Simultaneous Bilateral Laparoscopic Cortical-sparing Adrenalectomy for Bilateral Pheochromocytomas in Multiple Endocrine Neoplasia Type 2

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Research Article

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Abstract

Background: laparoscopic or open cortical-sparing adrenalectomy (LCSA or OCSA; CSA) for treatment of bilateral pheochromocytomas (bPHEO) in multiple endocrine neoplasia type 2 (MEN2) offers a postoperative corticosteroid independence and is balanced against the risk of local recurrence. In this study, the optimal surgical approach and the value of the simultaneous bilateral LCSA/OCSA (SB-LCSA/ SB-OCSA) were further assessed.

Methods: A total of 31 patients (54.8% women) were diagnosed with bPHEO in MEN2 at a median age at initial presentation of 38 years (range, 23–78). Twenty- seven patients (87.1%) presented with synchronous. With the exception two patients respectively presenting MEN2A died of MTC metastasis or MEN2B declined surgery, each of other 29 underwent initial CSA, and in 23 (79.3%), of whom 18 had SB-LCSA and 5 had SB-OCSA duration of the same anesthesia (synchronous surgery); whereas metachronous CSA was in 6 (20.7%), including 1 had metachronous bilateral LCSA, 2 had metachronous bilateral OCSA (metachronous surgery) and 3 had LCSA/OCSA (hybrid) surgery.

Results: All 31 patients associated with *RET*-C634 mutations, as MEN2A (90.3%) and *RET*-M918T, as MEN2B (9.7%), respectively. No conversion and intraoperative or postoperative severe complications were necessary. There were less bleeding volume, and shorter hospitalizations between in SB-LCSA compared with those in SB-OCSA, as well as synchronous surgery versus metachronous (hybrid) surgery (all $P < 0.05$). An initial bilateral postoperative corticosteroid replacement was necessary in 14 patients (45.2%). During a median follow-up period of 7 years (range, 1.8–23), 3 of these patients (10.3%) showed a persistent/recurrent disease and needed reoperation.

Conclusions: CSA for bPHEO in MEN2 has a relatively low recurrence and avoids lifelong corticosteroid replacement in well over half the patients. SB-LCSA for treatment of these synchronous bPHEO is safe and feasible, should be recommended as a prioritized surgical approach of choice.

Background

Bilateral pheochromocytomas (bPHEO) are extremely rare, which may present either synchronously or metachronously. The overwhelming majority of these bPHEO only develop benign tumors, being usually one of the clinical presentations of a syndrome disease, and in 96% having a genetic predisposition [1–4]. That is, in approximately 89% patients have been shown to occur in multiple endocrine neoplasia type 2 (MEN2) caused by germline mutation of the *RET* (rearranged during transfection) proto-oncogene and von Hippel-Lindau (VHL) disease caused by *VHL* gene [1]. Other relatively less common genes associated with bPHEO include neurofibromatosis type 1 (*NF1)*, succinate dehydrogenase (SDH) complex subunit D (*SDHD*), *SDHA, SDHB, SDHC*, SDH assembly factor 2 (*SDHAF2*), MYC-associated factor X (*MAX)*, fumarate hydratase (FH), transmembrane protein 127 (*TMEM127*), and several recently reported genes not yet rigorous evaluation, such as *KIF1B*, *SLC25A11*, and *MDH2*, *etc* [1,4–9]. Notably, the *SDHB* mutation causing PHEO (paraganglioma) usually developed malignant (metastatic) in 40% or more of affected patients [9, 14].

Currently, the treatment of bPHEO may be performed approached via bilateral posterior, laparotomy incisions or laparoscopic resection, while adequate preoperative treatment with α-blockers. However, the standard management of bPHEO remains seemingly great challenge, whether total adrenalectomy or cortical-sparing (adrenal-sparing) adrenalectomy (CSA). Of which mainly concerns the risk of malignancy or the future recurrences from the remnant, potential for difficulty of reoperation and complications, and likelihood of corticosteroid-independence to be balanced against the risks associated with chronically treated adrenal cortical insufficiency after CSA, and the inconsistent evidence of retrospective studies of small sample size. Recently, several international multicentre studies revealed the results showed that laparoscopic/open operative CSA (LCSA/OCSA) should be the successful surgical approach of choice for patients with hereditary bPHEO [1–3, 12]. In particular, the bilateral LCSA (B-LCSA) approach should be considered a viable alternative option for these patients requiring surgical intervention [1–4, 10–14].

However, simultaneous bilateral laparoscopic or open CSA (*i.e.*, SB-LCSA or SB-OCSA) for bPHEO associated with MEN2, less practical experience has been reported so far [1–4,10–22]. In the present study, 31 patients who had bPHEO originating from MEN2 in Ethnic Han Chinese, of whom 29 underwent a variety of bilateral CSA including synchronous/metachronous, LCSA/OCSA. Through described their clinical presentation, genetic analysis, operative procedures as well as the surgical outcomes, and we further evaluated the safety and the value of applying SB-LCSA for the treatment of the MEN2-related bPHEO.

Methods

Participants

This is a retrospective analysis of a prospective collected data from November 1998 to April 2021. 53 of 258 patients (20.5%) belonging to unrelated 83 families found to present with MEN2-related PHEO, and in some of clinical data, as described previously [23–28]. The MEN2 diagnosis was established either from a genetic screening showing germline mutations of the *RET*, or, in early cases, from clinical features and a clear family history conducted, and confirmed by subsequent *RET* testing. In all individuals with MEN2, an initial clinical study,

biological/imaging monitoring and *RET* testing were carried out according to the published criteria, as reported previously [23–28]: each individual patient's clinical history/manifestations, physical examination, biochemical tests [including plasma and 24-h urinary catecholamines (adrenaline, noradrenaline, and dopamine), vanillyl mandelic acid, and after 2018, the addition of plasma metanephrines (MN) and normetanephrines (NMN) (MNs)]. Imaging examinations involved Doppler ultrasound (US), computed tomography (CT), T2-weighted magnetic resonance imaging (MRI), and emission CT, if indicated. The study protocol was approved by the Ethics Committee of the 903rd PLA Hospital, and written informed consent was obtained from all study subjects or their legal guardians.

Overall, the bPHEO was diagnosed in 31 out of 53 patients (58.5%) with MEN2-related PHEO depending on the biological/imaging examination and histopathological findings. In the 31 patients, of which 29 patients (93.5%) had surgical operation, and preoperative preparation was all carried out adequate time to normalize blood pressure using oral administration of alpha-blockers, varying doses of phenoxybenzamine or terazosin, as the first-choice to minimize perioperative cardiovascular complications. When there were poor blood pressure and heart rate control, additional nifedipine or propranolol/metoprolol was given, meanwhile also include a high-sodium diet and fluid intake preoperatively [10–14, 26, 29]. On the morning of the day of operation, phenoxybenzamine or terazosin was taken, while hydrocortisone 100 mg was also intravenously infused. During the operation, the arterial blood pressure was monitored continuously, and 100-200 mg of hydrocortisone was infused intravenously. The remaining other 2 patients presenting MEN2A with simultaneous bPHEO, one (P26; male, 78 years) opted for treatment with terazosin over surgery, and died of MTC lung and liver metastasis two years after the diagnosis of initial bPHEO; the other (P27; male, 25 years) declined further surgery for "watchful waiting" due to having no PHEO-related symptoms and family factor (Table 1, Fig. 1). While 7 of these surgeries had OCAS via a laparotomy or lateral retroperitoneal open approach, occurred prior to year 2008. After that, 19 patients had LCSA, and all of tumors were initial removed using transperitoneal approach. The remaining other 3 patients had been performed at least LCSA and/or OCAS, as a hybrid surgery (Table 1, 2).

Table 1
 Demographic, clinical and operative data of patients with MEN2 related bilateral pheochromocytomas

Patient (*NO.*)	Syn/Meta bPHEO (n, Syn%)	*RET* mutation	M/F	Age at operation (years)	Tumor size (cm), L/R	Surgery procedures	Multifocal (n, %)	Postoperative (n, %)		Follow-up※ (year)
								steroid dependency	recurrence	
P1	Syn	C634Y	M	56	6.0/5.5	SB-OCSA	Yes	—	—	17.5
P2		C634Y	M	38	2.0/7.0	SB-OCSA	Yes	—	—	15.0
P3		C634Y	M	42	3.2/4.6	SB-OCSA	Yes	Yes	—	16.5
P4		C634R	M	34	10.0/3.5	SB-OCSA	Yes	Yes	—	23.0
P5		C634Y	F	28	5.0/3.8	SB-OCSA	—	Yes	—	15.3
P6		C634Y	M	48	2.5/1.5	SB-LCSA	Yes	—	—	9.0
P7		C634Y	M	42	4.4/2.5	SB-LCSA	Yes	—	—	2.5
P8		C634G	F	45	4.0/4.0	SB-LCSA	Yes	—	—	5.5
P9		C634Y	M	42	2.2/2.8	SB-LCSA	—	—	—	7.0
P10		C634Y	F	38	3.3/3.8	SB-LCSA	Yes	—	—	6.0
P11		C634R	F	46	2.9/4.3	SB-LCSA	Yes	—	—	4.0
P12		C634Y	M	58	8.5/5.5	SB-LCSA	Yes	Yes	—	1.8
P13		C634Y	M	35	2.8/2.8	SB-LCSA	—	Yes	—	11.0
P14		C634Y	M	36	6.0/5.2	SB-LCSA	Yes	Yes	—	10.0
P15		C634Y	F	49	3.6/1.1	SB-LCSA	Yes	Yes	—	6.0
P16		C634Y	F	32	5.0/3.8	SB-LCSA	Yes	Yes	—	11.0
P17		M918T	F	23	6.0/5.0	SB-LCSA	Yes	Yes	—	3.5
P18		M918T	F	50	8.1/5.1	SB-LCSA	Yes	Yes	—	3.0
P19		C634G	F	52	3.0/3.5	SB-LCSA	Yes	—	—	3.8
P20		C634F	F	34	2.1/2.7	SB-LCSA	—	—	—	6.0
P21		C634Y	F	30	5.2/2.2	SB-LCSA	Yes	—	—	2.3
P22		C634S	F	37	1.2/3.5	SB-LCSA	—	—	—	5.0
P23		C634W	F	34	4.5/1.5	SB-LCSA	Yes	—	—	2.5
P24		C634Y	F	45 (two-step)	2.3/2.9	R-OCSA/L-LCSA	Yes	Yes	Yes	10.0

Syn, synchronous; Meta, metachronous; bPHEO, bilateral pheochromocytomas; M, male; F, Female. CSA, cortical-sparing adrenalectomy; LCSA, laparoscopic CSA;

SB-LCSA, synchronous bilateral LCSA; MB-LCSA, metachronous bilateral LCSA; OCSA, open CSA; SB-OCSA, synchronous bilateral OCSA;

MB-OCSA, metachronous bilateral OCSA.

-, negative.

/ ,

▲, F %.

#, Median age at initial diagnosis of bPHEO.

§, Number and proportion of patients had operation.

※, From the time of initial bilateral CSA to present.

*, Median of follow-up and time ranges except for two patients (P26 and P27) having no surgery.

Patient (*NO.*)	Syn/Meta bPHEO (n, Syn%)	*RET* mutation	M/F	Age at operation (years)	Tumor size (cm), L/R	Surgery procedures	Multifocal (n, %)	Postoperative (n, %)		Follow-up※ (year)
								steroid dependency	recurrence	
P25		C634R	F	24 (two-step)// 29/40	6.0/3.7	MB-OCSA// R-OCSA/L-LCSA/	Yes	Yes	Yes	15.3
P26		C634Y	M	78	3.0/3.4	Died	/	/	/	2.0
P27		M918T	M	25	1.7/1.8	Refused	/	/	/	0.3
P28	*Meta*	C634R	M	37/41	2.0/4.0	L-LCSA/R-LCSA	Yes	—	—	4.0
P29		C634Y	F	30/40	4.5/5.3	L-OCSA/ /SB-LCSA	Yes	Yes	Yes	7.0
P30		C634Y	F	27/44	7.5/11.0	R-OCSA/L-OCSA	Yes	Yes	—	20.2
P31		C634Y	M	44/49	4.3/4.5	R-OCSA/L-OCSA	Yes	—	—	16.0
Total	27/4 (87.1)	C634/M918T	14/17 (54.8▲)	38#	4/3.8	29/31 (93.5)§	24/31 29(82.8)	14/29 (48.3)	3/29 (10.7)	7.0 (1.8–23)*

Syn, synchronous; Meta, metachronous; bPHEO, bilateral pheochromocytomas; M, male; F, Female. CSA, cortical-sparing adrenalectomy; LCSA, laparoscopic CSA;

SB-LCSA, synchronous bilateral LCSA; MB-LCSA, metachronous bilateral LCSA; OCSA, open CSA; SB-OCSA, synchronous bilateral OCSA;

MB-OCSA, metachronous bilateral OCSA.

-, negative.

/ ,

▲, F %.

#, Median age at initial diagnosis of bPHEO.

§, Number and proportion of patients had operation.

※, From the time of initial bilateral CSA to present.

*, Median of follow-up and time ranges except for two patients (P26 and P27) having no surgery.

Table 2
 Characteristics of synchronous versus metachronous presentation of bilateral pheochromocytomas

Variables	Synchronous PHEO※	Metachronous PHEO※	*P* value
Patient, no., (%)	27 (87.1%)	4 (12.9%)	
Gender (Male/Female)	12/15	2/2	0.829
Mean age at diagnosis (year)	40.8 ± 12.0	43.5 ± 4.0	0.660
Median age at surgery (year)	38	42.5	
RET mutation (no.)	27	4	
C634F/G/Y/R/S/W (no.)	24	4	
M918T (no.)	3	0	
Adrenergic symptoms*			
Symptomatic	22	2	0.158
Asymptomatic	5	2	
Tumor size (cm)			
Mean	3.9 ± 1.9	5.4 ± 2.7	0.055
Median	3.5	4.5	
Tumor multicentric, no., (%)	20 (64.5%)	4 (12.9%)	0.248
Surgery procedures	25	4	
LCSA (no.)	18	1	
OCSA (no.)	5	2	
hybrid (no.)	2	1	
PHEO, pheochromocytomas; CSA, cortical-sparing adrenalectomy; LCSA, laparoscopic CSA;			
OCSA, open CSA;Hybrid, both have OCSA and LCSA.			
#, available data.			
* Including hypertension, palpitations/tachycardia, headaches, perspiration, *etc*.			
※Initial synchronous or metachronous PHEO.			

Intraoperative blood loss volume was defined being the total amount of blood lost (from skin incision to the end of surgery). Length of hospital stay was defined as being the length of postoperative stay in the department. Evaluating complications were classified using the modified Clavien-Dindo classification (CDC, Grade I–V) [30]. Whereas not to evaluate length of operation due to a relatively longer time-span. Overall survival was assessed from the date of initial PHEO diagnosis to the time of last follow-up.

Surgical approach

Intravenous inhalation combined with endotracheal general anesthesia was used. SB-LCSA/metachronous B-LCSA (*i.e.*, MB-LCSA), synchronous/metachronous bilateral OCSA (*i.e.*, SB-OCSA or MB-OCSA), or hybrid LCSA/OCSA, was respectively performed (Fig. 1). LCSA were all performed transabdominally in the range 40°~70° lateral supine positions: placed either on left or right (easy side) lateral supine position for the first CSA and then changed to the contralateral supine for the second procedure; Left LCSA procedures were performed with 3-trocar technique and in right LCSA a fourth trocar was added for retraction of the liver when it is necessary [12, 21, 31]. OCSA were via transperitoneal supine position or posterior retroperitoneal approach. In SB-OCSA cases, during the surgical procedure patients' supine position need to not change, to the contrary MB-OCSA always need.

Combined with preoperative imaging information, careful exploration was carried out to avoid leaving PHEO tumor, and trying to preserve as much as possible uninvolved adrenals tissue during the operation. After the operative wound was completely hemostasis, gel sponge or absorbable hemostatic gauze was placed, and 2 drainage tubes were placed on both sides.

RET screening using targeted sequencing

Briefly, peripheral blood genomic DNA samples obtained from at least including 258 individuals in 83 families were prepared for targeted sequencing using an Illumina HiSeq 2000 Analyzer. The methods used for DNA target capture, enrichment, elution, and targeted sequencing were previously described [25, 27, 28]. The targeted sequencing results were further validated by Sanger sequencing using an ABI 3700 Genetic Analyzer (Perkin-Elmer, Fremont, CA).

Statistical analysis

All data were analyzed with IBM SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). The frequency of occurrence, percentages, and comparisons of enumeration variables were assessed by the chi-square test ($\chi 2$) or Fisher's exact test and Student's *t*-test for comparison between independent treatment groups. A *p* value less than 0.05 as the difference was considered statistically significant.

Results

Clinical and diagnostic data

Of all 31 patients with bPHEO, 17 (54.8%) were women (Table 1). The median age at initial diagnosis of bPHEO was 38 years (range, 23–78). Median tumor size was 3.8 cm (range, 1.1–11.0), and the tumor was larger than 5.0 cm in 38.7% of cases (Fig. 2A–2D). While 27 patients (87.1%) presented with initial synchronous PHEO, and 4 patients (12.9%) with initial metachronous PHEO [the incidence of a contralateral PHEO was 4, 5, 10 and 17 years after the first diagnosis/surgery of unilateral PHEO (mean, 9 years)]. However, the mean age at diagnosis was no significantly different between patients with simultaneous or metachronous [(40.8 ± 12.0) versus (43.5 ± 4.0) years, $P = 0.660$), although patients with metachronous PHEO seemingly presented at a median age older 4.5 years than synchronous's (Table 1–3). Additional, at time of diagnosis of initial PHEO, 7 patients (22.6%) were asymptomatic and 24 (77.4%) presented with adrenergic symptoms, including hypertension (n = 24), headaches (n = 9), palpitations/tachycardia, (n = 7), perspiration (n = 2), and paroxysms (n = 12). Among 25 patients (80.6%) had available biochemical data, of which 14/25 (56%) presented elevated catecholamines/ MNs in plasma or urine. The diagnosis was made according to clinical features suggestive of PHEO in 20 patients (64.5%), and according to mutation-based in 11 others (4 also had clinical features of the disease) (35.5%), which shown that the mean size of PHEO was 5.7 ± 2.0 cm in the patients discovered due to symptoms, larger than PHEO detected through mutation-based screening (mean size: 3.2 ± 1.5 cm) ($P = 0.003$) (data not shown). The characteristics of synchronous versus metachronous presentation of bPHEO in 31 patients are summarized in Table 1 and Table 2.

Table 3
The presence of perioperation and postoperation in synchronous/metachronous surgery

Variables	Synchronous surgery	Metachronous surgery	*P* value
Patient (no.)	23 (79.3%)	6 (20.7%)	
Gender (Male/Female)	10/13	2/4	0.653
Mean age at surgery (year)	40.4 ± 9.0	37.5 ± 8.1	0.360
Median age at surgery (year)	38	40	
Tumor size (cm)			
Mean	4.1 ± 1.9	4.8 ± 2.5	0.245
Median	3.8	4.4	
LCSA/OCSA (no.)	36/10	6/9	0.005
Times of recovery (day)	19.5 ± 4.2	40.2 ± 8.9	0.000
Length of hospitalization (day)	11.4 ± 4.5	20.3 ± 8.4	0.016
Postoperative			
Complications*	0	0	
Steroid replacement	10	4	**0.313**
Recurrence, n., (%)	0	3	**0.000**
Metastasis, n., (%)	0	0	
Follow-up (years)	7.8 ± 5.6	10.0 ± 4.8	0.381
B-LCSA/B-OCSA, bilateral laparoscopic cortical-sparing adrenalectomy/bilateral open cortical-sparing adrenalectomy.			
*Clavien-Dindo classification, ≥ Grade.			

Moreover, all 31 patients presenting with bPHEO only associated with 11 and 16 exons of *RET*, predominantly in exon 11 mutation, and in 28 subjects (90.3%) harboring *RET*-C634F/G/R/S/W/Y mutation was found, respectively followed by a C634Y (61.3%, 19/31), C634R (12.9%, 4/31), C634W (3.2%, 1/31), C634G (6.5%, 2/31), C634F (3.2%, 1/31) and C634S (3.2%, 1/31), were affected by MEN2A, belong to 14 unrelated families. The remaining other 3 subjects (9.7%) carrying *RET*-M918T in exon 16 were confirmed, belong to 3 different MEN2B families (Table 1, 2). Comparison of the mean age at bPHEO diagnosis was no significantly different between patients with C634 and M918T mutations [40.9 ± 11.4 versus 32.7 ± 15.0 years; *P* = 0.256), as well as the mean tumor size had no significantly different (4.0 ± 2.0 versus 4.6 ± 2.5 cm; *P* = 0.502), though those with *RET*-M918T occurred relatively younger 8 years and approximately larger 0.6 cm (Table 1). But also the diagnosis of initial PHEO was made after the diagnosis of medullary thyroid carcinoma (MTC) in 18 cases (58.1%), simultaneously in 5 cases (16.1%), and prior to the diagnosis of MTC in the 8 remaining cases (25.8%). The diagnosis of bPHEO, all of these 31 patients, had been the diagnosis of MTC (100%), and in the youngest patient, aged 23 years, diagnosis was simultaneous and presented with *RET*-M918T.

Surgical procedures

With the exception of two patients (P26 and P27) that did not undergo surgery, each of other 29 patients (93.5%) underwent a variety of bilateral CSA, in 23 patients (79.3%) initial CSA was synchronously performed on both side, of whom 18 had SB-LCSA and 5 had SB-OCSA duration of the same anesthesia; whereas metachronous bilateral CSA was in 6 cases (20.7%), including 1 had MB-LCSA, 2 had MB-OCSA and 3 had LCSA/OCSA hybrid surgery, respectively (Table 1, Fig. 1). Of all followed dissection and ligation of the adrenal central vein during the operation (Table 1, 2). To be more specific, the surgical approach was initial LCSA in 19 cases [SB-LCSA in 18 subjects with simultaneous, and MB-LCSA in 1 patients with metachronous PHEO, respectively]. The LCSA approach was performed via transabdominal route and used for these 19 patients. OCSA was initial in 7 patients [5 SB-OCSA in 5 patients with simultaneous, 2 MB-OCSA in 2 patients with metachronous PHEO, respectively], and performed using transperitoneal supine position in 5 and posterior retroperitoneal approach in 2, respectively (Table 1, 2 and Fig. 1). The remaining other 3 individuals, one (P24) presenting synchronous bPHEO, had OCSA (right) and LCSA (left) interval 3 months (two-step surgery) in 2012; whereas the other (P29) had initial unilateral PHEO, underwent initial OCSA (left) via retroperitoneal in 2009; in 2020, due to recurrences of the left and newly developed on the right PHEO (Fig. 2C, 2D), SB-LCSA (second surgery) was performed. Unfortunately, the third patient (P25) had initial simultaneous PHEO, underwent MB-OCSA interval 1 months in 2002, second right OCSA or left LCSA was respectively performed in 2007 and 2018, due to recurrences of the right or left PHEO — All in all, a total of 61 adrenal operations (30 right; 31 left) were performed, and were conducted using the LCSA (n = 42) or OCSA (n = 19), including the LCSA/OCAS hybrid surgical procedures (n = 3) (Table 1–3, and Fig. 1).

The perioperative information including preoperative, intraoperative and postoperative variables was compared between synchronous and metachronous CSA. Synchronous CSA had significantly less recurrence rate and shorted length of hospitalization than metachronous CSA (Table 3), as well as SB-LCSA had all significantly less blood loss, and shorted hospitalization than SB-OCSA or SB-OCSA/hybrid surgery (Table 4; The latter data not shown). Meanwhile the differences in surgical parameters were not statistically significant between synchronous and metachronous CSA, or SB-LCSA and SB-OCSA (Table 3, 4).

Table 4
Factors related to perioperation and postoperation in simultaneous bilateral laparoscopic or open surgery

Variables	SB-LCSA	SB-OCSA	*P* value
Patient (no.)	18 (78.3%)	5 (21.7%)	
Gender (Male/Female)	6/12	4/1	0.062
Mean age at surgery (year)	40.6 ± 8.9	39.6 ± 10.5	0.831
BMI (kg/m^2)	21.8 ± 2.7	22.0 ± 1.7	0.906
Tumor size (cm)			
Mean	3.8 ± 1.7	5.1 ± 2.3	0.060
Median	3.5	4.8	
ASA score (I/II/III/IV/V)	6/11/1/0/0	0/5/0/0/0	
Blood loss (ml)	75.0 ± 27.4	242.0 ± 100.8	0.003
Length of hospitalization (day)	10.0 ± 2.9	13.2 ± 1.6	0.046
Postoperative			
Complications*	0	0	
Steroid replacement, n (%)	7 (38.9%)	3 (60%)	0.397
Recurrence, n (%)	0	0	
Follow-up (mean, years)	5.3 ± 3.2	10.6 ± 5.4	0.000
CSA, cortical-sparing adrenalectomy; SB-LCSA, synchronous bilateral laparoscopic CSA;			
SB-OCSA, synchronous bilateral open CSA; Hybrid, laparoscopic and open CSA.			
*, Clavien-Dindo classification, ≥ Grade Ⅲ.			

Postoperatively, all 29 subjects had histopathology verifying bPHEO, and in 24 patients (82.8%) of them had initial multi-centric tumors, primary respectively noted in MEN2A (n = 22) and MEN2B (n = 2), and on the left in 19, right in 17 and bilateral multifocal in 12 (Table 1). The most number of PHEO was 9, of which 4 on the left and 5 on the right, in a 56-year-old patient with C634Y mutation (P1; Table 1). No conversion to an open procedure was necessary. No serious intraoperative and postoperative complications (CDC, ≥ Grade Ⅲ) were recorded. Notably, laparoscopic manipulation and surgical removal of the PHEO resulted in 8 peaks of hypertension (SBP >180 mmHg), associated in 4 cases with bouts of sinus tachycardia and in 2 low peaks of hypotension (SBP < 60 mmHg) in spite of initial ligation of the adrenal central vein.

Outcomes

Patients were all followed for a median of 7 years (range, 1.8–23) from the time of initial CSA, and in 14 of them (48.3%) need for lifelong steroid [glucocorticoid (prednisone or hydrocortisone) and mineralocorticoid] replacement (Table 1), and in 2 (6.9%) of them, respectively suffered transient adrenal insufficiency and over supplementation during the adjustment of drug dosage within 3 and 6 months post-operatively, but none developed the risk of addisonian crisis.

The presence of recurrent PHEO was diagnosed in 3 patients (10.7%; P29, P25, and P24), of whom 1 (P29) had recurrence or developed contralateral PHEO at 10 years postoperatively, and the other 1 (P25) had bilateral recurrences at respectively 4 and 16 years after the first operation; 2 were subjected to reoperation with no postoperative complications. In addition, 1 (P24) had unilateral recurrence (tumor size, 1.5cm) at 3 years after MB-LCSA, but declined surgery (Table 1). The former (P29) was diagnosed as recurrence due to adrenal symptoms, and latter two (P25 and P24) were found recurrence due to reexaminations, with no lateral predisposition (2 left adrenal bed and 2 right adrenal bed), and the 3 patients all with MEN2A, mean time of recurrence was about 8 years (range, 3–16). Moreover, none of the tumors were metastatic (malignant).

Discussion

To our knowledge, the present study is the first to detail the clinical presentation, management and outcomes of patients with MEN2-related bPHEO in an ethnic Han Chinese cohort. We found bilateral disease in approximately 59% of patients with PHEO, which is similar to that Castinetti *et al.*[2] previously reported where accounts for 61%. In this series, bilateral disease only associated with *RET*-C634 mutations, as MEN2A (90%) and *RET*-M918T, as MEN2B (10%), but absence of other mutations of *RET*, showing a relatively single mutation genotype [2, 13, 21, 32] (Table 1, 2). Our finding also revealed that bPHEO was exclusively benign, synchronously involving both adrenal glands in about four fifths, in approximately 23% diagnosed at an asymptomatic stage, and the mean tumor size was 3.8 cm, while those observed in patients with PHEO found through mutation-based screening less than symptomatic PHEO ($P = 0.003$) [10, 32]. Multifocal about 83%, and affected patients were mostly initial operated on before 40 years of age [2, 3, 10, 13]. However, it should still highlight the need for an optimal surgical procedure of choice to manage these patients, in spite of these PHEO-related deaths occur less frequently. In contrast, previously, the majority of studies mainly focusing on a more common cause of death and the outcome of MTC in these patients [2, 3, 10, 13], the use of prophylactic thyroidectomy in genotype-specific age, or extent of thyroidectomy based on genotype and serum calcitonin levels had became routine and formal practice guidelines recommended [1–4,9–13,23–26,33,34].

By contrast, the second major component PHEO of MEN2 could be treated by laparoscopic excision already established conventional procedure, which should be removed prior to surgery for either MTC or hyperparathyroidism [13, 14, 34]. In the last two decades, also, laparoscopic bilateral adrenalectomy for bPHEO showed a sharp reduction of intraoperative haemodynamic instability, providing an equal chance to cure hypertension, and less intraoperative blood loss, lower overall complication rates, while also caused a faster, better postoperative recovery and a better cosmetic result rather than the open approach [11–14, 20, 35, 36]. In this study, the similar results were also revealed that less bleeding volume and shorter hospitalizations, which are possible with LCSA compared with those in OCSA or hybrid surgery (all $P < 0.05$; Table 1–4, and Fig. 1). As for CSA approach for treatment of PHEO, should only be considered as an alternative procedure or a relatively weak recommendation, but not become established in the routine MEN2 practice guidelines [11–14, 34, 38, 39]. Of these mainly concerns the risk of remnant recurrences, reoperation, metastases, and likelihood of corticosteroid independence after CSA. Nevertheless, CSA as a feasible surgical approach for unilateral/bilateral PHEO in MEN2 patients was still performed by numerous clinicians [1–4,10,12,15–23,26,33,37–40]. A recent multicentre study of 563 MEN2 patients with PHEO, which includes some patients from our cohort, showed that malignant disease was in less than 1%, bPHEO with CSA in one or two operated glands associated with recurrence in 5% out of 114 patients and of whom 57% did not required steroid dependency at a median of 9.5 years (range, 1–28) postoperatively [2]. Another multicentre study of bPHEO (n = 625), of in 505 of 526 tested patients (96%) with germline mutations were detected that the majority of patients had *RET* mutations rather than *VHL* or other gene mutations (282 versus 184 versus 39, respectively), showed that CSA is associated with recurrence in 13% and malignant disease in 2% of patients at follow-up of a median of 8 years (IQR 4–17) [1]. In this series, of which 29 patients underwent LCSA or OCSA, trying to preserve most of the uninvolved adrenals using PHEO enucleation or subtotal adrenalectomy (CSA) with as much as possible rim (0.5 to 1.0 cm) of normal adrenal tissue. Postoperatively, in approximately 48% out of these patients still required lifetime steroid replacement, and in 2 of them (6.9%) suffered transient complications of steroid dosage. Meanwhile, about 10% out of these patients experienced tumor recurrence, showing that real recurrences are typically found about 8 years (range, 3–16) or later after CSA, but lacking metastatic or PHEO-related death (0%) (Table 1, 3, 4, and Fig. 1). It is noticeable that, nearly total adrenalectomy is sometimes inevitable when a large tumor (such as P30) is in an unfavorable location or when multifocal tumors (P24) are present or reoperation for recurrent PHEO (P25, P29) by laparoscopic procedure. Interestingly, however, patients (P1), who with 9 small multifocal tumors underwent PHEO enucleation, did not require steroid replacement follow-up 17.5 years postoperatively (Table 1). It seemingly to imply that enucleation may be more beneficial to preserving vascularized adrenal cortical tissue/function than subtotal adrenalectomy — preserving at least 10–15% of one remnant of properly vascularised adrenal cortical tissue appear to offer adrenal stress capacity [22, 31, 36]. However, the long-term follow up for at least 10 years should be still need in all these patients due to a persisting disease, because of the risk of recurrent PHEO is about 20% within 20 years after CSA [10, 11, 13]. Nevertheless, LCSA or OCSA approach did not decrease survival and imply that offers excellent oncologic and functional outcomes, particularly, LCSA (including robotic surgery [37]) as a safe and effective surgical management for the treatment of bilateral and/or multifocal PHEO (even for tumors measuring > 6 cm [36]) in MEN2 should be routine considered to utilize or might be more prone to recommend [1–4,10,15–23,26, 33,35–40].

Additionally, treating patients with synchronous bPHEO can be challenging, and there is no uniform standard surgical approach whether synchronous or two-stage (metachronous) procedures. Following laparoscopic device innovation, the accumulation of sufficient experience and proficient surgical skill, synchronous surgery including SB-LCSA was increasingly used in clinical practice for treating these bPHEO [10, 15–23, 41]. Walz *et al.* [16] reported that 15 patients with bPHEO (the tumor size of average 4.6 cm; 2 cases of recurrent PHEO on one side) underwent synchroenous bilateral laparoscopic adrenalectomy, of whom 14 (93.3%) were successfully removed bilateral tumors duration of the same anesthesia. In another case the procedures were split due to cardiac arrhythmias during laparoscopic removal of a 12 cm right-sided PHEO, and the contralateral 3 cm tumor was extirpated 5 weeks later retroperitoneoscopically. Kittah *et al.* [10] reported 98.7% out of 75 patients with synchronous PHEO (41 MEN2, 13 VHL, 7 NF1 and 14 other PHEO; the median tumor size of 3.0 cm), of who 74 underwent a simultaneous

bilateral adrenal surgery, and in 18 (24%) of them, a simultaneous bilateral CSA was successfully performed. Nine (44.4%) of the 18 patients required steroid replacement, 3 (16.7%) had recurrent at a median of 16.2 years (range, 3.6–51.9), and 2 developed metastatic PHEO 20 years postoperatively. Contrary to the present study, 27 patients (87.1%) had initial synchronous PHEO. Of these, 23 were simultaneous successfully removed bPHEO, where the median size of tumors were 3.8 cm, and 10 (43.5%) of them, required steroid replacement at a median follow-up of 10.5 years (range, 1.8–23), whereas none of them had recurrent and metastatic postoperatively (Table 1, 3, 4). Despite, there were 38.9% out of 18 underwent SB-LCSA, or 60% out of 5 underwent SB-OCSA, who respectively required steroid replacement, and the mean tumor size was (3.8 ± 1.7) or (5.1 ± 2.3) cm, yet had no significantly different (P = 0.397; P = 0.060). SB-LCSA can be safely performed and used for synchronous bPHEO surgery, which had advantages of less blood loss and shorter hospitalizations than MB-OCSA (Table 4). Moreover, in other 1 cases (P28) of recurrent PHEO (1.2 cm) on one side and developed contralateral PHEO (5.3 cm) was also subjected to SB-LCSA (Table 1). However, re-operation seems harder than primary operations mainly due to adhesions, but there can also be performed laparoscopically. SB-LCSA or SB-OCSA is technically safe and feasible [10,12,16–19], in particular, SB-LCSA can be considered as preferential choice in the surgical management for synchronous bPHEO in MEN2, even for recurrent PHEO as potential options.

With regard to whether the adrenal central vein should be preserved duration of the CSA. From our data and from descriptions by previous studies, there seems unnecessary to deliberately preserve the central adrenal vein [16, 18, 22]. However, it may be important not to excessive separate the remnant adrenal gland from the adjacent space, since the vascular bed adjacent to the remnant adrenal gland is integral to the preservation of its function. Correspondingly evidence of the presence of successful adrenal auto-transplantation was low [10, 16, 18, 22, 42]. In addition, it is not necessary to beforehand dissociate or ligate the central vein. In general, the surrounding adrenal tissue can be separated at a distance of 0.5–1.0 cm from PHEO by harmonic scalpel. Especially when the preoperative CT/MRI scan showed that the PHEO was large and the splenic/renal vessels were obviously compressed and deformed, it should be preferentially separated from the surrounding tissue vessels along the surface of PHEO capsule, and the central vein could be ligated after the boundary was clear (Fig. 2A, 2B). Meanwhile once the specimen removed, it should need to be carefully examined and preliminary assessment of whether there is an adequate disease-free margin around PHEO.

Conclusions

The integration of the clinical and molecular genetic diagnosis of MEN2 into routine practice can provide valuable information for establishing a precise treatment plan and procuring an optimized guidance for the long-term follow-up surveillance [9–11, 43–45]. SB-LCSA with preserving adrenocortical function for the treatment of synchronous bPHEO in MEN2 patient is safe and feasible, should be considered as a prioritized surgical approach of choice.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the Ethics Committee of the 903rd PLA Hospital and written informed consent was obtained from all study subjects.

Consent for publication

Consent for publication was obtained from all study subjects or their legal guardians.

Availability of data and materials

The original contributions presented in the study are in the article material. Further inquiries can be directed to the corresponding authors.

Competing interests

No competing financial interests exist.

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Authors' contributions

X-P Q conceived and designed the experiments. X-P Q, X-D F, F D, F L, B-J L, H-Y J, K Z, K-E W and Y Z conducted the experiments and analyzed the data. X-P Q and Q-Y Q wrote the manuscript, K-E W and Y Z reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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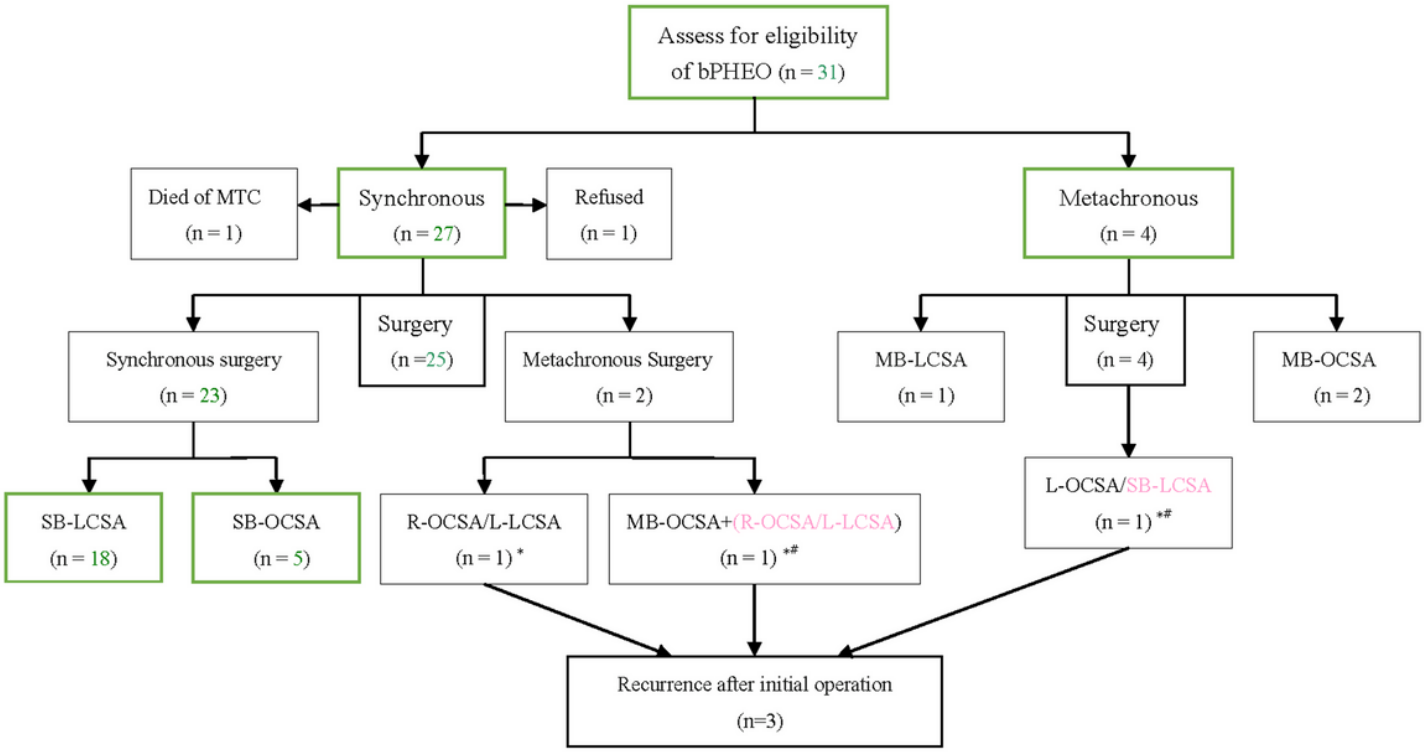
Figures



*bPHEO, bilateral pheochromocytomas; R, right; L, left; CSA, cortical-sparing adrenalectomy; LCSA, laparoscopic CSA; SB-LCSA, synchronous bilateral LCSA; MB-LCSA, metachronous bilateral LCSA; OCSA, open CSA; SB-OCSA, synchronous bilateral OCSA; MB-OCSA, metachronous bilateral OCSA; *, three patients had local recurrent; #, in 2 patients who underwent reoperation.*

Figure 1

Study population and outcome by type of operative intervention in those who had surgical intervention.

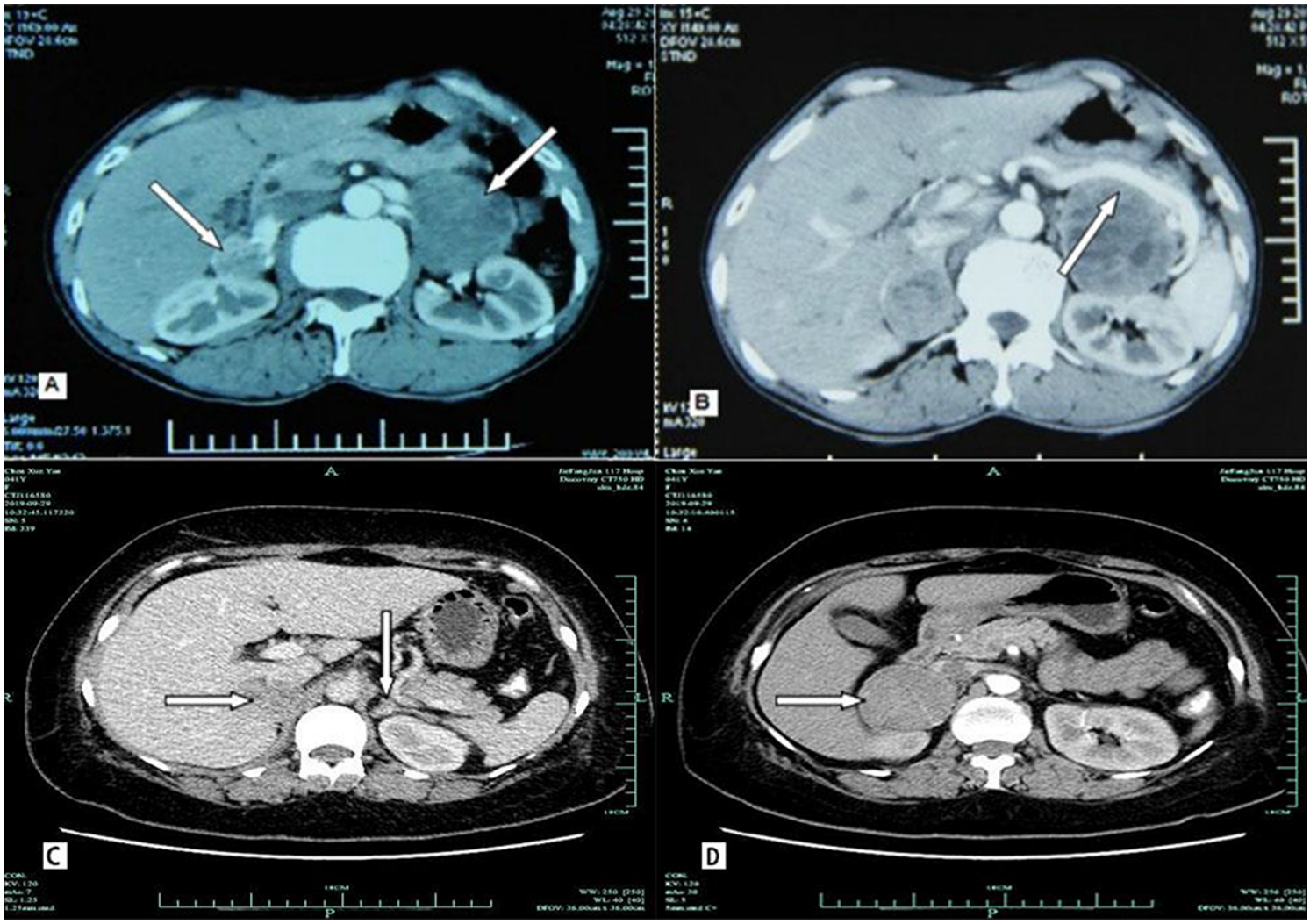


Figure 2

The imaging examination of computerized tomography scanning using Ultravist® 300 disclosed hypoechoic nodules in bilateral adrenal glands. A, B) A 36-year-old male patient (P14; RET-C634Y) presenting with primary bilateral multifocal pheochromocytoma. A) CT scanning showed irregular enhancement of multiple nodules with intact capsule in both adrenal glands. B) Contrast-enhanced CT imaging revealed inhomogeneous nodules with well-defined and heterogeneous enhancement in both adrenal glands [white arrows]. Maximum diameter of tumors was 6.0 ×5.3 × 4.8 cm in the left, and in the right, maximum diameter was 5.2 × 4.5 × 3.0 cm, while having multiple low density lesions with no obvious enhancement, respectively. No areas of obvious necrosis or hemorrhage are observed. The splenic artery and vein showed compression and displacement [white arrow]. C, D) A 40-year-old female patient (P29; RET-C634Y) having bilateral pheochromocytoma. C) Contrast-enhanced CT scanning showed that two primary inhomogeneous nodular and heterogeneous mild/moderate enhancement in the right adrenal [white arrows]. A nodule (1.2 × 0.8 × 0.6 cm) with equal density in the left adrenal gland was enhanced to the same extent as the normal adrenal tissue [white arrows], as possibility of recurrence of pheochromocytoma. D) The larger one with clear boundary in the right adrenal was about 5.3 × 4.3 × 3.0 cm in diameter [white arrows].