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Original Article

Long-term Results of Initial Gamma Knife Radiosurgery for Acromegaly: A Retrospective Cohort Study

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Abstract

Background and objectives: Acromegaly requires multimodal management. While surgery is first-line, many patients have persistent/recurrent disease. Gamma knife radiosurgery (GKRS) offers precise radiation, but data on its use as initial therapy remain limited. This study aimed to review the outcomes and report on our experience in treating patients with acromegaly using initial GKRS.

Methods: We retrospectively identified 33 patients with acromegaly who underwent GKRS from 1993 until 2016 at the Department of Radiotherapy, the Second Affiliated Hospital of Guangzhou Medical University. These patients had complete endocrine, radiological, and imaging data before and after GKRS. Furthermore, univariate and multivariate analysis was utilized to analyze the potential prognostic factors of endocrine remission and new-onset hypopituitarism.

Results: Thirty-three patients were enrolled in the study. Fifteen patients (45.5%) were males and 18 (54.5%) were females. The median age was 44.0 years (range, 24.9–66.2 years). During a median follow-up of 65.6 months (range, 12.9–297.6), the median margin dose for GKRS was 15.0 Gy (range, 10.8–20.3 Gy). Endocrine remission was achieved in nine of the 33 patients (27.3%) over a mean follow-up of 85.1 months (range, 12.9–161.3). No prognostic factors demonstrated a significant association with endocrine remission. New-onset hypopituitarism occurred in eight patients (24.2%) after GKRS. The tumor control rate was 100%. Only one patient developed worsening visual dysfunction. No new cranial neuropathy was noted.

Conclusions: Initial GKRS for acromegaly provided effective tumor control and partial endocrine remission with a favorable safety profile, notably a low rate of new-onset hypopituitarism, representing a viable treatment option.

Introduction

Acromegaly is a debilitating endocrine disorder secondary to a growth hormone (GH)–secreting pituitary adenoma. The chronic hypersecretion of GH and its primary mediator, insulin-like growth factor-1 (IGF-1), leads to a wide range of systemic complications, including cardiomyopathy, diabetes mellitus, hypertension, obstructive sleep apnoea, and arthropathy, significantly increasing the risk of overall morbidity and mortality if left untreated.[1] The ultimate goal of treatment is not only to eliminate the mass effect of the tumor but, more critically, to restore normal levels of GH and IGF-1, thereby reversing the metabolic sequelae and improving long-term outcomes, while preserving or improving residual pituitary function.

Transsphenoidal surgery remains the recommended primary treatment for most patients with acromegaly, particularly for those with microadenomas or well-circumscribed macroadenomas, offering the potential for immediate biochemical remission.[2] How-

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ever, the therapeutic landscape is complex. For patients with invasive tumors where complete surgical resection is unlikely, those with contraindications to surgery, or in cases where a patient declines surgery, primary medical therapy with somatostatin receptor ligands or GH receptor antagonists is often considered. Nevertheless, the high cost and potential lifelong requirement of medication present significant challenges. In such scenarios, radiosurgery, particularly gamma knife radiosurgery (GKRS), has emerged as a widely considered alternative or adjuvant intervention. It is most commonly employed for treating residual tumor mass following incomplete surgery or for tumors refractory to medical therapy.[3–5]

The existing body of literature, comprising numerous studies,[6–8] has established the role of GKRS as a safe and effective modality for achieving long-term tumor control and biochemical remission in acromegaly. These studies have reported endocrine remission rates varying widely, often influenced by factors such as pre-radiosurgery IGF-1 levels, the use of suppressive medications during the latency period, and the radiation dose to the tumor margin. Despite this wealth of data, a critical gap remains regarding the long-term efficacy and safety of GKRS when utilized as an initial primary treatment strategy, bypassing surgery altogether. Drawing upon over 26 years of experience at our high-volume institution, we conducted a large, single-center retrospective study to evaluate these precise long-term outcomes. This study analyzed a cohort of 33 acromegaly patients treated with initial GKRS at our center between 1993 and 2016. We aimed to rigorously evaluate the treatment's effectiveness by assessing rates of endocrine remission and tumor control, documenting complications, and identifying key factors predictive of both remission and new-onset hypopituitarism.

Materials and methods

Patients

This retrospective study was conducted between 2018 and 2021. Patients who received treatment between December 1993 and December 2016 were included, and no additional follow-up data beyond this timeframe were collected during the research period. A retrospective analysis was performed on the medical records of 2,557 patients who underwent GKRS for pituitary adenoma in the Department of Radiotherapy at the Second Affiliated Hospital of Guangzhou Medical University. This study was carried out in accordance with the recommendations of the ethical standards of the 2024 Declaration of Helsinki and its subsequent amendments. The protocol was approved by the Institutional Review Board of the Second Affiliated Hospital of Guangzhou Medical University (Approval No. 2019-hg-ks-08). Individual consent for this retrospective analysis was waived.

To define a clear and homogeneous study cohort for assessing the efficacy of initial GKRS, the following criteria were applied: Inclusion criteria: (1) Diagnosis of acromegaly secondary to a GH-secreting pituitary adenoma, confirmed by clinical features, biochemical testing, and magnetic resonance imaging (MRI). (2) Underwent GKRS as the primary and intentional initial treatment for acromegaly. (3) Deemed unsuitable for, or declined, neurosurgical intervention, as documented in the medical record. (4) Availability of complete baseline endocrinological and radiological data prior to GKRS. (5) A minimum post-GKRS follow-up duration of 12 months for both endocrine and imaging assessments. Exclusion criteria: (1) Previous surgical resection (transsphenoidal or transcranial) or radiotherapy to the sellar region prior to GKRS. (2) Presence of other pituitary tumor types (e.g., prolactinoma, non-functioning adenoma) or plurihormonal adenomas where acromegaly was not the dominant clinical presentation. (3) Insufficient follow-up data (less than 12 months) or loss to follow-up. (4) Patients with giant adenomas (≥40 mm) presenting with severe visual compromise requiring urgent surgical decompression at presentation.

Among the 2,557 patients, 751 had sufficient follow-up data lasting more than 12 months. Ultimately, a total of 33 acromegaly patients who met the above criteria and were not candidates for neurosurgical intervention were enrolled in this study. All patients underwent complete endocrinological and imaging evaluations both before and after GKRS (Fig. 1). The diagnosis of acromegaly was established in accordance with relevant guidelines,[2] based on clinical manifestations, endocrine hormone assessments, and MRI evidence of a pituitary tumor. As a single-arm retrospective study, no control group was included.

Endocrine and imaging evaluations

A complete pituitary hormonal assessment was performed before and after GKRS. This comprised measuring: 1) GH and prolactin; 2) the hypothalamic–pituitary–thyroid axis (FT3, FT4, TSH); 3) the hypothalamic–pituitary–adrenal axis (cortisol, adrenocorticotropic hormone); and 4) the hypothalamic–pituitary–gonadal axis (follicle-stimulating hormone), luteinizing hormone, testosterone in men, estradiol in women). Endocrine remission was defined as a random GH level < 1 ng/mL.[9,10] For the purpose of this study, new-onset hypopituitarism was considered present if a patient required hormone replacement or manifested a new deficiency in any pituitary axis post-GKRS.[11] A diagnosis of hypothyroidism required a low FT4 level (normal range: 12.00–22.00 pmol/L) paired with a TSH level that was low, within the normal range, or mildly elevated (normal range: 0.27–4.2 μIU/mL). Hypocortisolism was defined if the morning cortisol level was <100 nmol/L with a concomitant low adrenocorticotropic hormone level. Hypogonadism was defined as follows: for males, low testosterone (0.18–0.78 nmol/L) without elevated luteinizing hormone / follicle-stimulating hormone; for premenopausal females, amenorrhea with low estradiol (0–206 pmol/L) and low gonadotropins; and for postmenopausal females, the absence of elevated gonadotropins.[10,11] Hormonal parameters were measured using commercial kits.

Radiological assessment utilized pre- and post-GKRS pituitary MRI. Tumor size was stratified according to the following criteria: microadenomas were defined as those with a diameter under 10 mm, macroadenomas as greater than 10 mm, large macroadenomas as greater than 20 mm, and giant adenomas as exceeding 40 mm. The tumor dimensions were measured and recorded in three orthogonal planes: transverse (hereinafter referred to as TR), anteroposterior (hereinafter referred to as AP), and craniocaudal (hereinafter referred to as CC). Tumor volumes were estimated using the following formula: $V = (\pi \times [TR \times AP \times CC])/6$.[12] Volumetric criteria for tumor response were defined as: progression (≥20% volume increase or regrowth), shrinkage (>20% volume decrease), or stability (volume change within ±20%).[13] Favorable treatment response, termed "tumor control," encompassed both shrinkage and stability.[12,14] Furthermore, suprasellar extension was considered present when the tumor was within a 2 mm distance of the optic structures. Parasellar invasion was defined as Knosp grade 3 or 4.

GKRS technique

All GKRS procedures were conducted using a Leksell model B unit prior to April 2014 and a Perfexion model (Elekta Instrument, Inc.) thereafter. Following the application of a Leksell stereotactic

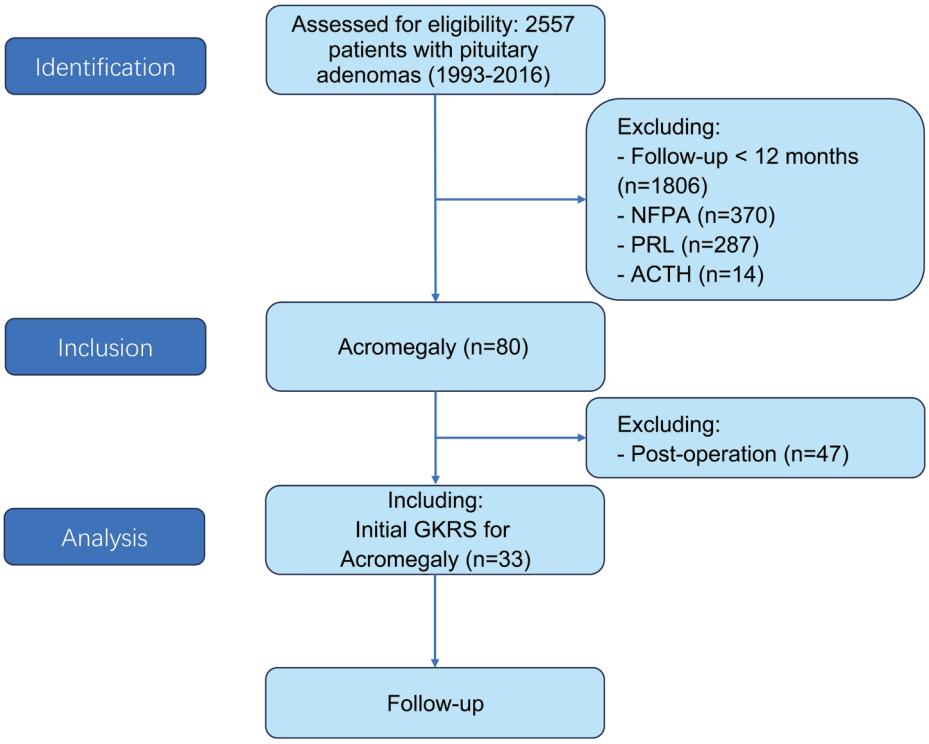

Fig. 1. Flowchart of the study. ACTH, adrenocorticotropic hormone; GKRS, gamma knife radiosurgery; NFPA, non-functioning pituitary adenoma; PRL, prolactin.

frame under local anesthesia, thin-slice, contrast-enhanced MRI of the sella was acquired for treatment planning. A multidisciplinary team comprising a neurosurgeon, radiation oncologist, and medical physicist then formulated the treatment plan. The prescribed dose was determined based on tumor volume, proximity to the optic apparatus, and prior radiation history. Critical dose constraints were set at ≤9 Gy for the optic nerves and chiasm, and ≤15 Gy for the lateral cavernous sinus. To optimize dose conformality, the 4-mm and 8-mm collimators were predominantly utilized.

Statistical analysis

Statistical analyses were performed using SPSS (v21.0), wherein the normality of continuous variables was evaluated with the Kolmogorov–Smirnov test; normally distributed data are expressed as mean ± standard error of the mean. The median (IQR) was used to describe variables not normally distributed. Univariate and multivariate analyses of the potential prognostic factors (age, sex, parasellar invasion, suprasellar invasion, tumor margin dose, tumor volume, preexisting hypopituitarism, and antisecretory therapy) associated with endocrine remission and new-onset hypopituitarism were performed using log-rank test statistics and a stepwise forward likelihood ratio method in Cox proportional hazards models. Kaplan–Meier analysis was used to assess endocrine remission and new-onset hypopituitarism. A P-value < 0.05 was considered statistically significant.

Results

Population and characteristics

A total of 33 patients (18 female and 15 male), median age 44.0 years (range: 24.9–66.2), were included in this analysis. The median clinical follow-up was 65.6 months (range: 12.9–297.6), and the median tumor volume was 2.14 cm^3 (range: 0.1–29.0). Of these patients, 16 (48.5%) had macroadenomas, 12 (36.4%) had large macroadenomas, and two (6.1%) had giant adenomas. Five patients (15.2%) had parasellar invasion, and 14 (42.4%) showed suprasellar invasion. Five patients presented with visual field defects or decreased visual acuity. Hypopituitarism was present in 16 patients (48.5%) before GKRS, including 11 with hypogonadism, four with hypothyroidism, and four with hypocortisolism. In this series, the median tumor margin radiation dose was 15.0 Gy (range: 10.8–20.3 Gy), the median maximum radiation dose was 36 Gy (range: 24–45 Gy), and the median prescription isodose was 40% (range: 30–55%). The baseline characteristics of GKRS treatment are presented in Table 1.

Clinical outcomes of GKRS

Endocrine remission was achieved in nine patients (27.3%) after GKRS, with a median time to remission of 85.1 months (range: 12.9–161.3 months) (Fig. 2a). Among all patients, the overall incidence of new-onset hypopituitarism was 24.2% (n = 8). Specifically, new-onset hypogonadism occurred in five patients, hypothyroidism in three, and hypocortisolism in four. At a median of 64.5 months (range: 12.9–143.4), patients developed new-onset hypopituitarism (Fig. 2b). Tumor shrinkage was observed in 32 patients (97.0%), and tumor stability in one patient (3.0%). No patient experienced tumor progression. Visual function deterioration occurred in one patient (3.0%) at 48.0 months of follow-up. None of the patients developed cranial nerve dysfunction after GKRS (Table 2). A univariable analysis was performed to assess the following potential prognostic factors: sex, age, parasellar invasion,

Table 1. Characteristics of 33 patients with acromegaly and GKRS parameters

Characteristic	Value
Male/Female, n (%)	15/18 (45.5/54.5)
Median age, (range), years	44.0 (24.9–66.2)
Median follow-up length, (range), months	65.6 (12.9–297.6)
Tumor size, n (%)	
Microadenoma	3 (9.1)
Macroadenoma	16(48.5)
Large macroadenoma	12(36.4)
Giant adenoma	2(6.1)
Median tumor volume, (range), cm^3	2.14 (0.1–29.0)
Parasellar invasion, n (%)	5 (15.2)
Suprasellar invasion, n (%)	14 (42.4)
Visual function before GKRS, n (%)	
Normal	28 (84.8)
Visual field defect and/or acuity decrease	5 (15.2)
Endocrine function, n (%)	
Baseline hypopituitarism	16 (48.5)
Hypogonadism	11
Hypothyroidism	4
Hypocortisolism	4
Normal endocrine function	17 (51.5)
Pre-GKRS cranial nerve dysfunction, n (%)	0
GKRS parameters	
Median tumor margin radiation dose, (range), Gy	15.0 (10.8–20.3)
Median maximum radiation dose, (range), Gy	36 (24–45)
Median prescription isodose, (range), %	40 (30–55)

GKRS, gamma knife radiosurgery.

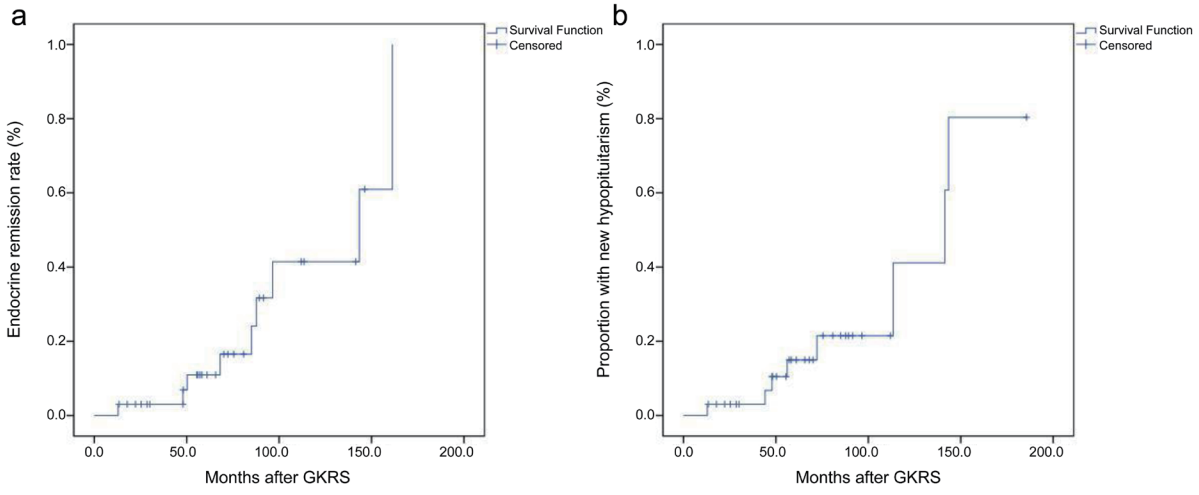

Fig. 2. Kaplan-Meier analysis of treatment outcomes. (a) Cumulative endocrine remission rate over time following initial GKRS. (b) Cumulative incidence of new-onset hypopituitarism during follow-up. GKRS, gamma knife radiosurgery.

Table 2. Clinical outcomes of 33 patients who underwent initial GKRS for acromegaly

Parameter	No. of patients (%)	Time in months (median, range)
Endocrine remission	9 (27.3)	85.1 (12.9–161.3)
Tumor response		
Shrinkage	32 (97.0)	
Stability	1 (3.0)	
Progression	0	
Complication		
New-onset hypopituitarism	8 (24.2)	64.5 (12.9–143.4)
Hypogonadism	5	
Hypothyroidism	3	
Hypocortisolism	4	
Visual function deterioration*	1 (3.0)	48.0
Cranial nerve dysfunction	0	

*Visual function deterioration includes visual acuity decrease, visual field defect, or both. GKRS, gamma knife radiosurgery.

suprasellar invasion, tumor volume, tumor margin dose, preexisting hypopituitarism, and antisecretory medication. No significant prognostic factors for endocrine remission or new-onset hypopituitarism were identified in univariate analysis (Table 3).

Discussion

Surgical resection remains the mainstay treatment for acromegaly, enabling rapid reduction of tumor burden and GH levels.[15,16] However, it is not suitable for all patients due to significant comorbidities, advanced age, or patient preference. GKRS has thus emerged as an alternative treatment option. Previous literature reports widely varying outcomes of GKRS in acromegaly, largely influenced by differences in endocrine remission criteria and study design.

As summarized in Table 4,[7,17,18] retrospective studies on initial GKRS for acromegaly have reported endocrine remission rates ranging from 21% to 96%, with median or mean margin doses between 23.7 Gy and 31.3 Gy, and follow-up periods ranging from

Table 3. Results of univariate and multivariate analysis for endocrine remission and new-onset hypopituitarism after GKRS

Variables	Endocrine remission	New-onset hypopituitarism
	Univariate, *P*	Univariate, *P*
Age (≥44 years)	0.858	0.384
Sex (male VS female)	0.404	0.727
Parasellar invasion	0.388	0.311
Suprasellar invasion	0.207	0.155
Tumor margin dose (<15 Gy)	0.542	0.525
Tumor volume (≥4 cm^3)	0.427	0.634
Preexisting hypopituitarism	0.204	0.247
Antisecretory medicine	0.251	0.922

Statistically significant ($P < 0.05$). GKRS, gamma knife radiosurgery.

Table 4. Literature review of initial GKRS for acromegaly

Study	Patients, n	Tumor margin dose (Gy)	Follow-up (months)	Endocrine remission rate	New hypopituitary	Remission criteria
Mohammed *et al*., 2019[7]	26	Median 23.7	Median 83.5	42% at 5-year	15.3%	IGF-1 normalization off meds
Shrivastava *et al*., 2005[18]	19	Mean 30	Mean 61	21%	NS	IGF-1 normalization; GH < 2 ng/mL
Thorén *et al*., 1991[17]	7	NS	Mean 96	42.8%	None	GH < 2 ng/mL
Present study	33	Median 15	Median 65.6	27.3%	24.2%	GH < 1 ng/mL

GH, growth hormone; GKRS, gamma knife radiosurgery; IGF-1, insulin-like growth factor-1; NS, not specified.

61 to 96 months.[17,19] Notably, variations in remission criteria significantly affect reported outcomes. Castinetti *et al*.[19] and Thorén *et al*.[17] applied stricter criteria (GH < 2 ng/mL or normalized IGF-1), yielding remission rates of 21% and 42.8%, respectively. These studies were conducted prior to the 2010 consensus, which established modern criteria: normalization of IGF-1 for age and sex, and random GH < 1.0 ng/mL. A more recent study by Mohammed *et al*.,[7] which adhered to the 2010 criteria, reported a 42% endocrine remission rate with a median margin dose of 23.7 Gy. Nonetheless, the generalizability of these findings remains limited due to small sample sizes and methodological heterogeneity.

In our study, endocrine remission was achieved in nine of 33 patients (27.3%), consistent with the broad range reported in previous literature.[7,20] The median tumor margin dose used in our cohort was 15 Gy—lower than doses in some other studies[7]—reflecting a deliberate trade-off between tumor control and preservation of visual function, especially given the proximity of many tumors to the optic apparatus. Although we analyzed potential prognostic factors such as age, sex, parasellar invasion, suprasellar extension, margin dose, tumor volume, and use of antisecretory medication, no significant predictors of endocrine remission were identified, which was similar to previous studies,[21] likely due to limited sample size, relatively short follow-up, and clinical heterogeneity.

We found that all the patients had tumor control by imaging evaluation after GKRS, the results in line with the previous study reported by Mohammed *et al*.[7] None of the patients showed tumor progression at the last time of follow-up. In comparison to other previous findings that the rate of tumor control was 42.0–100%,[7,17,20,22] our study showed a relatively successful rate of tumor control.

The development of new hypopituitarism represents the most common long-term sequela of GKRS for acromegaly, with a documented incidence ranging from 6% to 30.4%.[23–26] At 24.2% (8/33), the rate of new-onset hypopituitarism post-GKRS in our study was within the range reported by other institutions.[27,28] The literature on risk factors for post-GKRS hypopituitarism implicates technical parameters of the procedure itself, with the prescription isodose level being frequently cited as a key prognostic variable.[18,29,30] Our analysis revealed no significant association between the prognostic factors analyzed and the development of new-onset hypopituitarism.

We acknowledge several limitations of our study. Its retrospective design introduces potential selection and treatment biases. Histopathological data were unavailable, which might have offered prognostic insights. Variability in GH assay methods across time and institutions may also affect endocrine outcome consistency. Furthermore, the role of somatostatin analogs was not thoroughly analyzed, which may influence endocrine results. Finally, the small sample size limited statistical power for subgroup and regression analyses.

Conclusions

Our study suggests that initial GKRS represents a viable treatment option for acromegaly patients who are not optimal candidates for surgical resection. It provides high rates of tumor control and a reasonable rate of endocrine remission, coupled with an acceptable safety profile, particularly regarding pituitary function. Nevertheless, longer follow-up and larger prospective studies using standardized modern remission criteria are needed to better define the role of GKRS in the multidisciplinary management of acromegaly.

Acknowledgments

None.

Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Study supervision (JXY), conception and design (JXY, JYF), data acquisition (JMF, YLL, ZJW), data analysis and interpretation (JMF, ZJW), drafting of the article (JMF, ZJW), critical revision of the article (YHD). All authors have read and approved the final version of the manuscript.

Ethical statement

This study was carried out in accordance with the recommendations of the ethical standards of the 2024 Declaration of Helsinki and its subsequent amendments. The protocol was approved by the Institutional Review Board of the Second Affiliated Hospital of Guangzhou Medical University (Approval No. 2019-hg-ks-08). Individual consent for this retrospective analysis was waived.

Data sharing statement

The dataset used in support of the findings of this study are available from the corresponding author at Josse_yu@foxmail.com upon request.

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