Histol Histopathol (2020) 35: 721-728

http://www.hh.um.es

Histology and Histopathology
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Overexpression of YES1 is associated with favorable prognosis and increased platinum-sensitivity in patients with epithelial ovarian cancer

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Summary. Aims. The prognostic application of YES1 in epithelial ovarian cancer (EOC) is currently unclear. We aimed to investigate the expression of YES1 and its correlation with survival outcome in patients with EOC. Methods. A retrospective study of patients diagnosed with EOC at the Cancer Center, Sun Yat-Sen University, Guangzhou, China between 2002 and 2013 was conducted. The immunohistochemical expression of YES1 was assessed using tissue microarray. Survival rates were analyzed by the Kaplan-Meier method and were compared between groups using the log-rank test. Multivariate analyses were performed using the Cox proportional hazards model. Results. A total of 132 patients with EOC were enrolled. Patients in the YES1-high group exhibited significantly better OS and PFS, compared with those in the YES1-low group (P=0.02 and P=0.03, respectively). Further univariate and multivariate regression analyses indicated YES1 as an independent prognostic factor for the OS of patients with EOC. Notably, within the high YES1 expression group, 40 cases (74.1%) were of the platinum-sensitive group while 14 (25.9%) overlapped were of the platinum-resistant group. Conversely, in the low YES1 expression group, 11 cases (47.8%) were platinum-sensitive, and 12 (52.2%) platinum-resistant. Overall, patients within the high YES1 expression group were deemed significantly more sensitive to platinum-based chemotherapy than the low YES1 expression group (P=0.03), and YES1 levels were consistently and significantly higher in the platinum-sensitive group. Conclusions. High YES1 cytoplasmic expression in EOC patient tissue is significantly correlated with favorable prognosis. Patients with high YES1 expression tend to be sensitive to platinum-based chemotherapy.

Key words: YES1, OS, PFS, Platinum-sensitivity, Epithelial Ovarian Cancer

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DOI: 10.14670/HH-18-203

Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death among gynecologic malignancies in women, with patients generally diagnosed in advanced stages of the disease and predisposed to a high rate of mortality (Borley et al., 2012; Bray et al., 2018). The standard treatment for EOC is staging surgery or maximal debulking surgery followed with chemotherapy (Bristow et al., 2013, 2015; Ledermann et al., 2013; Erickson et al., 2014). While platinum-based drugs are widely used in primary chemotherapy for patients with ovarian carcinoma, currently no clinical biomarkers exist for the prediction of a patient's sensitivity to platinum-based treatment (Ozols et al., 2003; Pignata et al., 2011). From a clinical standpoint, upon a patient's recurrence, their likelihood of responding to treatment by platinum-based chemotherapy is largely dependent on the platinum-free interval, which is calculated as the time of the patient's last platinum administration to the time of cancer

recurrence (Markman et al., 2006; Sharma et al., 2009). If the carcinoma recurs within 6 months of the last platinum administration, it is considered to be 'platinum-resistant', whereas if recurrence occurs more than 6 months after the last platinum administration it is considered to be 'platinum-sensitive' (Markman et al., 1991).

EOC patients' sensitivity to platinum-based chemotherapy is an independent prognostic factor for their overall and progression-free survival (Raja et al., 2013). However, it is difficult to predict prior to first recurrence. As such, 'platinum-resistant' patients are usually identified retrospectively, after the recurrence of their cancer or failure to respond to initial platinum-based chemotherapy (Kyrgiou et al., 2006). Identifying predictors of patients' response to platinum-based chemotherapy would be greatly beneficial toward aiding with the selection of sensitive patients for chemotherapy and sparing resistant patients the toxicity of the process, and will also allow for the customization of treatments and clinical stratification of patients with EOC. Currently, however, no reliable methods exist to either determine or predict platinum sensitivity.

The v-yes-1 Yamaguchi sarcoma viral oncogene homolog 1, alternatively known as YES1, is the cellular homolog of the Yamaguchi sarcoma virus oncogene (Overholtzer et al., 2006; Dong et al., 2007). YES1 belongs to the Src kinase family, and its tyrosine kinase activity has been shown to be elevated in colonic adenomas compared with that in adjacent normal mucosa. In addition, a number of studies have identified up-regulation of YES1 as important for the growth and transformation of intestinal cells (Barraclough et al., 2007), and recently, YES1 has been discovered as a key molecule associated with chemoresistance in multiple cancers (Takeda et al., 2017; Lu et al., 2018; Chen et al., 2018; Fan et al., 2018). According to Takeda's study, YES1 was overexpressed and activated in breast cancer cell lines. Knockdown of YES1 by siRNA sensitized breast cancer cell lines to trastuzumab and lapatinib (Takeda et al., 2017). On the other hand, several studies suggest YES1 may exert tumor-suppressing functions. Knockdown of YES1 suppressed anoikis, increased migration/ invasion *in vitro*, and enhanced tumor growth in nude mice (Yuan et al., 2008). To date, studies on the role of YES1 in ovarian cancer development remain sparse, and the potential predictive function of YES1 expression on patients' survival and platinum-sensitivity remains obscure.

Thus, the aim of this study was to determine whether YES1 can serve as a novel biomarker for prognosis and predictive potential and platinum-sensitivity in EOC patients.

Materials and methods

Clinical samples

One hundred and thirty-two patients with epithelial ovarian cancer between 2002 and 2013 at the Cancer Center, Sun Yat-Sen University, Guangzhou, China were enrolled for this study. Briefly, women were eligible if they had a histologically or cytologically confirmed epithelial ovarian cancer, including serous, mucinous and endometrioid carcinoma, etc. All patients had undergone staging surgery or maximal debulking surgery (defined as residual disease measured <3 cm in largest diameter) and then received at least four cycles of platinum-based chemotherapy. The cohort's demographic, clinical, and pathological characteristics are shown in Table 1. This study was approved by the Ethical Committee of the Cancer Center, Sun Yat-Sen University (Guangzhou, China).

Among these patients, 82 patients which had recurrence were further divided into three categories: 1) progressed while receiving or within 4 weeks of receiving at least four cycles of platinum-based chemotherapy (defined as platinum-refractory, n=5), 2) recurred during 1–6 months after completion of the aforementioned platinum therapy (defined as platinum-resistant recurrence, n=26), 3) recurred more than 6 months after completion of the platinum-based therapy (defined as platinum-sensitive recurrence, n=51).

Epithelial ovarian cancer tissues were dissected from the resected tumors, which were confirmed by pathologic review. All samples were obtained from the Tissue Bank of Cancer Center, Sun Yat-Sen University. Epithelial ovarian cancer specimens were evaluated by an experienced pathologist and were staged according to the Federation of Gynecology (Mutch and Prat, 2014) and Obstetrics classification guidelines (Kurman, 2014). Grading and histopathology subtyping of epithelial ovarian cancer specimens was assigned based on criteria of the World Health Organization. Follow-up data was available for all patients. The duration of follow-up ranged from 5 to 164 months with a median follow-up period of 52 months. At last contact, 56 of the patients had died.

Tissue microarray

Hematoxylin and eosin–stained sections from each paraffin-embedded, formalin-fixed block were used to define diagnostic areas; 2-5 (average, 4) random representative 0.6-mm cores were obtained from each case and inserted in a grid pattern into a recipient paraffin block using a tissue arrayer (Beecher Instruments, Silver Spring, MD, USA) (Zhou et al., 2016).

Immunohistochemistry

Formalin-fixed, paraffin-embedded tissue were cut into 4-μm sections, deparaffinized in xylene, rehydrated through graded ethanol, then underwent endogenous peroxidase quenching in 0.3% hydrogen peroxide, antigen retrieval by pressure cooking in a 10 mM citrate buffer (pH 6.0), and incubation with primary antibody

against YES1 (Saierbio, China, 1:100) at 4°C overnight. Immunohistochemical staining was then implemented using a two-step EnVision System (Dako Cytomation). The sections were counterstained with hematoxylin. All runs included a no primary antibody negative control (Hans et al., 2004).

Evaluation of immunohistochemical variable

All of the stained slides were scanned using a digital slide scanner (Aperio VERSA 200, Leica, Germany) and eSlides were created. Expression of YES1 was then evaluated using the Aperio ImageScope (Aperio Technologies Inc., CA). Briefly, the level of YES1 was determined by a Histo-score (H-score), which included a semiquantitative assessment of both fraction of positive cells and intensity of staining. The intensity score was defined as no staining (0), weak (1), moderate (2) or strong (3) staining. The fraction score was based on the proportion of positively stained cells (0-100%). The H-score for each case was calculated as follows: H-score=1×(% of cells with intensity 1) + 2×(% of cells with intensity 2) + 3×(% of cells with intensity 3), which ranged from 0 to 3 and represented the level of YES1.

Statistical analysis

Statistical analyses were performed using the SPSS v19.0 software (IBM, USA). The relationship between YES1 expression and clinicopathological characteristics was assessed using Pearson's χ^2 test. Survival curves were plotted using the Kaplan-Meier method and compared using the log-rank test. Multivariate survival analyses were performed for all parameters that were significant in the univariate analysis using the Cox regression model. A two-sided probability value of <0.05 was considered statistically significant.

Results

Patient demographics and clinical characteristics

A total of 132 patients with epithelial ovarian cancer (EOC) were enrolled in this study. The duration of follow-up ranged from 5 to 164 months, with a median follow-up period of 52 months. At last contact, 56 patients had died. The 5-year overall survival (OS) rate for the 132 EOC patients was 47%, whereas the 5-year progress-free survival (PFS) was 25%.

YES1 Expression was associated with OS and PFS of EOC patients

The expression of YES1 was analyzed by immunohistochemistry. As shown, cytoplasmic expression of YES1 was observed in tumor cells (Fig. 1A). The positive rate of YES1 in tumor tissues is 96.2% (127/132). Thirty-three cases were cataloged into strong expressing group. Moreover, we also analyzed the expression of YES1 in fallopian tube epithelial. Four

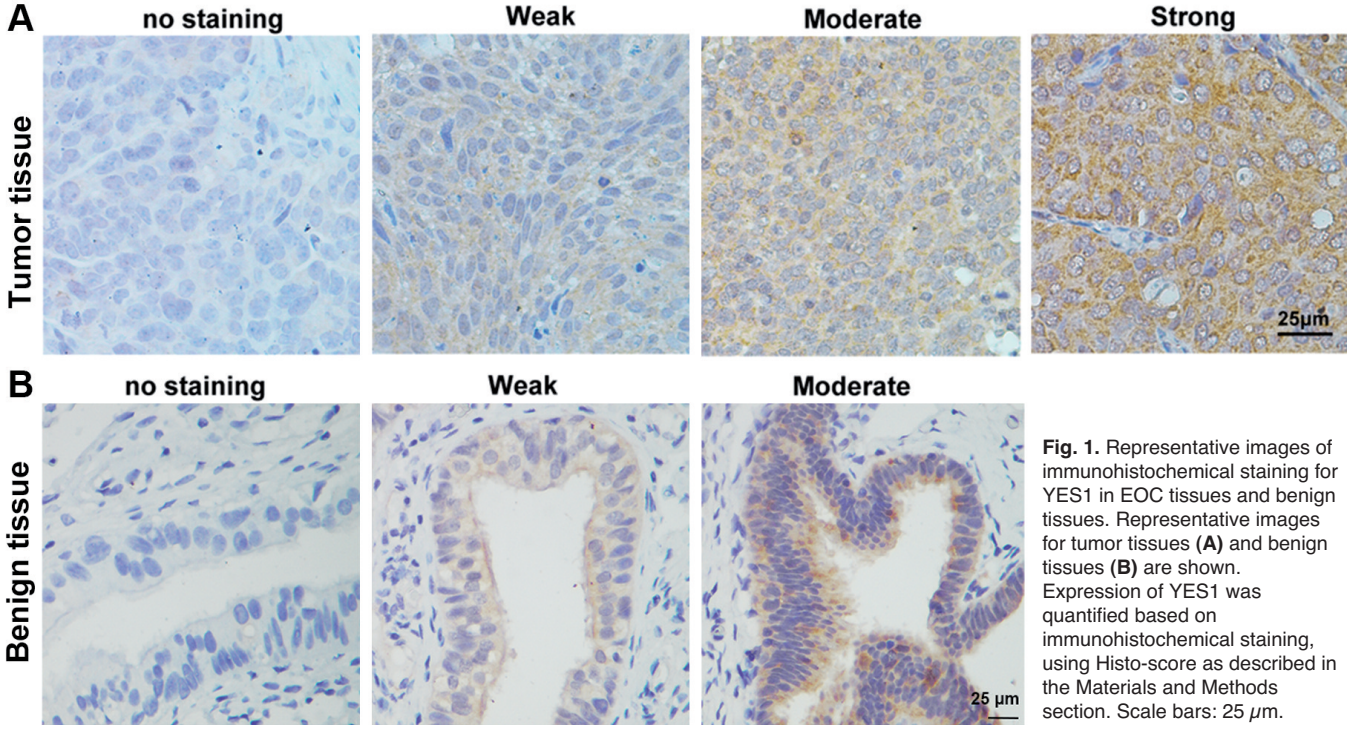

Fig. 1. Representative images of immunohistochemical staining for YES1 in EOC tissues and benign tissues. Representative images for tumor tissues **(A)** and benign tissues **(B)** are shown. Expression of YES1 was quantified based on immunohistochemical staining, using Histo-score as described in the Materials and Methods section. Scale bars: 25 μm.

corresponding benign tissues with fallopian tube epithelial were analyzed (Fig. 1B). The positive rate of YES1 in benign tissues was 3 out of 4. One sample presented a moderate level of YES1 and two other samples had weak YES1 levels. No strong signal was observed in benign tissues.

To further analyze the prognostic role of YES1, its expression was quantified by a H-score method as

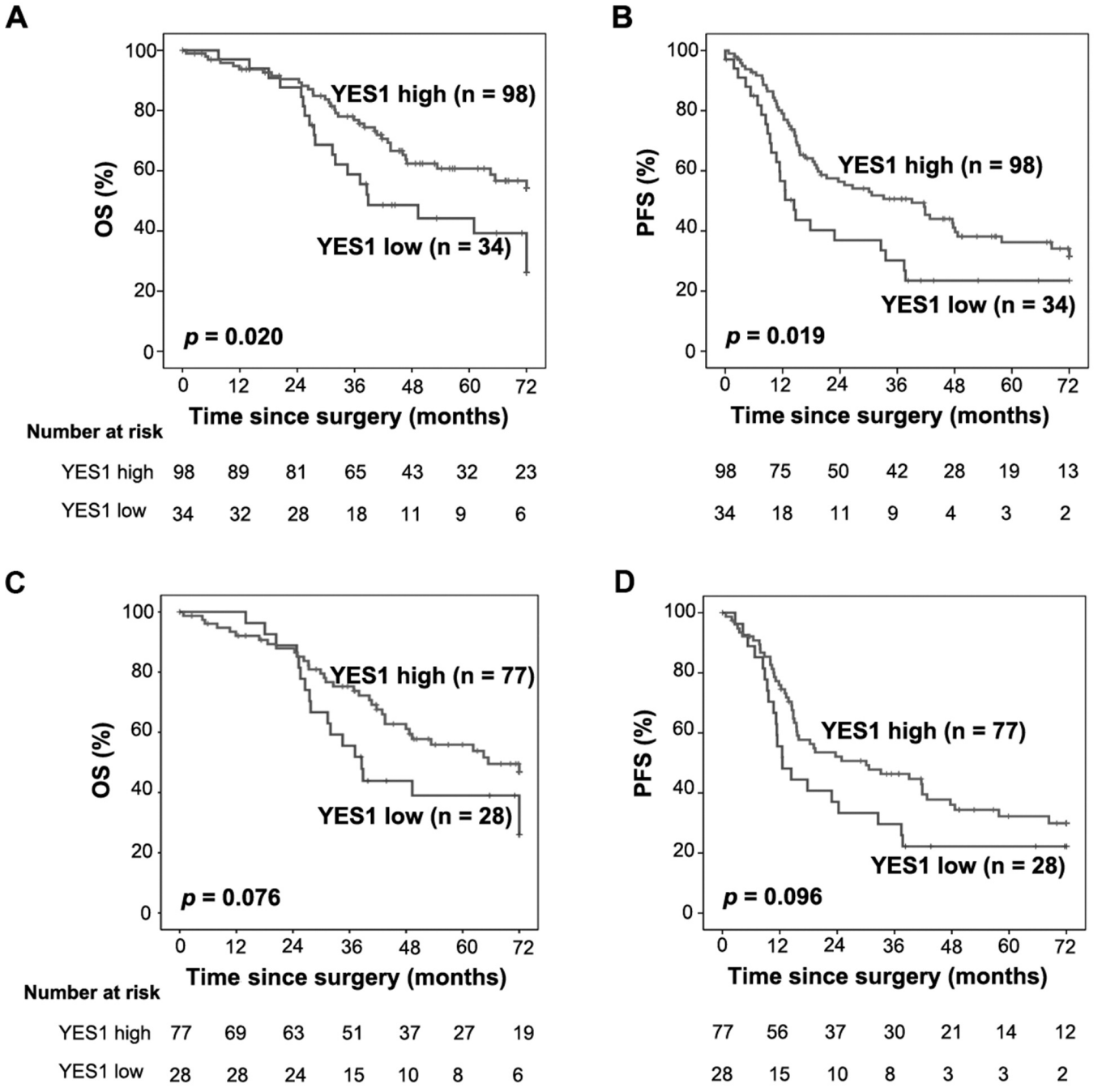

Fig. 2. Survival analysis of YES1 expression in EOC patients and HGSOC patients. **A-B.** Overall survival curves (OS, **A**) and Progress free survival curves (PFS, **B**) in EOC patients (n=132) were analyzed. A minimum P-value was acquired by log-rank survival analysis using a series of percentile values as cutoff points, based on YES1 levels. The 26th percentile was the most appropriate point for separating the YES1-high (N=98) from the YES1-low (N=34) expression group. **C-D.** Overall survival curves (OS, **C**) and Progress free survival curves (PFS, **D**) in HGSOC patients (n=105) were analyzed. The point for separating the YES1-high (N=77) from the YES1-low (N=28) expression group is based on Fig. 2A-B.

described in Methods. A minimum P-value approach was adopted to determine the most appropriate point in separating the YES1-high from the YES1-low expression group within the log-rank survival analysis, using a series of percentile YES1 levels as cutoff points. As shown, patients in the YES1-high group (n=98) fared significantly better in terms of both OS and PFS, compared with those in the YES1-low group (n=34) (Fig. 2A,B, P=0.020,=0.019). As the majority in this study are patients with high-grade serous ovarian carcinoma (HGSOC, 105/132), we also analyzed the prognostic effect of YES1 in this specific subgroup. Consistently, in the HGSOC patients, Kaplan-Meier curves showed an association between higher YES1 level and favorable OS or PFS (Fig. 2C,D). However, this difference was not statistically significant, which may be due to the small number of patients in each group.

Furthermore, univariate analysis showed that YES1, FIGO stage, histological grade, tumor recurrence, and cytoreductive surgery were factors significantly associated with overall survival (P<0.05) (Table 1). Analysis by Cox multivariate regression found that YES1 expression, pathological type, FIGO stage and residual disease were independent prognostic factors for patients' OS (Table 2). In addition, the relationship between YES1 expression and patient characteristics was analyzed (Table 3), and no significant association was observed.

Correlation of platinum sensitivity with YES1 expression

Platinum resistance is a major contributive factor for rapid EOC recurrence and poor patient survival. To analyze whether YES1 expression was associated with platinum resistance, patients with disease recurrence were divided into platinum-sensitive and -resistant groups. In the platinum-sensitive group (n=51), the disease did not recur within 6 months of the last instance

Table 1. Univariate analyses of factors associated with OS of EOC patients.

Variables	No. of Cases	Survival (%)	P*
Age (y)			
45 or younger	35	42	
Older than 45	97	48	0.202
Pathological type			
Serous	124	46	
Mucinous	4	75	
Endometrioid	2	50	
Other	2	5	0.45
FIGO stage			
I	21	100	
II	19	69	
III	77	28	
IV	15	9	0.0001
Histological grade			
G1	2	100	
G2	19	82	
G3	111	38	0.011
Residual disease			
<1cm	108	54	
≥1cm	24	23	0.0001
Recurrence			
Yes	82	20	
No	50	100	0.0001
YES1 expression			
High	98	53	
Low	34	28	0.020

*: P values were calculated using univariate Cox proportional hazards regression.

Table 2. Multivariate analyses of factors associated with OS of EOC patients.

Variables	P*	HR*	95% CI*
Pathological type (Serous vs Other)	0.017	0.261	0.086-0.79
FIGO stage (I,II VS III,IV)	0.0001	7.852	2.733-22.558
Histological grade (G1,G2 VS G3)	0.239	2.102	0.61-7.241
Residual disease (<1cm VS ≥1cm)	0.011	2.193	1.195-4.026
YES1 expression (High VS Low)	0.015	0.496	0.282-0.871

*: HR (hazard ratio) and P values were calculated using multivariate Cox proportional hazards regression; 95% CI, 95% confidence interval.

Table 3. Correlation of YES1 expression with clinicopathological features of EOC Patients.

Variables	Cases	Yes1-low	Yes1-high	P*
Age (y)				
45 or younger	35	9	26	
Older than 45	97	25	72	0.995
Pathological type				
Serous	124	32	92	
Mucinous	4	1	3	
Endometrioid	2	0	2	
Other	2	1	1	0.727
FIGO stage				
I	21	3	18	
II	19	5	14	
III	77	21	56	
IV	15	5	10	0.574
Histological grade				
G1	2	1	1	
G2	19	3	16	
G3	111	30	81	0.428
Residual disease				
<1cm	108	27	81	
≥1cm	24	7	17	0.673
Recurrence				
Yes	82	24	58	
No	50	10	40	0.238

*: P values were calculated using Pearson's χ^2 test.

of platinum administration, whereas in the platinum-resistant group, the disease recurred within 6 months (n=26). Notably, within the high YES1 expression group, 40 cases (74.1%) were in the platinum-sensitive group while 14 (25.9%) were in the platinum-resistant group. On the other hand, in the low YES1 expression group, 11 cases (47.8%) fell under the platinum-sensitive group and 12 (52.2%) were in the platinum-resistant group. The high YES1 expression group was significantly more sensitive to platinum-based chemotherapy than the low group (P=0.03, Fig. 3A). Moreover, upon further comparison of YES1 expression between patients from platinum-sensitive and –resistant groups, YES1 was consistently found to be significantly higher expressed in platinum-sensitive patients (Fig. 3B). These data suggest that a higher level of YES1 was associated with increased sensitivity to platinum, which may contribute favorably toward the survival of EOC patients. However, this notion still needs further validation on more patients.

Discussion

YES1 has been a focus subject of research due to its prognostic and therapeutic implications in the progression of various cancers (Xu et al., 2009; Wang et al., 2010). However, the role of YES1 and especially its prognostic application in ovarian cancer remains largely unclear. In this study, we found that high YES1 cytoplasmic expression in epithelial ovarian cancer tissue correlated significantly with favorable prognosis. In addition, patients with high YES1 expression tended to be sensitive to platinum based chemotherapy.

YES1 is a notable member of the Src family of tyrosine kinases, and has been suggested to regulate integration of different signaling pathways (Edgar, 2006; Dong et al., 2007). Actually, YES1 may function as an oncogene or a tumor suppressor depending on cell context (Overholtzer et al., 2006; Barraclough et al., 2007; Yuan et al., 2008). Currently, the oncogenic role of YES1 in tumor progression is supported by the existing correlation between decreased YES1 expression and impaired growth abilities of several malignancies, including malignant mesothelioma, rhabdomyosarcoma, and pancreatic cancer (Kubo et al., 2009; Yeung et al., 2013; Sato et al., 2014). Additionally, YES1 amplification has also been known as a mechanism through which resistance to EGFR inhibitors develops in lung cancer (Fan et al., 2018). On the other hand, YES1 may also act as a tumor-suppressor gene. Knockdown of YES1 by shRNA in breast cell lines suppressed cell anoikis, increased cell migration/invasion in vitros, and enhanced tumor growth in nude mice (Yuan et al., 2008). Other studies found that the downregulation of YES1 expression in gastric cancer tissue compared with that in adjacent normal tissue, or high cytoplasmic YES1 expression in tumor tissue, correlated significantly with lower TNM stages and lower histological grades in squamous cell carcinoma (Lu et al., 2018). The role of YES1 in the context of ovarian cancer is as of yet unclear; currently, only two studies have been published that analyzed the effect of YES1 on EOC cells *in vitro*, with inconsistent results (Konecny et al., 2009; Li et al., 2015). One study showed that OC cell lines with high expression of YES1 were particularly sensitive to dasatinib-induced cell apoptosis and cell cycle arrest, while the other showed that knockdown of YES1 reduced proliferation of EOC cells. Ultimately, the *in vivo* or prognostic role of YES1 in OC is still unknown. Our data establishes that EOC patients with high YES1 expression possess significantly more favorable overall and progression-free survival than patients with low YES1 expression. These findings suggest that YES1 may serve a substantial function in the regulation of tumor suppression in EOC. As for the different effect of YES1 on the tumor cells, it may be attributed to

A

Platinum Sensitivity	YES1 expression		*p*
	low	high	
Sensitive	11	40	0.03
Resistant	12	14	

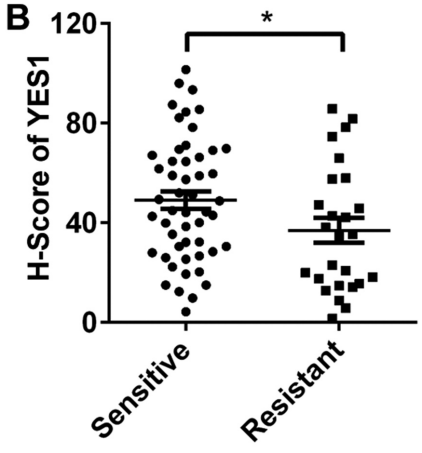

Fig. 3. YES1 levels correlated significantly with platinum sensitivity in patients with ovarian cancer. A Pearson's χ^2 test **(A)** and Student's T test **(B)** were employed. The 26th percentile was the separating point for the YES1-high (N=98) and the YES1-low (N=34) expression groups, as in Fig. 2.

difference in cellular contexts and further investigations in future are required.

Furthermore, our data show a significant correlation between YES1 expression and platinum sensitivity in patients with ovarian cancer. Patients with high YES1 expression tended to be sensitive to platinum based chemotherapy. Together with the previous report that OC cell lines with high expression of YES1 were particularly sensitive to dasatinib *in vitro* (Konecny et al., 2009), our data may suggest that a higher level of YES1 may sensitize the tumor cells to apoptosis or cell-cycle-arrest stimulators. Moreover, YES1 may stand as a potential predictive marker of whether platinum-based chemotherapy is likely to be effective in patients with ovarian carcinoma. Understanding the predictors of response to platinum based chemotherapy may help us select patients sensitive to chemotherapy while sparing resistant patients from exposure to the unnecessary toxicity of platinum based chemotherapy, and also allows for customization of treatments and clinical stratification of patients with ovarian cancer. In addition, reports have shown that YES1 enhances chemoresistance both *in vitro* and *in vivo*, and that (Takeda et al., 2017; Chen et al., 2018; Fan et al., 2018; Lu et al., 2018) downregulation of YES1 led to increased chemotherapy-induced cell death. As such, further *in vitro* and *in vivo* analyses of YES1 function on OC are warranted.

In summary, YES1 expression may serve as a predictive marker for the efficacy of platinum based chemotherapy and for survival in patients with ovarian cancer, the knowledge of which can be greatly contributive toward improving the prognosis of such patients. Planning is currently underway for further investigation regarding the involved molecular mechanisms.

Acknowledgements. This work was supported by the National Natural Science Foundation of China under grant numbers 81672863; the Project of State Key Laboratory of Oncology in South China under grant number 030041060004; the Project of Guangzhou Science and Technology Plan under grant number 2014J4100238; and the Science and Technology Plan Program of Guangdong Province under grant number 2016A020215080.

Conflict of Interest. No potential conflict of interest relevant to this article was reported.

Disclaimer. No potential conflict of interest relevant to this article was reported.

References

Barraclough J., Hodgkinson C., Hogg A., Dive C. and Welman A. (2007). Increases in c-Yes expression level and activity promote motility but not proliferation of human colorectal carcinoma cells. Neoplasia 9, 745-754.

Borley J., Wilhelm-Benartzi C., Brown R. and Ghaem-Maghami S. (2012). Does tumour biology determine surgical success in the treatment of epithelial ovarian cancer? A systematic literature review. Br. J. Cancer 107, 1069-1074.

Bray F., Ferlay J., Soerjomataram I., Siegel R.L., Torre L.A. and Jemal A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 68, 394-424.

Bristow R.E., Chang, J., Ziogas A. and Anton-Culver H. (2013). Adherence to treatment guidelines for ovarian cancer as a measure of quality care. Obstet. Gynecol. 121, 1226-1234.

Bristow R.E., Chang, J., Ziogas A., Campos B., Chavez L.R. and Anton-Culver H. (2015). Impact of National Cancer Institute Comprehensive Cancer Centers on ovarian cancer treatment and survival. J. Am. Coll. Surg. 220, 940-950.

Chen L., Cao H. and Feng, Y. (2018). MiR-199a suppresses prostate cancer paclitaxel resistance by targeting YES1. World J. Urol. 36, 357-365.

Dong J., Feldmann G., Huang J., Wu S., Zhang N., Comerford S.A., Gayyed M.F., Anders R.A., Maitra A. and Pan D. (2007). Elucidation of a universal size-control mechanism in Drosophila and mammals. Cell 130, 1120-1133.

Edgar B.A. (2006). From cell structure to transcription: Hippo forges a new path. Cell 124, 267-273.

Erickson B.K., Martin J.Y., Shah M.M., Straughn J.J. and Leath C.R. (2014). Reasons for failure to deliver National Comprehensive Cancer Network (NCCN)-adherent care in the treatment of epithelial ovarian cancer at an NCCN cancer center. Gynecol. Oncol. 133, 142-146.

Fan P.D., Narzisi G., Jayaprakash A.D., Venturini E., Robine N., Smibert P., Germer S., Yu H.A., Jordan E.J., Paik P.K., Janjigian Y.Y., Chaft J.E., Wang L., Jungbluth A.A., Middha S., Spraggon L., Qiao H., Lovly C.M., Kris M.G., Riely G.J., Politi K., Varmus H. and Ladanyi M. (2018). YES1 amplification is a mechanism of acquired resistance to EGFR inhibitors identified by transposon mutagenesis and clinical genomics. Proc. Natl. Acad. Sci. USA 115, E6030-E6038.

Hans C.P., Weisenburger D.D., Greiner T.C., Gascoyne R.D., Delabie J., Ott G., Muller-Hermelink H.K., Campo E., Braziel R.M., Jaffe E.S., Pan Z., Farinha P., Smith L.M., Falini B., Banham A.H., Rosenwald A., Staudt L.M., Connors J.M., Armitage J.O. and Chan W.C. (2004). Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 103, 275-282.

Konecny G.E., Glas R., Dering J., Manivong K., Qi J., Finn R.S., Yang G.R., Hong K.L., Ginther C., Winterhoff B., Gao G., Brugge J. and Slamon D.J. (2009). Activity of the multikinase inhibitor dasatinib against ovarian cancer cells. Br. J. Cancer 101, 1699-1708.

Kubo T., Kuroda Y., Kokubu A., Hosoda F., Arai Y., Hiraoka N., Hirohashi S. and Shibata T. (2009). Resequencing analysis of the human tyrosine kinase gene family in pancreatic cancer. Pancreas 38, e200-e206.

Kurman R.J., Carcangiu M.L., Herrington C.S. and Young R.H. editors. (2014). WHO Classification of Tumours of Female Reproductive Organs. 4th ed. Geneva: WHO; 2014

Kyrgiou M., Salanti G., Pavlidis N., Paraskevaidis E. and Ioannidis J.P. (2006). Survival benefits with diverse chemotherapy regimens for ovarian cancer: meta-analysis of multiple treatments. J. Natl. Cancer Inst. 98, 1655-1663.

Ledermann J.A., Raja F.A., Fotopoulou C., Gonzalez-Martin A., Colombo N. and Sessa C. (2013). Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for

diagnosis, treatment and follow-up. Ann. Oncol. 24 Suppl 6, i24-i32.

Li L., He L., Zhao J.L., Xiao J., Liu M., Li X. and Tang H. (2015). MiR-17-5p up-regulates YES1 to modulate the cell cycle progression and apoptosis in ovarian cancer cell lines. J. Cell Biochem. 116, 1050-1059.

Lu T., Sun L. and Zhu X. (2018). Yes-associated protein enhances proliferation and attenuates sensitivity to cisplatin in human gastric cancer cells. Biomed. Pharmacother. 105, 1269-1275.

Markman M., Rothman R., Hakes T., Reichman B., Hoskins W., Rubin S., Jones W., Almadrones L. and Lewis J.J. (1991). Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. J. Clin. Oncol 9, 389-393.

Markman M., Blessing J., Rubin S.C., Connor J., Hanjani P. and Waggoner S. (2006). Phase II trial of weekly paclitaxel (80 mg/m^2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. Gynecol. Oncol. 101, 436-440.

Mutch D.G. and Prat J. (2014). 2014 FIGO staging for ovarian, fallopian tube and peritoneal cancer. Gynecol. Oncol. 133, 401-404.

Overholtzer M., Zhang J., Smolen G.A., Muir B., Li W., Sgroi D.C., Deng C.X., Brugge J.S. and Haber D.A. (2006). Transforming properties of YAP, a candidate oncogene on the chromosome 11q22 amplicon. Proc. Natl. Acad. Sci. USA 103, 12405-12410.

Ozols R.F., Bundy B.N., Greer B.E., Fowler J.M., Clarke-Pearson D., Burger R.A., Mannel R. S., DeGeest K., Hartenbach E.M. and Baergen R. (2003). Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J. Clin. Oncol. 21, 3194-3200.

Pignata S., Scambia G., Ferrandina G., Savarese A., Sorio R., Breda E., Gebbia V., Musso P., Frigerio L., Del M.P., Lombardi A.V., Febbraro A., Scollo P., Ferro A., Tamberi S., Brandes A., Ravaioli A., Valerio M.R., Aitini, E., Natale D., Scaltriti L., Greggi S., Pisano, C., Lorusso D., Salutari V., Legge F., Di Maio M., Morabito A., Gallo C. and Perrone F. (2011). Carboplatin plus paclitaxel versus carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: the MITO-2 randomized phase III trial. J. Clin. Oncol. 29, 3628-3635.

Raja F.A., Counsell, N., Colombo N., Pfisterer J., du Bois A., Parmar M.K., Vergote I.B., Gonzalez-Martin A., Alberts D.S., Plante M., Torri V. and Ledermann J.A. (2013). Platinum versus platinum-combination chemotherapy in platinum-sensitive recurrent ovarian cancer: a meta-analysis using individual patient data. Ann. Oncol. 24, 3028-3034.

Sato A., Virgona N., Ando A., Ota M. and Yano T. (2014). A redox-silent analogue of tocotrienol inhibits cobalt (II) chloride-induced VEGF expression via Yes signaling in mesothelioma cells. Biol. Pharm. Bull 37, 865-870.

Sharma R., Graham J., Mitchell H., Brooks A., Blagden S. and Gabra H. (2009). Extended weekly dose-dense paclitaxel/carboplatin is feasible and active in heavily pre-treated platinum-resistant recurrent ovarian cancer. Br. J. Cancer 100, 707-712.

Takeda T., Yamamoto H., Kanzaki H., Suzawa K., Yoshioka T., Tomida S., Cui X., Murali R., Namba K., Sato H., Torigoe H., Watanabe M., Shien K., Soh J., Asano H., Tsukuda K., Kitamura Y., Miyoshi S., Sendo T. and Toyooka S. (2017). Yes1 signaling mediates the resistance to Trastuzumab/Lap atinib in breast cancer. PLoS One 12, e171356.

Wang Y., Dong Q., Zhang Q., Li Z., Wang E. and Qiu X. (2010). Overexpression of yes-associated protein contributes to progression and poor prognosis of non-small-cell lung cancer. Cancer Sci. 101, 1279-1285.

Xu M.Z., Yao T.J., Lee N.P., Ng I.O., Chan Y.T., Zender L., Lowe S.W., Poon R.T. and Luk J.M. (2009). Yes-associated protein is an independent prognostic marker in hepatocellular carcinoma. Cancer 115, 4576-4585.

Yeung C.L., Ngo V.N., Grohar P.J., Arnaldez F.I., Asante A., Wan X., Khan J., Hewitt S.M., Khanna C., Staudt L.M. and Helman L.J. (2013). Loss-of-function screen in rhabdomyosarcoma identifies CRKL-YES as a critical signal for tumor growth. Oncogene 32, 5429-5438.

Yuan M., Tomlinson V., Lara R., Holliday D., Chelala C., Harada T., Gangeswaran, R., Manson-Bishop C., Smith P., Danovi S.A., Pardo O., Crook T., Mein C.A., Lemoine N.R., Jones L.J. and Basu S. (2008). Yes-associated protein (YAP) functions as a tumor suppressor in breast. Cell Death Differ. 15, 1752-1759.

Zhou Y., Huang Y., Cao X., Xu J., Zhang L., Wang J., Huang L., Huang S., Yuan L., Jia W., Yu X., Luo R. and Zheng M. (2016). WNT2 promotes cervical carcinoma metastasis and induction of epithelial-mesenchymal transition. PLoS One 11, e160414.

Accepted January 23, 2020