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ARTICLE

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Pseudomyxoma Peritonei of Appendiceal Origin - 801 Cases from a Single Institution in China

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ABSTRACT

Aim: As more and more centers has published their treatment results of pseudomyxoma peritonei (PMP) with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), the data from China is missing. Myxoma Department of Aerospace Hospital is the biggest center treating PMP in China. The purpose of this study is to report the early and long-term outcomes for PMP from this single center. **Methods:** 801 appendix-derived PMP out of 1008 consecutive patients treated in Myxoma Department of Aerospace Hospital between 2008 and 2019 were retrospectively analyzed. **Results:** Complete cytoreductive surgery (CCRS) was achieved in 240 (30%) patients with median PCI of 14(1~39), and the rest had maximal tumor debulking (MTD), HIPEC was implemented in 96.3% of CCRS and 78.6% of MTD. The major morbidity (grade III/IV) was 11.4% and the 30-day operative mortality is 0.7%. The 5- and 10-year OS of CCRS was 76.9% and 64.1%, which is significantly higher than MTD (5-, 10-year OS as 36.1%, 27.1%; $p<0.001$). On the univariate analysis, all prognostic factors (gender, PSS, interval time, prior chemotherapy, prior HIPEC, Peritoneal Cancer Index (PCI), completeness of cytoreduction (CC), HIPEC, pathology, present of serous ascites) were found to be associated with overall survival except for age. On multivariate analysis, only PCI>20, MTD, high pathologic grade and without HIPEC were independent factors predicting poorer prognosis. **Conclusions:** CCRS +HIPEC can benefit PMP well with controllable risks. MTD+HIPEC may benefit PMP as well when CCRS cannot be achieved after fully asscessment by an experienced peritoneal maglignacy center, but the surgery should be performed as limited as possible.

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1. Introduction

PMP is an extremely rare clinical condition caused by the widespread implantation of mucinous tumor cells in the abdominal cavity through "redistribution phenomenon" described by professor Sugarbaker [1], and it usually had a relatively long and slow progressing natural course. These relatively inert cells mostly come from appendiceal mucinous neoplasms counting about 87.2%~94% according to previous studies [2-5]. Without appropriate treatment, the quality of life and prognosis can be really poor among these patients. In early report of 44 PMP patients treated by debulking surgery or combined with radiation therapy in Mayo Clinic, 35 died after tracing for 5 years [6]. And the later researches reported a 76% and 91% recurrence rate without the comprehensive treatment plan of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) [7,8], and mostly occurred in 2.5 years. As the latter combined panel gradually applied in clinical treatment, we had already got some achievements. The 10-year overall survival was as high as 54~70% when complete CRS(CCRS) can be achieved according to large sample size studies more recently, combined with HIPEC undoubtedly [9-12].

Though CRS+HIPEC has become the "gold standard" for PMP among almost all peritoneal malignany diagnosis and treatment centers, it still not widely recognized by other surgeons due to its relatively high mobility and mortality and lack of randomized controlled trails (RCT) [13-15]. Cause of the rarity of PMP and the long nature course, RCT may not be implemented and even for a very long time in the future. Thus, a lot high volume center had published their research results, but data from China is still missing.

The Myxoma Department of Aerospace Hospital is currently the largest PMP diagnosis and treatment center in China. More than 1000 PMPs have been treated in this center since 2008. Although there are still major limitations on knowledge of PMP in China and patients with early stage or local metastasis are rarely seen in our center, we still wish to share our treatment experience and summarize the current situation of PMP in China.

2. Method

2.1 Patients and Preoperative Management

A prospective database of all patients (N=1008) in our tertiary care center treated for PMP between Jan 2008 and Dec 2019 was retrospectively analyzed. Exclusion criteria are as follows: (1) without surgery as the first treatment strategy; (2) underwent palliative surgery simply to relieve clinical symptoms or accepted "open and close" surgery; (3) PMP originated from extra-appendix. The definition and pathological classification for PMP are based on the PSOGI experts' consensus in 2016 as follows [16]:

(1) Acellular mucin;

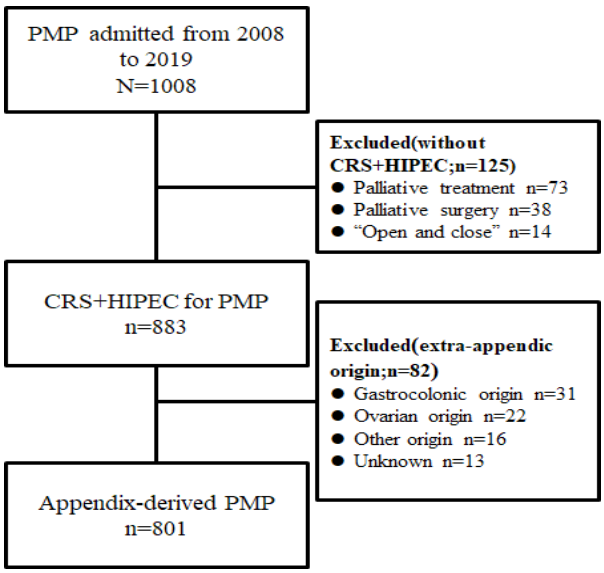
(2) Low-grade mucinous carcinoma peritonei (LGMCP);

(3) High-grade mucinous carcinoma peritonei (HGMCP);

(4) High-grade mucinous carcinoma peritonei with signet ring cells (HGMCP-S)

The films without accurate classification were re-read by pathologist.

Enhanced abdomino-pelvic CT with oral contrast angent, serum tumor marker tests (CA19-9, CA125, CEA), gastroscopy, colonoscopy, cardiopulmonary function evaluation were routinely implemented before surgery.



Flow-chat

2.2 Surgical Strategy

A midline incision was adopted for all PMP patients. At first, the abdominal cavity was fully explored and the extent of tumor burden was carefully calculated and using Peritoneal Cancer Index (PCI) [17]. Peritonectomy combined with visceral resections intending to remove all the macroscopic tumors as much as possible was processed as Sugarbaker previously described [18,19], taking into account its expected morbidity/mortality. The completeness of cytoreduction (CC) is as follows: CC-0: no visible residue; residual tumor: CC-1: <2.5mm; CC-2: 2.5mm~2.5cm; CC-3: > 2.5cm when CC-0/1 is defined as complete cytoreductive surgery (CCRS) and

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CC-2/3 as maximal tumor debulking surgery (MTD) with unresectable focus [20].

MTD in our department took place in the following 2 situations:

(1) the small bowel is widely involved with the remaining less than 1.5 metres or mesenteric involving caused retraction;

(2) tumors invade the serosa of stomach circumference or hepatic pedicle.

In the follow-up period for these patients with MTD, only if severe clinical symptoms which may seriously affected quality of life occurred (such as obstruction, fistula et.al), another operation was chosen cautiously.

2.3 Hyperthermic Intraperitoneal Chemotherapy

HIPEC was performed after CRS and before digestive tract reconstruction with a closed procedure. The circulation speed was controlled at 800~1000ml/min, inlet temperature was controlled at 43.5°C when the outlet was above 41°C during the therapy for 60min. MMC 30mg/cisplatin 60~80mg was used with a solvent of physiological saline.

3. Data Collection and Analysis

All patients were followed up every 3 to 6 months in the first 5 years after surgery with enhanced abdomino-pelvic CT and tumor marker evaluation (CEA/CA125/CA19-9) in our center, and then annually after 5 years. The outset of follow-up was the date of surgery in our hospital, and the overall survival (OS) was counted. The follow-up period was until Feb, 2019. Perioperative data and follow-up results were collected statistically after. Post-operative complications were graded by Clavien-Dindo criteria, with grade III-IV as the major complication and grade V as the perioperative death (30-day) [21].

Statistical analysis was performed using SPSS 25.0. The *t*-test was used for the measurement data and Rank sum test (Mann-Whitney *U* test) for those which do not meet the normal distribution. The x^2- test was used for the count data. The overall survival was compared using Kaplan-Meier method by log-rank test. The prognostic univariate and multivariate analysis were performed using the *cox* proportional hazard model. P <0.05 was defined as significant.

4. Results

4.1 Clinicopathologic Features

From Jan 2008 to Dec 2019, 1008 patients diagnosed as PMP were treated in the Myxoma Department of Aerospace Hospital. And 801 of them who received the comprehensive plan of CRS and HIPEC and pathologically confirmed as appendix origin were included in this study. 627(78.3%) had received more than one surgical procedure before with a median interval time of 16 months. 172(21.5%) had previously received HIPEC and 246(30.7%) received system chemotherapy without CRS. The patient characteristics are shown in Table 1.

Table 1. characteristics of patient underwent CRS+HIPEC with appendix-derived PMP

Variable		n(N=801)	%
gender	male	322	40.20%
	female	479	59.80%
age	mean(range)	58(17~82)	
PSS	0	174	21.70%
	1	219	27.30%
	2	118	14.70%
	3	290	36.20%
interval time[a]	≤12m	336	41.90%
	>12m	465	58.10%
Prior chemotherpy	without	555	69.30%
	with	246	30.70%
Prior HIPEC[b]	without	629	78.50%
	with	172	21.50%
CEA(ng/ml)	median(quartile range)	31(6.7~94.2)	
CA125(U/ml)	median(quartile range)	46.5(22.1~93.9)	
CA19-9(U/ml)	median(quartile range)	45(10~249)	
PCI	median(range)	28(1~39)	
PCI	0-9	106	13.20%
	10-19	72	9%
	20-29	284	35.50%
	30-39	339	42.30%
CC	CC-0	101	12.60%
	CC-1	139	17.40%
	CC-2	237	29.60%
	CC-3	324	40.40%
HIPEC	without	129	16.10%
	with	672	83.90%
pathology	acellular	20	2.50%
	LGMCP	504	62.90%
	HGMCP	181	22.60%
	HGMCP-S	54	6.70%
	unknown	42	5.20%
ascites	mucious	274	34.20%
	serous	253	31.60%
	mixed	87	10.90%
	without	187	23.30%

Notes:
[a], the time from diagnosis of PMP to CRS+HIPEC in our department; [b], previously received HIPEC without CRS.

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CCRS was achieved in 240 (30%) patients dispite a median PCI of 14(1~39), of which 30.8% (74/240) were 20-29 and 5.4% (13/240) were above 30. CC-2 and CC-3 happened in 237(29.6%) and 324 (40.4%) patients each with the median PCI of 27 and 32($p<0.001$). HIPEC was implemented in 96.3% of CCRS and 78.6% of MTD. Except for 42 patients remained unclear pathological grade, low-grade PMP is the most common pathological type accounting for 66.4% (504/759). CCRS was achieved in 27.6% (65/235) and 32.8% (172/352) of patients in the HGMCP+/-S group and acellular/LGMCP group, respectively, with no significant difference between the two groups.

Ascites can be detected in 76.7% and mostly mucious or mixed, but serous ascites existed in 31.6%. And we found serous ascites associated with the grade of tumors (acellular/LGMCP vs HGMCP+/-S: 37.8% vs 55.3%, $p<0.001$). Also, the high-grade+/-S were with significantly higher tumor marker levels (median; CEA: 36.4 ng/ml vs 28.7ng/ml, $p=0.008$; CA125: 66.5U/ml vs 38.5 U/ml, $p<0.001$;CA19-9: 90.7U/ml vs 36.8U/ml, $p<0.001$). Overall, the mean operation time was 476 min (105~859) and the median blood loss is 1500ml (20~11000).

4.2 Morbidity and Mortality

The major morbidity (grade III/IV) was 11.4% (91/801) in the entire cohort. Intestinal fistula and anastomotic leakage were the most common counting for 44% (40/91), followed by post-operative pleural effusion (24.2%;22/91) and intra-abdominal bleeding (7.7%;7/91). Six patients died within 30 days after surgery, 3 died of abdominal infection, 2 died of respiratory failure, and 1 died of renal failure. The 30-day operative mortality is 0.7%. Comparing CCRS with MTD, the overall severe perioperative complications were slightly higher in MTD group (15.7% vs 9.6%, $p=0.059$).

4.3 Survival Outcomes

Excluding 63(7.9%) patients with inadequate follow-up information from the survival analysis, the median follow-up for the rest is 39 months (1-143). The 3-, 5-and 10-year overall-survival (OS) was 62.7%, 47%and 37.9% for the whole patient population. The 5- and 10-year OS was 76.9% and 64.1% when CCRS occurred, which is significantly higher than MTD (5-, 10-year OS as 36.1%, 27.1%; $p<0.001$). And CC-0 has a much better prognosis than CC-1($p<0.01$) (Figure 1). The benefit seemed also to be found in CC-2 than CC-3(5-year OS 37% vs 30%, $p=0.034$), but the significant difference disappeared when adjusted by tumor grade, HIPEC and PCI ($p=0.506$; HR=0.900, 95%CI: 0.659-1.228).

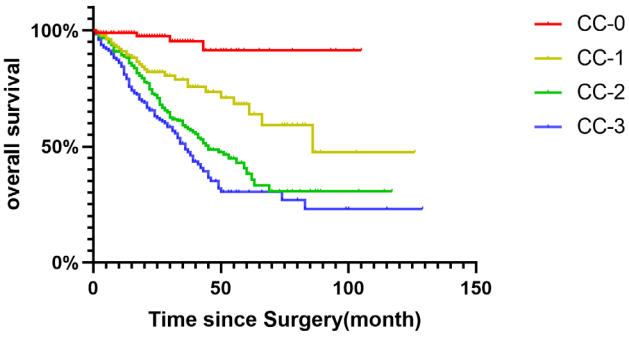

Figure 1. Overall survival by completeness of cytoreduction(CC)

The median OS of MTD combined with or without HIPEC was 44 months and 24 months ($p<0.001$). The survival advantage of HIPEC is more pronounced in MTD without serous ascites ($p<0.001$) (Figure 2) compared with the opposite ($p=0.118$) (Figure 3).

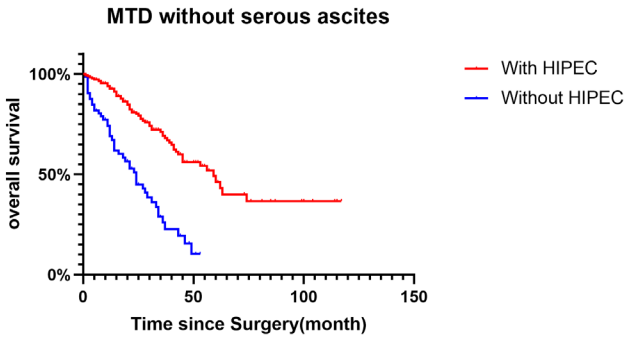

Figure 2. Overall survival by HIPEC for MTD without serous ascites

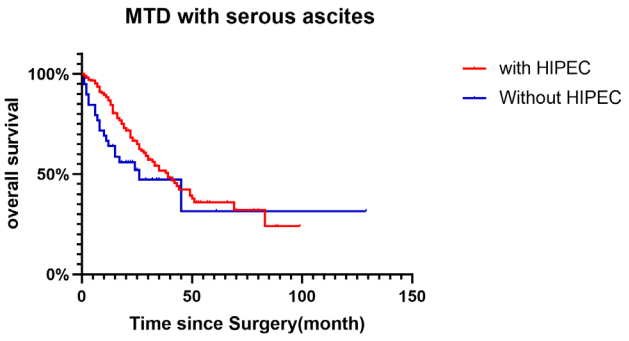

Figure 3. Overall survival by HIPEC for MTD with serous ascites

No deaths occurred among the patients diagnosed with acellular mucin and significant survival difference can be found between each grade (Figure 4). The worst prognosis was associated with HGMCP-S with a median OS of 21

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months. The median OS for LGMCP and HGMCP was 83 months and 39 months (p<0.001).

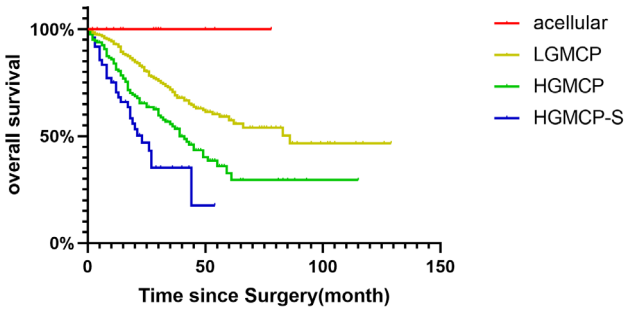

Figure 4. Overall survival by different pathological grades

On the univariate analysis, all prognostic factors were found to be associated with OS except for age, as outlined in Table 2. On multivariate analysis, PCI≤20, CCRS, acellular/LGMCP and HIPEC were independent factors predicting a better prognosis (Figure 5).

Table 2. Univariable and multivariable analysis for overall survival after CRS+HIPEC

		Univariable OS		Mutivariable OS	
		HR(95%CI)	p	HR(95%CI)	p
Gender	female	0.754 (0.588-0.966)	0.025	0.750 (0.553-1.018)	0.065
Age		1.007 (0.996-1.019	0.227		
PSS	0/1	0.712 (0.555-0.914)	0.008	0.911 (0.651-1.274)	0.586
Interval time	≤12m	0.69 (0.532-0.895)	0.005	1.101 (0.797-1.52)	0.561
Prior chemotherpy	without	0.541 (0.421-0.694)	<0.001	0.783 (0.583-1.051)	0.104
Prior HIPEC	without	0.66 (0.493-0.882)	0.005	0.913 (0.65-1.282)	0.6
PCI	≤20	0.283 (0.188-0.425)	<0.001	0.48 (0.295-0.781)	0.003
CC	0-1	0.291 (0.202-0.418)	<0.001	0.607 (0.395-0.933)	0.023
HIPEC	with	0.348 (0.264-0.459)	<0.001	0.473 (0.373-0.659)	<0.001
pathology	Low-grade	0.456 (0.351-0.593)	<0.001	0.493 (0.373-0.65)	<0.001
Serous ascites	without	0.594 (0.463-0.761)	<0.001	0.79 (0.597-1.044)	0.098

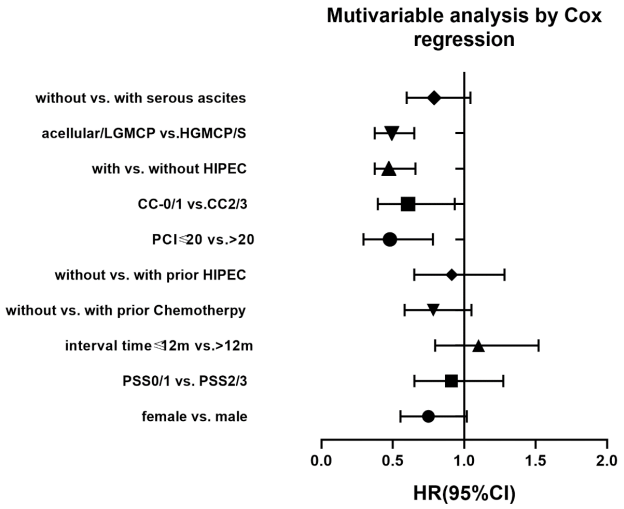

Figure 5. Forest plots of cox regression

5. Discussion

AS Sugarbaker proposed the peritonectomy technique and the comprehensive treatment model of CRS + HIPEC in the 1990s, more and more centers have reported the good survival outcomes and prognostic factors of CCRS + HIPEC for PMP, but few centers had treated more than 500 cases [2,9-12,14,15,22]. Prior to this study, professional team of Li Yan from Shijitan hospital has already pubilished their results which evaluated the safety of CRS + HIPEC in PMP and summarized its clinicopathological features [23,24], but still the data from China is lacking. Department of Myxoma of the Space Center Hospital is currently the largest PMP treatment center in China. This article aimed to summarize and share the experience of this single center with a large volume.

The 5-year and 10-year survival rates of patients who achieved CCRS and MTD in this study were 76.9%, 64.1%, and 36.1%, 27.1%, the overall major morbidity was 11.4%, and the 30-day perioperative mortality was 0.7 %, Which is similar to previous researches [10-12]. CC or HIPEC may be not presented as independent factors in several centers [11,12], but the long-term prognosis of all CCRSs were excellent and there is no doubt that in selected patients to achieve CCRS as much as possible to improve the long-term survival with the controllable risks.

However, based on the current situation in China, a vast majority of patients have a huge tumor burden in the abdominal cavity at the time of consultation, and the stomach and small intestine are seriously involved and lost the possibility of CCRS. Previous study has reported CRS+HIPEC in 100 patients which with PCI≥28 and the radical resection rate was 54% [25]. In another research, the rate of CCRS even in HGMCP with a median PCI

of 32 can reach 84% [26]. It is undeniable that we have a large gap with them. At present, we still have major limitations when dealing with tumors involved in hepatic pedicle. However, few studies have focused on this part of patients with MTD. Considering the relatively higher risk than traditional treatment, whether MTD + HIPEC should be performed is still ongoing debate [15,27]. Although some researchers believe that MTD can still benefit PMP in longer OS and improved quality of life, it cannot be proved without suitable controls [28,29]. In this study, the proportion of MTD is huge. Although the residual tumors of CC-2 are significantly smaller and lower tumor burden post-operation, we failed to prove CC-2's significant survival advantage over CC-3, consistent with the earlier data reported by Sugarbaker [30]. For patients who cannot reach CCRS, it seems that expanding the scope of surgical resection does not obtain any survival benefit. Theoretically, the penetration depth of HIPEC cannot cover the residual tumors after MTD and HIPEC was not recommended by previous studies. Of the 174 MTDs reported by Glehen et al., the 5-year OS of patients who did not receive HIPEC treatment is only 10%, compared to 32%. On multivariate analysis HIPEC was an independent factor for OS in MTD in their study [31]. Although some studies suggest that the presence of serous ascites should be considered for HIPEC [11], the results of this study showed that MTD combined with HIPEC can still achieve longer survival when PMP without serous ascites. More importantly, the Patients with serous ascites do not seem to benefit from HIPEC ($p = 0.118$).

HGMCP+/-S were usually associated with serous ascites (55.3%) and significantly higher tumor marker levels (CEA, CA125, CA19-9), while acellular / LGMCP were usually mucinous. That can be used in preoperative and intraoperative judgment. Although there was no significant difference in the proportion of CCRS in different pathological grades, the prognosis of HGMCP+/-S, especially HGMCP-S was much worse than acellular / LGMCP. The median survival of HGMCP-S after CRS + HIPEC in this study was only 21 months. C. Mumzo-Zuluaga [26] reported 65 cases of HGMCP-S with the median survival of 2.2 years, though 83% of the cases reached CCRS. HGMCP+/-S were independent predictor of poorer survival here had been proved previously [11,12,28,32].

PCI is also one of the independent risk factors affecting OS, as H. Anderasson and O. Glehen reported [15,33]. The worse prognosis of high PCI is considered to be associated with lower CCRS probability. Based on the result of a multi-center study with the currently largest sample size, even in patients with PCI> 30, 10-year OS can still reach 68% if achieved CCRS [10]. Therefore, for patients with high tumor burden, if there is a possibility of complete resection after assessment by an experienced center, CRS + HIPEC should be implanted for the optimal prognosis.

Overall, CCRS +HIPEC should always be the primary goal for PMPs regardless of PCI and pathology. Once CCRS cannot be achieved after fully evaluation in the experienced peritoneal maglignacy center, MTD+HIPEC should be performed but as limited as possible to minimize the surgical trauma.

Of course, this study has major limitations. First of all, as the average rate of CCRS reported by S.Kusamura was 84.4% [34], obviously we still have a very long way to go. Most of the appendixes were previously removed but without clear pathological classification, the pathological grades of appendiceal mucinous neoplasm were unknown. Also, as a retrospective study, partial data loss (such as lymph node metastasis status, recurrence data *et al*.) and case selection bias might be factors affecting the results. Whether PMP with limited metastasis just around appendix can benefit more or not from CCRS+HIPEC cannot be proved in this study.

Surgery techniques and the understanding of PMP have been constantly improving worldwide as time goes, but still a lot of things remained unclear. We have treated PMP with increasing numbers and the annual volume nearly 200 in recent years. This article filled the blanks of China and we are looking forward for the development in future.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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