Oncology and Translational Medicine
DOI 10.1007/s10330-017-0241-1
December 2017, Vol. 3, No. 6, P–P

ORIGINAL ARTICLE

Comparative analysis of ATP-based tumor chemosensitivity assay-directed chemotherapy versus physician-decided chemotherapy in platinum-resistant recurrent ovarian cancer*

Ning Li[1], Yutao Gao[1], Wei Zhang[2], Xiaoguang Li[1], Bin Li[1], Haimei Tian[2], Yanfen Li[2], Lingying Wu[1] (✉)

[1] Department of Gynecological Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China
[2] Biological Testing Center, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Abstract

Objective The aim of the study was to evaluate the role of ATP-based tumor chemosensitivity assay (ATP-TCA) in patients with platinum-resistant recurrent ovarian cancer (PRROC).

Methods A total of 43 patients with PRROC who underwent chemotherapy based on the results of ATP-TCA in the Cancer Hospital, Chinese Academy of Medical Sciences were included in the present study. As controls, we selected another 43 patients with PRROC who were treated at the physician's discretion within the same time period and had the same clinical characteristics as the patients in the ATP-TCA group. Log-rank test and Cox proportional hazards model were adopted for analysis.

Results A total of 86 patients were retrospectively analyzed in the present study. Patients were routinely monitored to evaluate the rate of progression-free survival (PFS). The median follow-up time was 13 months. The PFS for the ATP-TCA and control groups was 5 and 3 months, respectively (P = 0.027). Multivariate analysis showed that the type of treatment was an independent prognostic factor for PFS (P = 0.040; HR: 0.623; 95% CI: 0.313–0.973). Subgroup analysis showed that among patients with a treatment-free interval (TFI) of ≥ 3 months (n = 50), those in the ATP-TCA group had longer PFS than those in the control group (7 vs 4 months, P = 0.010). Meanwhile, the median PFS of patients who underwent ≤ 2 prior chemotherapy regimens (PCR, n = 52) in the ATP-TCA and control groups was 6 months and 4 months, respectively (P = 0.025).

Conclusion ATP-TCA-directed chemotherapy might improve the PFS in PRROC. In particular, the survival benefit from ATP-TCA is higher in patients with a TFI of ≥ 3 months or treated with ≤ 2 PCR.

Received: 2 October 2017
Revised: 3 November 2017
Accepted: 7 December 2017

Key words: epithelial ovarian cancer; platinum-resistance; recurrence; ATP-based tumor chemosensitivity assay (ATP-TCA)

The prognosis of epithelial ovarian cancer is rather poor. The 5-year survival rate for patients with advanced ovarian cancer remains at approximately 30%–40%, and chemoresistance after relapse is among the main causes. Currently, second-line chemotherapy for patients with platinum-resistant recurrent ovarian cancer (PRROC) is selected mainly based on the clinical experience of the physicians, results of clinical trials, and guidelines from related international organizations. Several cytotoxic agents for patients with PRROC are available, including docetaxel, topotecan, gemcitabine (GEM), liposomal doxorubicin, paclitaxel (weekly therapy), and etoposide (oral). Previous reports have shown that the overall response rate of second-line chemotherapy is approximately 20%–30% [1–3]. Patients who show no response to certain chemotherapeutics might respond to

✉ Correspondence to: Lingying Wu. Email: wulingying@csco.org.cn
* Supported by a grant from the Capital's Funds for Health Improvement and Research (No. Z131107002213013).

another, suggesting considerable clinical heterogeneity in tumor chemosensitivity. According to literature, a portion of patients still achieve complete remission after receiving second-line chemotherapy and has prolonged progression-free survival (PFS) of more than 5 years [3–5]. However, how to select the most effective cytotoxic drugs or drug combinations for individualized treatment remains to be solved.

A chemosensitivity assay assesses tumor responses to a particular chemotherapeutic agent by using cells primarily cultured from the tumor specimen. This allows for the identification of agents with a strong anti-tumor activity, and those with no anti-tumor activity are excluded. The result of a chemosensitivity assay provides the basis for clinical decision-making concerning chemotherapeutic regimens. Both the American Society of Clinical Oncology [6] and National Comprehensive Cancer Network [7] encourage researchers to conduct clinical trials related to chemosensitivity assay.

Several types of chemosensitivity assays have been reported. The ATP-based tumor chemosensitivity assay (ATP-TCA) was developed based on the principle that the amount of endogenous ATP in cells instantly reflects cell viability and the number of viable cells. Therefore, intracellular ATP content can be used to evaluate the anti-tumor effect of various chemotherapy drugs. In 1988, Sevin *et al* [8] at the University of Miami employed ATP-TCA for the first time to examine the chemosensitivity of ovarian cancer tissues. Since then, many studies have indicated a good correlation between the results of ATP-TCA and clinical responses in patients with ovarian cancer. However, the results of ATP-TCA were not completely consistent with the clinical response of patients with ovarian cancer in different study populations. This indicates that ATP-TCA might play a role in only a particular group of patients. A series of studies reported that chemosensitivity testing on primary ovarian cancer prior to the initial chemotherapy failed to improve the PFS and overall survival (OS) [9–12]. Initial paclitaxel (PTX)/platinum chemotherapy usually achieves a response rate of over 70% in epithelial ovarian cancer. It is highly likely that conducting ATP-TCA would not challenge the primary care for additional therapeutic benefit. Therefore, identifying patients who can benefit from ATP-TCA is important. Our previous retrospective study has shown that patients with PRROC benefit limitedly from experience-guided chemotherapy [13]. By contrast, ATP-TCA-guided chemotherapy extended PFS by 3 months (ATP-TCA guided group vs. experience-based group: 5 months vs. 2 months, respectively) [13]. Based on our previous findings, the present study further evaluated the role of ATP-TCA in the treatment of PRROC and aimed to identify the patient population who require ATP-TCA.

Materials and methods

Patients' eligibility

Patients with ROC who were admitted to Cancer Hospital, Chinese Academy of Medical Sciences between July 2010 and June 2013 were included in the present study, if the following inclusion criteria were met: (1) patients were previously histologically diagnosed with epithelial ovarian cancer; (2) patients had PRROC (the last chemotherapy was a platinum-containing regimen, and the time interval from completion of the last chemotherapy to progression or recurrence was ≤ 6 months); (3) tumor specimens or aspirates from malignant ascites/pleural effusion could be obtained for ATP-TCA; (4) patients had a Karnofsky performance status score of 60–100 points; and (5) the expected survival was more than 4 months.

Forty-three patients with PRROC were assigned to the ATP-TCA-guided chemotherapy group. This study was approved by the Cancer Hospital, Chinese Academy of Medical Sciences Institutional Review Board. All patients signed a written informed consent form. To decrease the bias from other clinical factors, we selected another 43 patients with PRROC who were treated based on the physician's discretion within the same time period and had similar clinical characteristics such as age, tumor stage, histology, grade, number of prior chemotherapy regimens (PCR) and cycles, treatment-free interval (TFI), and residual disease (if patients underwent secondary cytoreductive surgery) to the patients in ATP-TCA group as controls. TFI was calculated as the time interval from the last chemotherapy to recurrence before study enrollment. The TFI of the patients who progressed during the last chemotherapy was considered as 0.

ATP-TCA method

Tissue/cells for ATP-TCA were obtained either during the operation or from malignant effusions. Within 30 minutes, the samples were sent to the Biological Testing Center of our hospital where the ATP-TCA was conducted. The rest of the tumor tissue or abdominal/pleural effusion samples were collected for routine pathological and cytological examinations.

Detection reagents, instruments, and methods

The detection kit was purchased from Jin Zijing Biomedical Technology Co., Ltd (Beijing, China). The fluorescence scanner was purchased from Hamamatsu Photonics Co., Ltd (Beijing, China). The experimental procedure was conducted in strict accordance with the manufacturer's instructions. All tests were completed at the Biological Testing Center of our hospital. Briefly, cells were dissociated from solid tumor samples via enzymatic digestion overnight and purified via density

centrifugation. Density centrifugation was also used to obtain cells from ascites/pleural effusion aspirate. The cells were resuspended in a complete assay medium and were then plated at 20 000 cells/well in polypropylene 96-well plates. In general, sufficient ovarian cancer cells were available for testing 14 different drugs or drug combinations at 6 concentrations. Triplicate wells were set up for each drug dose, ranging from 6.25% to 200% of peak plasma concentrations (PPC) for each drug or drug combination. At the end of a 5-day incubation period, the ATP content of the cells was measured using the luciferin-luciferase assay. Results were deemed evaluable if the following criteria were fulfilled:

(1) Histological and/or cytological diagnosis of ovarian carcinoma on the assay specimen with > 20% malignant cells; (2) No inhibition medium. Only control value > 20 nmol/L ATP and maximum inhibitor control ≤ 1% of medium; (3) Concentration responsiveness to agents previously shown to exhibit such responsiveness in the assay; and (4) Absence of fungal or bacterial contamination.

Evaluation criteria for the ATP-TCA results

The results of the ATP-TCA were evaluated using the sensitivity index (SI) method. SI was calculated according to the following formula: SI = 600 − Σ(tumor growth inhibition rates at 6 drug concentrations). The 6 concentrations utilized in the present study were 200%, 100%, 50%, 25%, 12.5%, and 6.25% of PPC of the drug. As published previously [8], an SI value of ≤ 150 and 150–250 is defined as being highly sensitive and sensitive to the drug, respectively, whereas an SI value of > 250 is defined as being resistant.

Chemotherapy regimens

The chemotherapy drugs and drug combinations used for ATP-TCA testing were as follows: PTX, pegylated liposomal doxorubicin (PLD), topotecan, GEM, PTX + PLD, PLD + oxaliplatin (L-OHP), PTX + nedaplatin (NDP), GEM + NDP, GEM + epirubicin (E-ADM), PTX + ifosfamide (IFO), IFO + E-ADM, etoposide (VP-16) + L-OHP, IFO + VP-16, irinotecan + NDP, and PTX + topotecan + cisplatin. Based on the results of ATP-TCA, the patients in the experimental group were given a chemotherapy regimen with the lowest SI. In the event of two regimens producing similarly strong *in vitro* sensitivity, the physician was requested to select the least toxic alternative. If the best regimen was contraindicated for any reason, the next best regimen was selected at the physician's discretion. For patients in the control group, the chemotherapy regimens were determined by the physician mainly based on the patients' treatment history, side effects, and clinical status, among other factors. The chemotherapeutic dose in both groups was calculated using a similar method. None of the patients received targeted therapy at this time of recurrence.

Response evaluation

Patients were prospectively monitored for PFS. Serum cancer antigen 125 (CA125) was routinely assessed within 1 week before the start of each cycle of chemotherapy. Computed tomography scanning or magnetic resonance imaging was performed every 2 cycles or when disease progression was suspected based on physical examination or patient symptoms. Patients were regarded as evaluable if a minimum of 2 cycles of chemotherapy were administered. The efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors [14] for patients with radiologic relapse and the Rustin criteria [15] for patients with CA125 elevation only. All chemotherapy regimens were continued for 4–6 cycles in responders and in patients with stable disease. After completion of chemotherapy, all patients were followed up routinely every 3 months through physical examination, serum CA125 evaluation, and imaging examination. The date of the last follow-up was June 24, 2014. PFS was calculated from the start of chemotherapy to progression or lost to follow-up.

Statistical analysis

The SPSS 19.0 software was used to perform statistical analyses. PFS was calculated using the Kaplan-Meier method, and the difference between the experimental group and control groups was analyzed using the log-rank test. Multivariate analysis was conducted using the Cox proportional hazards model. The Fisher exact probability or χ^2 test was used to analyze frequency data. $P < 0.05$ was considered statistically significant.

Results

A total of 86 patients with PRROC were retrospectively analyzed in the present study. Forty-three patients were in the ATP-TCA group, and the other 43 were in the control group. Patients in the control group were selected from the same time period and had the same clinical characteristics as those in the ATP-TCA group. The median age at diagnosis was 53 years. Table 1 shows the clinical and pathological characteristics of all the patients. The specimens utilized in the ATP-TCA test included tumors tissues (30/43, 69.8%) and ascites/pleural effusion aspirate (13/43, 30.2%).

Chemotherapy regimens

The 5 most frequently used regimens in the ATP-TCA group were PTX (paclitaxel) + PLD/E-ADM (n = 12), PTX + NDP (nedaplatin) (n = 10), PLD + L-OHP (n = 5), PTX

Table 1 The clinicopathologic characteristics of all the patients (*n*)

	ATP-TCA	Control
Number of cases	43	43
Median age at diagnosis (years)	55 (26–75)	52 (30–72)
Grade		
2 and 3	42	38
NA	1	5
Histological type		
Serous adenocarcinoma	32	25
Adenocarcinoma	9	16
Clear cell carcinoma	1	1
Transitional cell carcinoma	1	1
Median TFI (months)	3	3
Median No. of prior CT regimens	2 (1–6)	2 (1–6)
Median No. of prior CT cycles	13 (4–32)	15 (4–38)
Secondary cytoreductive surgery		
No surgery/residual disease > 1 cm	22	15
Residual disease ≤ 1 cm	14	14

Note: CT, chemotherapy; NA, not available; PFS, progression free survival; TFI, treatment free interval

+ topotecan + DDP (cisplatin) (*n* = 5), and GEM + NDP/DDP (*n* = 5). Similarly, the 5 most frequently employed chemotherapy regimens in the control group were PTX + NDP (*n* = 10), PTX + PLD (*n* = 5), PLD + L-OHP/NDP (*n* = 5), IFO + E-ADM (*n* = 4), and GEM + NDP/DDP (*n* = 3). Other chemotherapy regimens included the single agent PLD, topotecan, and oral vp16. Table 2 shows the regimens and doses used in the present study. All patients received at least two cycles of chemotherapy after enrollment.

Survival outcomes

After a median follow-up of 13 months (range, 3–46 months), 84 patients experienced relapse or tumor progression, while the other two patients had not yet shown signs of progression until the last follow-up. The overall median PFS was 4 months. The PFS for the ATP-TCA group and the control group was 5 and 3 months, respectively ($P = 0.027$). Forty-six patients died of disease, and 40 patients were still alive.

Univariate analysis showed that the prognostic factors for PFS included age ($P = 0.041$), TFI ($P = 0.012$), the number of PCR ($P = 0.015$), treatment (according to ATP-TCA or physician's choice) ($P = 0.027$), and residual disease (patients who did not receive secondary cytoreduction were classified as suboptimal cytoreduction) ($P = 0.001$). The number of cycles of PCR had no impact on PFS ($P = 0.466$). The independent prognostic factors for PFS under multivariate analysis were residual disease [$P = 0.006$; hazard ratio (HR): 2.024, 95% confidence interval (CI): 1.219–3.362] and treatment ($P = 0.040$; HR: 0.623; 95% CI: 0.313–0.973).

Table 3 PFS comparison in subgroup analysis

PFS	ATP-TCA (month)	Control (month)	*P* value
Treatment free interval			
≥ 3 months	7 (*n* = 25)	4 (*n* = 25)	0.010
< 3 months	3 (*n* = 18)	2 (*n* = 18)	0.353
No. of prior chemotherapy regimen			
1–2	6 (*n* = 28)	4 (*n* = 28)	0.025
≥ 3	3 (*n* = 15)	2 (*n* = 15)	0.517
Secondary cytoreductive surgery			
No surgery/residual disease > 1 cm	4 (*n* = 28)	3 (*n* = 27)	0.025
Residual disease ≤ 1 cm	7 (*n* = 15)	6 (*n* = 16)	0.521

Subgroup analysis of PFS

Table 3 summarizes the results of subgroup analysis. The median PFS of patients in the ATP-TCA group and control group who had a TFI of ≥ 3 months ($n = 50$) was 7 and 4 months, respectively ($P = 0.010$) (Fig. 1). Meanwhile, the median PFS for patients in the ATP-TCA group and the control group who had a TFI of < 3 months was 3 and 2 months, respectively ($P = 0.353$).

The median PFS of patients in the ATP-TCA group

Table 2 Mainly used regimens of chemotherapy

Regimen	Dosage
Doxil	40 mg/m^2 d1, IV, q4wk
Topotecan	1–1.5 mg/m^2 d1, 2, 3, 4, 5, IV, q3wk
Paclitaxel	80 mg/m^2 d1, 8,15, IV, q3wk
Epirubicin + paclitaxel	Epirubicin 25 mg/m^2, d1, 2, IV + paclitaxel 175 mg/m^2 d1, IV, q3wk
Doxil + paclitaxel	Doxil 25 mg/m^2 IVI, d1, IV + paclitaxel 175 mg/m^2 d1, IV, q3wk
Paclitaxel + nedaplatin	paclitaxel 175 mg/m^2 d1, IV + nedaplatin 80 mg/m^2 d1, IV, q3wk
Cisplatin + gemcitabine	Cisplatin 75 mg/m^2 d1, IV + gemcitabine 1000 mg/m^2 d1, 8, IV, q3wk
Nedaplatin + gemcitabine	Nedaplatin 80 mg/m^2 d1, IV + gemcitabine 1000 mg/m^2 d1, 8, IV, q3wk
Doxil + L-OHP	Doxil 25 mg/m^2 IV, d1 + L-OHP 135 mg/m^2 d1, IV, q3wk
Doxil + nedaplatin	Doxil 25 mg/m^2 IV, d1 + nedaplatin 80 mg/m^2 d1, IV, q3wk
Paclitaxel + topotecan + cisplatin	paclitaxel 100 mg/m^2 d1, IV + topotecan 1 mg/m^2 d1–4, IV + cisplatin 25 mg/m^2, d1, 2, IV, q3wk
Ifosfamide + epirubicin	Ifosfamide 1.5 g/m^2 d1–3, IV + epirubicin 25 mg/m^2, d1, 2, IV, q3wk

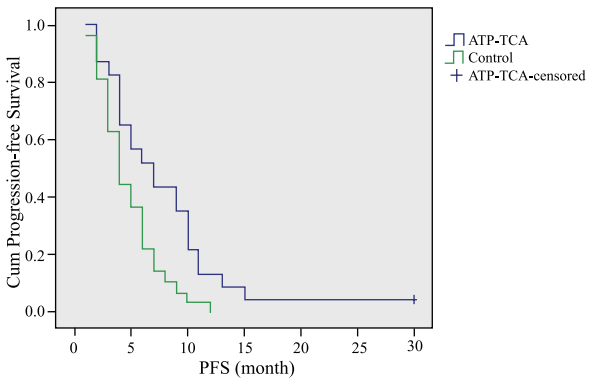

Fig. 1 Comparison of PFS in the subgroup of patients with a TFI of ≥ 3 months (P = 0.010)

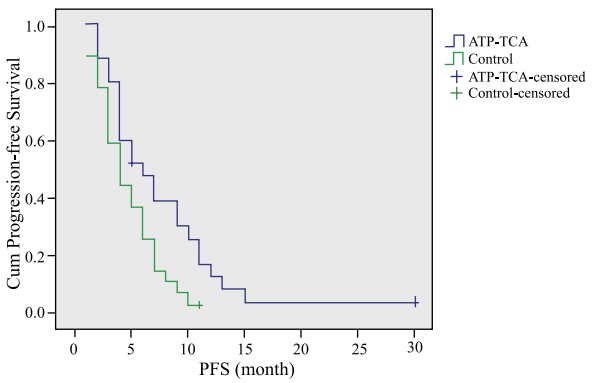

Fig. 2 Comparison of PFS in the subgroup of patients treated with ≤ 2 prior chemotherapy regimens (P = 0.025)

and control group who received ≤ 2 cycles of PCR (n = 52) was 6 and 4 months, respectively (P = 0.025) (Fig. 2). The median PFS for patients in the ATP-TCA group and the control group who received ≥ 3 PCR was 3 and 2 months, respectively (P = 0.517).

Among the patients who did not undergo secondary cytoreduction and who experienced suboptimal cytoreduction (n = 55), those in ATP-TCA and the control groups had a median PFS of 4 and 3 months, respectively (P = 0.025). The patients in the ATP-TCA group and the control group who achieved optimal cytoreduction had a median PFS of 7 and 6 months, respectively (P = 0.521).

Discussion

At present, predicting the effective chemotherapeutic regimen for patients based only on the pathological types, grade, history of prior chemotherapy, and other clinical characteristics is difficult. On the other hand, at the molecular level, reliable markers capable of predicting the efficacy of various cytotoxic drugs are still lacking. Thus, any method for testing chemosensitivity is welcome in the treatment of ROC. Rutherford *et al* reported an improved PFS and OS for patients with ROC treated with chemoresponse assay-sensitive agents [16].

Treatment options for PRROC include multiple cytotoxic agents, such as weekly paclitaxel, GEM, PLD and topotecan, that have different mechanisms of action. ATP-TCA is useful in guiding the selection of optimal chemotherapy regimen. Consistent with a previous study [13], the present study demonstrated that the overall PFS was prolonged in patients with PRROC who received ATP-TCA-directed chemotherapy compared with patients treated based on the physician's choice.

Cree *et al* conducted a prospective, randomized study to determine the response rate and PFS in patients with PRROC who received chemotherapy based on the physician's choice in comparison with ATP-TCA-guided chemotherapy [17]. The results show that the PFS in the ATP-TCA group was slightly but not statistically significantly longer than that in the physician's choice group (104 days vs 93 days, P < 0.14). As the number of PCR and cycles increases and the TFI shortens, subsequent chemotherapy would be less effective. For patients with ROC who received ≥ 4 PCR, other cytotoxic drugs are barely active. Any chemosensitivity assay – molecular or cellular – is only as good as the effective drugs that are available. This means that ATP-TCA and other drug-sensitivity testing can theoretically provide no benefit for patients who are resistant to all the cytotoxic agents. Cree *et al* failed to show the statistically significant difference of PFS between the groups possibly because they did not perform a subgroup analysis to exclude the patients with multi-drug resistance.

The subgroup analysis of the present study confirmed that patients who previously received at least 3 chemotherapy regimens (PFS: 3 vs. 2 months, P = 0.517) and those with TFI less than 3 months (PFS: 3 vs. 2 months, P = 0.353) did not benefit from ATP-TCA. The results of ATP-TCA in the above patient subgroup patients showed that no or few regimens were highly sensitive or sensitive. On the other hand, in patients who had a TFI of ≥ 3 months and previously received only ≤ 2 chemotherapy regimens, ATP-TCA guided chemotherapy prolonged the PFS by 2–3 months compared with the control group. These results provided more indication in selecting patients for ATP-TCA.

The significance of secondary cytoreductive surgery in patients with platinum-resistant cancer was less explored in previous literature. In the present study, among the 37 patients who underwent secondary cytoreduction, 75.7% (28/37) achieved optimal cytoreduction (residual disease < 1 cm). Moreover, multivariate analysis showed that residual disease was an independent prognostic factor in PRROC. Patients with residual disease < 1 cm had better treatment outcome than the others. Among the patients

who achieved optimal cytoreduction, those in the ATP-TCA group had a slightly longer PFS than those in the control group, but the difference was not statistically significant (7 vs. 6 months, respectively). Meanwhile, the PFS of the patients who did not undergo secondary cytoreductive surgery or who failed to achieve optimal cytoreduction was statistically different between the ATP-TCA group and the control group. However, the PFS was only extended by one month (4 vs. 3 months). The role of ATP-TCA in this patient population needs further evaluation.

In the present study, most patients underwent combination chemotherapy because a single agent was less sensitive (higher SI score) than the combination regimens in ATP-TCA. The ratio of patients receiving combination chemotherapy was comparable between the experimental group and the control group. Drug safety between the two groups were not compared in our study because the same doses of chemotherapy were administered in both the experimental and control groups. None of the patients in the present study died due to adverse events.

Conclusions

The ATP-TCA resulted in favorable PFS when used as a predictive assay to individualize chemotherapy regimens in patients with PRROC, particularly in patients who had a TFI of ≥ 3 months and received ≤ 2 PCR. These findings are worth further confirmation via prospective randomized trials.

Acknowledgement

We thank Dr. Ying Huang for her comments on this paper.

Conflict of interest

The authors indicated no potential conflicts of interest.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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DOI 10.1007/s10330-017-0241-1
Cite this article as: Li N, Gao YT, Zhang W, *et al*. Comparative analysis of ATP-based tumor chemosensitivity assay-directed chemotherapy versus physician-decided chemotherapy in platinum-resistant recurrent ovarian cancer. Oncol Transl Med, 2017, 3: –.