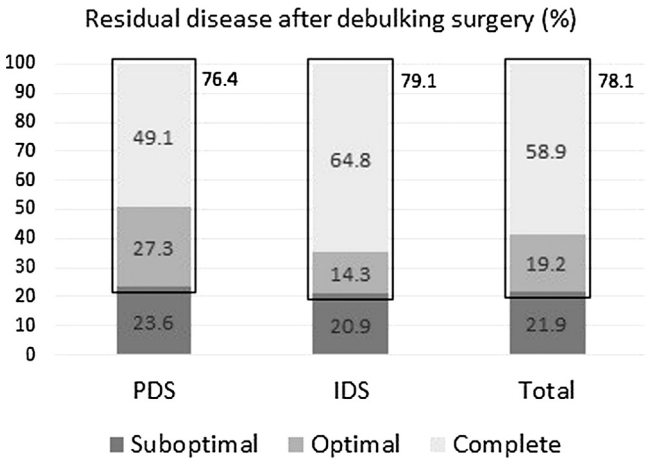


Fig. 1. Patient selection procedure.

Table 1
Baseline characteristics.

Baseline characteristics		Primary debulking, n (%) n = 55	Interval debulking, n (%) n = 91	p-value
Age in years, median (iqr)		57 (50–66)	62 (56–69)	0.017
Performance status	Healthy	23 (41.8)	30 (33.0)	0.566
	Comorbidity present	26 (47.3)	42 (46.2)	
	Serous	43 (78.2)	72 (79.1)	0.420
	Mucinous	3 (5.5)	1 (1.1)	
Histological type	Clear cell	0 (0.0)	1 (1.1)	
	Endometrioid	4 (7.3)	3 (3.3)	
	Poor-differentiated	5 (9.1)	8 (8.8)	
	IIIa	3 (5.5)	2 (2.2)	0.129
FIGO stage	IIIb	7 (12.7)	11 (12.1)	
	IIIc	38 (69.1)	52 (57.1)	
	IV	7 (12.7)	26 (28.6)	
CA-125 at entry, median (iqr)		755 (213–3256)	998 (308–3161)	0.475
	Omental, peritoneal deposits	29 (52.7)	27 (29.7)	0.116
Tumour localisation on CT-scan at diagnosis	Capsular disease on liver, spleen, diaphragm	2 (3.6)	8 (8.8)	
	Parenchymal disease liver, spleen	4 (7.3)	11 (12.1)	
	Pleural effusion, distant metastases	10 (18.2)	17 (18.7)	

iqr = inter quartile range.



Graph 1. Overview of postoperative residual disease (in%).

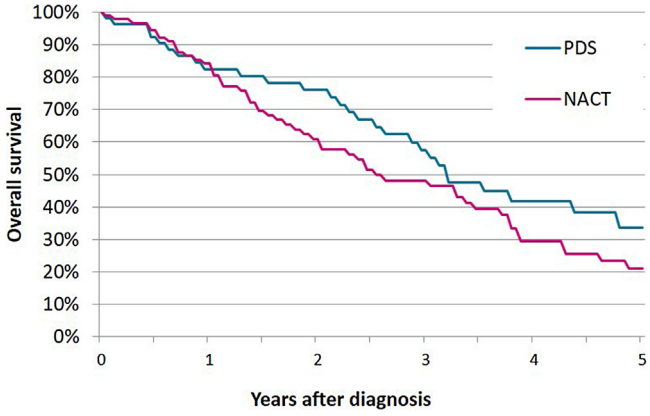


Fig 2. Overall survival for primary and interval debulking surgery.

Survival outcome was significantly different between groups based on surgical result. In case of PDS, median survival for a complete, optimal, and suboptimal result was 58, 38, 23 months respectively (Fig. 3). In case of IDS, median survival for a complete, optimal, and suboptimal result was 44, 19 and 21 months respectively (Fig. 4). Within the PDS group, the complete and optimal debulking group had a significant prognostic advantage over suboptimal debulking (p = 0.035). No difference was observed between complete and optimal debulking in this group (p = 0.589). Surprisingly, in the IDS group this comparison did show a significant difference. Patients who had complete debulking showed better survival outcome compared to those with optimal debulking (p = 0.013). No difference was found between IDS patients with optimal and suboptimal debulking (p = 0.825). This is illustrated clearly in Fig. 4.

We performed univariable and multivariable cox regression analyses for age, FIGO stage, performance status and residual disease in order to compensate for possible confounders. Both age and residual disease showed significant influence on survival in our series. However, there was still no difference in OS between PDS and IDS even after correcting for age (HR 1.18, 0.74–1.88). Age does impact the OS in PDS patients; complete/optimal versus suboptimal is now insignificant (HR 2.18, 0.97–4.91). In IDS patients correcting for age does not change our output (complete versus incomplete HR 2.17, 1.23–3.82).

Comments

Our findings emphasize the importance of complete tumour resection, since this was related to the best survival outcome. We did not find a significant difference in survival between PDS and IDS. Most interesting, in patients treated with neoadjuvant chemotherapy, optimal debulking (remnants 1–10 mm) has no survival benefit over suboptimal debulking surgery. Therefore, it's reasonable to question the value of operating on these patients when complete resection does not seem to be feasible in the first place.

The median survival of EOC stage III–IV ranges from 25 to 44.4 months in literature, for PDS 22.6-41.1 months and for IDS between 24.1 and 33 months [8,10–12,14–18,20–22]. These numbers are in line with our own median survival rates (37, 38 and 31 months, respectively). A 5-year survival rate was not always mentioned but ranged from 16 to 38.3% in literature, which is consistent with our own 5-year OS of 25.6% [8,10–12,14–17,20–22].

Though, the planning of the surgical treatment of advanced stage EOC (either PDS or IDS) remains debated, we did not find a

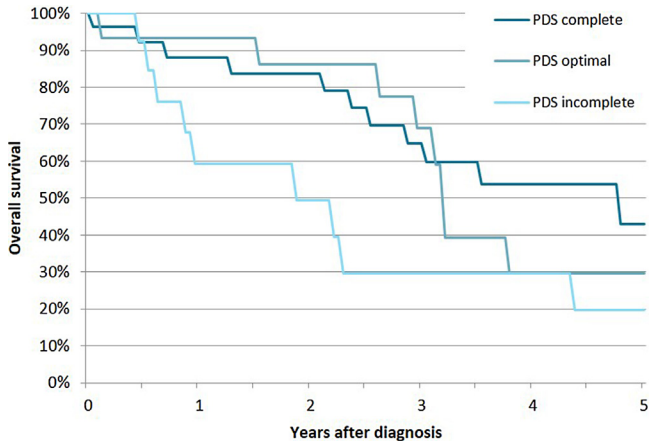


Fig. 3. Overall survival for primary debulking surgery.

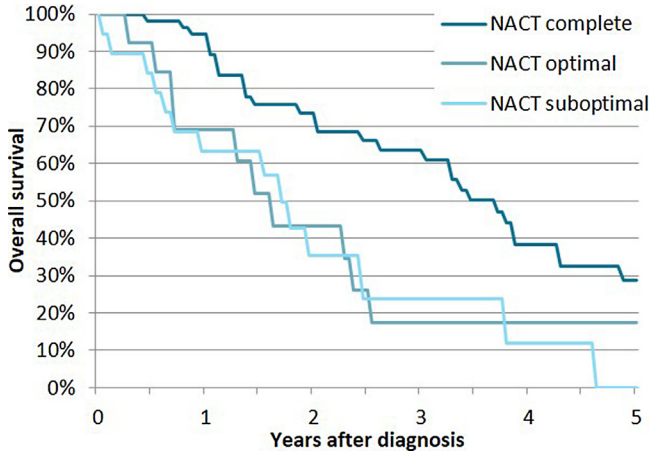


Fig 4. Overall survival for interval debulking surgery.

significant difference in OS between patients with primary and interval debulking surgery overall.

A meta-analysis of retrospective studies showed that NAC followed by IDS was associated with inferior overall survival compared to PDS followed by chemotherapy [9]. Because the study designs of the included research papers were non randomised, important prognostic factors like extent of disease and performance status were not taken into account in determining survival. It is clear that these factors influence the treatment approach as well as directly associated with a poor prognosis. Another meta-analysis found that NAC with IDS was not inferior to PDS and led to a higher rate of complete cytoreduction, despite unfavourable conditions in this patient group. However, this did not result in an improved survival outcome in these patients [11]. Makar et al. [23] analysed all large studies available on this subject and came to the conclusion that patients should be categorised into five subgroups according to specific tumour type behaviour and characteristics. This classification results in an advice for a particular treatment plan.

Our surgical results are consistent with international standards, probably due to the effective approach we follow to identify suitable patients for PDS. Although we do not categorize patients, we do assess both radiological findings and molecular tumour characteristics like Makar [23], and PDS is still considered first choice. Only in case of extended unresectable disease or poor performance status, patients are planned for NAC and IDS. This strategy was also described as successful in a study of van Meurs et al. [24], who analysed baseline characteristics of patients included in the EORTC trial. Otherwise, applying the categories of Makar, which takes into account more specific details of the disease, could be a first step to consensus worldwide.

Vergote et al. [8] conducted the first RCT regarding primary and interval debulking surgery in 2010 and found that NAC followed by surgery was not inferior to PDS followed by chemotherapy. No significant difference was found in OS, though less post-operative deaths, less infections and less major haemorrhages were reported in the IDS-group. Optimal surgical results (residual lesions $<$10 mm) were higher in the IDS-group, although, this did not influence the survival rates. These findings were confirmed by the CHORUS trial of Kehoe et al. [17]. Patients who were primarily debulked to zero macroscopic disease showed the best survival outcome. Although this doesn't mean that these patients have a worse survival when starting with chemotherapy, it was concluded that at present the goal remains to ensure that every patient who is eligible for complete primary surgery would ideally be identified and treated as such [25]. In our population complete cytoreduction during PDS resulted in an OS of 58 months, versus 44 months after complete IDS. Patient selection plays a part here, though this OS was not significantly different ($p = 0.401$). Complete versus optimal PDS was not significantly different either, probably due to the low number of PDS patients included.

In contrast to the PDS group, patients in the IDS group, who were optimally debulked to a residual tumour of 1–10 mm had no prognostic advantage over patients with a tumour residual larger than 10 mm, even when corrected for age. These data are in agreement with other retrospective studies [12,15,16].

The development of chemo-resistance in the IDS group could be a possible explanation for this finding [23,26]. The period between NAC and IDS gives the highly aggressive ovarian tumour cells a chance to mutate into a chemo-resistant type, which would limit the effect of chemotherapy and narrow down any other options. Surgery can affect the tumour cells as well, since a smaller tumour volume tends to have better perfusion, which accelerates tumour mitosis and growth[27]. Finally, we should realise that both the large majority of patients in whom a suboptimal or optimal debulking is obtained after NAC, probably belong to the suboptimal debulking group in case they underwent PDS. Thus, the definition of "optimal" in IDS following NAC should be different from PDS to indicate similar good or expected better survival [12].

One should realise that the prognostic value of the surgical outcome in patients with PDS cannot simply be translated to patients with IDS, that is surgery after previous chemotherapy. The group of patients who started with chemotherapy, which was based on among others age, performance status, and radiological findings, may have had a worse prognosis beforehand. A retrospective study of Kaban et al. [28] describes other independent prognostic factors in patients receiving NAC and interval debulking for advanced ovarian cancer: the presence of macroscopic tumour in the omentum after NAC and $>$4 NAC cycles. These items could be helpful when estimating prognosis. Also, a chemotherapy response score (CRS) was introduced by Böhm et al. [29] and externally validated to improve survival estimation in our target population. The CRS system appeared to be useful and reproducible for assessing NAC response in the cohort of Lee et al. [30].

In order to make sure complete resection is feasible in IDS patients, a laparoscopic procedure could be performed before starting neoadjuvant chemotherapy [31] or after a couple of cycles before interval debulking surgery. One can evaluate the actual response to chemotherapy and decide to go ahead with surgery, to give a few more cycles or to switch to another cytotoxic regimen. This strategy is already incorporated in several medical centres in

Spain, Mexico, and the USA [32]. In case of an excellent response debulking surgery could even be performed laparoscopically, which would dramatically decrease postoperative morbidity and mortality rates. Melamed et al. [33] reviewed a population of 3071 women with EOC stage IIIC or IV who received debulking surgery, of whom 450 (15%) laparoscopically. No difference in 3-year survival was found and hospitalization was slightly shorter in the laparoscopic group (4 versus 5 days, $P < 0.001$). A pilot study by Favero et al. [34] showed that laparoscopic cytoreductive surgery is feasible and effective, but recommend that these results should be confirmed by a larger prospective trial before clinical application.

Due to its retrospective design, we couldn't control possible confounding factors, which could affect the outcomes we assessed. These include the cytotoxic regimen used in number of cycles, doses, timing and the need for second line chemotherapy. Although mean age was the only significant baseline difference between the two groups, it is still possible that our IDS patients had worse prognosis at baseline, due to deliberate patient selection process. Also the surgical results are subject to the surgeon's personal estimation of residual tumour, and therefore not entirely objective. We decided to exclude non-epithelial ovarian cancers; therefore our study is only applicable to advanced epithelial ovarian cancer.

In conclusion, our study contributes to the growing number of publications regarding the treatment of advanced EOC and confirms the relation between residual tumour size and survival outcome. Complete tumour resection to zero macroscopic disease should always be the goal in debulking surgery. If this cannot be achieved in patients with IDS, optimal surgery may not result in any survival advantage over suboptimal debulking surgery and might not be worth the peri-operative risks. For future perspective we should develop a more accurate definition for the outcome of debulking surgery after neoadjuvant chemotherapy.

Disclosure

All authors certify that there is no conflict of interest with any financial, research, and academic organization, with regards to the research work discussed in the manuscript.

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