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European Journal of Obstetrics & Gynecology and Reproductive Biology 223 (2018) 98–102

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

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

Full length article

Neoadjuvant chemotherapy or primary debulking surgery in FIGO IIIC and IV patients; results from a survey study in the Netherlands

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ARTICLE INFO

Article history:
Received 20 December 2017
Received in revised form 26 February 2018
Accepted 27 February 2018

Keywords:
Epithelial ovarian cancer
Primary debulking surgery
Neoadjuvant chemotherapy
Survey

ABSTRACT

Introduction: Primary debulking surgery (PDS) followed by adjuvant chemotherapy is historically recommended as first line treatment for advanced stage ovarian cancer. Two randomized controlled trials, however, showed similar efficacy and reduced toxicity with neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS). Nevertheless, uptake of NACT-IDS varies widely between hospitals, which cannot be explained by difference in patient populations. In this survey, we therefore aimed to evaluate the views on NACT-IDS among all Dutch gynaecologists and medical oncologists involved in the treatment of ovarian cancer.
Study design: An e-mail link to the online questionnaire was sent to all medical oncologists and gynaecologists in the Netherlands, regardless of their (sub)specializations. The data was analysed using descriptive statistics and chi-square tests were used to analyse differences between groups.
Results: Three-hundred-forty physicians were invited to fill out the questionnaire. After two reminders, 167 of them responded (49%). Among the responders, 82% of the gynaecologists versus 93% of the medical oncologists considered the available evidence sufficiently convincing to treat advanced stage ovarian cancer patients with NACT-IDS ($p = 0.076$). Moreover, 33% of gynaecologists and 62% of medical oncologists preferred NACT-IDS to PDS as first line treatment ($p = 0.001$). While most responders (86%) indicated that selecting the right patients for NACT-IDS is difficult, those with bulky disease, FIGO stage IV or metastases near the porta hepatica were most likely to undergo NACT-IDS.
Conclusion: The majority of Dutch gynaecologists and medical oncologists adopted NACT-IDS as an alternative treatment approach for advanced stage primary ovarian cancer. About two-thirds of medical oncologists and one-third of gynaecologists prefer NACT-IDS to PDS as first line treatment in this setting. Improving patient selection is considered of paramount importance.

Introduction

The outcome for patients with advanced stage epithelial ovarian cancer (EOC) is generally poor, with five-year survival rates of 25%–35% [1]. There is a lively debate about the most optimal treatment for these patients. The mainstay of therapeutic regimens consists of debulking surgery combined with platinum-based combination chemotherapy. Historically, primary debulking surgery followed by adjuvant chemotherapy (PDS) is recommended as first line treatment. Over the last two decades, an alternative regiment consisting of neoadjuvant chemotherapy followed by interval debulking surgery and adjuvant chemotherapy (NACT-IDS) emerged [2].

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https://doi.org/10.1016/j.ejogrb.2018.02.029
0301-2115/

In 2010, the randomized controlled trial of Vergote et al. compared the use of NACT-IDS versus PDS in patients with bulky FIGO IIIC and IV EOC. This study demonstrated that overall survival and progression free survival after NACT-IDS were similar compared to PDS [3], while perioperative morbidity and mortality were reduced after NACT-IDS. Just before publication of the results of this trial the opinion of gynaecologists and medical oncologists among the American Society of Gynaecologic Oncology (SGO) with respect to the preferred treatment was evaluated. It was concluded that most members did not treat their patients with NACT-IDS and did not consider the available evidence sufficient for this treatment sequence [4]. In 2011, the opinion of the European Society of Gynaecological Oncology (ESGO) members was evaluated, and a majority believed there was sufficient evidence to treat FIGO IIIC and IV patients with NACT-IDS. However, there was a large variation between countries (e.g. 16% in Germany versus 100% in Belgium) [5].

More recently, the CHORUS trial of Kehoe et al. confirmed the non-inferiority of NACT-IDS [6]. In addition, multiple international retrospective studies also demonstrated less perioperative morbidity and mortality after interval debulking surgery [7–9]. Nevertheless, the use of NACT-IDS remains a topic of debate, partly because findings from observational studies indicate that patients with no residual disease after PDS might have a better survival than those with no residual disease after IDS [7,8,10]. Furthermore, it is argued that the choice of treatment (PDS versus NACT-IDS), and the amount of residual disease after (interval) debulking surgery, is strongly related to the expertise of the surgical team.

Dutch hospitals are classified according to their level of specialization as general, semi-specialized, or specialized hospitals (including all University hospitals) [11]. Since 2012, surgical care for ovarian cancer is centralized in the Netherlands and debulking surgery is solely executed in hospitals that perform a minimum of twenty debulking surgeries annually. These are semi-specialized or specialized hospitals, and the distinction between the two types of hospitals is defined by the employment of gynaecological oncologists. After a regular training in gynaecology and following an additional two-year fellowship in gynaecologic oncology, the Dutch Society of Gynaecologic Oncology can certify members as gynaecological oncologists. In semi-specialized hospitals, gynaecological oncologists participate in each debulking surgery together with semi-specialized gynaecologists. Medical oncologists administer (neo-)adjuvant chemotherapy in practically all hospitals, regardless of their specialization. The initial diagnosis of ovarian cancer can be made in all Dutch hospitals, by either gynaecologists or medical oncologists. Subsequently, but before the initiation of treatment, all patients are discussed in a multidisciplinary tumour board meeting by gynaecological oncologists, medical oncologists, pathologists, radiologists and radiotherapists for the optimal treatment strategy, as recommended by the ESGO [12].

The use of NACT-IDS increased over the last years in the Netherlands, but the uptake of NACT-IDS varies widely between hospitals which cannot be explained by differences in patient populations [13]. In this survey, we aimed to evaluate the views on NACT-IDS among all Dutch gynaecologists and medical oncologists involved in the treatment of ovarian cancer.

Methods

Questionnaire

A digital questionnaire was used to perform this survey in the Netherlands. It was send to gynaecologists and medical oncologists in all Dutch hospitals, regardless of their (sub)specialization. A link to the survey was send by e-mail. Responders received their first e-mail, which explained the purpose of the study and a link to the survey program in January 2016. To increase the response rate, all non-responders received a reminder after three and six weeks. Not all responders filled in a complete questionnaire, and these responders also received a reminder to complete their questionnaire after eight weeks.

Questions were based on the two previous survey studies [4,5]. Responders were asked about demographics, experience, diagnostic techniques, definitions of the outcome of debulking surgery, chemotherapy protocols and their use and believe in NACT-IDS. The questionnaire is provided as a Supplementary file together with the CHERRY checklist to establish the validity of this questionnaire (S1, S2) [14].

Statistical analysis

The answers were summarized using descriptive statistics. Not all questions had to be answered, therefore the number of responses varies between questions. Percentages were calculated based on the number of answers to each questions. Respondents from specialized and semi-specialized hospitals were categorized as one group, and compared to responders from general hospitals. Chi-square tests were used to analyse differences between groups. A p-value <0.05 was considered statistically significant for all analyses. Statistical analyses were performed using STATA/SE (version 14.1; STATA CORP., College Station, Texas, USA).

Results

Three-hundred-forty physicians were invited to fill out the questionnaire, 167 physicians responded (167/340 = 49%). Most responders were gynaecologists (Table 1). Of all respondents, 28% of gynaecologists and 12% of medical oncologists were employed at (semi-)specialized hospitals. The vast majority had more than five years of experience with the treatment of ovarian cancer patients (84%) and treated 5 to 20 newly diagnosed patients a year (60%, Table 1).

Evidence for NACT-IDS

Most responders considered the available evidence as sufficient to treat advanced stage EOC patients with NACT-IDS (82% of gynaecologists and 93% of medical oncologists, p = 0.076). In addition, there was no difference between responders from

Table 1
Demographics of respondents on the online survey in the Netherlands.

	N (%)
Specialization	
Gynaecologists	101 (60.5)
Medical oncologist	66 (39.5)
Type of hospital	
Specialized	47 (28.1)
Semi-specialized	20 (12.0)
General	100 (59.9)
Experience	
<5 years	27 (17.1)
5–10 years	37 (23.4)
11–15 years	36 (22.8)
>15 years	58 (36.7)
Number of EOC patients a year	
<5	12 (7.6)
5–10	48 (30.4)
11–20	46 (29.1)
21–35	26 (16.5)
36–50	9 (5.7)
>50	7 (4.4)
Other	10 (6.3)

Table 2
Scores of patients and tumour characteristics that benefit from NACT-IDS.

	Score [a]
FIGO IV	2.56
Bulky disease upper abdomen	2.44
Metastasis porta hepatica	2.40
Serious comorbidity	2.22
Inevitable bowel resection	2.22
FIGO IIIC	2.07
Large amount of ascites	2.05
Diaphragm involvement	2.03
Spleen metastasis	1.93
Extreme high CA-125 values	1.50

[a] Respondents could answer on a Likert scale (0–4); the number of responses on every specific number of the Likert scale were multiplied by this value and the total sum was divided by the number of responses (n = 167).

specialized, semi-specialized and general hospitals (84%, 88% and 88% respectively, p = 0.836). Patients with FIGO stage IV, bulky disease in the upper abdomen or metastasis near the porta hepatica were most prone to undergo neoadjuvant chemotherapy, but patients with an extremely high CA125 or spleen involvement had a higher probability to undergo primary debulking surgery (Table 2).

Before the publication of the EORTC trial, already 15% of gynaecologists and 55% of medical oncologists considered NACT-IDS as a treatment option ($p < 0.001$). In general hospitals, this percentage was higher for both gynaecologists and medical oncologists (Table 3). After the publication of the EORTC and CHORUS trials, the adoption of NACT-IDS increased within all groups to a comparable adoption rate (Table 3).

Opinions about whether NACT-IDS should be the preferred treatment for all FIGO IIIC and IV patients were diverse. Whereas a minority of gynaecologists (33%) thought that NACT-IDS should be first choice of treatment in this selected group of patients, most medical oncologists believed that it should be first choice (62%, Table 3). In addition, 16% of gynaecological oncologists and 46% of medical-oncologists from specialized hospitals preferred NACT-IDS.

Diagnostic process

Most physicians based their decision to schedule patients for primary debulking surgery or neoadjuvant chemotherapy on preoperative imaging (94%). Computed tomography (CT) scans (79%), transvaginal or transabdominal ultrasounds (46%) and diagnostic laparoscopy (46%) were reported as most useful techniques. Diagnostic laparoscopy was not used as standard diagnostic work-up, although some physicians performed this technique to establish the probability to achieve a complete or optimal primary debulking surgery. Positron emission tomography-CT (PET-CT) (2%), magnetic resonance imaging (MRI) scans (5%) and thoracoscopy (1%) were rarely used. In addition to preoperative imaging, a majority of responders (56%) stated that age and performance status also influenced the choice between PDS and NACT-IDS. Nevertheless, most responders (86%) indicated that prediction of the outcome of debulking surgery based on pre-operative imaging was unreliable. This estimation did not differ between gynaecologist and medical oncologists (90% and 80% respectively, p = 0.073), or between types of hospitals (p = 0.863).

Surgery

The definitions of complete and optimal debulking surgery are known by the majority of responders, 91% of responders defined a complete debulking surgery as no macroscopic residual disease and 81% of responders defined an optimal debulking as ≤1 cm residual disease in maximal diameter. Medical oncologists more often than gynaecologist thought that optimal debulking was defined by less than 0.5 cm residual disease (21% and 6% respectively), or as no macroscopic residual disease (13% and 3% respectively). Gynaecological oncologists and medical oncologists from specialized hospitals defined it adequately in 94% and 71% respectively.

Most responders estimated the number of patients treated with PDS as first line therapy within their hospitals between 11% and 40% (48.2%) and only 5.6% estimated that more than 90% of their patients were treated with PDS. A substantial number of responders did not know the percentage of complete or optimal debulking surgeries in their hospital (57–60%).

Chemotherapy

There was a large overlap for chemotherapy regimens in both neoadjuvant chemotherapy and adjuvant chemotherapy. Most responders chose for the combination of three-weekly carboplatin and paclitaxel for both PDS and NACT-IDS (87% and 84% respectively). General gynaecologists more often answered 'I do not know' compared to (semi)-specialized gynaecologists and all medical oncologists for first line chemotherapy protocol (PDS: 16% vs. 2% vs. 0%, NACT: 26% vs. 4% vs. 2% respectively). For patients treated with NACT-IDS, the preferred number of neoadjuvant cycles is three (88%), only 3% varied the number of neoadjuvant cycles based on chemotherapy response. After optimal and suboptimal debulking surgery, most responders chose for three adjuvant cycles (91% and 88% respectively) and a minority chose for more than three cycles (4% and 7% respectively). Other chemotherapy regimens that were used in daily practice were weekly carboplatin and weekly paclitaxel (42% PDS and 37% NACT-IDS), carboplatin monotherapy (43% PDS and 36% NACT-IDS) and intraperitoneal chemotherapy (18% PDS and 3% NACT-IDS).

Table 3
Use and adoption of NACT-IDS by gynaecologists and medical-oncologists, stratified by type of hospital.

	(Semi-)specialized gynaecologists [a]	General gynaecologists	(Semi-)specialized medical oncologists [a]	General medical oncologists	p-value [b]
Sufficient evidence for NACT-IDS					
Before Vergote trial	2 (4.8)	10 (27.0)	6 (46.2)	22 (57.9)	**<0.001**
Present	38 (86.4)	31 (77.5)	12 (80.0)	39 (97.5)	0.061
NACT-IDS as preferred treatment					**0.001**
Yes	10 (22.7)	18 (45.0)	8 (53.3)	26 (65.0)	
No	34 (77.3)	22 (55.0)	7 (46.7)	14 (35.0)	

[a] Responders from semi-specialized and specialized hospitals were categorized as one group and depicted under a.
[b] Chi-square test.

Discussion

In this survey study, we evaluated the views of Dutch gynaecologists and medical oncologists on NACT-IDS for advanced stage primary ovarian cancer. The study was executed as an update of two earlier survey studies among the SGO and ESGO members. Our results show that a substantial number of responders consider NACT-IDS as an alternative treatment approach for patients with FIGO IIIC or IV disease. In addition, the majority of medical oncologists prefer NACT-IDS to PDS in this group, whereas gynaecologists still more often opt for PDS as first line treatment.

The decision to schedule patients for PDS or NACT-IDS is mainly based on pre-operative imaging in relation to the probability of a successful debulking surgery ($\leq$1 cm of residual disease in maximal diameter). In concordance with the previous survey studies, however, the majority of physicians indicated that the outcome of debulking surgery could not reliably be predicted [4,5]. Bulky disease in the upper abdomen, FIGO stage IV disease, metastases near the porta hepatica, poor performance status, and an inevitable bowel resection were the most commonly mentioned additional reasons to choose NACT-IDS.

A prior survey among SGO members, conducted in 2009 before the publication of the EORTC trial, concluded that responders considered the available evidence in favour of NACT-IDS as insufficient (82%). In a second survey conducted shortly after publication of the EORTC trial, the ESGO members were more convinced of the available evidence, with 70% accepting NACT-IDS as an alternative treatment option. This latter study, however, reported large variation between European countries in their use of NACT-IDS (e.g. 16% in Germany versus 100% in Belgium) [5]. At present, our results are in line with the results of the ESGO survey, with an adoption rate of 86%. In addition, most responders started to use NACT-IDS after the publication of the EORTC trial. This is supported by the increase in the use of NACT-IDS over the last years in the Netherlands [13].

The CHORUS trial and the EORTC trial showed similar overall- and progression- free survival for patients after PDS and NACT-IDS, but postoperative morbidity was lower after NACT-IDS [3,6]. This raises the question why NACT-IDS is not considered the preferred treatment for all FIGO IIIC and IV patients. Among the SGO members in 2009, 74% thought PDS should be the preferred treatment, unfortunately this was not evaluated among the ESGO members. Our results show more diversion. Still, 55% of all responders were convinced of PDS as first line treatment, although there was a significant difference between gynaecologists and medical oncologists (67% and 38% respectively, $p = 0.001$).

The diversity in uptake of NACT-IDS may reflect the ongoing discussion regarding the results of the clinical trials. These studies are critically evaluated as the non-inferiority outcome might be caused by the rather low percentages of patients with no macroscopic residual disease after debulking surgery. Consequently, survival rates in these studies were lower when compared to international non-randomized studies [15–17]. These outcomes may suggests that NACT-IDS could be an alternative approach in patients with extended tumour burden and a low probability to complete PDS, as the amount of residual disease after debulking surgery is the most prognostic factor for prolonged overall survival [2,3,6]. However, if the likelihood to no macroscopic residual disease is high, NACT-IDS should not be the first choice of treatment for these patients, which is supported by the majority of gynaecologists and medical oncologists from specialized hospitals. Besides evidence-based rationale, logistic reasons may also play a role in the use of NACT-IDS in the Netherlands. As the surgical treatment is centralized, extended wait lists for surgery or reduced intensive care capacity might be reasons to start with NACT in general hospitals.

The addition of intraperitoneal chemotherapy to the primary treatment improves overall survival in patients who underwent PDS with minimal residual disease [18–21]. This treatment is accompanied with an increase in side effects [21], so optimal patient selection and adequate experience with intraperitoneal chemotherapy are crucial. In our study, 18% of responders used intraperitoneal chemotherapy after primary surgery in Dutch daily practice. The possibility of intraperitoneal chemotherapy after successful PDS may persuade physicians to pursue PDS in order to improve outcomes for EOC patients. Furthermore there are several trials that investigate the efficacy and safety of hyperthermic intraperitoneal chemotherapy (HIPEC) during interval debulking surgery, such as the CHORINE trial (NCT01628380) and the OVIHIPEC trial (NCT00426257) [22,23]. In our study only 3% of responders used intraperitoneal chemotherapy during interval debulking surgery in daily practice, probably related to the OVIHIPEC trial. This was lower compared to the SGO members (42–49% depending on the outcome of surgery), but comparable to the ESGO members (2.6%). The addition of HIPEC during interval debulking surgery may be a valuable treatment opportunity in patients who cannot be optimally debulked in a primary setting [23].

Our study has some limitations. We used the same questionnaire as the two prior surveys, which has not been validated however, and added some non-validated questions. As a result, we cannot be certain that the results reliably reflect daily practice [24]. Furthermore, our overall response rate was only 49% (167/340). Since we could not identify the opinions of the non-responders, the results of this survey may not be generalizable. In addition, we included gynaecologists and medical oncologist from all Dutch hospitals. While increasing the sample size and reflecting the views of physicians in the entire country, experience and knowledge about the most recent developments in ovarian cancer treatment may be lacking in responders from general hospitals. This is reflected by the percentage of gynaecologists and medical oncologists from general hospitals that were not aware of the key RCTs for advanced ovarian cancer patients (data not shown) [3,6].

This survey study contributes to the debate about the timing of surgery in advanced ovarian cancer. The adoption rate of neoadjuvant chemotherapy is high for advanced ovarian cancer patients in the Netherlands, and even first choice of treatment in FIGO IIIC and IV patients according to a majority of medical oncologists. Semi-specialized gynaecologists, however, still more often opt for PDS as first line treatment, and this choice seems to depend on the probability of successful surgery in the primary setting. This emphasizes the great importance of our selection processes to ensure that every patient undergoes the most optimal treatment.

Conflict of interest statement

None.

Funding

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

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ejogrb.2018.02.029.

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