Gynecologic Oncology Reports 20 (2017) 47–50

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

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

Survey article

The role of neoadjuvant chemotherapy in the management of patients with advanced stage ovarian cancer: Survey results from members of the society of gynecologic oncologists, a 5-year follow-up

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ARTICLE INFO

Article history:
Received 24 May 2016
Received in revised form 9 February 2017
Accepted 10 February 2017
Available online 16 February 2017

1. Introduction

Ovarian cancer is the leading cause of death among patients with gynecologic malignancies (Dewdney et al., 2010; Chiva et al., 2016; Gomez-Hidalgo et al., 2015a; Aletti et al., 2006; Markauskas et al., 2014; Rauh-Hain et al., 2012; Vergote et al., 2010; Le et al., 2011), most women (70–80%) present with stage III–IV disease (Dewdney et al., 2010). Largely, this results from lack of specific symptoms and reliable early detection methods.

Surgery and chemotherapy are gold standard for newly diagnosed ovarian cancer (Dewdney et al., 2010; Markauskas et al., 2014; Rauh-Hain et al., 2012; Vergote et al., 1998; Chi et al., 2012; Zheng and Gao, 2012). Primary debulking surgery (PDS) and surgical staging, followed by platinum/taxane chemotherapy is the standard of care (Dewdney et al., 2010; Gomez-Hidalgo et al., 2015a). Recently, studies on neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) for advanced ovarian cancer question the standard approach (Dewdney et al., 2010; Chiva et al., 2016; Markauskas et al., 2014; Rauh-Hain et al., 2012; Vergote et al., 2010, 1998; Chi et al., 2012; Zheng and Gao, 2012; Sato and Itamochi, 2014; Kehoe et al., 2015).

Residual disease is a well-known prognostic factor for survival, justifying extensive cytoreductive surgery (Dewdney et al., 2010; Chiva et al., 2016; Aletti et al., 2006; Bristow et al., 2002). Patients benefit most from surgical intervention when complete cytoreduction is achieved (Gomez-Hidalgo et al., 2015a). This is often difficult based on disease burden, location, and medical co-morbidities (Dewdney et al., 2010). No single modality consistently and accurately predicts complete cytoreduction, nor identifies patients who benefit most from surgical intervention.

Retrospective studies show NACT/IDS requires less radical procedures than PDS and results in higher rates of complete resection, less mortality and equivalent overall survival (Chiva et al., 2016; Markauskas et al., 2014; Rauh-Hain et al., 2012; Vergote et al., 1998; Chi et al., 2012; Zheng and Gao, 2012; Sato and Itamochi, 2014). However, several studies failed to demonstrate benefit of IDS among patients whose disease couldn't be optimally debulked after 3 courses of chemotherapy (Chiva et al., 2016; Rose et al., 2004). Both the EORTC and CHORUS trials where PDS/chemotherapy and NACT/IDS were studied, demonstrated survival with NACT/IDS was not inferior to PDS/chemotherapy for patients with stage IIIC-IV disease (Vergote et al., 2010; Kehoe et al., 2015).

Originally, this survey was sent in 2010, prior to publication of above clinical trials. In 2010, most responding Society of Gynecologic Oncologists (SGO) members didn't treat patients with NACT/IDS, nor did they consider available evidence sufficient to support this approach (Dewdney et al., 2010). SGO members were re-surveyed to assess patterns of care regarding NACT/IDS for advanced ovarian, fallopian tube, and primary peritoneal carcinoma. Our objective was to identify patterns of care in advanced ovarian cancer and compare them to responses in 2010.

2. Methods/materials

The Rush University Institutional Review Board (15042003-IRB01) approved of this study and it was completed through administration of a non-validated electronic survey. We utilized the same electronic survey from 2010 (Supplemental Fig. 1). We assessed demographics, practice characteristics, current opinions, initial approaches to management of ovarian cancer, and evaluated indications for NACT/IDS. Membership list was obtained from SGO by completion of their online E-survey application. The 20-item survey was distributed in English to working e-mail addresses (n = 1835), and results were collected using commercially

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http://dx.doi.org/10.1016/j.gore.2017.02.005

available online software (http://www.surveymonkey.com). An opt-out option was provided.

Demographics were summarized with descriptive statistics. Statistical analysis was performed using frequency distributions and Chi-square test to detect differences between groups. Data from 2015 was assumed independent from 2010.

3. Results

3.1. Demographics

267 responses were obtained from 1835 working e-mail addresses (response rate, 15%). Recipients who opted out (n = 112) were not included in analysis. Most were male (56%) and with >15 years experience (35%) (Table 1). Most were gynecologic oncologists; 2.5% identified as medical oncologists. Most, (60%) identified practice type as "academic", 24% as "private with academic affiliation", 13% as "private", 2% as "military", and 1% as "other". Most, (89%) practice in the USA, 1% in Canada, 4% in Europe and 6% in Asia, Central/South America or Australia/New Zealand (Table 1). Majority (80%) manages ovarian cancer both as a surgeon and oncologist; 17% state role limited to surgical intervention (Table 1). Many (42%) state they see 5–15 new patients with ovarian cancer per month and 44% reported <5 new patients per month.

3.2. Self-reported rates

Most stated rate of optimal primary cytoreduction > 60%, 35% reported a rate between 61 and 80% and 41% reported a rate > 80% (Table 2). Only 15% identified rate < 60% (Table 2). A significant difference of reported optimal cytoreduction was found between males/females, years of experience, but not practice type (Table 2). Of note, corresponding data from 2010 can be found in Supplemental Fig. 2.

Most (64%) used NACT between 11 and 40% of the time for treatment of stage IIIC/IV disease, 25% used NACT < 10%, and 11% used NACT > 40% of the time for treatment of stage IIIC/IV disease (Table 2).

Table 1
Demographics of respondents.

	2010		2015	
	N	%	N	%
1. *Years of practice since fellowship*[a,b]				
Fellow in-training	26	7.7	23	9.2
<5 years	77	22.8	74	29.5
5–10 years	56	16.6	44	17.5
11–15 years	44	13.1	23	9.2
>15 years	134	39.8	87	34.7
2. *Specialty*[a]				
Gynecologic oncology	331	98.2	245	97.6
Medical oncology	6	1.8	6	2.4
Radiation oncology	0	0	0	0
3. *Current practice type*[a]				
Academic	196	59.2	148	59
Private with academic affiliation	86	26	61	24.3
Private	43	13	32	12.8
Military	6	1.8	4	1.6
4. *Location*[a,b]				
USA	318	94.6	223	88.8
Canada	4	1.2	2	0.8
Europe	8	2.4	10	3.98
Other	6	1.8	16	6.4
5. *Gender*[a,b]				
Male	224	66.7	141	56.2
Female	113	33.3	110	43.8

[a] 15 non-respondents.
[b] Variance in response based on years of practice since fellowship, location, and gender was statistically significant p-value < 0.05.

3.3. Diagnosis

Many, (50%) didn't think it possible to predict optimal cytoreduction pre-operatively; when asked which modality is most helpful, 59% identified CT scan, 24% said diagnostic laparoscopy and 0.5% said CA-125.

Many respondents (95%) identified medically inoperable candidates, patients with unresectable intraparenchymal liver disease (82%), and women with bulky upper abdominal disease on pre-operative imaging (63%) as likely to benefit from NACT/IDS. Only 8% thought patients with extreme values of CA-125 were likely to benefit.

3.4. Treatment

All respondents would use carboplatin/paclitaxel for NACT. Number of cycles to give prior to surgery varied; 54% said 3 cycles, 42% said it would depend on response (Table 3). Many (47%), believed patients who received NACT with complete response should undergo an exploratory laparotomy with total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) even in the absence of gross disease (Table 3). Others (39%) stated patients should undergo laparoscopic exploration with total laparoscopic hysterectomy (TLH) and BSO in the absence of gross disease (Table 3).

If gross disease was found and optimal cytoreduction was achieved, 32% would continue with same IV chemotherapy and 42% would place a port and treat with at least two cycles of intraperitoneal (IP) chemotherapy (Table 3). Others (19%) would continue with more IV chemotherapy regardless of result (Table 3).

If microscopic disease was found, 51% would continue with same IV chemotherapy treatment, and 43% would treat with at least 2 cycles of IP chemotherapy (Table 3).

3.5. Evidence

Respondents didn't consider available evidence sufficient to justify NACT/IDS (68%). Additionally, the majority doesn't think it should be the preferred treatment (79%).

4. Discussion

Standard of care for newly diagnosed ovarian cancer is surgery and chemotherapy (Dewdney et al., 2010; Markauskas et al., 2014; Rauh-Hain et al., 2012; Vergote et al., 1998; Chi et al., 2012; Zheng and Gao, 2012); the optimal order has sparked controversy (Dewdney et al., 2010; Chiva et al., 2016; Markauskas et al., 2014; Rauh-Hain et al., 2012; Vergote et al., 2010, 1998; Chi et al., 2012; Zheng and Gao, 2012; Kehoe et al., 2015). Our objective was to determine whether opinions have changed regarding the use of NACT/IDS in advanced stage ovarian cancer among members of the SGO.

The EORTC trial by Vergote et al., randomized patients with stage IIIC/IV epithelial ovarian cancer to PDS/chemotherapy or NACT/IDS (Chiva et al., 2016; Vergote et al., 2010). Overall survival (OS) and progression free survival (PFS) were similar in both groups with median OS being 29 and 30 months respectively (Vergote et al., 2010). Median PFS in both groups was 12 months (Vergote et al., 2010). Authors concluded NACT/IDS was not inferior to PDS/chemotherapy for patients with stage IIIC/IV disease (Vergote et al., 2010).

The CHORUS trial by Kehoe et al., randomized women with suspected stage III/IV ovarian cancer to PDS/chemotherapy or NACT/IDS (Kehoe et al., 2015). Survival was similar in both groups although lower than predicted (Kehoe et al., 2015). Median OS was 22.6 months and 24.1 months respectively (Kehoe et al., 2015). Median PFS was 12 v 10.7 in favor of the NACT/IDS group (Kehoe et al., 2015). Authors concluded survival with NACT/IDS was non-inferior to PDS/chemotherapy in stage III/IV disease (Kehoe et al., 2015).

A large retrospective study by Chiva et al. compared the survival impact of complete cytoreduction after PDS and IDS in patients with

Table 2
Responses to selected questions according to years of experience, practice type and sex.

	Years of experience			Practice type				Sex	
	Fellow	<10 years	>10 years	Private	Private w/affiliation	Military/other	Academic	Male	Female
1. *Rate of optimal primary cytoreduction*[a]									
<20%	0 (0%)	2 (1.8%)	1 (1%)	1 (3.2%)	0 (0%)	0 (0%)	2 (1.4%)	1 (0.7%)	2 (1.9%)
21–40%	0 (0)%	3 (2.8%)	2 (1.9%)	0 (0%)	2 (3.5%)	0 (0%)	3 (2.1%)	3 (2.2%)	2 (1.9%)
41–60%	3 (13.6%)	15 (13.8%)	10 (9.6%)	3 (9.7%)	10 (17.2%)	1 (10%)	14 (9.9%)	20 (14.7%)	8 (7.6%)
61–80%	6 (27.3%)	34 (31.2%)	44 (42.3%)	14 (45.2%)	19 (32.8%)	5 (50%)	46 (32.4%)	53 (39.0%)	31 (29.5%)
>80%	9 (40.9%)	46 (42.2%)	45 (43.2%)	12 (38.7%)	25 (43.1%)	3 (30%)	60 (42.3%)	52 (38.2%)	48 (45.7%)
I don't know	4 (18.2%)	9 (8.3%)	2 (1.9%)	0 (0%)	2 (3.5%)	0 (0%)	13 (9.2%)	4 (2.9%)	11 (10.5%)
2. *Percentage of your patients who receive NACT*									
None	0 (0%)	2 (1.8%)	1 (0.9%)	0 (0%)	1 (1.7%)	0 (0%)	2 (1.4%)	2 (1.5%)	1 (1%)
1–10%	2 (10%)	18 (15.9%)	39 (36.8%)	7 (22.6%)	23 (39.7%)	1 (10%)	28 (20%)	38 (27.9%)	21 (20.4%)
11–15%	7 (35%)	47 (41.6%)	39 (36.8%)	11 (35.5%)	19 (32.8%)	6 (60%)	57 (40.7%)	47 (34.6%)	46 (44.7%)
26–40%	10 (50%)	33 (29.2%)	16 (15.1%)	9 (29.0%)	9 (15.5%)	1 (10%)	40 (28.6%)	34 (25%)	25 (24.3%)
41–60%	0 (0%)	11 (9.7%)	9 (8.5%)	2 (6.5%)	5 (8.6%)	2 (20%)	11 (7.9%)	13 (9.6%)	7 (6.8%)
61–75%	1 (5%)	2 (1.8%)	2 (1.9%)	2 (6.5%)	1 (1.7%)	0 (0%)	2 (1.4%)	2 (1.5%)	3 (2.9%)
>75%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3. *Accurately determine pre-op if a patient can be optimally cytoreduced*									
Yes	7 (35%)	38 (33.6%)	38 (35.8%)	11 (35.5%)	25 (43.1%)	4 (40%)	43 (30.7%)	43 (31.6%)	40 (38.8%)
No	8 (40%)	51 (45.1%)	60 (56.6%)	13 (41.9%)	28 (48.3%)	6 (60%)	72 (51.4%)	80 (58.8%)	39 (37.9%)
I don't know	5 (25%)	24 (21.2%)	8 (7.5%)	7 (22.6%)	5 (8.6%)	0 (0%)	25 (17.9%)	13 (9.6%)	24 (23.3%)

[a] Variance in response based on experience level and gender was statistically significant $p < 0.05$.

advanced ovarian cancer (Chiva et al., 2016). Of patients reviewed, 87% underwent PDS and 16.3% NACT/IDS (Chiva et al., 2016). One third were considered completely resected with microscopic disease (Chiva et al., 2016). After PDS, weighted average of median OS and PFS was 43 and 17 months, respectively (Chiva et al., 2016). After IDS, median OS and PFS were 33 and 14 months (Chiva et al., 2016). Authors concluded IDS didn't improve nor ensure equal benefit of complete PDS (Chiva et al., 2016).

Table 3
Responses to treatment questions.

	2010		2015	
	N	%[a]	N	%[a]
1. How many cycles before you operate?				
Standard 3 cycles	173	53.6	128	53.8
Standard 4 cycles	21	6.5	7	2.9
Variable; depends on response	135	41.8	101	42.5
6 cycles or more	5	1.5	2	0.8
2. After NACT with a complete response, you:				
LSC exploration, cytoreduction only if gross disease	12	3.8	11	4.7
Ex-lap, cytoreduction if gross residual	26	8.2	9	3.8
LSC exploration, TLH/BSO even in absence of gross disease[b]	66	20.8	92	39.2
Ex lap with TAH/BSO even in absence of gross disease[b]	225	70.8	111	47.2
Not undergo surgical exploration	5	1.6	1	0.4
Other	24	7.5	11	4.7
3. After NACT with gross residual on ID, you:				
If optimally cytoreduced place a port and treat with at least 2 IP cycles	136	42.2	98	42.1
If optimally cytoreduced continue IV chemo	139	43.2	75	32.2
Switch IV treatment to _____	16	5	2	0.9
Treat with IP regardless of cytoreductive result	1	0.3	4	1.7
Treat with more IV regardless of cytoreductive result	59	18.3	45	19.3
4. After NACT with microscopic disease on ID, you:				
At least 2 cycles of IP	157	48.9	99	42.9
Continue with same type of IV	164	51.5	118	51.1
Switch IV treatment to _____	12	3.7	7	3
Offer no treatment and start disease surveillance	2	0.6	3	1.3

Key
LSC = laparoscopic; TLH = total laparoscopic hysterectomy; BSO = bilateral salpingo-oophorectomy; TAH = total abdominal hysterectomy; IV = intravenous; IP = intraperitoneal.
[a] Percentages are based on the number of participants responding to each question, some participants marked multiple answers.
[b] denotes statistically significant difference between years $p < 0.0001$ by two-sample *t*-test.

A substantial fraction of members use intraperitoneal (IP) chemotherapy to complete therapy for women with gross (42%) or minimal (43%) disease after NACT/IDS; this has slightly declined since 2010 where 42% would treat gross disease and 49% would treat residual disease with IP chemotherapy. Results of the OV21/PETROC study demonstrate use of IP carboplatin following NACT/IDS is well tolerated and associated with lower PD9 rate compared to IV therapy, supporting our results (Mackay et al., 2016).

Fewer respondents feel they cannot accurately predict pre-operatively whether a patient can be optimally cytoreduced (50% in 2015, 62% in 2010) (Dewdney et al., 2010). CT scan remains most helpful (59% in 2015, 63% in 2010), diagnostic laparoscopy has increased in favor (24% in 2015, 19% in 2010) while CA-125 has decreased (0.5% in 2015, 18% in 2010) (Dewdney et al., 2010). Existing studies highlight diagnostic laparoscopy for assessing feasibility of optimal PDS/IDS. The Fagotti laparoscopy-based scoring system is a validated predictive index using the distribution of intra-abdominal disease for prediction of optimal cytoreduction. Cost of implementation is a concern and should serve as a hypothesis for future studies (Fagotti et al., 2005; Gomez-Hidalgo et al., 2015b).

Demographics of respondents are somewhat different from 2010. Notably, proportion of men to women, and increase in respondents from Central/South America or Australia/New Zealand (Table 1) (Dewdney et al., 2010). Demographics are overall consistent with the membership distribution of the SGO, with majorities from the USA identifying as academic gynecologic oncologists. Observed differences are likely secondary to response rates (15% in 2015, 30% in 2010).

Respondents reported a remarkably high number of new cases each month; 42% reported 5–15 new patients each month (47% in 2010). This extrapolates to 6720–20,160 new patients with ovarian cancer seen by 112 providers each year; a gross over-estimate as only an estimated 21,000 new cases were diagnosed in the US in 2015. This was also true in 2010.

Perceived rates of optimal cytoreduction were high, with 42% stating complete cytoreduction rate >80%, and 35% stating rate was 61–80% (Table 2). High reported cytoreduction rates were also seen in 2010 where 42% stated rate between 61 and 80% and 39% stated >80%. This too is a gross overestimate as this level of complete cytoreduction is likely unattainable. Perceived rates of optimal cytoreduction were similar between less (<10 years) and more experienced (>10 years)

respondents with perceived rates being 41% and 42% respectively (Table 2). This differs from 2010 where perceived rates were 15% more in less experienced respondents (Dewdney et al., 2010). This was thought to be due to aggressive surgical debulking being a newer trend (Dewdney et al., 2010). Rates of optimal cytoreduction were different between men/women (Table 2). This was not seen in 2010 (Dewdney et al., 2010) and likely results from different response rates, but does warrant further investigation.

NACT/IDS is utilized more than in 2010; roughly 60% used NACT < 10% in 2010 only 25% of respondents use NACT < 10% of the time now (Table 2) (Dewdney et al., 2010). Use of NACT/IDS was similar among respondents identifying as "academic" and "private" where 20% and 22%, respectively, used NACT < 10% of the time (Table 2). This differs from 2010 where 70% of "private" and 56% of "academic" respondents used NACT < 10% (Dewdney et al., 2010). Generalizability of these results is difficult due to significantly fewer "private" participants, as was true in 2010 (Dewdney et al., 2010).

Many (47%) would perform an exploratory laparotomy with TAH-BSO in the absence of gross visible disease (71% in 2010) (Table 3) (Dewdney et al., 2010). Others (39%) would perform a TLH-BSO in the absence of gross visible disease (21% in 2010) (Table 3) (Dewdney et al., 2010). The differences in both laparoscopic v open abdominal approach between 2010 and 2015 were statistically significant and demonstrates the increasing role of laparoscopy (Gomez-Hidalgo et al., 2015a).

Our study has several limitations. Questions were developed by the authors, and not validated. Lack of validation makes misinterpretation possible. In addition, our response rate was only 15% making it difficult to generalize findings. Additionally, majority of respondents practice in academic settings, making our results biased, representing a more academic picture. While this limitation is important to note, most SGO members practice in an academic setting.

Despite published randomized controlled trials and retrospective reviews of NACT/ID versus PDS/chemotherapy, most SGO members don't utilize this approach, nor do they consider evidence sufficient to support regular use. This was true in 2010; however, fewer respondents feel evidence is insufficient to support use of NACT/IDS (68% 2015, 82% 2010) (Dewdney et al., 2010). In this selected survey population, primarily based in the U.S., it appears we are still biased against the use of NACT/IDS; however this may be slowly changing as evidenced by the 2010 study. Barriers to greater implementation of NACT/IDS into regular practice should be evaluated in future studies. The results of our study should be used as a benchmark to continue monitoring practice patterns in the treatment of ovarian cancer.

Conflict of interest statement

The authors declare no conflict of interest.

We have no sources of support to disclose.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.gore.2017.02.005.

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