and prospective clinical studies are underway in Hong Kong [4] and Malaysia [5].

Japan has been late to address HBOC. The HBOC Awareness and Coordination Subcommittee was launched in 2013 within the Gynecological Hereditary Breast and Ovarian Cancer Committee of the Japan Society of Obstetrics and Gynecology (JSGO).

A survey of gynecologic oncologists was conducted in order to characterize the state of care and awareness of information provision for HBOC in Japan and to identify information necessary to enhance HBOC care.

Methods

Selection of participants

All gynecologic oncologists certified by the Japan Society of Gynecologic Oncology (JSGO) as specialists in the treatment of ovarian cancer in Japan were included in the survey. A total of 613 gynecologic oncologists, including those certified in 2012, was selected. The survey was conducted with the permission of the JSGO.

Measures

The study questionnaire was developed by two breast oncologists (H.B., and C.S.), a gynecologic oncologists (T.S.), and a certified genetic counselor (N.T.). It was validated by two external gynecologic oncologists via communication by e-mail. The 44 questions involved the background of the respondent, the facilities at the respondent's institution, how the family history interview is conducted, awareness of and practice behavior toward HBOC, performance of genetic testing, and performance of risk-reducing salpingo-oophorectomy (RRSO) (Table 1). Gynecologic oncologists were asked to indicate agreement with the statement on a five-point Likert scale (strongly agree, agree, somewhat disagree, disagree completely, unsure) to question B1–8, D3–4, E5–7 (Table 1) and on a four-point Likert scale (always, frequently, occasionally, rarely) to question B9–10, C1–4 (Table 1).

Procedures

The study was conducted according to government guidelines for epidemiological research. The name and affiliation of the survey recipients were collected from the JSGO website and with the assistance of the JSGO secretariat. An anonymous survey form was sent with a postage-paid return envelope to 613 gynecologic oncologists. The survey forms were mailed on April 8, 2013. The responses postmarked by April 30 were included in the analyses. The

Table 1 Questionnaire statements

A Demographics and medical background

1. What is your sex?
2. What is your age?
3. When did you graduate from medical school?
4. Are you a medical genetics specialist?
5. What is your religious background?
6. What kind of institution do you practice in?
7. Is your institution a community-based hospital for cancer care?
8. How many gynecologic oncologists are in your practice setting including you?
9. Are you the chief of the gynecology department in your practice setting?
10. Is there a department of breast surgery in your practice setting?
11. In a typical week, how many invasive gynecologic cancer surgeries are performed in your practice setting?
12. In a typical week, how many invasive gynecologic cancer patients who visit for the first time are examined in your practice setting?
13. Do you have a family history of cancer?
14. Is there a genetic counseling clinic in your practice setting?
15. Are there any medical genetics specialists in your practice setting?
16. Are there any genetic counselors in your practice setting?
17. Do you know of any department of genetics or other service that refers patients for genetic counseling?
18. In your practice setting, are there any medical genetics specialists or certified genetic counselors able to consult with patients about hereditary cancer?
19. Is information for explaining HBOC to patients available to you when required?

B Attitude toward hereditary cancer

1. I am interested in HBOC.
2. It is important to provide care with HBOC in mind.
3. I administer care with HBOC in mind.
4. I want to be involved in the care of HBOC.
5. I am able to inform patients about HBOC.
6. I am able to provide counseling to patients about HBOC genetic testing.
7. I would refer an ovarian, tubal, or peritoneal cancer patient presenting with a family history of (breast or ovarian) cancer to the department of genetics.
8. I would refer a serous ovarian, tubal, or peritoneal cancer patient presenting without a family history of (breast or ovarian) cancer to the department of genetics.
9. I provide printed information on hereditary cancer and departments of genetics to patients I suspect of having a hereditary cancer.
10. I recommend patients that I suspect of having a hereditary cancer visit the department of genetics.

C Practice behavior

1. I collect family history information (who, when, what type) when caring for cancer patients.

2. We discuss the risk of hereditary cancer of patients during case review meetings and conferences.
3. A patient with ovarian, tubal, or peritoneal cancer has consulted with me about genetics.
4. A patient with endometrial cancer has consulted with me about genetics.

D Genetic test

1. What do you consider an appropriate charge for BRCA1/BRCA2 genetic testing?
2. Do you perform genetic testing for hereditary cancer?
3. Patients with suspected HBOC should undergo genetic testing.
4. I would undergo genetic testing if I were suspected of having HBOC.

E Risk-reducing salpingo-oophorectomy (RRSO)

1. I perform RRSO.
2. About how many RRSOs do you perform annually?
3. Where are RRSO recipients referred from?
4. How are RRSOs performed (routine care, clinical studies, other)?
5. RRSO is appropriate for breast cancer patients who are positive for the BRCA mutation and have a family history of ovarian cancer.
6. RRSO is appropriate for breast cancer patients who are positive for the BRCA mutation but have no family history of ovarian cancer.
7. If I were given a diagnosis of HBOC, I would recommend RRSO for all unaffected relatives.

consent of the participants was unnecessary because the survey was anonymous. No monetary gift was awarded to those who completed the survey.

Data analysis

The people answering "strongly agree" or "agree" in response to questions B1–8 (Table 1), which involve the practice behaviors that factor in HBOC, were considered positive respondents. The people answering "always" or "frequently" in response to questions B9 and 10 (Table 1), which involve providing information on hereditary cancer and recommending that patients visit the department of genetics, were considered positive respondents. Fisher's exact test was used for correlation analysis between practice behaviors toward hereditary cancer and respondent backgrounds and between performing genetic testing and the backgrounds of the responding institutions. Univariate and multivariate analyses were conducted with a logistic regression model, and odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated. Multivariate analysis was performed for factors having a significant difference on univariate analysis. If it was found to be multicollinearity correlated among the factors, we selected the factor having the lower P value. All analyses were conducted using IBM SPSS statistics version 21. All P values were two-sided, and the statistical significance level was set at $P < 0.05$.

Results

Response rate

The response rate was calculated as the number of gynecologic oncologists completing the survey (n = 307) divided by the initial sample size (n = 613), for a 50.1 % response rate.

Background characteristics of the respondents

Of the respondents, 88 % was men and 12 % was women. Moreover, 10.1 % was younger than 40 years of age, 35.8 % was 40–49 years, 40.1 % was 50–59 years, and 12.7 % was 60 years of age or older. The median year of graduation from medical school was 1987 and ranged from 1947 to 2004. Ten of the respondents (3.3 %) were medical genetics specialists. 37.8 % of the respondents worked in a university hospital, and 75.2 % worked in a community-base hospital for cancer care. 60.4 % of the respondents worked at an institutions with 2 or fewer gynecologic oncologists. Next, 82.7 % of the respondents worked at an institution with a department of breast surgery (or with an examination by breast oncologist), 12.7 % worked at an institution where general surgeons treated breast cancer patients, and 3.9 % worked at an institution that did not offer breast cancer treatment. Moreover, 5.5 % of the respondents' institutions performed no gynecologic oncology surgeries per week, 22.5 % performed <1, 21.8 % performed 1–2, 24.4 % performed 2–3, 17.3 % performed 3–5, 6.2 % performed 5–10, and 1.3 % performed more than 10. The number of initially examined gynecologic oncology patients per week was 0 in 4.6 % of the respondents' institutions, fewer than 1 in 34.5 %, 1–2 in 30.0 %, 2–3 in 16.3 %, 3–5 in 11.4 %, and 5–10 in 2.9 %. Finally, 30.6 % of the respondents' institutions had a department of genetics, 40.4 % had a medical genetics specialist, and 19.9 % had a certified genetic counselor.

Characteristics of the institutes from which responses were received

A total of 172 respondents completed the questionnaires from the 331 institutions sent a survey (52.0 %). The background characteristics of the institutions from which responses were received are shown in Table 2. Of the 172 institutions, 54.7 % was general hospitals, 26.7 % was

Table 2 Characteristics of institutions from which responses were received

Characteristic	Number	%
Total number of institutions from which responses were received	172	
Type of affiliation		
Cancer center	12	7.0
General hospital	94	54.7
University hospital	46	26.7
Private clinic	7	4.1
Others	13	7.6
Community-based hospital for cancer care	111	64.5
Number of gynecological oncologists		
1	93	54.1
2	40	23.3
3	24	14
≥4	15	8.7
Department of breast surgery		
Present	135	78.5
Absent	27	15.7
Breast cancer treatment is not offered	10	5.8
Number of gynecologic oncology surgeries (per week)		
0–1	68	39.6
1–2	42	24.4
2–3	37	21.5
≥3	24	13.9
Unknown	1	0.6
Number of first examination patients (per week)		
0–1	76	44.2
1–2	44	25.6
2–3	25	14.5
≥3	27	15.7
Department of genetics	33	19.2
Medical genetics specialists	50	29.1
Certified genetic counselors	21	12.2

university hospitals, and 7.0 % was cancer centers. Moreover, 135 institutions (78.5 %) had a department of breast surgery. Thirty-three of the institutions (19.2 %) had a department of genetics, 50 (29.1 %) had a medical genetics specialist on staff, and 21 (12.2 %) had a certified genetic counselor.

Attitude toward hereditary cancer

The results of the survey forms on hereditary cancer by the 307 respondents are shown in Fig. 1. The percentages of oncologists responding affirmatively to "I am interested in HBOC" and "It is important to provide care with HBOC in mind" were 93.2 and 96.8 %, respectively. However, the percentages of oncologists responding positive to "I administer care with HBOC in mind," "I want to be involved in the care of HBOC," and "I am able to inform patients about HBOC" were lower, at 64.4, 58.5, and 63.1 %, respectively, and only 18.0 and 10.1 % of the respondents, respectively, were involved in the clinical care of HBOC as indicated by positive responses to "I am able to provide counseling to patients about HBOC genetic testing" and "I provide printed information on hereditary cancer and departments of genetics to patients I suspect of having a hereditary cancer."

Next, 75.2 % of the oncologists responded positive to "I would refer an ovarian, tubal, or peritoneal cancer patient presenting with a family history of (breast or ovarian) cancer to the department of genetics," with 18.0 % responding positive to "I would refer a serous ovarian, tubal, or peritoneal cancer patient presenting without a family history of (breast or ovarian) cancer to the department of genetics," but 14.1 % responded positive to "I recommend that patients I suspect of having a hereditary cancer visit the department of genetics."

With regard to the oncologists responding positive to question B9, which involves the provision of printed information on hereditary cancer to patients suspected of having a hereditary cancer, 4.4 % worked at an institution with no department of genetics, 5.9 % worked with no medical genetics specialist on staff, and 5.2 % worked with no certified genetic counselor on staff, while 23.4 % worked at an institution with a department of genetics, 16.9 % worked with a medical genetics specialist on staff, and 26.2 % worked with a certified genetic counselor on staff (Table 3). The last three were significantly higher than the first three. Because it found to be multicollinearity among institutions with a department of genetics and institutions with a genetic medical specialist on staff, we selected the factor which had the lower p value of the two. And multivariate analysis was conducted with the two factors of institutions with a department of genetics and institutions with a certified genetic counselor on staff. With regard to question B10, the percentages of respondents stating that they recommend that patients they suspect of having a hereditary cancer visit the department of genetics were significantly higher among the oncologists working at institutions with three or more gynecologic oncologists on staff, institutions with a department of genetics, institutions with a medical genetics specialist on staff, and institutions with a certified genetic counselor on staff and the oncologists who graduated from medical school in 1990 or after (Table 3). Multivariate analysis was conducted with four of these factors, excluding institutions with a medical genetics specialist on staff for the reason given in relation to question B9. For both questions B9 and B10, significantly more oncologists working in an institution with a department of genetics answered positive.

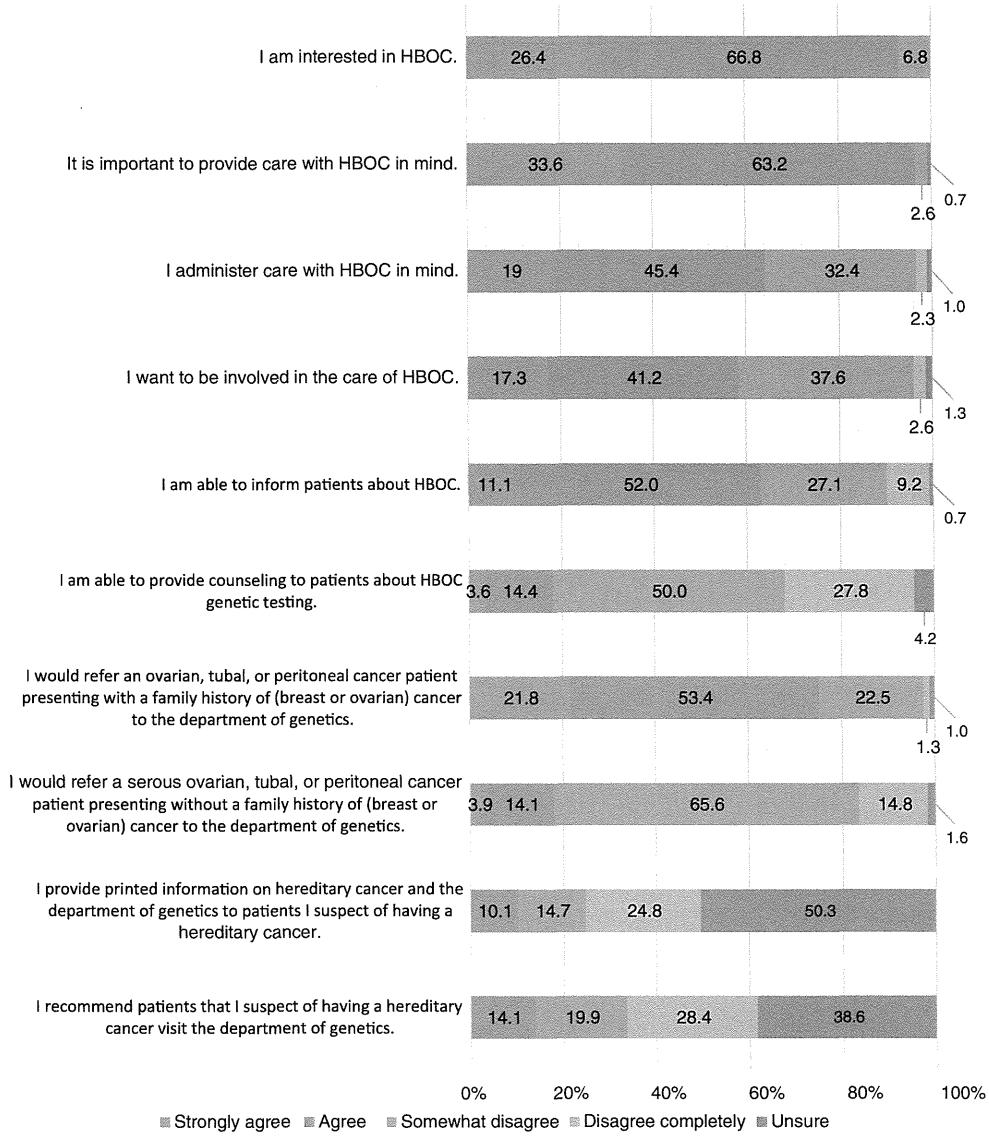


Fig. 1 Attitude toward hereditary cancer

Practice behavior

When asked how frequently they collect family history information, 60.5 % responded they always do, 23.5 % responded they frequently do, 12.7 % responded that they occasionally do, and 3.3 % responded they rarely do. The person collecting the family history information was a doctor in 73.8 % of the cases, a nurse in 16.6 % of the cases, a certified genetic counselor in 2.2 % of the cases, and another person in 7.4 % of the cases. Overall, 73.9 % of the respondents reported collecting a family history information at only the initial examination, and 2.2 % stated that they asked for periodic updates. With regard to the extent of the interview, 15.6 % of the respondents stated "only with an interview form," 36.4 % asked "Does any family member have cancer?", 17.0 % stated "as self-reported by the patient," and 26.9 % stated "with as much detail about the type and age of cancer as possible." Finally, 52 % of the respondents reported that a patient with ovarian, tubal, or peritoneal cancer had consulted with them about genetics.

Genetic testing

The results of univariate and multivariate analyses of the status of genetic testing and institutional background factors are shown in Table 4. A total of 29 institutions (16.9 %) conducted genetic testing for BRCA1/2. Univariate analysis showed that performance of genetic testing was significantly higher at university hospitals, community-base hospital for cancer care, and other institutions that care for many cancer patients, institutions with many gynecologic oncologists on staff, institutions with a department of breast surgery, institutions with many cancer

Table 3 Factors associated with positive attitude toward hereditary cancer

Variable	I provide my patients with materials about hereditary cancer when I suspect that my patients may have hereditary cancer					I suggest my patients have a genetic medical examination when I suspect that my patients may have hereditary cancer				
	Univariate analysis			Multivariate analysis[a]		Univariate analysis			Multivariate analysis[a]	
	N	%	*P*	*P*	OR (95 % CI)	N	%	*P*	*P*	OR (95 % CI)
Sex			0.322					0.131		
Female (n = 37)	5	13.5				8	21.6			
Male (n = 267)	26	9.8				35	13.2			
Age (years)			0.487					0.125		
≤49 (n = 141)	15	10.6				24	17.0			
≥50 (n = 163)	16	9.9				19	11.7			
Year graduated from medical school			0.462					0.024	0.193	
≤1989 (n = 134)	16	11.9				17	12.7			1.00
≥1990 (n = 169)	14	8.3				25	14.8			1.72 (0.76–3.88)
Medical genetics specialists			0.270					0.038		
Yes (n = 10)	2	20.0				4	40.0			
No (n = 297)	29	9.8				39	13.2			
Type of affiliation			0.546					0.353		
University hospital (n = 116)	12	10.3				18	15.5			
Others (n = 191)	19	10.1				25	13.3			
Number of gynecological oncologists			0.086					0.006	0.566	
1–2 (n = 186)	21	8.7				27	11.2			1.00
≥3 (n = 120)	10	15.6				16	25.0			0.75 (0.28–1.99)
Department of breast surgery			0.077					0.230		
Present (n = 254)	29	11.5				38	15.0			
Absent (n = 51)	2	3.8				5	9.6			
Number of gynecological oncology surgeries (per week)			0.124					0.090		
0–2 (n = 153)	12	7.9				17	11.2			
≥2 (n = 151)	19	12.6				26	17.2			
Number of first examination patients (per week)			0.343					0.067		
0–2 (n = 212)	20	9.5				25	11.8			
≥2 (n = 94)	11	11.7				18	19.1			
Department of genetics			<0.001	0.004				<0.001	0.014	
Present (n = 93)	22	23.4			4.26 (1.07–17.07)	30	31.9			5.55 (1.42–21.64)
Absent (n = 207)	9	4.4			1.00	13	6.3			1.00
Medical genetics specialists			0.003					0.002		
Present (n = 123)	21	16.9				28	22.6			
Absent (n = 154)	9	5.9				14	9.2			
Certified genetic counselors			<0.001	0.257				<0.001	0.269	
Present (n = 60)	16	26.2			2.18 (0.57–8.38)	23	37.7			2.02 (0.58–7.02)
Absent (n = 192)	10	5.2			1.00	15	7.9			1.00
Family history of cancer			0.377					0.182		
Present (n = 188)	18	9.6				22	11.7			
Absent (n = 105)	12	11.4				17	16.2			

[a] In the presence of multicollinearity among the factors, we selected the factor having the lower *P* value for the multivariate analysis. *N* Number of respondents answering "strongly agree" or "agree", *OR* Odds ratios, *CI* 95 % confidence intervals

Table 4 Factors associated genetic testing

Variable	Univariate analysis			Multivariate analysis[a]	
	Number	%	*P*	*P*	OR (95 % CI)
Type of affiliation			0.014		
University hospital	13	31.7			
Others	16	14.0			
Community-based hospital for cancer care			0.007	0.838	
Yes	25	24.5			1.17 (0.26–5.24)
No	4	7.5			1.00
Number of gynecological oncologists			0.005	0.933	
1–2	22	15.6			1.00
≥3	7	50.0			0.93 (0.15–5.67)
Department of breast surgery			0.025	0.931	
Present	27	22.1			1.08 (0.18–6.73)
Absent	2	6.1			1.00
Number of gynecological oncology surgeries (per week)			0.001	0.603	
0–2	11	11.1			1.00
≥2	18	32.7			1.40 (0.39–5.04)
Number of first examination patients (per week)			0.002		
0–2	13	12.0			
≥2	16	34.0			
Department of genetics			<0.001	0.001	
Present	19	63.3			18.85 (3.49–101.83)
Absent	10	8.1			1.00
Medical genetics specialists			<0.001		
Present	20	45.5			
Absent	8	8.1			
Certified genetic counselors			<0.001	0.651	
Present	13	68.4			1.48 (0.27–8.13)
Absent	14	11.7			1.00

[a] In the presence of multicollinearity among the factors, we selected the factor having the lower *P* value for the multivariate analysis. *OR* Odds ratios, *CI* 95 % confidence intervals

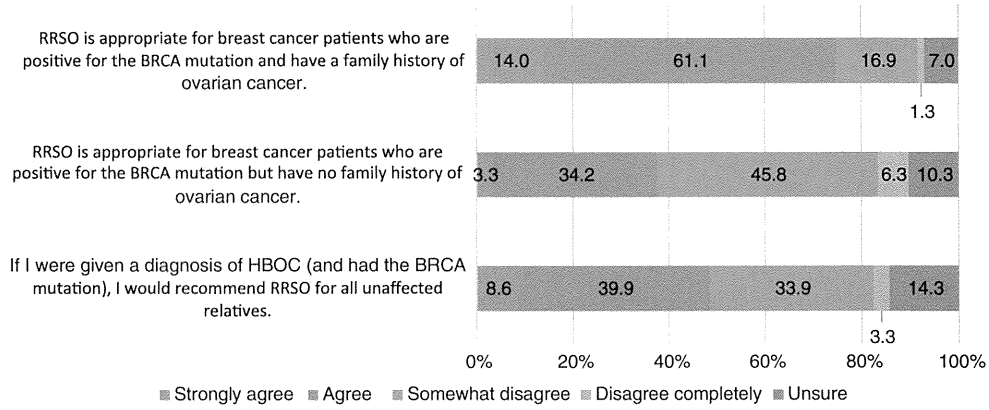
patients, and institutions with a well-established system for a department of genetics. There were close correlations between university hospitals and designated cancer hospitals, the number of initial examinations of gynecologic cancer patients and number of surgeries, and the presence of a department of genetics and the presence of a medical genetics specialist, so the ones with the lower *P* values were selected for the following multivariate analysis. Multivariate analysis was conducted with the six factors of whether or not the institution was the community-base hospital for cancer care, the number of gynecologic oncologists on staff, whether a department of breast surgery was present, the number of gynecologic oncology surgeries performed, whether or not a department of genetics was present, and whether or not a certified genetic counselor was present. Genetic testing was performed independently significantly more frequently at institutions with a department of genetics.

The BRCA1/BRCA2 testing available in Japan is not covered by insurance. Tests for the proband cost around ¥200,000, nearly equivalent to US$2,000 (US$1 = ¥100). The median charge the respondents considered appropriate for testing was ¥50,000 (US$500), ranging from ¥1,000 to ¥350,000 (US$10 to US$3,500). Moreover, 77.1 % of the respondents indicated that patients with suspected HBOC should undergo genetic testing, and 73.8 % indicated that they would undergo genetic testing if they were suspected of having HBOC.

Risk-reducing salpingo-oophorectomy (RRSO)

Risk-reducing salpingo-oophorectomy (RRSO) was performed at eight institutions (4.7 %). Four institutions performed one RRSO annually, and two institutions performed two RRSOs annually. Three and five RRSOs were performed annually at one institution each.

Fig. 2 Attitude toward RRSO



Overall, 74.8 % of the respondents answered positive to "RRSO is appropriate for breast cancer patients who are positive for the BRCA mutation and have a family history of ovarian cancer," but 37.4 % responded positive to "RRSO is appropriate for breast cancer patients who are positive for the BRCA mutation but have no family history of ovarian cancer" (Fig. 2). Moreover, 48.5 % of the respondents answered positive to "If I were given a diagnosis of HBOC (and had the BRCA mutation), I would recommend RRSO for all unaffected relatives." The rates of positive responses to these questions among the respondents working at an institution with a department of genetics were 80.4 % ($P = 0.095$), 51.1 % ($P = 0.001$), and 59.8 % ($P = 0.005$), respectively.

Discussion

No nationwide survey on HBOC had been conducted among obstetricians and gynecologists in Japan. The relatively high response rate of 50.1 % suggests that gynecologic oncologists have a high interest in HBOC.

Overall, 93.2 % of the respondents indicated they were interested in HBOC, and 96.8 % indicated that it is important to provide care with HBOC in mind, thus the survey respondents have a high interest in HBOC. These figures indicate a steadily growing interest with information being repeatedly provided in educational seminars and other events by the JSOG and JSGO. However, the survey may suffer from a participation bias, with respondents being interested in HBOC than non-respondents. With about 60 % of respondents stating "I administer care with HBOC in mind" and "I want to be involved in the care of HBOC," only 2 in 3 doctors is able to explain HBOC to patients, fewer than 1 in 5 doctors is able to give counseling to patients, 1 in 10 doctors provides printed information to patients suspected of having a hereditary cancer, and 1 in 7 doctors recommends that patients suspected of having a hereditary cancer visit the department of genetics. The survey showed the reality that few doctors provide HBOC information to patients, in contrast to the high awareness of HBOC among gynecologic oncologists. In this study, regrettably, because we did not investigate gynecologic oncologists' knowledge of HBOC, we were unable to assess the relationship between their knowledge and attitude toward HBOC.

Significantly more oncologists working in an institution with a department of genetics provided printed information on hereditary cancer to patients and recommended that such patients visit the department of genetics. This indicates that the presence of a department of genetics is required to establish a proper system for managing HBOC. Among 843 breast cancer specialists in Japan, a survey of the practice patterns regarding cancer genetic issues for young breast cancer patients was conducted in 2010 [6]. The study indicated that physicians working in a facility with a multi-disciplinary team and cancer genetic services had positive attitudes and behavior regarding referral to cancer genetic specialists. Only 30.6 % of the respondents and 19.2 % of the responding institutions had a department of genetics. These figures highlight the need to develop a proper management structure for HBOC and other hereditary cancer in Japan. However, medical genetics specialists and certified genetic counselors, the member of departments of genetics, were on staff in only 29.1 and 12.2 % of the institutions, respectively. Japan has only 951 medical genetics specialists (as of October 2013) [7] and 138 certified genetic counselors (as of February 2013) [8]. Moreover, many specialize in fetal diagnostics, with few likely specializing in oncology. Cancer genetics specialists are still lacking.

The present survey showed that the actual cost of BRCA1/2 genetic testing for the proband is highly disparate from the cost gynecologic oncologists consider appropriate. The high cost of genetic testing is one factor hindering wider use. In Western countries, genetic testing

are already covered under health insurance, and genetic analysis of BRCA is widely used when planing treatment procedures, cancer prevention, or surveillance. In South Korea, genetic testing are covered under health insurance. The patient may undergo testing by paying but 5 % of the US$882 cost (about 4,000–5,000 Japanese yen), so about 90 % of people who need genetic testing actually undergo testing. A database of BRCA-positive patients is being developed in the country. It appears time to consider Japanese health insurance to cover BRCA1/2 genetic testing for high-risk individuals and relatives of the proband.

Genetic testing is significant not in that they detect mutation carriers but in that they help manage the health of individuals by subsequently planning surveillance and cancer prevention [2]. However, in a randomized controlled trial of ovarian cancer screening in 78,216 participants, it was concluded that, in the general population, screening with serum CA125 measurement and transvaginal ultrasound did not reduce ovarian cancer mortality [9]. HBOC-related ovarian cancer is more likely to be of serous histology [10], but Horiuchi stated the following. Eleven patients with a diagnosis of serous ovarian adenocarcinoma underwent transvaginal ultrasound 2–12 months (median: 3 months) before the diagnosis. The findings were normal for 9, 1 had benign cystic lesions, and 1 had endometriosis, but the disease in stage III developed at the time of diagnosis in 8 of these patients [11]. With no established screening for the early detection of ovarian cancer [12], RRSO is the most effective measure for preventing ovarian cancer in carriers of the BRCA1/2 mutation [13–16]. Fewer than 5 % of institutions perform RRSO in Japan. Assuming that the number of procedures is similar in the institutions that did not respond, only about 30 procedures are performed annually in Japan, partially because RRSO is not covered under health insurance. Since the effect of ovarian cancer screening is poor, the need for development of services which allows BRCA1/2 mutation carriers to undergo RRSO if they expect should be discussed. Aiming for the accreditation of advanced medical care might be a good first step toward such a service.

Conclusions

The present survey showed that, although many oncologists have a positive attitude toward genetic testing, genetic testing is currently available at few institutions. The provision of information to patients, recommending that patients visit the department of genetics, and the performance of genetic testing were dependent on whether a department of genetics was present in the respondent's institution. It is important to develop human resources and cancer genetic services with medical genetics specialists and certified genetic counselors.

The survey also found that RRSO is not widely performed in Japan. Since the effect of ovarian cancer screening is poor for BRCA1/2 mutation carriers and unaffected persons likely to have this mutation, debate about RRSO must be advanced so that RRSO is available for those requesting it.

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Conflict of interest The authors declare that they have no conflict of interest.

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クリニカルカンファレンス 5（腫瘍）—標準治療になるのに何が不足か？—

1. 上皮性進行卵巣癌に対するネオアジュバント化学療法

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Neoadjuvant Chemotherapy for Advanced Ovarian Cancer

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1. はじめに

進行卵巣癌に対する標準治療は，最初に手術を行い術後に化学療法を行う手術先行治療である．5 年生存率 20%～30% 以下と，予後不良なこの疾患の治療成績改善を目指した治療の一つに術前化学療法（NAC：neoadjuvant chemotherapy）がある．NAC 療法について解説を行い（ここでは，NAC で始まり，腫瘍縮小手術，術後化学療法と続く治療全体を NAC 療法と呼ぶ），NAC 療法が進行卵巣癌の標準治療となるための課題についても解説する．

2. 標準治療と NAC 療法

進行卵巣癌に対する標準治療は，原発臓器，組織型の診断，進行期の診断，転移病巣の切除を目的として，初回腫瘍縮小手術（PDS：primary debulking surgery）を行い，残存腫瘍径 1～2cm 未満の optimal 手術が達成できれば化学療法を 6～8 コース追加，1～2cm を越える残存の suboptimal となれば，化学療法 3～4 コースを行い，IDS（interval debulking surgery）と呼ばれる腫瘍縮小手術を再度行い，さらに化学療法を 3～4 コース追加して臨床的寛解を目指す．Optimal が達成できれば suboptimal に比べて良好な予後が得られることが多数報告され，optimal を目指して最初に手術を行う治療が標準治療となった．

一方 NAC 療法は，臨床診断，細胞診，組織診などにより対象疾患を確認し，2～6 コースの NAC，IDS さらに 2～6 コースの術後化学療法を行い臨床的寛解を目指す治療である．従来，PDS にて，試験開腹に終わった場合や，全身状態不良で手術困難，画像診断（CT）にて，初回 optimal 不能，腹腔鏡診断にて，初回 optimal 不能された症例に対する代替的な治療であった．

3. 標準治療と NAC 療法の後方視的比較

この NAC 療法と標準治療を比較した多くの後方視的研究が報告された．多くは，NAC 療法群の方が進行した症例，PS 不良，高齢者を多く含んだ対象での比較であった．にも関わらず，NAC 療法群では，（PDS と同様の optimal 定義を用いると，）有意に高率に optimal 手術が達成できて，予後の改善には至らないが，有意差のない遜色のな

Key Words: Neoadjuvant chemotherapy, Primary debulking surgery, Interval debulking surgery, Phase III trial
今回の論文に関して，開示すべき利益相反状態はありません．

い予後が示された．また，NAC療法群では，有意な出血量，輸血割合，周囲臓器合併切除，重篤な合併症の減少，有意な手術時間，ICU滞在期間，入院期間の短縮を認めた．理論的にNAC療法は標準治療の種々の欠点を補う特徴を有しており，有効性が期待される治療であるが，NAC療法にも，問題点が指摘される．腫瘍縮小手術の機会を逸する可能性，薬剤耐性出現の可能性の増加，過度の術式縮小による根治性を損なう可能性，対象疾患の診断が不正確となる可能性，などである．NAC療法の有効性を確認するためには，前方視的な検討が必要と考えられた．

4. 第Ⅱ相feasibility試験

JCOG（Japan Clinical Oncology Group）ではNAC療法の有用性を検証するための第Ⅲ相試験の前段階として第Ⅱ相試験であるJCOG0206を行った．画像診断，細胞診によりⅢ/Ⅳ期卵巣癌，卵管癌，腹膜癌と診断された症例を登録し，全例で腹腔鏡にて臨床的診断の正誤を確認，正診と判断された症例に対して，4コースのNAC，IDS，4コースの術後化学療法からなるNAC療法を行った．化学療法は標準的なTC療法を行った．適格規準としては，他疾患の混入を減らすため，腫瘍マーカーCA125，CEAに関しても規準を設けた．登録はほぼ順調で，予定の1か月遅れで登録を完了できた．有効性に関して，NAC療法が行われた53例中22例（42%）において画像上完全奏効かつCA125<20が得られ，NAC療法は有効と判断された．臨床診断に関しては，56例中3例が腹腔鏡診断によりⅠ/Ⅱ期と診断されたが，全例が卵巣，卵管，腹膜原発で，かつ卵巣の表層上皮性間質性腫瘍相当の癌であり，総合的な正診割合は95%であった．以上より臨床的診断によりNAC療法の対象者を適切に診断可能と判断された．また，NAC療法施行症例のMST（median survival time）45M，PFS（progression free survival）は14Mと良好であった．

5. 第Ⅲ相試験

JCOGでは第Ⅱ相feasibility試験の良好な結果を受けて，NAC療法と標準治療との第Ⅲ相無作為化比較試験であるJCOG0602試験を2006年から開始した．対象は0206とほぼ同様で，今回は登録後，診断的腹腔鏡は施行せず，標準治療群（PDS群）あるいはNAC群に割り付けられた．NAC群の治療は0206と同様，PDS群では術後化療8コースで，状況により4コース後IDSを行うこととした．試験デザインは非劣性試験で，NAC群が有効性で劣らず，治療侵襲の軽減など他の指標で上回ることを期待した．当初の予定より遅れたものの，2011年10月に登録を完了し，現在経過観察中である．同様の試験は，EORTC（European Organization for Research and Treatment of Cancer）やRCOG/MRC-CTU（Royal College of Obstetricians and Gynecologists / Medical Research Council Clinical Trials Unit，試験名はCHORUS [Chemotherapy or Upfront Surgery]），インドなどで行われた．4つの試験は，悪性疾患の確認方法，化学療法の種類，回数などに特徴があるが，デザインはいずれも非劣性であった．EORTC試験は，2010年に最終結果がpublishされ，NAC療法のMST 30MはIDSの29Mと遜色ないことが示され，CHORUS試験ではNAC療法のMST 24.5Mは標準治療の22.8Mと同等の治療成績であることが，2013年のASCO（American Society of Clinical Oncology）で報告された．JCOG試験などで，同様の結果が示されれば，NAC療法は進行卵巣癌の標準治療となり得ると考えられる．

6. NAC療法の課題

NAC療法は有用な治療であると期待されるが，その適用には，特に標準治療として行うには，解決すべき課題が残されている．NAC療法での手術侵襲の軽減の証明と，NAC療法対象疾患の診断，臨床進行期の診断などである．3点につき以下に解説を行う．

7. NAC療法における手術侵襲の軽減（表1）

過去の後方視的検討では，輸血量の減少，周囲臓器合併切除の減少，入院期間の短縮など手術侵

【表1】 NAC療法と標準治療の手術侵襲の比較

	EORTC 55971(2010)		CHORUS(2013, ASCO報告)	
割り付け群	PDS群 (n=336)	NAC療法群 (n=334)	PDS群 (n=276)	NAC療法群 (n=274)
手術時間	165 min (10～720)	180 min (30～560)	NA	NA
周術期死亡	2.5%	0.7%	NA	NA
出血 Grade 3/4	7.4%	4.1%	3%	7%
血管 Grade 3/4	2.5%	0%	2%	0%
感染 Grade 3/4	8.1%	1.7%	6%	3%
消化管瘻	1.0%	0.3%	NA	NA
2週以内退院割合	NA	NA	74%	92%

EORTC：European Organization for Research and Treatment of Cancer, CHORUS：Chemotherapy or Upfront Surgery, ASCO：American Society of Clinical Oncology, NA：not available

【表2】 NAC症例の臨床的進行期診断

	JCOG0206		CHORUS(PDS群)	
	術前診断	腹腔鏡診断	登録前	登録後
I	0	1	0	0
IIA	0	2*	0	2
IIB			0	5
IIC			0	5
IIIA	0	0	0	7
IIIB	0	4	0	8
IIIC	38	31	NA	174
IV	18	18	NA	41
不明	0	0	NA	8
I-IIIB	0	7 (12.5%)	0	27 (10.8%)
症例数	56	56	250	250

*2例のうち1例は開腹を行いIIIB期であることが確認された.

襲の軽減が示されてきた．EORTC試験では周術期死亡，出血，血管，感染，消化管瘻などの有害事象の頻度低下の傾向を認めたが，統計的な解析は行われておらず，手術侵襲の軽減は証明されていない．CHORUS試験においては，NAC群の方がむしろ出血の頻度の増加を認めている．血栓塞栓症や，感染はNAC群で頻度が減少する傾向が示されているが，抄録を見る限りでは統計的解析は行われていない．しかしながら，NAC群が非劣性試験で標準治療に勝るためには，治療侵襲の軽減の証明は，必須である．JCOGでは，経過観察5年以降に予定される最終解析に先立って，手術侵襲に関する統計的検討を予定している．

8. NAC療法症例における進行期診断(表2)

治療前にStaging laparotomyを行わないNAC療法では，手術所見で進行期診断を行うことが出来ない．JCOG0206試験では，登録時IIIC/IV期と診断された56例中，腹腔鏡診断でI/II期が3例(うち1例は開腹に切り替えIIIB期が確認された)であったが，他にIIIB期の症例も4例含まれており，12.5%がIIIB期以下であった．CHORUS試験ではIIIC/IV期として登録されPDS群となった250例中，27例(11%)にIIA-IIIB期症例が含まれていた．以上のように，進行期分類の亜分類まで正確に臨床的に診断することは困難である．ただし，NAC療法を標準治療として行うためには，NAC療法症例に正確に適応出来る進行期分類が必要であり，JCOGでは，まず臨床的診断でどの程度現在の手術進行期診断が可能であるか，JCOG0602登録症例にて検討する予定である．

9. NAC対象疾患の診断(表3)

JCOG0206試験では，細胞診を含む臨床的診断により登録された56例に対して診断的腹腔鏡を行い，生検にて上皮性卵巣癌に矛盾しない腺癌であることが確認された．原発診断臓器診断におい

【表3】 NAC症例の対象疾患の診断

	JCOG0206	EORTC	CHORUS
登録の条件	細胞診	組織診 or 細胞診	組織診，細胞診とも不要
最終診断			
卵巣癌	47*	NA	184
卵管癌	7*	NA	1
腹膜癌	12*	NA	15
上記いずれか	NA	NA	60
癌肉腫		5	
子宮体癌		4	
消化器腫瘍		2	3
卵巣境界悪性腫瘍		2	2
子宮頸癌		1	
奇形腫		1	
横紋筋肉腫		1	
腹膜偽粘液腫		1	1
原発不明癌			1
子宮筋腫			1
悪性所見なし			3
不明		5	3
対象外疾患割合	0%(0/56)	2.5%(17/670)	6%(11/274)

*重複を許容，NA：not available

ても，画像診断，細胞診，腫瘍マーカーを併用することにより，56例全例が，卵巣，卵管，腹膜(重複を許容)いずれかの原発である事が確認された．また，開腹手術，画像ガイド下生検，あるいは細胞診(＋腫瘍マーカー)を要するEORTC試験では対象疾患の診断の誤りは670例中，17例(2.5%)のみであった．一方，画像診断と腫瘍マーカーのみで登録可能で細胞診，組織診は不要としたCHORUS試験では，NAC群274例中少なくとも11例(6%)に他疾患の登録が認められた．LPM(low potential malignancy)2例や良性疾患4例も含まれていた．最低限，診断には細胞診を併用することが望ましく，標準治療としてNAC療法が広く行われるならば，周知が必要であると考えられた．

10. おわりに

NAC療法はEORTC，CHORUSの2つの試験で標準治療に比してOSの非劣性が示されており，JCOG試験の最終結果が待たれる．NAC療法が進行卵巣癌に対する標準治療になるためには，NAC療法における治療侵襲の軽減の程度の確認，NAC症例に適応できる臨床進行期診断の確立，NAC対象症例の臨床的診断方法の周知が必要であると考えられる．

進行卵巣癌に対する術前化学療法の臨床試験

恩田貴志*

進行卵巣癌の予後改善の期待がかかる治療として，化学療法先行治療(NAC療法)が第Ⅲ相ランダム化比較試験で検討されている。EORTCやMRC-CTUの試験結果により，化学療法先行治療で標準治療と遜色のない(非劣性の)予後と治療侵襲の軽減傾向が示され，JCOG試験では化学療法先行治療全体あるいはIDSにおいて，手術回数，手術時間，出血量，輸血量などの有意な減少が示されている。今後JCOG試験の予後に関する最終結果，臨床診断による進行期診断の可能性の検討結果および新たに計画されている第Ⅲ相ランダム化比較試験の結果などが待たれる。

はじめに

婦人科悪性腫瘍のなかで，卵巣癌は最も予後不良な疾患として知られている。理由の1つは，早期発見が困難であり，60～70%の症例が診断時点で進行癌であることが挙げられる。進行卵巣癌の予後は極めて不良で，一般的な施設では5年生存率20～30%程度とされている。卵巣癌に対する標準治療は，最初に手術を行い，術後に化学療法を行う手術先行治療であるが，進行卵巣癌に対して標準治療を行う場合の種々の問題点も指摘されている。この疾患の予後改善が期待される治療の1つとして，術前化学療法(neoadjuvant chemotherapy：NAC)が挙げられる。日本臨床腫瘍研究グループ(Japan Clinical Oncology Group：JCOG)の婦人科腫瘍研究グループでは，化学療法先行治療の有用性を検証するため，第Ⅲ相ランダム化比較試験を行った。本稿では，進行卵巣癌に対するNACの臨床試験について解説を行う。

1．標準治療とNAC療法(図1)

進行卵巣癌に対する標準治療は，最初に手術を行う手術先行治療である。この手術は，原発臓器の診断，組織型の診断，進行期の診断など診断目的(staging laparotomyと呼ばれる)と，転移病巣の可及的切除の治療目的を合わせて行われ，初回腫瘍縮小手術(primary debulking surgery：PDS)と呼ばれる。標準治療では，PDSで残存腫瘍径1 cm未満のoptimal手術が達成できれば化学療法を6～8コース追加，残存が1 cmを越えるsuboptimal手術となれば，化学療法3～4コース後，IDS(interval debulking surgery)と呼ばれる腫瘍縮小手術を再度試み，化学療法をさらに3～4コース追加して臨床的寛解を目指す。Griffithsら[1]が初回の手術における残存腫瘍径と卵巣癌の予後が関連することを示して以降，optimal手術症例の予後がsuboptimal手術症例に比べて良好であることが多くの報告により確認され，初めにoptimalを目

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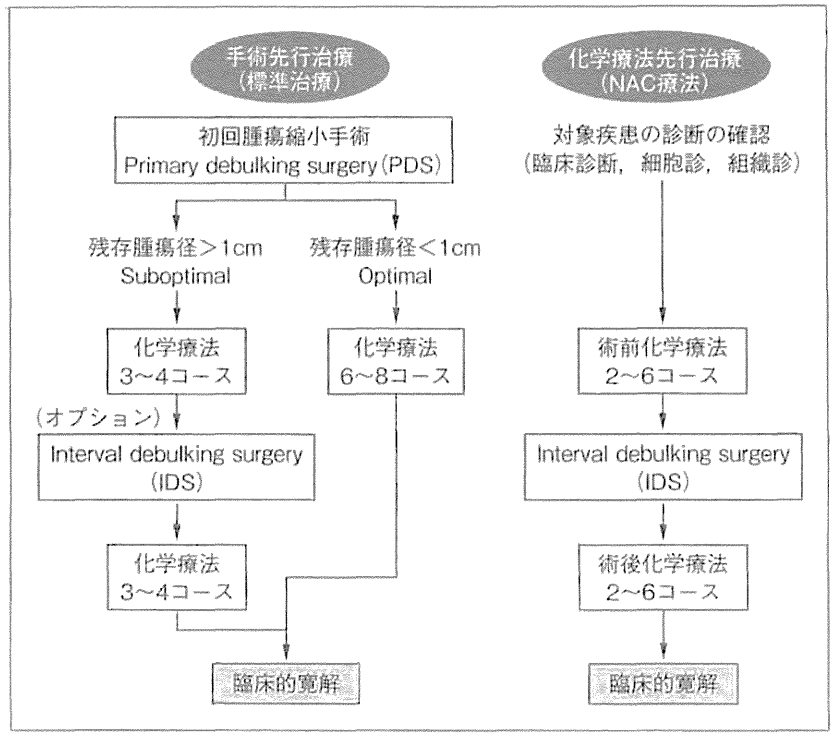

図1 手術先行治療(標準治療)と化学療法先行治療(NAC 療法)

指して PDS を行う手術先行治療が標準治療として確立されてきた。IDS に関しては，欧州の臨床試験グループ European Organization for Research and Treatment of Cancer(EORTC)が行った大規模比較試験[2]により，PDS で suboptimal に終わった症例に対して IDS を行うことで，化学療法のみを行った場合に比べ予後の改善が得られることが示されて，標準治療の一部となったが，米国の臨床試験グループ Gynecologic Oncology Group(GOG)による同様のデザインの大規模比較試験[3]では IDS の有用性が否定された。現時点では PDS 時に十分な debulking の努力がなされずに suboptimal に終わった症例に対してのみ選択される option と考えられている。

一方，化学療法先行治療(NAC 療法)は，従来 PDS にて debulking に至らず生検のみの試験開腹に終わった症例，全身状態不良で手術不能の症例，画像診断あるいは腹腔鏡診断により optimal 手術不能と判断された症例に対して，標準治療が不能であるために代替的に行われていた治療であり，臨床診断，細胞診，組織診などにより対象疾患を確認し，2～6 コースの NAC，IDS，さらに 2～6 コースの術後化学療法を行い，臨床的寛解を目指す治療である。術前の NAC，術後の追加化学療法の至適コース数に関しては，臨床試験の結果により決定されたコース数ではなく今後検討されるべき課題の 1 つであるが，標準治療との比較の臨床試験では，ともに 3～4 コースと設定されている。化学療法の種類に関しては，特に NAC 療法に適したレジメンが存在するわけではなく，標準治療と同様の化学療法が選択される。

2．標準治療と NAC 療法の non-randomized の比較

1991 年に Jacob ら[4]が，NAC 療法と標準治療を比較した後方視的研究を報告して以降，同様の比較研究が多数報告された。大部分の報告は後方視的検討で，一部に前方視的検討も見られたが，いずれも non-randomized の比較であり，NAC 療法群の方が進行した症例，PS 不良症例，

高齢者を多く含んだ不平等な対象での比較であった。にもかかわらず，NAC療法群では，標準治療群に比べて高率にoptimal手術が可能で，改善までは得られないものの，標準治療群と同等の予後が多くの報告で示された。同時に，NAC療法群では，標準治療群に比べて，特に手術関連の治療侵襲の軽減(出血量，輸血割合，周囲臓器合併切除，重篤な合併症などの減少，手術時間，ICU滞在期間，入院期間など短縮)を認めた。これらの結果により，NAC療法は進行卵巣癌に対して治療侵襲が少なく，(同等の対象で比較すれば)予後の改善も期待できる治療として注目を集め，このNAC療法の有効性の検討が必要と考えられるようになった。

3．EORTCの臨床試験

Vergoteら[5]は，単施設の検討として進行卵巣癌症例を対象として，切除可能性を試験開腹あるいは腹腔鏡により判断し，切除可能例には手術先行治療，切除不能例にはNAC療法を施すという方針で行った1989～1997年の治療成績(N＝173)を，NAC療法導入以前の，全例に手術先行治療を施すという方針で行っていた1980～1988年の治療成績(N＝112)と比較し，NAC療法導入後のほうが全体として予後良好(3年生存率，42% vs 26%)であったと報告している。時代により，化学療法や手術手技などにも違いはあると考えられるが，NAC療法は進行卵巣癌に対する標準治療として検討に値する結果と考えられた。この結果により，卵巣癌・卵管癌・腹膜癌ⅢC/Ⅳ期を対象に第Ⅲ相ランダム化比較試験EORTC55971[6]がVergoteを研究代表者として開始された。診断的腹腔鏡，試験開腹により対象疾患の診断を確認し登録を行った(症例登録が不良のため，試験途中の改訂により，穿刺細胞診と画像診断，腫瘍マーカーの組み合わせでの登録を可能としている)。卵管癌・腹膜癌は，組織学的所見，化学療法感受性，予後が卵巣癌とほぼ同一であり，卵巣・卵管の摘出なしでは鑑別診断困難であることから対象に含められた。登録例は，NAC群とPDS群に割り振られ，NAC群では，3コースの化学療法の後，腫瘍縮小手術(IDS)を行い，術後3コースの化学療法の追加，PDS群ではPDSの後，6コースの化学療法である。PDSにおいてsuboptimalに終わった症例では，化学療法3コース後にIDSを行った。化学療法としては，プラチナ製剤〔シスプラチン(CDDP)またはカルボプラチン(CBDCA)〕＋タキサン製剤〔パクリタキセル(PTX)またはドセタキセル(DTX)〕の組み合わせとした。NAC療法群で，手術侵襲の軽減が期待されることから，NAC療法の非劣性を検証するデザインで行われた。この臨床試験は1998年に開始し，2006年に登録を完了，結果が2010年に論文としてpublishされた。表1に示すように，NAC群の予後は標準治療と遜色なく，また，治療侵襲の軽減傾向が示された。

4．MRC-CTUの臨床試験

英国のMRC-CTU(Medical Research Council Clinical Trials Unit)は，当初からEORTC試験の結果とのメタ解析を予定した第Ⅱ/Ⅲ相試験であるCHORUS(Chemotherapy or Upfront Surgery)試験を行った(第Ⅲ相部分は2004年より開始，2010年に登録完了)。化学療法はCBDCAを含むレジメンで，両群とも6コースの予定，やはりNAC療法群の非劣性を示すデザインで行われた。対象はEORTC同様進行卵巣癌・卵管癌・腹膜癌であるが，この試験の特徴の1つと考えられることは，細胞診や組織診により悪性所見を確認しなくても，画像診断と腫瘍マーカー所見により登録可能としたことである。この試験の結果は正式にはpublishに至っていないが，2013年に米国の臨床腫瘍学会American Society of Clinical Oncology(ASCO)で発表された[7]。EORTC試験同様，NAC群の予後は標準治療群とほぼ同等で，治療侵襲の軽減が示された(表1)。

5．JCOGの臨床試験

1 第Ⅱ相feasibility試験

JCOGではNAC療法の有用性を検証するた

表3 先行する第Ⅲ相ランダム化比較試験の結果

EORTC55971 (2010 publish)			CHORUS (2013 ASCO presentation)		
割り付け治療	PDS(n=336)	NACT(n=334)	割り付け群	PDS(n=276)	NACT(n=274)
割り付け治療施行割合	92%	96%	割り付け治療施行割合	90%	92%
手術時間(min)	165(10-720)	180(30-560)	手術時間(min)	120(30-450)	120(30-330)
残存<1 cm (完全切除含む)	41.6%	80.6%	残存<1 cm (完全切除含む)	41%	75%
完全切除割合	19.4%	51.2%	完全切除割合	15%	35%
周術期死亡	2.5%	0.7%	周術期死亡	5.6%	0.5%
出血 G3/4	7.4%	4.1%	出血 G3/4	3%	7%
血管 G3/4	2.5%	0%	血栓塞栓症 G3/4	2%	0%
感染 G3/4	8.1%	1.7%	感染 G3/4	6%	3%
消化管瘻	1.0%	0.3%		—	—
			化学療法後何らかの G3/4	48%	40%
	——	——	術後何らかの G3/4	24%	14%
			2w 以内退院割合	74%	92%
PFS	12M	12M	PFS	10.2M	11.7M
OS	29M	30M	OS	22.8M	24.5M

(EORTC55971 は文献 6, CHORUS は文献 7 より引用)

めの第Ⅲ相試験の前段階として，NAC 療法が第Ⅲ相試験の試験治療として相応しいかを検証する事を第 1 の目的に，まず第Ⅱ相試験である JCOG0206 を 2002 年から行った[8]。画像診断，細胞診により Ⅲ/Ⅳ期卵巣癌，卵管癌，腹膜癌と診断された症例を登録し，全例で腹腔鏡にて臨床的診断の正誤を確認。正診と判断された症例に対して NAC 療法を行った。また，消化器癌など他疾患の混入を減らすため，腫瘍マーカー CA125，CEA に関しても規準を設けた。腹腔鏡を施行した理由は，本試験の第2の目的である，(第Ⅲ相試験において登録前に手術を行わなくても)臨床的診断により適切に対象疾患を診断できることを確認するためである。化学療法は標準的な TC 療法(PTX＋CBDCA)とし，進行癌であることを考慮して術前，術後とも 4 コースの設定とした。表 2 に有効性および臨床診断の正診割合に関する結果を示す。この結果，NAC 療法は第Ⅲ相試験の試験治療として相応しい治療と判断され，臨床的診断により NAC 療法の対象者を適切に診断可能と判断された。また，NAC 療法施行症例の MST(median survival time)は 45 M，PFS(progression free survival)は 14 M と良好であった。

2 第Ⅲ相ランダム化比較試験

この良好な結果を受けて，NAC 療法と標準治療との第Ⅲ相ランダム化比較試験である JCOG0602 試験を 2006 年から開始した 9)。対象は 0206 とほぼ同様で，登録症例は，診断的腹腔鏡を受けることなく手術先行治療あるいは化学療法先行治療に割り付けられた。NAC 群の治療は 0206 と同様，PDS 群では術後化療 8 コー

表2 JCOG0206 試験の結果概要

NAC 療法の有効性	
IDS 施行割合	89%(47/53)
残存腫瘍<1 cm	72%(38/53)
残存腫瘍 0	55%(29/53)
完全腫瘍消失*	42%(22/53)
腹腔鏡前臨床診断の正診割合	
原発診断，組織型の正診割合	100%(56/56)
進行期診断の正診割合	95%(53/56)
総合正診割合	95%(53/56)

*画像診断にて完全奏効かつ CA125<20(本試験で規定した endpoint)

スで，状況により 4 コース後 IDS を行うこととした。試験デザインは非劣性試験で，NAC 群が有効性で劣らず，治療侵襲の軽減など他の指標で上回ることを期待した。また，臨床的診断による進行期診断に関して JCOG0206 試験よりも詳細な解析を行う予定としている。当初の予定より約 2 年遅れて 2011 年 10 月に 301 例の登録を完了し，現在 5 年間の経過観察中である。

6．第Ⅲ相試験の結果と課題

1 NAC 群の治療成績

EORTC55971[6]，CHORUS[7]試験とも，NAC 療法群は標準治療群と比べて，遜色のない PFS，OS を示しており，NAC 群の予後における非劣性は示されたと考えられる(表 1)。ただし，これらの結果には，問題点も指摘されている。両試験とも PDS の完全切除割合(15～19%)や残存<1 cm の割合(41～42%)が低く，また手術時間中央値が短い(120～180 min)ことから十分な手術が行われておらず，標準治療が NAC 療法と近い治療となっていることが指摘されている。また，両試験とも予後が不良であり(OS が 22～30 M 程度)，不十分な手術を示唆すると同時に，結果をⅢ/Ⅳ期の標準治療として一般化できない高度進行例や PS 不良例の結果となっていることが指摘されている。今後，米国を中心に，高度の手術成績を誇る施設に限定した同様の比較試験が計画されており，JCOG 試験結果と共に結果が期待される。

2 治療侵襲の軽減

EORTC55971[6]試験では周術期死亡，出血，血管，感染，消化管瘻などの有害事象の頻度低下の傾向を認めたが，統計的な解析は行われておらず，手術侵襲の軽減は証明されていない。CHORUS[7]試験においては，周術期死亡，血栓塞栓症や，感染，化学療法後有害事象，術後有害事象，NAC 群で頻度が減少し，術後 2 週以内の退院割合は NAC 群で上昇する傾向が見られたが，手術における出血の頻度は増加がみられる。抄録を見る限りでは統計的解析は行われていないようで，治療侵襲の軽減は証明されたとは言いがたい。JCOG では，最終解析に先立ち，治療侵襲の軽減に関する解析を行い，2014 年の ASCO で報告を行った[10]。手術回数，手術時間，他臓器合併切除割合，リンパ節郭清施行割合，出血量，腹水排泄量，赤血球製剤輸血頻度，Alb 製剤輸血頻度，術後合併症，化学療法後合併症などを，標準治療と NAC 療法あるいは標準治療の PDS と NAC 療法の IDS で比較を行った。NAC 療法群では有意に高率にリンパ節郭清が行われていたが，多くの指標で標準治療に比べて治療侵襲の統計的に有意な軽減を示す結果であった。

3 臨床診断による進行期診断について

治療前に Staging laparotomy を行わない NAC 療法では，手術所見で進行期診断を行うことができない。JCOG0206[8]試験では，登録時Ⅲ/Ⅳ期と診断された 56 例中，腹腔鏡診断で 53 例(95%)がⅢ/Ⅳ期であることが確認された(他に，腹腔鏡で Ⅰ/Ⅱ期と考えられた 3 例のうち 1 例は開腹に切り替えⅢB 期が確認された)。CHORUS[7]試験ではⅢC/Ⅳ期として PDS 群に登録され，開腹所見による進行期データの得られた 242 例中，230 例(95%)がⅢ/Ⅳ期症例であった。臨床診断により，Ⅲ/Ⅳ期症例を診断することはほぼ可能と考えられる。ただし，Ⅲ期のなかでもⅢA/ⅢB 期症例も含まれており，臨床診断により亜分類まで正確に診断することは

困難である。NAC 療法が進行卵巣癌の標準治療となる場合，適応症例の臨床進行期を適切に診断することが必要であるが，JCOG0602 試験では，まずは臨床的診断でどの程度現在の手術進行期診断が適応可能であるか，0206 試験よりも詳細な検討を予定している。

おわりに

NAC 療法は EORTC55971，CHORUS の 2 つの試験で標準治療に比して OS の非劣性が示されており，また JCOG 試験により治療侵襲の有意な軽減が示されている。今後，JCOG 試験の予後の最終解析結果が待たれる。同時に，高度な手術施行施設限定の比較試験の成り行きや，JCOG による臨床診断による手術進行期診断の適応の可能性の解析結果も待たれるところである。

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ORIGINAL ARTICLE

4-step 4-h carboplatin desensitization protocol for patients with gynecological malignancies showing platinum hypersensitivity: a retrospective study

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Abstract
Background Platinum agents are essential for treating gynecological malignancies, particularly ovarian cancer. However, multiple carboplatin doses may cause hypersensitivity reactions (HSRs). Carboplatin desensitization prevents life-threatening HSRs and promotes the successful completion of planned chemotherapy.
Methods Since January 2010, carboplatin desensitization was performed at our institution. Solutions with 1/1000, 1/100, and 1/10 dilutions of carboplatin and an undiluted solution were prepared in 250 mL of 5 % glucose. Each solution was administered as a 1-h intravenous infusion (4-step 4-h protocol). This retrospective analysis was approved by the institutional review board.
Results From January 2010 to December 2013, 20 patients with gynecological malignancies (median age 62 years, range 43–74 years) received desensitization treatment. The International Federation of Gynecology and Obstetrics stages at presentation were I, II, III, and IV in 1, 1, 15, 13 patients, respectively. During first-line and second-line treatments, 3 and 17 patients, respectively, experienced carboplatin-induced HSRs. The median carboplatin cycle number was 11 (range 2–16). In the first desensitization cycle, 17 (85 %) patients completed treatment without adverse events, 2 experienced Grade 1 HSRs but completed treatment, and 1 experienced Grade 3 HSR and discontinued treatment. The first desensitization cycle completion rate was 95 %. Of 83 desensitization cycles administered, 79 (95.2 %) were completed. No treatment-related deaths occurred.
Conclusions Most patients completed the planned chemotherapy. Our protocol could be conducted safely with shorter duration and simpler procedures than previous protocols. Carboplatin desensitization seems beneficial for patients with a history of carboplatin-induced HSRs; however, the risk of HSR recurrence still remains. Desensitization should therefore be performed only by well-trained staff.

Keywords Ovarian cancer · Desensitization · Carboplatin · Hypersensitivity reaction · Gynecological malignancy

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Introduction

Platinum agents such as cisplatin and carboplatin are among the most efficacious drugs for treating gynecological malignancies of the ovary, cervix, and uterine corpus [1–3]. In patients with ovarian cancer in particular, if the interval between the end of platinum therapy and recurrence is >6 months (the so-called platinum-sensitive relapse period) [4], carboplatin rechallenge may improve overall survival [5–7]. Nonetheless, platinum agents may

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