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A survey method using three indicators (total, regimen, and each line contribution periods) to understand the actual treatment status for patients with recurrent ovarian cancer in real-world clinical practice

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Abstract

Background

There is no indicator to evaluate the “usefulness” of anticancer treatment for recurrent ovarian cancer in clinical practice.

Methods

To evaluate “usefulness,” we propose three indicators: “total,” “regimen,” and “each line contribution periods.” These indicators were applied to 183 patients with recurrent ovarian cancer who were classified as platinum-sensitive or platinum-resistant and had received anticancer treatment.

Results

Many of the patients with platinum-sensitive recurrence received platinum-based drugs with long “regimen contribution periods,” which were further prolonged by adding molecularly targeted drugs. Patients with platinum-resistant recurrence had shorter “regimen contribution periods.” “Each line contribution period” follow-up revealed that in patients with platinum-sensitive recurrence, taxane and carboplatin were administered more frequently in the first to third lines of treatment, whereas nedaplatin was administered more frequently in the fourth to sixth lines of treatment. In patients with platinum-resistant recurrence, platinum-based agents were administered at a frequency comparable to that of non-platinum as first-line treatment. Because the histological type affected prognosis, the “regimen contribution period” was examined using three histological types. In patients with platinum-sensitive recurrence clear cell carcinoma, taxane+carboplatin+bevacizumab and gemcitabine had longer “regimen contribution period” than taxane+carboplatin. In patients with platinum-resistant recurrence high-grade serous carcinoma, taxane+carboplatin had a longer “regimen contribution period” than non-platinum agents.

Conclusion

Using these three indicators, the “usefulness” of regimens or treatments in clinical practice was able to be evaluated wonderfully. However, the “regimen” and “each line contribution periods” are not suitable for statistical analysis; thus, they are used for visual judgment using box-and-whisker plots.

Introduction

Chemotherapy plays an important role in the treatment of recurrent ovarian cancer. Many cytotoxic anticancer agents and molecularly targeted drugs (MTDs) are available, and various combinations of these agents have been developed, potentially improving prognosis. Guidelines categorize recurrence into platinum-sensitive recurrence (PSR) and platinum-resistant recurrence (PRR) and describe the treatments for each type [1]. Generally, treatment is performed in accordance with the guidelines; however, there is no detailed information regarding the selection of anticancer drugs after recurrence. Although the guidelines are based on clinical trials [2, 3], the usefulness of anticancer drugs in real-world clinical practice differs from their effectiveness in clinical trials. In clinical practice, usefulness includes not only effectiveness but also other factors, such as side effects, ease of use, and patient convenience. Therefore, a retrospective analysis is necessary to evaluate the usefulness of treatment and determine how to use drugs in actual clinical practice.

Two issues are associated with determining the appropriate administration of anticancer drugs. One issue is that there are no indicators for evaluating the usefulness of anticancer drugs in clinical practice. Indicators, such as overall survival or progression-free survival, cannot be used to evaluate the efficacy of anticancer drugs [4]. The Response Evaluation Criteria in Solid Tumor is difficult to use in retrospective studies [5]. Another issue is that palliative care does not affect the usefulness of anticancer treatment. To address these two issues, we propose three new indicators. Using the indicators, we can retrospectively aggregate and analyze the administration of anticancer drugs or regimens in clinical practice. This study aimed to understand the actual treatment status for patients with recurrent ovarian cancer practice using a survey method with three indicators.

Patients and Methods

This study comprised 183 patients with recurrent ovarian cancer who underwent initial surgery between 2005 and 2020 at Nagoya University Hospital, were able to distinguish between PSR and PRR, and received recurrent chemotherapy. The follow-up was conducted until the end of December 2025. Clinical information was collected from the patients’ electronic medical records. As older cases before the classification of atypia grades for serous carcinoma were included, the histological type was reconfirmed by two pathologists.

We defined three indicators to quantify the usefulness of anticancer treatment after recurrence in clinical practice (Figure 1). At first, the common part “contributed period (CP)” was defined as the sum of the administration period and the drug holiday period. The CP immediately before devoting oneself to palliative care or before death was limited to the administration period, including the final day, and excluded the drug holiday period. The period during which anticancer treatment and palliative care were administered in combination was included in the CP. Next, three indicators were defined by dividing the CP into three types. The “total contribution period (TCP)” was defined as the period from the start date of recurrence treatment to the final day of anticancer treatment. The final day was the day of anticancer therapy and was included in the TCP. The “each line contribution period (ECP)” was defined as the CP for each line of the regimen. Consequently, “TCP” can be divided into several “ECPs.” In many cases, the administration of several regimens is repeated several times because of cancer recurrence. When the same regimen was repeated, the “regimen contribution period (RCP)” was calculated as the sum of the ECPs of the same regimen.

The number of months was calculated by dividing the number of days by 365 and multiplying it by 12 months. Patient information was compiled using Excel (chi-squared test), and statistical analyses (Kaplan–Meier, log-rank test, Cox hazard model, box-and-whisker plots) were performed using the Mac statistical analysis version 3.0 software (ESUMI Co., Ltd., Tokyo, Japan). Box-and-whisker plots show RCPs or ECPs, with the regimen names and the number of cases listed in each row. It only displayed regimens that had been provided to three or more patients. Because statistical analysis of group comparisons in RCP and ECP is unsuitable, the judgment will be based on the appearance of the plots.

The administered regimens and their abbreviations were as follows: taxanes+carboplatin (TxC) [6], taxans were added to TxC as maintenance therapy (TxCTx) [7], taxan (Tx) [8], irinotecan (CPT) [9], pegylated liposomal doxorubicin (PLD) [10-12], nogitecan (NGT) [10, 13], gemcitabine (Gem) [12], irinotecan+cisplatin (CPT-P) [14], pegylated liposomal doxorubicin+carboplatin (PLD-C) [15], nedaplatin (Ned) [16], etoposide administered orally (Oral ETP) [17], cisplatin+other cell killing anticancer drugs (Pt+others), added surgery with chemotherapy (+Op) [18, 19], added as simultaneous administration and maintenance treatment with bevacizumab (+B) [20, 21], added as maintenance treatment with poly (ADP-ribose) polymerase (PARP) inhibitors (+Pi) [22, 23], and added treatment with both bevacizumab and PARP inhibitors (+B+Pi).

Results

The patient characteristics of the 183 patients with recurrent ovarian cancer are shown in Table 1. The PSR and PRR groups were compared using five parameters. There was a significant difference in the stage distribution (p<0.001) and residual tumors after surgery (p<0.001). There were no significant differences in the age distribution (p=0.98), neoadjuvant chemotherapy (p=0.89), and histological type (p=0.11). The PSR and PRR groups exhibited different characteristics. Therefore, separate analyses were performed.

For the PSR and PRR groups, the survival rates after recurrence (SAR) and survival rates of TCP were compared using Kaplan–Meier survival curves and the log-rank test (Figure 2). The difference between the PSR and PRR groups was clear, as shown in the figure. In each of the PSR or PRR groups, the TCP curves laid below the SAR curves, respectively. The log-rank test between TCP and SAR showed significant differences in PSR (p=0.017) and PRR (p=0.008). TCP and SAR were similar but different. The numbers of confirmed alive, dead, completion of anticancer treatments, and lost to follow-up cases are shown in Table 2. The numbers of patients who lost to follow-up after completion of anticancer treatment in the PSR and PRR groups were 22 and 15, respectively. These cases can be analyzed as those for which follow-up was terminated to evaluate the usefulness of anticancer drug treatment.

Survival analysis using the TCP is shown in Tables 3 and 4 for the patients with PSR and PRR, respectively. There were no significant differences in TCP survival rates with respect to age, early or advanced International Federation of Gynecology and Obstetrics stage, neoadjuvant chemotherapy, or the state of the residual tumor at the end of surgery in each group of patients with PSR and PRR. Histological type influenced the TCP. The TCP for clear cell carcinoma (CCC) and mucinous carcinoma in patients with PSR showed significantly poorer prognoses than high-grade serous carcinoma (HGSC) according to the univariate and multivariate analyses of Cox proportional hazards model in Tables 3. The TCP for CCC in patients with PRR showed significantly poorer prognosis than HGSC according to univariate analysis in Table 4. As shown here, it is possible to analyze the TCP survival rate parameters.

In the box-and-whisker plots of the RCP, the patients with PSR and PRR are shown in Figure 3a and 3b, respectively. In both figures, the upper rows represent platinum-based regimens, whereas the lower rows represent non-platinum regimens. The order of regimen names was based on the main medications used. In Figure 3a, among the platinum-based regimens, TxC was the most commonly administered (64 patients). Ned was also administered to 42 patients, which was a largely significant number of patients. Among the non-platinum agents, PLD, Gem, Tx, CPT, and NGT were also frequently administered. The platinum-based regimens with RCPs longer than that of TxC were TxC+Op, TxC+Pi, TxC+B, and Ned+Pi. The non-platinum regimens, except for Tx+B and Tx+Op, showed shorter RCPs than the TxC regimen. RCPs were longer in patients treated with MTDs, such as bevacizumab or PARP inhibitors. In Figure 3b, despite the PRR, 23 and 21 patients received TxC and Ned, which compromised platinum agents, respectively. Gem and PLD, which are non-platinum agents, were administered in 35 and 29 patients, respectively. The RCPs were short in all the regimen groups. Using the RCP, we obtained a comprehensive understanding of recurrent chemotherapy.

Figure 4 shows the box-and-whisker plots of ECP and the change in ECPs due to repeated regimen lines for recurrence from the first to the sixth lines. The PSR and PRR cases are shown in Figure 4a and 4b, respectively. The order of the regimens in the plots was determined using the same rules as those shown in Figure 3. As treatment progressed in both patients with PSR and PRR, the number of patients per line decreased and the ECPs shortened. In patients with PSR shown in Figure 4a, TxC was frequently used in the first to third lines, whereas Ned was frequently used in the fourth to sixth lines. Patients administered with PARP inhibitors were observed in the first and second-lines, but not in the third line or beyond. However, non-platinum agents were administered in the second line and beyond. Among the non-platinum drugs, Gem and PLD were the most frequently administered. In patients with PRR shown in Figure 4b, platinum-based regimens were used in many first-line treatments, and longer ECPs were observed in platinum-based regimens than in non-platinum regimens. MTDs were not administered for patients with PRR shown in the plots. Overall, the ECP was short in patients with PRR. Using the ECP allowed us to understand how relapse treatments changes as the line progresses.

Figure 5 shows the Kaplan–Meier survival curves and log-rank test using the TCP of CCC, endometrioid carcinoma (EC), and HGSC. Figure 5a shows the TCP survival curves for PSR, in which a significant difference was observed among the three histological types (p=0.014). Figure 4b shows the TCP survival curves of the PRR, in which no significant differences were observed among the three histological types (p=0.06). The curve for CCC was plotted below the HGSC curve, and a significant difference was observed between the two histological types (p=0.03). We believe that the prognosis varies depending on the histological type of PSR and PRR.

We examined the RCPs in CCC, EC, and HGSC for both patients with PSR and PRR using box-and-whisker plots (Figure 6). The order of the regimens in the plots was determined using the same rules as those shown in Figure 3. Twenty cases of PSR CCC were observed (Figure 6a). Because recurrent CCC cases were generally refractory, the average RCPs in the 11 patients treated with TxC was short (4.0 months). However, the average RCPs for TxC+B in th four

patients was 43.8 months. The average RCPs for Gem in the seven patients was 11.0 months. TxC+B and Gem may potentially extend the RCPs in PSR CCC. Nineteen cases of PSR EC were observed (Figure 6b). The average RCPs in patients receiving TxC was 24.3 months, including one case with an RCP 98.1 months. Therefore, TxC appears to be a good treatment option for PSR EC. Fifty-two cases of PSR HGSC were identified (Figure 6c). The patients who received TxC+Pi achieved an average RCP of approximately 28.2 months. The averages RCPs for non-platinum agents was <12 months. Thus, TxC+Pi may be a useful treatment option for PSR HGSC. Eighteen PRR CCC cases were identified (Figure 6d). Gem was administered in five patients, the average RCPs was 6.5 months, and the maximum RCP value was 20.5 months. Gem may extend the RCPs of PRR CCC in the same manner as PSR CCC. Only seven cases of PRR EC were identified (Figure 6e). Their prognoses were poor, and the RCPs were short. There were 38 cases of PRR HGSC (Figure 6f). The average RCPs for platinum-based regimens ranged from approximately 4.2 to 6.5 months, whereas the average RCPs for non-platinum regimens was 1.9–4.3 months. The RCPs of PRR were short for all histological types. Even in patients with PRR, many received regimens using platinum-based regimens: therefore, platinum-based regimens still rely upon in patients with PRR. These figures suggest that RCP can be used to identify the optimal regimen for each histological type.

Discussion

The introduction of MTDs in addition to cytotoxic anticancer drugs has increased the treatment options for recurrent ovarian cancer and improved prognosis. However, there is no effective method to retrospectively investigate the usefulness of anticancer drugs in clinical practice. Therefore, we presented three indicators TCP, RCP, and ECP. In this study, patients with recurrence were grouped into the PSR and PRR groups. The TCP mainly focuses on recurrent anticancer treatment, excluding palliative care, and is an indicator similar to but different from SAR. The TCP allows for the statistical analysis of prognosis based on five parameters. The RCP was useful in showing which treatments were administered overall after recurrence and whether they were useful. The ECP was useful in showing how the regimens changed as the treatment lines were repeated after recurrence. Furthermore, when classifying according to histological type, the RCP showed the treatment methods administered to each histological type. Unlike TCP, the RCP and ECP cannot be used for statistical analyses, and their weakness lies in their reliance on the visual interpretation of the figures. Notably, this study examined the usefulness of anticancer treatments, rather than their effectiveness. Moreover, the term “contribution period” encompasses not only the anticancer effects of each regimen or whole treatment but also the contributions to psychological and lifestyles aspects.

As shown in Figure 2, the TCP curves lie below the SAR curves for two reasons. One reason for this is that the TCP starts later and ends earlier than the SAR. Most anticancer treatments began after a radiological diagnosis of recurrence, and the TCP did not include palliative care. Another reason is that many patients were lost to follow-up because of palliative care transferred to other hospitals or home palliative care in the SAR curves. However, as TCP ended follow-up when cancer treatment is completed, there are fewer cases of lost to follow-up compared with SAR (Table 2). The SAR curves shows a slower decline in the initial period than the TCP curves.

Figure 3 shows that platinum-based regimens widely used for both patients with PSR and PRR. Their usefulness was enhanced by the addition of MTDs in patients with PSR, whereas only a few patients with PRR were treated with MTDs. Using outliers to identify cases exhibiting long RCPs, we may be able to collect these cases, examine their characteristics, and use them in future studies.

Figure 4a shows that MTDs appear to be helpful in extending the ECP only in first and second-line treatment. Ned, which is mainly administered in Japan, was used instead of TxC in the later stages of treatment. This indicates that Ned is a useful anticancer drug that is easy to administer, even as cancer repeatedly progresses. Non-platinum drugs are also administered as second-line treatment and beyond, but ECPs are short, and their usefulness is low. All the PRR cases shown in Figure 4b had short ECPs. The widespread use of platinum-based regimens as a first-line treatment for PRR was unexpected.

TCP analysis showed that the prognosis differed depending on the histological type (Figure 5). The RCP analysis in Figure 6 shows that the selection of anticancer drugs based on histological type is useful method. As shown in Figure 6a, TxC+B and Gem were potentially useful for PSR CCC. As shown in Figure 6d, unexpectedly, some patients with PRR CCC treated with Gem exhibited prolonged RCP. These facts demonstrate that there is an opportunity to use the currently available treatments even for recurrent CCC, although recurrent CCC is generally considered refractory. Figures 6b and 6c show that the treatments for PSR EC and HGSC were mainly both TxC and Ned. Figures 5b and 6e show that the prognosis for patients with PRR EC was poor, and the RCPs were short. If a larger number of patients are collected, it may be possible to identify regimens with longer RCPs. Figure 6f shows that PRR HGSC are significantly reliant on platinum-based drugs.

As the number of cases is limited, the period of case accumulation was extended. Over that long period, the drugs available on the market, trends in treatment methods, and surgeries and medication prescriptions have changed. Regarding RCP and ECP, accurate comparisons similar to those in prospective studies cannot be made because the case backgrounds for comparison are not aligned, and the selection of anticancer drugs is not randomized. Owing to these limitations, it is difficult to directly apply this data to routine clinical practice. However, this analytical method is useful for retrospectively understanding the reality of clinical practice.

We hope to expand it to include multi-center collaborative studies in the future. Recent advances in generative architectural intelligence have led to the development of electronic medical record systems with summarization functions and systems for aggregating cases [24]. Consequently, it will likely be possible to collect cases from multiple institutions within a shorter timeframe. As the number of cases increases, it will become possible to form a basis for the design of clinical trials, thereby proposing appropriate treatment plans based on these data. We hope that this analytical method will be widely adopted and useful to clinicians.

Declarations

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Data availability The data that support the findings of this study are not openly available owing to reasons of sensitivity but are available from the corresponding author upon reasonable request.

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval The study protocol was approved by the Ethics Committee of Nagoya University (Institute Review Board No. 2017-0494)

Consent to participate Written informed consent was obtained from each patient to study anticancer drug resistance in ovarian cancer.

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Tables

Table 1. Classification of 183 recurrent ovarian cancer cases according to 5 parameters.

Platinum Sensitivity	Sensitive (PSR)	Resistance (PRR)	Total
Total	109	74	183
Parameters			
FIGO stage			
I	23	1	24
II	6	3	9
III	67	55	122
IV	13	15	28
			p<0.001*
age (years old)			
≦50	37	26	63
51~60	34	23	57
61≦	38	25	63
			p=0.98
Neoadjuvant chemotherapy			
None	63	42	105
Administrated	46	32	78
			p=0.89
Surgery			
Complete	57	20	77
Incomplete-Optimal	29	15	44
Suboptimal	23	39	62
			p<0.001*
Histology			
High-Grade Serous	52	38	90
Clear cell	20	18	38
Endometrioid	19	7	26
Mucinous	3	3	6
Low-Grade Serous	5	0	5
Others	3	6	9
Unidentified	7	2	9
			p=0.11

* shows significant.

Table 2. Comparison of numbers of lost to follow-up cases between SAR and TCP.

			SAR		TCP		(a-b) Lost to follow-up after completion of anticancer treatment
	Total	Confirmed alive	Died	(a) Lost to follow-up	Completion of anticancer treatment	(b) Lost to follow-up	
PSR	109	24	57	28	79	6	22
PRR	74	1	57	16	72	1	15

Table 3. Analysis of TCP after recurrence in relation to clinical parameters in Platinum-Sensitive Recurrence

		Kaplan–Meier analysis		Cox proportional hazards model							
		Survival rate	Log-rank test	Univariate analysis				Multivariate analysis			
Parameter	Number	of TCP 5 years (%)	P-value	Hazard Ratio	95% confidence interval		P-value	Hazard Ratio	95% confidence interval		P-value
▯ Total	109	44.1	-								
▯ Age											
≦ 50	37	48.5	0.57	0.77	0.44	1.34	0.36	0.65	0.36	1.18	0.16
51 ≦ ≦ 60	34	37.3		1				1			
61 ≦	38	45.1		1.00	0.59	1.71	1.00	0.90	0.49	1.66	0.75
▯ FIGO stage (Early: stage I and II, or Advanced: stage III and IV)											
Early	29	43.3	0.60	1				1			
Advanced	80	44.4		0.88	0.53	1.43	0.60	0.81	0.37	1.77	0.60
▯ Neoadjuvant chemotherapy											
None	63	47.0	0.90	1				1			
Administrated	46	39.4		0.97	0.62	1.53	0.90	1.39	0.73	2.64	0.31
▯ Surgery											
Complete	57	41.5	0.83	1				1			
Incomplete Optimal	29	48.6		0.86	0.51	1.47	0.60	0.90	0.46	1.76	0.75
Suboptimal	23	45.9		1.04	0.59	1.86	0.88	1.26	0.59	2.71	0.55
▯ Histology											
High Grade Serous	52	48.4	0.073	1				1			
Clear cell	20	25.0	Analysis of five most common tissue types	1.94	1.07	3.50	0.028*	2.16	1.06	4.42	0.035*
Endometrioid	19	55.8		0.69	0.36	1.33	0.27	0.67	0.33	1.36	0.27
Low Grade Serous	5	60.0		0.85	0.30	2.42	0.77	0.71	0.23	2.26	0.57
Unidentified[a]	7	50.00		1.21	0.43	3.39	0.72	0.97	0.30	3.08	0.96
Mucinous	3	-		4.46	1.33	14.93	0.015*	4.72	1.28	17.45	0.020*
Others	3	-		0.98	0.24	4.10	0.98	0.88	0.20	3.92	0.86

TCP: Total contribution period. [a] shows “Unidentified after neoadjuvant chemotherapy”. * shows significant.

Table 4. Analysis of TCP after recurrence in relation to clinical parameters in Platinum-Resistance recurrence

		Kaplan-Meier analysis		Cox's proportional hazards model				
		Survival rate of TCP 1 year (%)	Log-rank test	Univariate analysis				
Parameter	Number		P-value	Hazard Ratio	95% confidence interval		P-value	
▯ Total	74	36.5						
▯ Age								
≦ 50	26	42.3	0.69	0.85	0.48	1.51	0.58	
51 ≦ ≦ 60	23	39.1		1				
61 ≦	25	28.0		1.09	0.62	1.92	0.77	
▯ FIGO stage (Early: stage I and II, or Advanced: stage III and IV)								
Early	4	50.0	0.15	1				
Advanced	70	35.7		2.31	0.71	7.51	0.16	
▯ Neoadjuvant chemotherapy								
None	42	31.0	0.11	1				
Administrated	32	43.8		0.69	0.43	1.10	0.12	
▯ Surgery								
Complete	20	40.0	0.35	1				1
Incomplete-Optimal	15	53.3		1.28	0.64	2.56	0.49	0.99
Suboptimal	39	28.2		1.51	0.86	2.65	0.15	1.13
▯ Histology								
High Grade Serous	38	44.7	0.081	1				1
Clear cell	18	16.7	Analysis of five most common tissue types	1.90	1.07	3.38	0.029*	1.51
Endometrioid	7	42.9		1.40	0.58	3.38	0.45	1.14
Others	6	33.3		1.02	0.42	2.48	0.96	0.91
Mucinous	3	66.7		0.33	0.079	1.42	0.14	0.32
Unidentified[a]	2	-		1.33	0.32	5.61	0.70	1.60
Low Grade Serous	0	-		-	-	-	-	-

TCP: Total contribution period. [a] shows “Unidentified after neoadjuvant chemotherapy”. * shows significant.

Figures

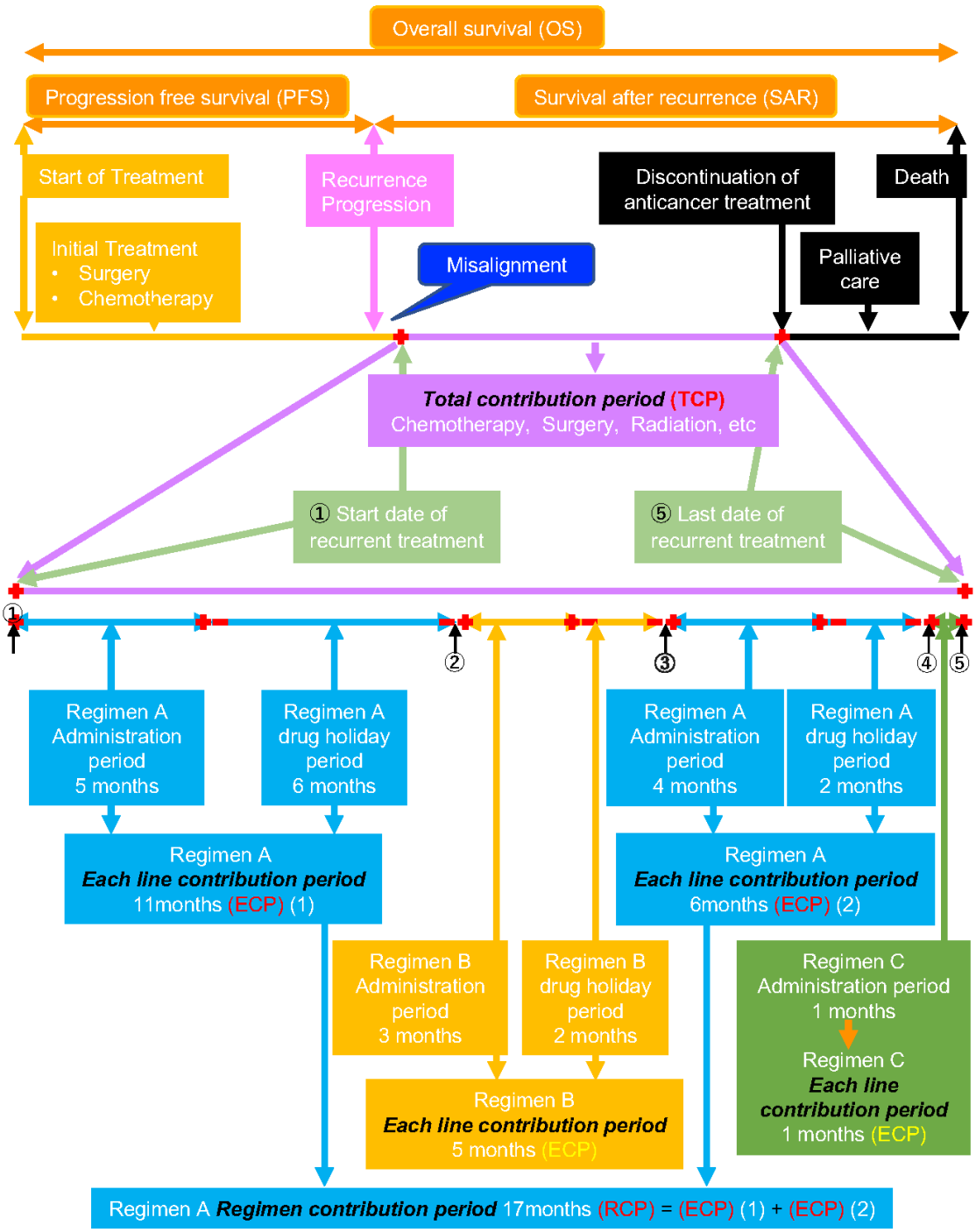


Figure 1

Definition of TCP, RCP, and ECP

TCP is defined as a number of months from the start date of anticancer treatment to the last date before palliative care □–□. The TCPexcluded the period from the relapse diagnosis date to the start of treatment and the palliative care period from the SAR period. In addition, TCP includes treatment periods of surgery alone, radiation alone, or proton therapy alone, as well as the treatment-free intervals that occur until the subsequent treatment begins. ECP is defined as a number of months from the start date of a regimen to the start date of the next regimen, that is, the sum of the medication period and the drug holiday period (regimen A 1st time □–□, 11 months, regimen A 2nd time □–□, 6 months: blue boxes, or regimen B □–□ 5 months: orange boxes). The regimen immediately prior to palliative care includes only the medication period for ECP, not the drug holiday period (regimen C □–□ 1 month: green boxes). The RCP was defined as the sum of the ECP of repeated identical regimens. (ECP of regimen A 1st time, 11 months+ECP of regimen A 2nd time, 6 months=ECP of

regimen A, 17 months). **+:** Red plus symbols indicate including the days of tips or ends of lines or arrows. **-:**Red minus symbols indicate excluding the days at the tips or ends of the arrows.

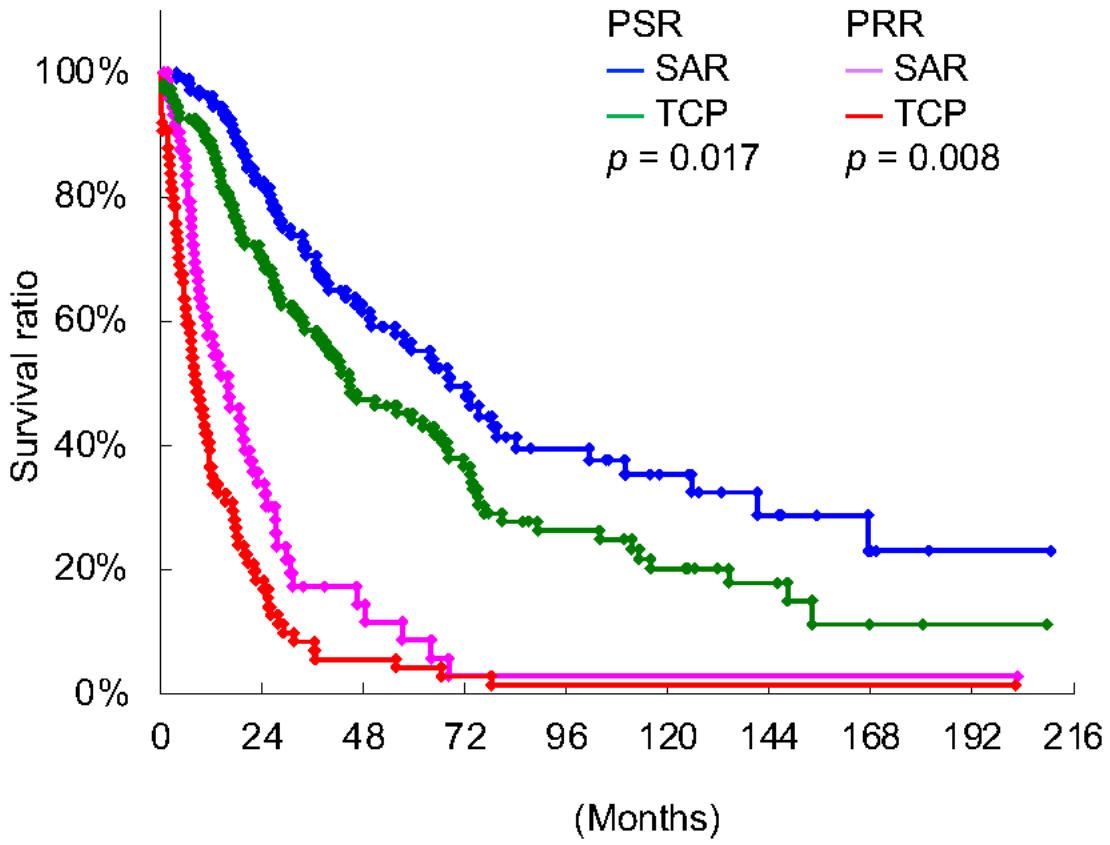


Figure 2

Comparison of "SAR" and "TCP" in PSR or PRR

A Kaplan–Meier curve of the SAR for PSR cases is shown with a blue line ——, and one of the TCP for PSR cases is shown with a green line ——. There was a significant difference between the SAR and the TCP (p=0.017). A Kaplan–Meier curve of the SAR for PRR cases was shown with pink line ——, and one of the TCP for PRR cases was shown with red line ——. There was significant difference between the SAR and the TCP (p = 0.008). Markers: ▯, ▯, ▯, and ▯ show the termination of follow-up because of missing of follow-up or December 31 2025. The numbers of survived, dead, completion of anticancer treatments, and lost to follow-up cases are shown in Table 2.

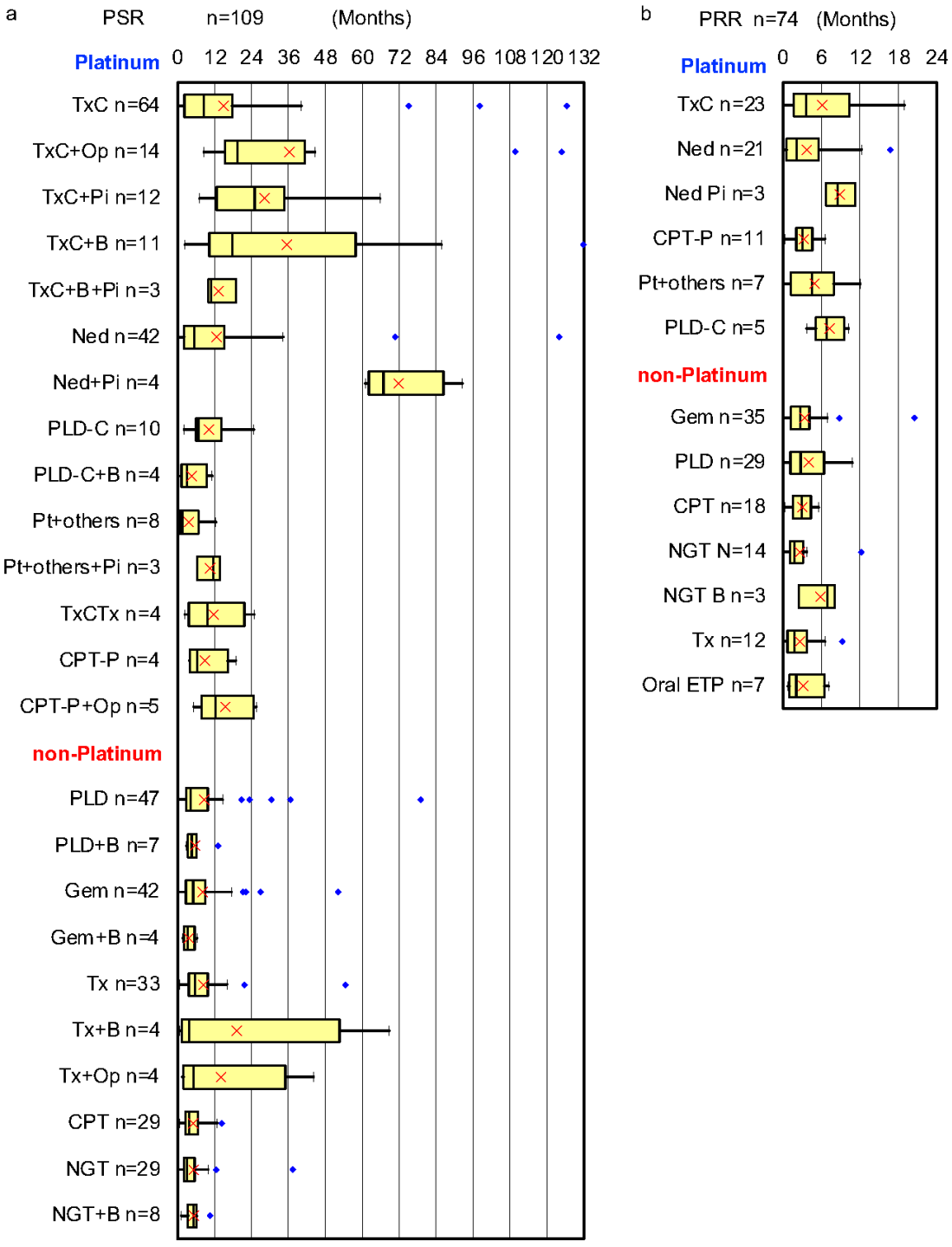


Figure 3

Box-and-whisker plots of RCPs

a: PSR cases. b: PRR cases. The upper rows represent platinum-based regimens, whereas the lower rows represent non-platinum regimens. The regimens were listed according to a group of major drugs. The figures show the regimens in which three or more patients received the treatment. × shows the average. shows the outlier. Abbreviations of regimens are shown in the “Patients and Methods” section.

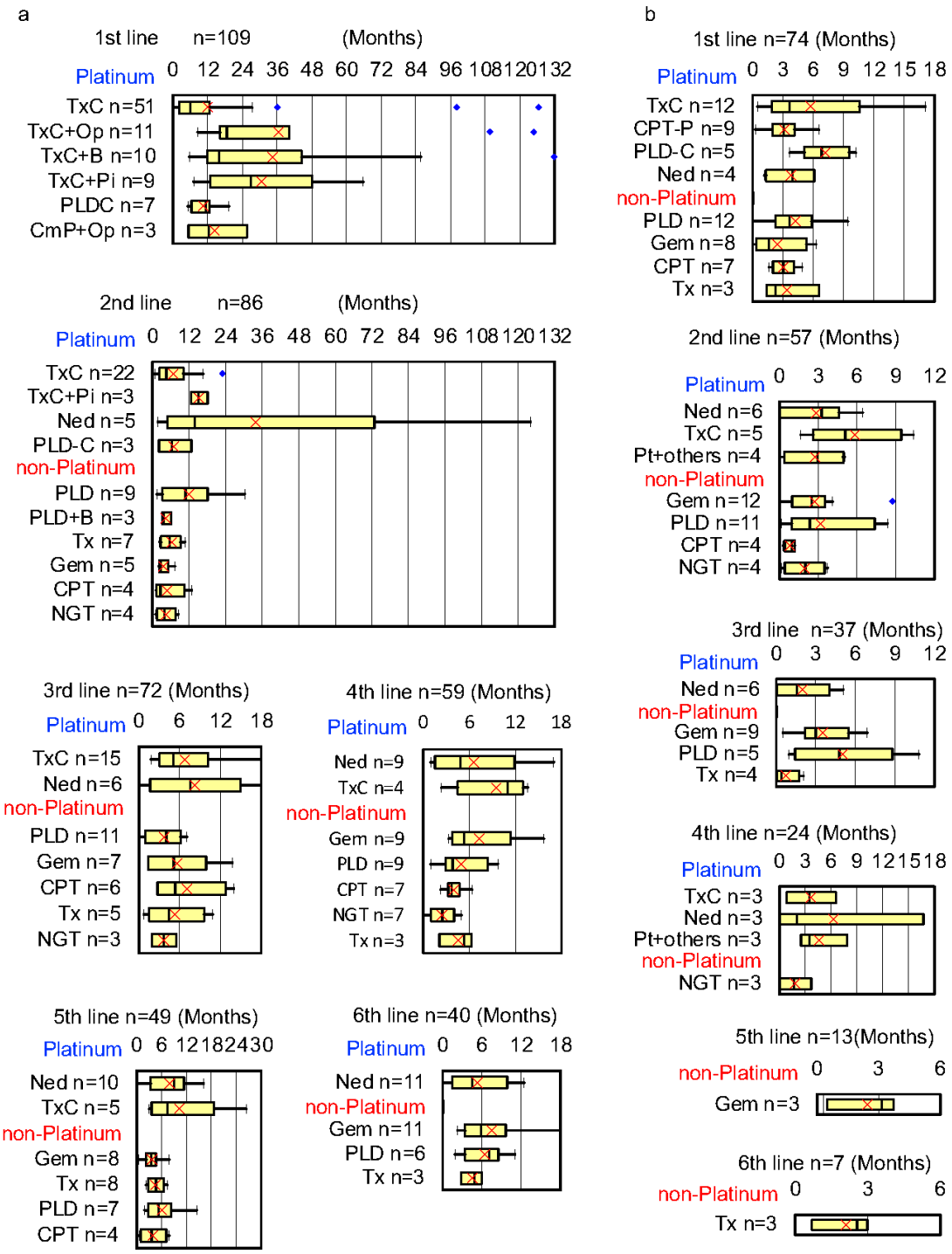


Figure 4

Box-and-whisker plots of ECPs, grouped line by line in order

a: PSR cases. b: PRR cases. The lines for chemotherapy administration are shown in the numerical order for each plot. The upper rows represent platinum-based regimens, whereas the lower rows represent non-platinum regimens. The regimens were listed according to a group of major drugs. The figure shows the regimens in which three or more patients received the treatment. × shows the average. ▯ shows the outlier. Abbreviations of regimens are shown in the "Patients and Methods" section.

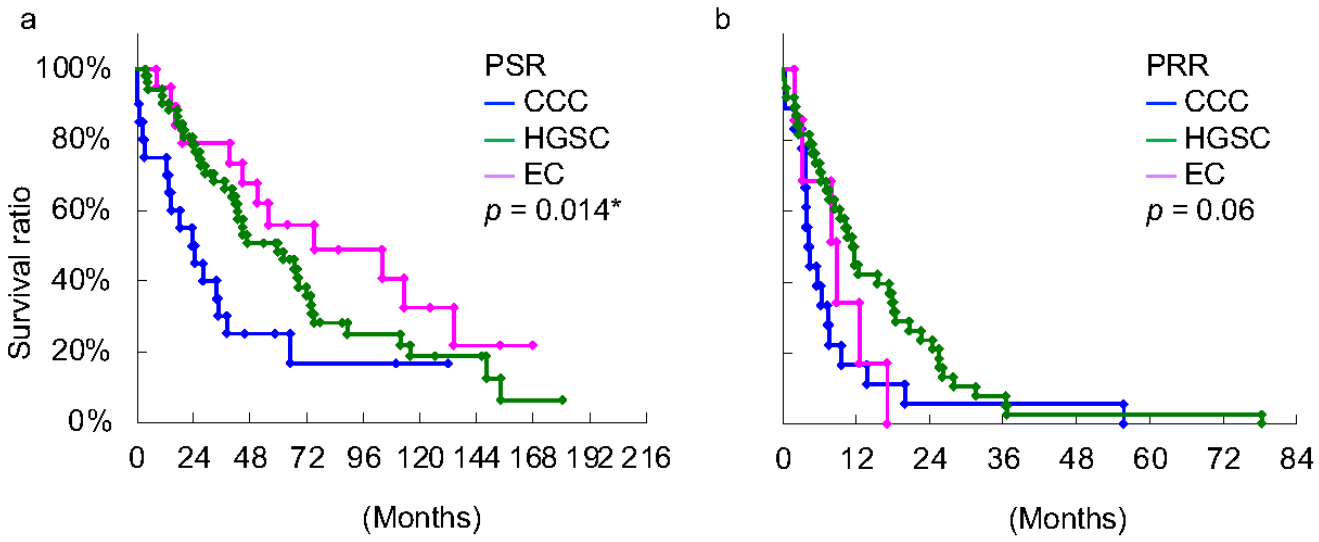


Figure 5

Kaplan-Meier survival curves and Log-rank tests of TCP in three major histological types

In both A and B graphs, blue line —— is "CCC," green line —— is "HGSC," and pink line —— is "EC." A: PSR. There was a significant difference among the three histological types (p=0.014). B: PRR. There were no significant differences among the three histological types (p=0.06). Comparison between the CCC and HGSC groups (p=0.03). Markers ▯, ▯, and ▯ show the termination of follow-up because of missing of follow-up or December 31, 2025. † signifies significance.

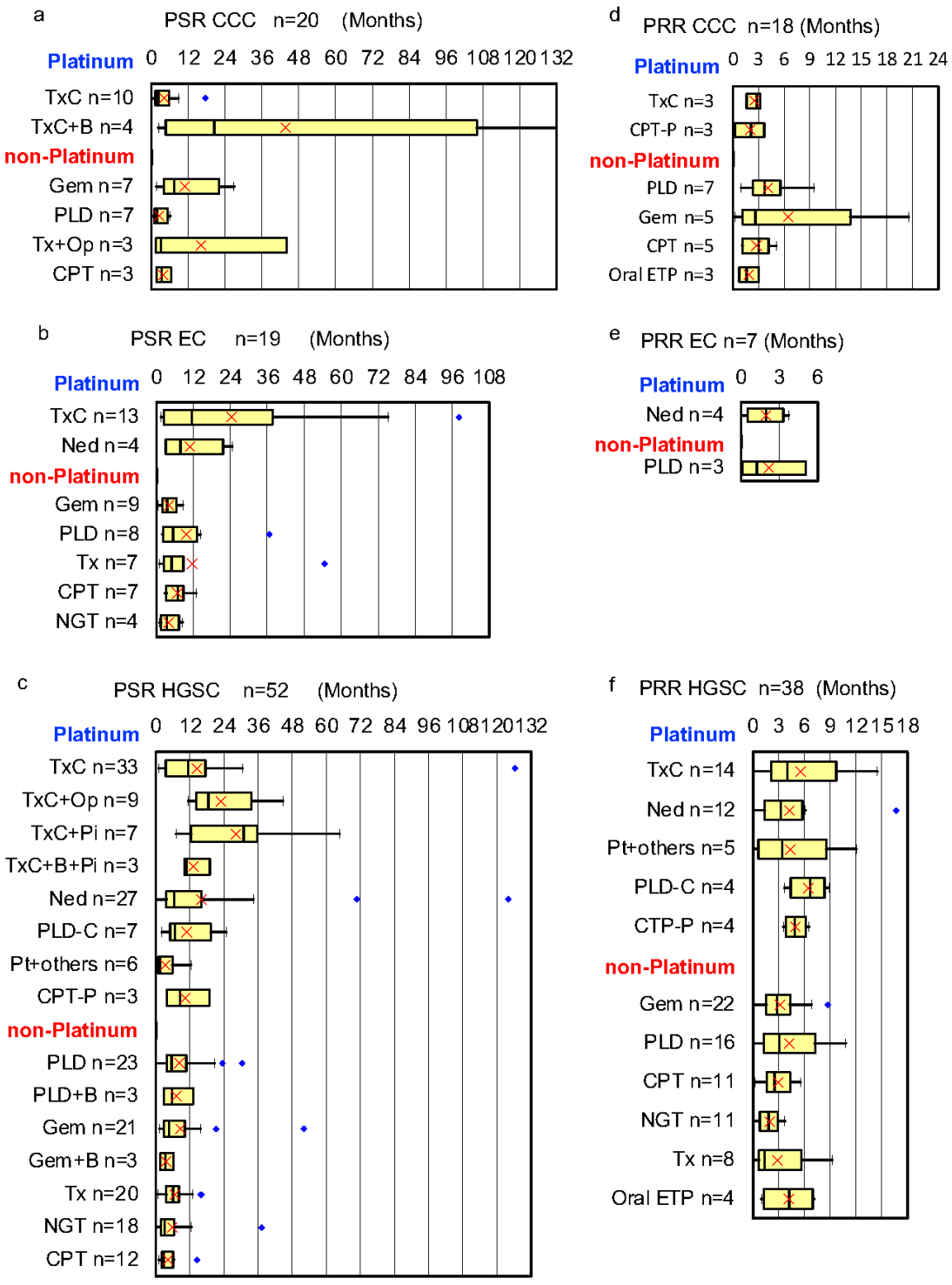


Figure 6

Box-and-whisker plots of RCPs divided by 3 histological types in PSR and PRR

A: PSR, CCC. B: PSR, EC. C: PSR, HGSC. D: PRR, CCC. E: PRR, EC. F: PRR, HGSC. The upper rows represent platinum-based regimens, whereas the lower rows represent non-platinum regimens. The figure shows the regimens in which three or more patients received the treatment. ×shows the average. ▯ shows the outlier. Abbreviations of regimens are shown in the “Patients and Methods” section.