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# Genitourinary small-cell carcinoma: 11-year treatment experience

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The predictive factors of prognosis and treatment strategies for small-cell carcinoma (SCC) of the urinary tract are controversial. This study was aimed to investigate the clinical experience and management of patients with SCC of the urinary tract. We collected data of patients who were diagnosed with genitourinary SCC (GSCC) between 2002 and 2013 and were treated in the Fudan University Shanghai Cancer Center. A total of 18 patients were diagnosed with GSCC of which 10 originated from the prostate, seven from the bladder and one from the adrenal gland. The mean follow-up time was 15.5 months and progression-free survival (PFS) was 9.3 months. Primary tumor resection was attempted in 13 of 18 patients (72.2%) in whom radical surgery was performed in six of 14 (42.9%) limited disease patients. Most of the patients (13, 72.2%) received cisplatin-based chemotherapy. Patients who had normal lactic dehydrogenase (LDH) levels showed a significantly higher median PFS and overall survival (OS) compared with patients with high LDH levels ( $P = 0.030$ ,  $P = 0.010$ ). Patients with limited disease treated with a radical operation experienced a non-significant ( $P = 0.211$ ) longer PFS compared with patients who were not treated, but this reached statistical significance after analyzing OS ( $P = 0.211$ ,  $P = 0.039$ ). Our patients showed a poor prognosis as reported previously. Serum LDH levels beyond the normal range indicate a poor prognosis. For GSCC patients who are diagnosed with limited disease, radical surgery is strongly recommended along with cisplatin-based chemotherapy.

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## INTRODUCTION

As a distinct histological and biological disease entity, small-cell carcinoma (SCC) usually originates from the lung. However, SCC arising from the genitourinary tract has occasionally been reported. The first case of SCC of the urinary system was reported in 1977 by Wenk *et al.*<sup>1</sup> SCC comprises <1% of primary bladder tumors<sup>2</sup> and <0.5% of prostate carcinomas.<sup>3</sup> Other genitourinary organs showing SSC, such as the adrenal gland, kidney, ureter, urethra and testicle, are even less incidental.<sup>3</sup>

Genitourinary SCC (GSCC) is usually characterized by an advanced stage at diagnosis and rapid clinical progression. Patients with localized disease are inclined to develop distant metastases after treatment.<sup>4</sup> Given the rarity of GSCC, there are few good quality clinical trials and most experience of GSCC is directly learned from SCC of small-cell lung carcinoma (SCLC). Most retrospective series and case reports on GSCC had a relatively small sample size.<sup>5</sup> Among the published articles on GSCC, most are research from the surveillance, epidemiology and end results (SEER) database and information on the patients is not detailed. The only prospective study on GSCC was a single-center non-randomized phase II study of 25 patients with small-cell urothelial cancer treated in a fashion analogous to SCLC.<sup>6</sup> Therefore, the effectiveness of some newly advocated treatment therapies, including radical surgery,

remains controversial. In addition, the importance of lactic dehydrogenase (LDH) in predicting the prognosis of GSCC is still unclear.

We report our clinical experience in a single center in the diagnosis and treatment of patients with GSCC during the past 11 years at Fudan University Shanghai Cancer Center. We analyzed data on characteristics, clinical behavior and treatment results of GSCC.

## MATERIALS AND METHODS

### Patient selection

All cases of GSCC were retrospectively reviewed in Fudan University Shanghai Cancer Center from August 2002 to July 2013. Patients were included when they had a pathological confirmation of GSCC, either by biopsy or at surgery. Patients were excluded if they had any evidence of tumors originating from the lung. Immunohistochemical analysis further assisted in confirming the diagnosis. Data from 18 patients were collected from clinical notes for patient demographics, primary site, stage (limited vs extensive), tumor node metastasis (TNM), treatment received and outcome. The length of follow-up was based on the response to telephone calls and progression-free survival (PFS) was based on data extracted from the clinical records. Living patients were censored at the date of the last follow-up. This study was approved by our Institutional Review Board and written informed consent was

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obtained from each patient before any study-specific investigation was performed.

### Staging

In the management of SCLC, a simplified staging approach known as the Veterans Affairs system separating “limited” and “extensive” disease was initially adopted, which is commonly used to stage GSCC.<sup>7</sup> However, in contrast to typical SCLC treatment, resection of the primary tumor can be part of the therapeutic strategy in GSCC. Therefore, resectability of the primary tumor should be taken into consideration when designating limited disease versus extensive disease. As a result, limited disease was defined as a tumor restricted to the primary urinary organ with or without locoregional lymph node metastasis. Locoregional lymph node metastasis can be resected or is confined to the true and false pelvis such that all disease is encompassable within the same radiation field. Extensive disease was defined as disease that does not adhere to the description for limited disease.<sup>8,9</sup> The TNM staging system advocated by the 2010 American Joint Committee on Cancer was also adopted for pathological staging. This system is used to stage common urinary tract carcinoma.

### Statistical analysis

To study the potential differences in PFS and overall survival (OS) related to different variables, Kaplan–Meier survival curves and the log-rank test were calculated using Statistical Package for the Social Sciences (SPSS) 19.0 software version 16.0 (SPSS Inc., Chicago, IL, USA).  $P < 0.05$  was deemed statistically significant.

## RESULTS

### Clinical features

The clinicopathological features of the 18 cases are summarized in **Table 1**. Of the 18 patients with GSCC, 10 originated from the prostate, seven from the bladder and one from the adrenal. H and E staining showed a cluster of closely packed small cells with hyperchromatic nuclei and a scanty cytoplasm. The presence of immunoreactivity against chromogranin A or synaptophysin in biopsy samples was examined for diagnostic confirmation. Among the pure prostate SCC patients, immunohistochemical analysis showed the absence of tissue-specific antigens (e.g., prostate-specific antigen (PSA) expression). A relatively high Ki67 expression suggested aggressive behavior of GSCC (**Figure 1**). Pathological study also showed SCC with mixed histology in seven of 18 cases (38.9%). The patients’ ages ranged from 44 to 76 years (mean, 63.7 years). The majority of the patients were men, with only one woman. Among the patients, the presenting symptom was closely related to the origin of SCC: the bladder was associated with hematuria, the prostate was associated with dysuria and the adrenal gland was not associated with any symptoms, which could only be discovered by a routine examination. Other accompanying symptoms were weight loss (22.2%, 4/18), backache (16.7%, 3/18) and abdominal pain (11.1%, 2/18), which were not specifically confined to a particular disease. Evidence of extensive disease was found in four cases (22.2%) and the most frequent distant sites of metastasis were the liver (75%, 3/4), bone (50%, 2/4), posterior peritoneum (50%, 2/4) and mediastinum (25%, 1/4). None of the patients presented with paraneoplastic syndromes or cranial metastasis during their follow-up. According to patients’ serum LDH levels at diagnosis, they were divided into two groups. One group consisted of patients whose LDH levels were within the normal range (61.1%, 11/18) and the other group consisted of patients with elevated serum LDH

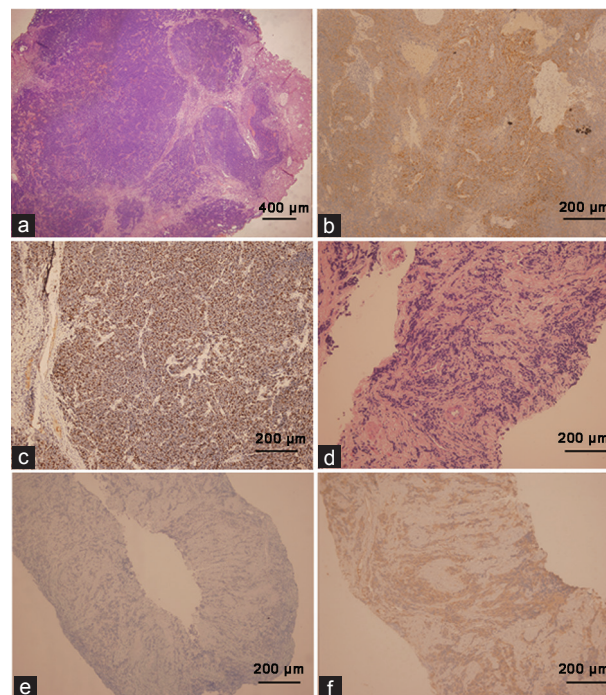
levels (38.9%, 7/18). The normal range of serum LDH was defined as from 100 to 300 U l<sup>-1</sup>.

### Pathological characteristics

The morphological criteria for diagnosis of SCC were based on the description of the World Health Organization. Diagnosis of SCC required the identification of a tumor with cohesive round to oval cells, a sparse cytoplasm, nuclei with “salt-and-pepper” chromatin, nuclear mounding and small or inconspicuous nucleoli. In addition, the tumor cells were examined for mitoses, apoptosis and necrosis. Immunoreactivity played a pivotal role in diagnosis of SCC, such as the presence of cyokeratins AE1-AE3, chromogranin A and synaptophysin. A high expression of Ki67 indicated aggressive behavior of SCC. In addition to the markers stated above, a negative reaction for PSA was another feature of SCC originating from the prostate (**Figure 1**).

### Treatment outcome

Treatment modalities in these patients included surgery, chemotherapy and radiation therapy, as well as hormonal therapy in some cases with prostatic adenocarcinoma. Most of the patients received combined modality therapies or treatment at different times in the disease course. Primary tumor resection was attempted in 13 of 18 patients (72.2%) in whom radical surgery was performed in six of 14 (42.9%) limited disease patients. Most of the patients (13, 72.2%) received cisplatin-based chemotherapy as adjuvant treatment. Besides cisplatin, etoposide was administered in nine (50%) patients, docetaxel in five (27.8%) and gemcitabine in two (11.1%). Cyclophosphamide and Adriamycin were rarely given. Radiation therapy was administered in six of



**Figure 1:** (a) Bladder small-cell carcinoma (SCC): H and E staining (original magnification,  $\times 40$ ); (b) Bladder SCC: chromogranin A immunohistochemical expression (original magnification,  $\times 100$ ); (c) Bladder SCC: Ki67 immunohistochemical expression (original magnification,  $\times 100$ ); (d) Prostate SCC: H and E staining (original magnification,  $\times 100$ ); (e) Prostate SCC: negative prostate-specific antigen immunohistochemical expression (original magnification,  $\times 100$ ); (f) Prostate SCC: synaptophysin immunohistochemical expression (original magnification,  $\times 100$ ).

**Table 1: Characteristics of the patients and therapeutic strategies used**

Patient	Primary site	Sex	Age	Presenting symptom	Stage	TNM	Surgery	Radical operation	Treatment therapy except surgery	Serum LDH beyond the normal range	OS	PFS
1	Prostate	Male	48	Dysuria	LD	T4N1M0	No	No	DPx6+EPx6+pelvic RT	No	28	15
2	Prostate	Male	64	Dysuria	LD	T3N0M0	RP	Yes	(DP+5-Fu)×11+etoposid ex12+palliative RT+HT	No	48	5
3	Prostate	Male	69	Dysuria, backaches, abdominal pain	ED	T4N1M1	No	No	DPx3	No	9	9
4	Prostate	Male	69	Dysuria	LD	T4N0M0	UCST+transverse colostomy	No	DPx3+pelvic RT	Yes	7	6
5	Prostate	Male	76	Dysuria	ED	T4N1M1	TURP	No	DPx2+EPx4+HT	No	14	2
6	Prostate	Male	59	Dysuria, weight loss	LD	T4N0M0	No	No	No	Yes	5	5
7	Prostate	Male	64	dysuria	LD	T4N1M0	RP+UCST	No	EPx6	Yes	11	6
8	Prostate	Male	62	Dysuria, backaches	NA	T3N1M0	RP	Yes	EPx4+HT	Yes	25	12
9	Prostate	Male	71	Dysuria, weight loss	NA	T4N1M0	TURP	No	EPx6+pelvic RT	No	35	26
10	Prostate	Male	63	dysuria	ED	T3N1M1	No	No	No	Yes	2	0
11	Bladder	Male	65	Hematuria, backaches	LD	T2N2M0	TURBT+RC	Yes	GPx3	No	41	36
12	Bladder	Female	75	Hematuria	LD	T2N0M0	TURBT	No	Pelvic RT	No	15	15
13	Bladder	Male	67	Hematuria, weight loss	LD	T4N2M0	RC+UCST	No	EPx2	Yes	4	4
14	Bladder	Male	63	Hematuria, abdominal pain	LD	T4N2M0	TURBT+RC	Yes	EPx3+CAPx2+pelvic RT	No	12	7
15	Bladder	Male	73	Hematuria	LD	T2N0M0	TURBT+RC	Yes	No	No	8	8
16	Bladder	Male	52	Hematuria, weight loss	LD	T3N2M0	TURBT+RC	Yes	GPx4	No	9	9
17	Bladder	Male	44	Hematuria	LD	T2N0M0	TURBT+ReTURBT	No	No	No	3	3
18	Adrenal	Male	63	No	ED	T3N1M1	No	No	EP	Yes	3	0

CAP: cyclophosphamide+adriamycin+cisplatin; DP: docetaxel+cisplatin; ED: extensive disease; EP: etoposide+cisplatin; GP: gemcitabine+isplatin; HT: hormonal therapy; LD: limited disease; RC: radical cystectomy; RP: radical prostatectomy; RT: radiation therapy; TURBT: transurethral resection of bladder; UCST: ureterocutaneostomy; TNM: tumor-node-metastasis; PFS: progression-free survival; OS: overall survival; LDH: lactic dehydrogenase; TURP: transurethral prostatectomy

18 cases (33.3%). Hormonal manipulation was attempted in three of the five patients (60%) with prostatic SCC mixed with adenocarcinoma.

The follow-up interval of these 18 patients ranged from 3 to 48 months (median, 15.5) and the median PFS was 9.3 months. At the last follow-up, 13 patients (72.2%) had died of GSCC, three (16.7%) were in good health and two (11.1%) were alive with disease. The median OS was 18.2 months in patients with prostate SCC and 13.1 months in patients with bladder SCC.

#### Comparison of clinical outcomes between groups

Evaluation of the 18 patients was completed to determine the patient and tumor characteristics and therapies that were associated with OS. As shown in **Figure 2a**, patients with normal LDH levels showed a significantly higher mean PFS compared with patients with serum LDH levels beyond the normal range (12.2 vs 4.7 months,  $P = 0.030$ ; **Figure 2a**). In OS analysis, patients with normal LDH levels also, <sup>16,17</sup> showed a survival benefit (20.0 months) compared with patients with high serum LDH levels (8.1 months,  $P = 0.010$ ; **Figure 2b**).

Limited disease patients treated with radical surgery appeared to experience a longer PFS compared with those without radical surgery (12.8 vs 7.6 months, **Figure 2c**), but this difference was not statistically significant ( $P = 0.211$ ). However, in OS analysis, limited disease patients treated with radical surgery lived longer than patients without radical surgery (23.8 vs 11.3 months,  $P = 0.039$ , **Figure 2d**).

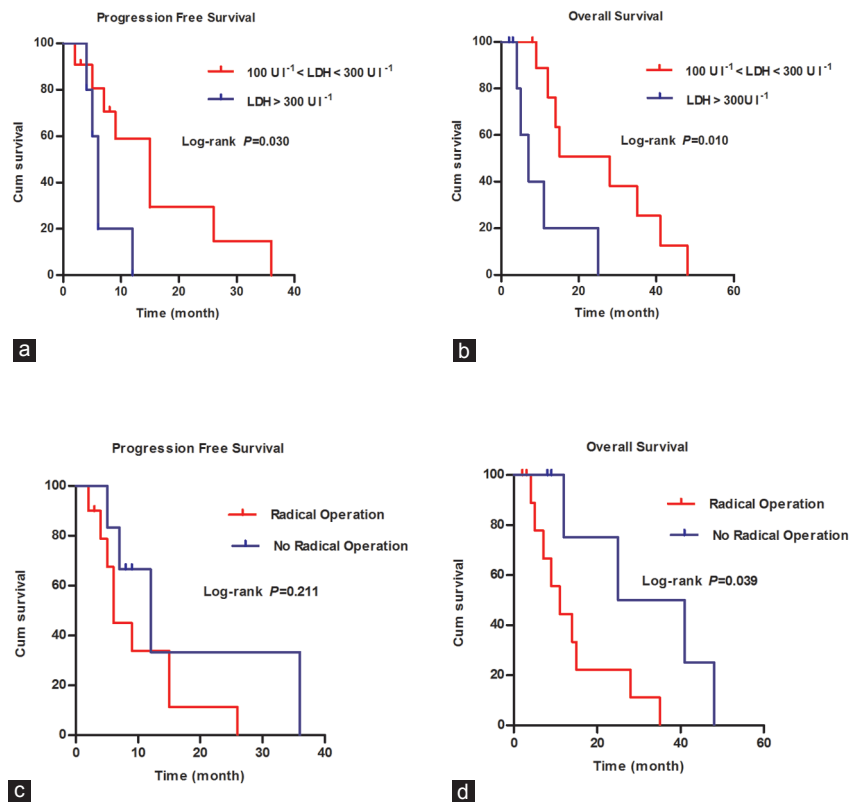
Other variables were also analyzed in relation to PFS and OS, such as differences based on the origin in various organs, limited disease versus extensive disease and lymph node metastasis versus a tumor confined to a specific organ. However, there were no significant differences in PFS and OS related to these variables. Patients with SCC mixed with other types of carcinoma appeared to live longer than patients with pure SCC (20.3 vs 13.1 months), but this did not reach statistical significance ( $P = 0.421$ ).

#### DISCUSSION

GSCC is a rare tumor, which behaves aggressively, with a 25% two-year survival and 8% five-year survival.<sup>10</sup> GSCC mostly occurs in elderly men instead of women, which was found in the present study and in previous series.<sup>11-14</sup>

The origin of extrapulmonary SCC remains controversial. Therefore, different theories have been postulated. The majority of authors accept the hypothesis that extrapulmonary SCC is derived from a multipotent stem cell with the ability to differentiate into various tissue types. This concept is indispensable to understand the nature of SCC because it is always diagnosed with a mixture of other malignancies, such as adenocarcinoma or transitional cell carcinoma. Cheng *et al.*<sup>15</sup> reported an identical pattern of allelic loss in coexisting SCC and urothelial carcinoma, suggesting a common progenitor cell of origin. Other theories, including the derivation of SCC from the neural crest line/amine precursor uptake and decarboxylation system and metaplasia from other high-grade malignancies, still need further validation.<sup>10,16,17</sup>

Due to the diverse origin of GSCC, the discrepancy of the presenting syndrome may lead to various diagnostic stages, which have never been previously reported. In our study, bladder SCC patients always presented with hematuria, the prostate was associated with dysuria and the adrenal gland was not associated with any symptoms (**Table 1**). Therefore, early diagnosis of prostate SCC and adrenal SCC may be difficult. Because early diagnosis of prostatic adenocarcinoma relies on abnormal elevation of PSA levels and prostate SCC patients' PSA levels generally remain at a low level, early diagnosis of prostate SCC is extremely difficult. However, in SCC originating from the bladder, our study showed that all of the patients visited the hospital for hematuria, which is similar to bladder transitional cell carcinoma. Therefore, bladder SCC patients



**Figure 2:** Kaplan–Meier progression free survival (PFS) and overall survival (OS) curves and the log-rank test by lactic dehydrogenase levels (a and b). Kaplan–Meier PFS and OS curves and the log-rank test by radical operation (c and d)

are usually diagnosed in the early stage. Our study also supports this discrepancy that 8/10 (80%) patients with prostate SCC were diagnosed as T4 and only 2/6 (30%) bladder SCC patients were diagnosed as T4. Furthermore, three prostate SCC patients were diagnosed with distant metastasis, which was not present in the bladder. These findings are consistent with some previous studies. In Deorah *et al.*'s cohort,<sup>18</sup> 47% of the prostate patients were diagnosed with distant metastasis. However, with regard to bladder patients, only 5% were reported in Choong *et al.*'s cohort of 44 patients.<sup>19</sup> Due to the limited related published articles, further research is required to validate this conclusion.

In our cohort, patients with SCC mixed with other tumors, such as adenocarcinoma or transitional cell carcinoma, experienced longer OS than patients with pure SCC (20.3 vs 13.1 months), but this difference did not reach statistical significance. This phenomenon has been sporadically reported by some authors. Deorah *et al.*<sup>18</sup> in their study have reported that concomitant well-to-moderately differentiated adenocarcinomas were associated with improved prognosis in SCC of the prostate after analyzing 241 prostate SCC patients from SEER database registries. We found that patients responded to hormonal therapy with shrinkage of prostate volume and a reduction in PSA levels. Therefore, we speculate that this difference between studies in OS of patients with SCC mixed with other tumors and those with pure SCC was due to the effectiveness of hormonal therapy. A study by Brammer *et al.*<sup>4</sup> also reported a benefit of survival with a combination of hormonal therapy for treatment of patients with prostate SCC mixed with adenocarcinoma. With regard to bladder SCC mixed with transitional cell carcinoma, patients were thought to benefit from

routine transurethral resection of a bladder tumor and intravesical instillation followed by surgery.

Some recent studies reported that an elevated serum LDH level at the time of diagnosis is a predictive factor of inferior PFS and OS. Previous studies have reported the prognostic value of serum LDH levels in other genitourinary organs.<sup>20,21</sup> However, the current study validates the clinical significance of this variable for GSCC. Spiess *et al.*<sup>22</sup> discovered that patients with a combination of low serum albumin levels and high LDH levels at the time of diagnosis have poorer PFS and disease-specific survival than other patients with SCC of the prostate (both  $P = 0.02$ ). Serum LDH levels in healthy people can fluctuate in a relatively normal range. Therefore, we divided our patients into two groups according to normal and high serum LDH levels. We found that high serum LDH levels were closely associated with a poor prognosis. However, further studies are still required to investigate this finding in more detail.

Different approaches have been proposed to prolong survival in patients diagnosed with GSCC. Our study suggested that patients who accepted radical surgery experienced a longer PFS and OS compared with those who did not accept radical surgery. However, this result is controversial among other previous studies. In Cheng *et al.*'s study<sup>23</sup> on 64 patients with SCC of the urinary bladder, 38 (59%) underwent radical cystectomy and no significant survival difference was found between patients who accepted radical surgery and those who did not ( $P = 0.65$ ). However, in some larger cohorts, radical surgery played an important role in treating GSCC patients who were diagnosed with limited disease. Schreiber *et al.*<sup>24</sup> in their study have reported that patients who

had SCC originating from the bladder could benefit from radical surgery in terms of OS compared with those who only underwent transurethral resection of urinary bladder tumor ( $P < 0.001$ ). After analyzing patients' clinical data, Mackey *et al.*<sup>3</sup> concluded that radical surgery is an independent factor associated with prolonged survival for prostate patients ( $P < 0.0001$ ; risk ratio, 0.34). Mackey *et al.*<sup>3</sup> also separately analyzed prostate SCC and bladder SCC and concluded that primary surgery is the only parameter that predicts the outcome of prostatic SCC ( $P < 0.01$ ; risk ratio, 0.46). Among all of the therapeutic approaches, cisplatin-based chemotherapy is commonly accepted as the most effective treatment for GSCC. However, no significant survival advantage was found in our study because of our limited cohort.

Most authors have reported a survival benefit of patients with bladder SCC over SCC of the prostate.<sup>3,9,10</sup> However, we did not find any such benefit in our cohort because of the small sample size. We believe that this discrepancy in survival benefit between studies should take the differences of diagnostic stage into consideration, because distant metastasis and advanced stages usually imply a poor prognosis. Due to the limited published case series on GSCC, further studies are required.

## CONCLUSIONS

GSCC is a rare aggressive malignancy, which leads to a poor prognosis of patients. Compared with SCC originating from the bladder, prostate SCC usually presents with advanced stages, which lead to a worse outcome because of the different presenting syndromes. Patients with GSCC mixed with other tumors, such as adenocarcinoma or transitional cell carcinoma, appear to live longer than patients with pure SCC. Patients who present with high serum LDH levels at the time of initial diagnosis appear to have a dismal prognosis. For patients with non-metastatic disease at the time of diagnosis, radical surgery is beneficial to prolong their OS. Because of the limited case series on GSCC, some treatment approaches are still controversial. Therefore, prospective multicenter trials with larger cohorts are urgently needed in the future.

## AUTHOR CONTRIBUTIONS

KC and BD designed the study, collected, analyzed and interpreted the clinical data and wrote and revised the manuscript. YYK and HLG helped with collecting and reviewing the pathological slides and revised the manuscript. DWY supervised the project and revised the manuscript. WJG helped to draft the manuscript. YYQ, HLZ, YZ and GHS collected part of the patients' clinical data and followed up patients. All authors approved the final version and agreed to publish the manuscript.

## COMPETING INTERESTS

All authors declare no competing financial interests.

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