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Bilateral inferior petrosal sinus sampling: Procedural data from a German single-center study

Sinus-petrosus-Blutentnahme: Prozedurale Daten einer unizentrischen Studie aus Deutschland

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Key words

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ABSTRACT

Purpose To assess radiation exposure and diagnostic performance of bilateral inferior petrosal sinus sampling for the distinction of pituitary and ectopic adrenocorticotropin-dependent Cushing's syndrome.

Materials and Methods Procedural data of bilateral inferior petrosal sinus procedures were retrospectively evaluated. The analysis included the patients' clinical and demographic data, procedural radiation exposure, and complication rates, sampling results, clinical course of the patients, and calculation of diagnostic performance data.

Results The cases of 46 patients diagnosed with adrenocorticotropin-dependent Cushing's syndrome were evaluated. Bilateral inferior petrosal sinus sampling was successfully performed in 97.8 % of the cases. The overall median procedure-related fluoroscopy time was 7.8 min. (range 3.2–36.2 min.), and the median procedural dose area product was 11.9 Gy*cm² (range 2.1–73.7 Gy*cm²). Radiation doses due to digital subtraction angiography series for visualization of the inferior petrosal sinus were 3.6 Gy*cm² (range 1.0–18.1 Gy*cm²). Radiation doses due to fluoroscopy had a higher impact on the overall radiation exposure and were significantly influenced by the patients' habitus. The sensitivity, specificity, and positive and negative predictive values were 84 %, 100 %, 100 %, and 72 % before stimulation with corticotropin-releasing hormone, and 97 %, 100 %, 100 %, and 93 % after stimulation. Concordance between magnetic resonance imaging studies and bilateral inferior petrosal sinus sampling results was only found in 35.6 % of the cases. The periprocedural complication rate was 2.2 %, with one patient experiencing vasovagal syncope during catheterization.

Conclusion Bilateral inferior petrosal sinus sampling is a safe procedure with high technical success rates und excellent diagnostic performance. The procedure-related radiation exposure shows large variations and depends on the complexity of cannulation as well as the patients' habitus. Fluoroscopy accounted for the largest proportion of radiation exposure. Acquisition of digital subtraction angiography series for the verification of correct catheter placement appears justified.

Key Points:

- Bilateral inferior petrosal sinus sampling with CRH stimulation provides high diagnostic performance in the distinction of pituitary and ectopic Cushing's syndrome.
- The associated radiation exposure is not negligible and is significantly influenced by the use of fluoroscopy and the patients' habitus.
- Digital subtraction angiography contributes less to the overall radiation dose and appears justified for the verification of correct catheter placement.

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ZUSAMMENFASSUNG

Ziel Bestimmung der Strahlenbelastung und diagnostischen Leistungsfähigkeit der Sinus-petrosus-Blutentnahme bei der Differenzierung von hypophysärem und ektopem Adrenocorticotropin-abhängigem Cushing-Syndrom.

Material und Methoden Prozedurbezogene unizentrische Daten der Sinus-petrosus-Blutentnahme wurden retrospektiv ausgewertet. Anhand klinischer und demografischer sowie prozedurbezogener Daten wurde neben der intraprozeduralen Strahlenbelastung die diagnostische Leistungsfähigkeit der Sinus-petrosus-Blutentnahme analysiert.

Ergebnisse Die Auswertung beinhaltete die Daten von 46 Patienten mit der Diagnose eines Adrenocorticotropin-abhängigen Cushing-Syndroms. Die bilaterale Blutentnahme gelang im ersten Versuch in 97,8 % der Fälle. Die mediane prozedurbezogene Durchleuchtungszeit belief sich auf 7,8 min (3,2–36,2 min), das Dosisflächenprodukt auf 11,9 Gy*cm^2 (2,1–73,7 Gy*cm^2). Dabei entfielen im Median 3,6 Gy*cm^2 (1,0–18,1 Gy*cm^2) auf die Akquisition von digitalen Subtraktionsangiografie-Serien. Die Strahlenbelastung durch Einsatz der Durchleuchtung hatte einen höheren Einfluss auf die Gesamtdosis und wurde signifikant durch den Habitus der Patienten beeinflusst. Sensitivität, Spezifität, positiver und negativer Vorhersagewert beliefen sich auf 84 %, 100 %, 100 %, und 72 % vor Corticotropin-Releasing-Hormon-Stimulation und auf 97 %, 100 %, 100 %, und 93 % danach. Eine Übereinstimmung der Ergebnisse der hypophysären Magnetresonanztomografie und der Sinus-petrosus-Blutentnahme-Ergebnisse lag in nur 35,6 % der Fälle vor. Die prozedurbezogene Komplikationsrate betrug 2,2 %, wobei ein Patient während der Katheterisierung eine vasovagale Synkope erlitt.

Schlussfolgerung Die Sinus-petrosus-Blutentnahme ist ein sicheres Verfahren mit hohen technischen Erfolgsraten und diagnostischer Leistungsfähigkeit. Die prozedurbezogene Strahlenbelastung zeigt eine breite Variabilität und wird durch die Komplexität der Sondierung sowie den Patientenhabitus beeinflusst. Die Akquisition von digitalen Subtraktionsangiografie-Serien zur Verifikation der korrekten Katheterplatzierung vor Blutentnahme kann basierend auf den vorliegenden Daten als gerechtfertigt bewertet werden.

Kernaussagen:

- Die bilaterale Sinus-petrosus-Blutentnahme bietet hohe diagnostische Wertigkeit bei der Unterscheidung des hypophysären und ektopen Cushing-Syndroms.
- Die damit assoziierte Strahlenbelastung ist nicht zu vernachlässigen und wird maßgeblich durch den Einsatz der Durchleuchtung und den Patientenhabitus beeinflusst.
- Die digitale Subtraktionsangiografie trägt zu einem geringeren Anteil zur Gesamtdosis bei und kann vor dem Hintergrund der Verifikation der korrekten Katheterlage als gerechtfertigt bewertet werden.

Introduction

Cushing's syndrome (CS) is an endocrine disease resulting from chronic glucocorticoid excess. Endogenous overproduction of cortisol may be adrenocorticotropin hormone (ACTH)-independent, usually caused by a cortisol-producing adrenal adenoma, or ACTH-dependent (the vast majority of cases). The latter is mainly attributed to ACTH-producing pituitary adenomas, also called Cushing's disease (CD). On the other hand, ectopic ACTH- or corticotropin-releasing hormone (CRH)-secreting neuroendocrine tumors might be a much less frequent origin of ACTH-dependent CS [1].

Since long-term consequences frequently include obesity, arterial hypertension, and diabetes, CS might be accompanied by relevant morbidity, mortality, and decreased quality of life [2]. Beside the evaluation of clinical presentation and symptoms, noninvasive laboratory assessment is the diagnostic cornerstone in suspected CS [3]. If ACTH-dependent CS is assumed, the correct distinction between CD and ectopic CS (ECS) is of paramount importance to pave the way to appropriate treatment.

Noninvasive methods to differentiate between CD and ECS are dynamic endocrine tests (like the CRH-stimulation test and the high-dose dexamethasone suppression test) and high-resolution, gadolinium-enhanced magnetic resonance imaging (MRI) of the sellar region [4]. While the former is characterized by low diagnostic accuracy, MRI is often not able to identify small pituitary lesions and carries the risk of misjudging non-functioning adenomas as the source of cortisol excess [5].

Bilateral inferior petrosal sinus sampling (BIPSS) is a minimally invasive procedure, considered the gold standard for distinguishing CD from ECS by measuring the pituitary hormone output directly [6, 7]. Many studies have already reported the benefits of BIPSS with special emphasis on the technical and clinical outcome [8]. However, concerning the diagnostic performance, some publications offer a high variability of sensitivity (85–100 %) and specificity values (67–100 %) [9, 10]. In addition, the procedure-related radiation exposure to the patient has not yet been explicitly addressed in the available literature.

Therefore, this study aims to compile the BIPSS data from our single-center institution with a special focus on the patients' radiation exposure and on technical and clinical aspects, thereby further elucidating the usefulness, safety, and impact of this procedure in the diagnostic workup of patients with ACTH-dependent CS.

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Materials and methods

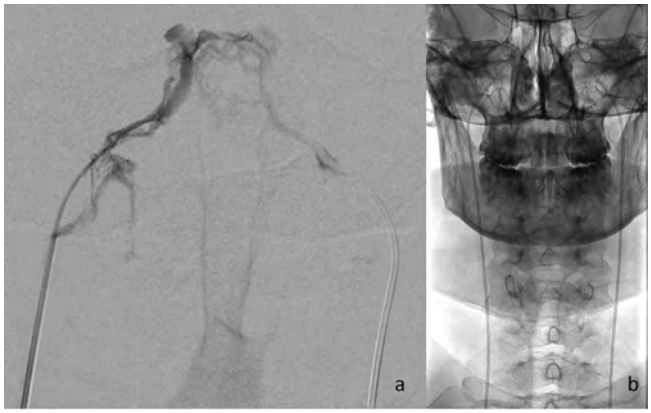
Study design and patient characteristics

To obtain a homogeneous dataset, only procedures performed with the same angiography units and identical beam geometry were considered. On this basis, a total of 46 patients with biochemically confirmed ACTH-dependent CS undergoing BIPSS at our institution between July 2009 and March 2021 were identified. Diagnosis of ACTH-dependent CS was performed according to established criteria including pathological results for serum cortisol during the 1-mg dexamethasone suppression test, late-night salivary or serum cortisol, and 24h-urinary free cortisol [6]. Definitive diagnosis of CD or ECS was based on histopathological analysis after transsphenoidal surgery or resection of an extrapituitary ACTH secreting tumor. Alternatively, clinical and biochemical remission of CS after transsphenoidal surgery was considered as indicative of a pituitary ACTH source, even if histopathological analysis did not identify a pituitary tumor. Informed consent for the procedure was obtained from each patient. The requirement for consent from the patients to be included in this retrospective study was waived by our institutional review board.

Sampling protocol and laboratory measurements

All BIPSS procedures were carried out by the same experienced board-certified interventional radiologist in our local angiography suites equipped with a state-of-the-art flat-panel detector C-arm angiographic system (Axiom Artis Zee, Siemens Healthineers, Forchheim, Germany) including dedicated low-dose settings and collimation filters for the acquisition of fluoroscopic, radiographic, and digital subtraction angiography (DSA) images (CARE Body, Siemens Healthineers, Forchheim, Germany). CARE Body is a standard comprehensive portfolio of tools to reduce radiation exposure. Those tools include adaption of pulses per second, minimization of entrance dose, radiation-free adjustment of collimation, radiation positioning without additional fluoroscopy, effective patient entrance dose during procedures, making dose visible, real-time patient entrance dose monitoring, comprehensive and improved dose reporting. All imaging was acquired in posterior-anterior projection with the following parameters: Tube potential 70 kVp, bodyweight-adapted tube current setting ranging from 160 to 465 mA, 48 cm field of view, standardized system dose 0.36 µGy per pulse, pulse rate of 7.5 pulses per second, DSA frame rate of 2 frames per second, and variable and automatically adjusted prefiltering ranging from 0.2 to 0.9 mm during fluoroscopy and from 0.0 to 0.9 mm during digital acquisition (referring to the absorption of the patient entrance dose along the path of the X-ray beam through the patient).

During the study period, changes to the systems' algorithms regarding enhanced image quality (CLEAR features, Siemens Healthineers, Forchheim, Germany) were not performed. Those features include shortening of pulse length, optimization of image brightness, reduction of motion artifacts, dose-adaptive noise reduction, enhanced visibility of vessel edges, real-time pixel-shifting for patient movement compensation, and enhanced image quality in Roadmap). Concerning radiation reduction tools, however, the following adaptions were made over time: CARE vision module (Siemens Healthineers, Forchheim, Germany; dose reduction by adapting the pulses per second) in March 2010, and CARE monitor/guard (Siemens Healthineers, Forchheim, Germany; real-time patient entrance dose monitoring/visual and audible warnings) in April 2017. After application of local anesthesia, bilateral antegrade transfemoral venous access was achieved using the Seldinger technique. The patients were not heparinized. Catheterization of both inferior petrosal sinuses was performed under fluoroscopy guidance. In most of the cases, a 0.035" guidewire (Radifocus, Terumo, Tokyo, Japan) and a 4F multipurpose catheter (Radifocus™ Optitorque™, Terumo Europe N. V., Leuven, Belgium) were used for the right side. For the left side a JB2 configurated catheter (Beacon™ tip, Cook, Bjaeverskov, Denmark) was preferably used to cannulate the left internal jugular vein, that was later exchanged for a 4F multipurpose catheter (Radifocus™ Optitorque™, Terumo Europe N. V., Leuven, Belgium) to catheterize the left inferior petrosal sinus. Alternatively, a 5F Kumpe (KMP) catheter (Beacon™ tip, Cook, Bjaeverskov, Denmark), a multipurpose angiographic (MPA) catheter (Beacon™ tip, Cook, Bjaeverskov, Denmark), or a headhunter 1 (H1) catheter (Beacon™ tip, Cook, Bjaeverskov, Denmark) were occasionally utilized. A small amount of contrast agent was applied and DSA was conducted bilaterally on the level of each sinus in all cases to verify correct catheter placement prior to venous sampling (▶ **Fig. 1**). 100 µg CRH (Ferring, Kiel, Germany) was applied as a bolus via a peripheral vein. Blood samples from the right and left inferior petrosal sinus and from peripheral venous access were collected simultaneously before CRH injection and after 2 as well as 5 minutes, respectively. Blood samples were collected in labelled EDTA tubes and were transferred to the endocrinology lab immediately



▶ **Fig. 1** Examples of selective catheterization during bilateral inferior petrosal sinus sampling. **a** Digital subtraction venography verifying the correct catheter placement in a 43-year-old female patient. **b** Bilateral catheter location in both inferior petrosal sinuses in a 37-year-old female patient.

▶ **Abb. 1** Beispielbilder der selektiven Sondierung während der Sinus-petrosus-Blutentnahme. **a** Digitales Subtraktionsvenogramm mit Kontrastmittelapplikation über den rechtsseitigen Sinus petrosus inferior zur Verifikation der richtigen Katheterlage bei einer 43-jährigen Patientin. **b** Bilaterale Platzierung der Katheter innerhalb der Sinus petrosi inferiores bei einer 37-jährigen Patientin.

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after each sampling approach. The proceeding of BIPSS was not changed during the study period.

The central/peripheral ACTH gradient at each time point was utilized to distinguish between a central or an ectopic source of ACTH excess. According to published criteria, a ratio of ≥ 2 before or of ≥ 3 after stimulation with CRH was regarded as a central ACTH source [11].

Lateralization of central hypersecretion was determined by the ACTH ratio between right and left inferior petrosal sinus sampling. A ratio of ≥ 1.4 before or after CRH stimulation indicated a right- or left-sided hormone-excreting adenoma. If the intersinus gradient was not evident, the hormone source was considered to be located in the pituitary center. If BIPSS indicated an ectopic ACTH source, further diagnostic evaluation was performed (e. g., positron emission tomography-computed tomography (PET-CT)).

Data evaluation and endpoint definition

Patient charts and medical records were reviewed to extract demographic, procedural, clinical, biochemical, radiological, and surgical data. Since many of the patients received further surgical treatment in external hospitals, efforts were made in these cases to request the surgical and histopathological reports.

The main focus of this study was procedure-related data, which included radiation values with fluoroscopy time (FT; min) and dose area product (DAP; Gy*cm^2). Radiation dose was further subdivided into fluoroscopy-associated dose and dose occurring during the visualization of the inferior petrosal sinuses utilizing DSA. Further analyzed procedural data included the number of acquired DSA series, the amount of contrast agent, the procedure's technical success, and complication rates.

Further emphasis was put on the diagnostic outcome of BIPSS, e. g., regarding location, lateralization, and concordance to available pituitary MRI results. Besides, basic patient characteristics, laboratory results and the presence of sinus abnormalities (e. g., a unilateral hypoplasia) were evaluated. Diagnostic performance data including sensitivity, specificity, positive and negative predictive value, and accuracy rates were calculated based on surgical and histopathological reports and/or the clinical course of the patients.

Statistical analysis

Descriptive data are presented as means ± standard deviation for normally distributed variables or medians with ranges for non-normalized variables, if appropriate. Categorical data are expressed as counts and percentages with n (%). For the assessment of normality, the Anderson-Darling test was used, rejecting the hypothesis of normality when the p-value is less than or equal to 0.05. Correlation analysis of ordinal and metrical data was performed with the test according to Spearman for non-normalized variables. For all evaluations, a p-value of less than 0.05 was considered to indicate significant differences. Statistical analysis and the evaluation of the data were performed with a specialized computer algorithm (Microsoft Excel V1908 and RStudio 1.2.5033).

Results

In total, the data of 46 adult patients, 35 females (76.1 %) and 11 (23.9 %) males, were included in this retrospective study. The median patient age was 49 years and ranged between 19 and 76 years. Basic patient characteristics data and laboratory results are shown in ▶ **Table 1**. The most common CS-related symptoms documented in the medical records were arterial hypertension, diabetes mellitus, obesity, and muscle atrophy.

Bilateral sampling could successfully be achieved on the first attempt in 45 out of 46 (97.8 %) cases. In one case, laboratory

▶ **Table 1** Clinical characteristics of patients with ACTH-dependent CS undergoing bilateral inferior petrosal sinus sampling.

▶ **Tab 1** Klinische Daten der Patienten mit ACTH-abhängigem CS, bei welchen eine Sinus-petrosus-Blutentnahme durchgeführt wurde.

Age (years)	48	(19–76)
Male:female ratio	11:35	
BMI (kg/m^2)	31.4	(16.3–56.7)
	n	%
Clinical presentation		
Hypertension	28	60.9
Adipositas/weight gain	33	71.7
Diabetes mellitus type 2	21	45.7
History of pituitary surgery	3	6.5
Outcome of pituitary MRI*		
Without adenoma	27	60
Macro- or microadenoma	18	40
▪ Left-sided	4	8.9
▪ Right-sided	10	22.2
▪ Middle of the gland	4	8.9
Presence of sinus hypoplasia		
▪ Left-sided	6	13.3
▪ Right-sided	1	2.2
	Median	Min.-max.
Biochemical profile		
Plasma ACTH (ng/L)	52.0	7.2–250
Serum cortisol (µg/dL)	21.0	4.8–61.1
Midnight serum cortisol (µg/dL)	15.3	2.5–51.9
Serum cortisol during the 1 mg dexamethasone suppression test (µg/dL)	16.8	2.3–99.2
24-h UFC (µg/dL)	217.6	22.3–2450.0

ACTH = adrenocorticotropin hormone; BMI = body mass index; CS = Cushing's syndrome; MRI = magnetic resonance imaging; UFC = urinary free cortisol
ACTH = Adrenocorticotropes Hormon; BMI = Body-Mass-Index; CS = Cushing-Syndrom; MRI = Magnetresonanztomografie; UFC = Freies Cortisol im 24-Stunden-Urin
* Preinterventional pituitary MRI studies were available in 45/46 (97.8 %) patients.

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results of the first BIPSS proved insufficient catheter positioning during the sampling. The procedure was successfully repeated four weeks after the first attempt.

The absolute median DAP for all procedures including the reintervention was 11.9 Gy*cm^2 and ranged between 2.1 and 73.7 Gy*cm^2. These dose values were derived from DSA acquisition (median of 3.6 Gy*cm^2; range 1.0–18.1 Gy*cm^2) and fluoroscopy (median 7.7 Gy*cm^2; range 1.1–70.3 Gy*cm^2). The median FT was 7.8 min. (range 3.2–36.2 min.). A significant positive correlation between the patient body mass index (BMI) and the total DAP (rho-value 0.569; $p < 0.0001$) was found. However, a significant correlation between BMI and FT was not observed (rho-value -0.194; $p = 0.197$). DAP based on fluoroscopy alone showed a more significant correlation with patient BMI than DSA-related DAP (rho-value 0.619; $p < 0.0001$ vs. rho-value 0.341; $p = 0.020$). The influence of fluoroscopy alone on the overall DAP was significantly higher than that of DSA alone (rho-value 0.974; $p < 0.0001$ vs. rho-value 0.547; $p = 0.004$). The highest dose levels found in our collective were associated with relevant obesity in terms of a BMI of ≥ 40 kg/m^2 in 9 patients, and technical difficulties due to jugular vein thrombosis in one case.

Preinterventionally, pituitary MRI studies were available in 45 out of 46 patients (97.8 %). In 18 cases (40.0 %), MRI indicated the presence of a micro- or macroadenoma, including three patients with final diagnosis of ECS and 15 with CS. Abnormalities of the venous sinus were found in seven patients (15.5 %), including hypoplasia of the left inferior petrosal sinus in six patients (13.3 %) and of the right inferior petrosal sinus in one case (2.2 %). MRI showed lateral intrasellar adenomas in 15/16 (93.8 %) cases, whereas in one case an adenoma located in the middle of the pituitary gland was described. Concordance between MRI studies and BIPSS results was only found in 35.6 % of cases with available MRI (16/45).

Based on histopathological results or the clinical and biochemical course, 13 patients (28.3 %) were finally diagnosed with an ectopic ACTH source (▶ **Table 2**). In seven of these patients, PET-CT scans of the chest, abdomen, and pelvis did not reveal any evidence of an ectopic ACTH-secreting tumor. Six patients finally underwent bilateral adrenalectomy, and three patients were treated conservatively. The cases with ECS and confirmed neuroendocrine tumor included four patients with pulmonary carcinoid tumor, and two patients with pancreatic neuroendocrine tumor. One patient with pulmonary carcinoid tumor was first treated with adrenalectomy and subsequently with pulmonary lobectomy.

BIPSS results predicted CD in 31 cases, whereas the sampling results indicated an ectopic source of ACTH hypersecretion in 15 patients (67.4 % vs. 32.6 %). A basal central/peripheral ACTH gradient ≥ 2 was found in 26 patients. After stimulation with CRH, a central/peripheral ACTH gradient ≥ 3 could be found in 28 patients two minutes and in 30 patients five minutes after CRH injection. The central/peripheral ACTH gradient was < 2 before stimulation and < 3 after stimulation in all patients with the final diagnosis of ECS. In five cases with confirmed CS, central/peripheral ACTH gradients were only indicative of a pituitary origin after CRH stimulation. Details on the diagnostic course of patients with ECS are given in ▶ **Table 3**.

During one procedure, a 30-year-old male patient experienced vasovagal syncope during catheterization and was immediately treated with manual resuscitation. The patient responded with a return of spontaneous circulation (ROSC) within 30 seconds. Apart from that, further complications did not occur during or following the procedures. None of the procedures was associated with permanent morbidity or mortality of the patients.

Discussion

BIPSS is considered the most sensitive instrument for determining the origin of ACTH secretion and is therefore regarded as the diagnostic gold standard in patients with ACTH-dependent CS. - Despite modern laboratory and imaging techniques, reliable identification of the underlying tumor in ACTH-dependent CS remains a diagnostic challenge. Misinterpretation of the source of ACTH secretion may have serious consequences like unnecessary surgery or delayed cure. The noninvasive imaging modality of choice for suspected CD remains pituitary MRI examination. Dedicated contrast-enhanced study protocols, preferably with high-magnetic field scanners, nowadays allow adenoma detection rates of up to 96 % [12]. While the problem of adenoma detection has been overcome as scanner technology continues to improve, the challenge of distinguishing between secreting and non-secreting pituitary incidentalomas remains [13]. Consistent with that, accuracy rates of MRI in the differentiation between central and ectopic CS reported in the literature range between 50 % and 58 % [14, 15]. In our study cohort, only 15/46 patients with the final diagnosis of central hypercortisolism had a positive pituitary MRI examination. At the same time, MRI detected adenoma-like pituitary lesions in 4/14 patients with the final diagnosis of an ectopic ACTH source. Without further diagnostic clarification, these patients might have been incorrectly assigned to pituitary surgery.

With a successful bilateral catheterization rate of 98 % in the first attempt, our overall technical success rate appears to be one of the highest reported in the literature [15, 16]. A possible explanation for that might be that only one experienced interventional radiologist performed all of the BIPSS procedures. As a technically demanding intervention, this procedure should be performed exclusively in centers with appropriate technical background and by operators with adequate clinical expertise [17]. Regarding the diagnostic performance data, accuracy rates between 90 % and 100 % can be found in the literature [18]. Previous studies and meta-analyses demonstrated improved diagnostic accuracy when CRH stimulation is performed [19, 20]. We found basal accuracy rates of 89 %, which could be further increased to 98 % by utilizing CRH stimulation in our cohort.

Some authors advocate the use of a microcatheter for sampling owing to the potential of blocking or diverting the sinus drainage when utilizing larger catheters [21]. Although microcatheters were not used in our study, a remarkable success rate was still achieved, possibly due to the preferential use of catheters with additional side holes. Accordingly, the risk of a wedging effect or catheter tip suction towards the vessel wall was obviously relevantly reduced.

The incidence of false-negative results in BIPSS (i. e., falsely indicating an ectopic ACTH source) is generally more common than that of false-positive results [22]. Reasons for this may be related

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▶ **Table 2** Procedural and diagnostic performance data for BIPSS and MRI.

▶ **Tab 2** Prozedurbezogene Daten und Ergebnisse der diagnostischen Güte der Sinus-petrosus-Blutentnahme und des MRT.

	n	%		
Primary technical success	45/46	97.8		
Complications	1/46	2.2		
Radiation data	Median	Min.-max.		
Overall FT (min.)	7.8	3.2–36.2		
Overall DAP (Gy*cm²)	11.9	2.1–73.7		
Number of DSA series (n)	2	2–8		
DSA-related DAP (Gy*cm²)	3.6	1.0–18.1		
Fluoroscopy-related DAP (Gy*cm²)	7.7	1.1–70.3		
Amount of contrast agent (ml)	10	5–50		
Final diagnosis	n	%		
Pituitary source	33	71.7		
Ectopic source	13	28.3		
BIPSS results				
Pituitary source	31	67.4		
Ectopic source	15	32.6		
ACTH gradients				
Basal c/p gradient ≥ 2	26			
c/p gradient ≥ 3				
▪ 2 minutes after stimulation	28			
▪ 5 minutes after stimulation	30			
Lateralization				
Right	17	54.8		
Left	9	29.1		
None	5	16.1		
Concordance between MRI and BIPSS	16	35.6		
Diagnostic performance of BIPSS	Before CRH	2 min. after CRH	5 min. after CRH	In total
Diagnostic accuracy (%)	89	89	94	98
Sensitivity (%)	84	84	91	97
Specificity (%)	100	100	100	100
Positive predictive value (%)	100	100	100	100
Negative predictive value (%)	72	72	81	93
Diagnostic performance of MRI				
Diagnostic accuracy (%)	47			
Sensitivity (%)	56			
Specificity (%)	23			
Positive predictive value (%)	64			
Negative predictive value (%)	18			

ACTH = adrenocorticotropin hormone; BIPSS = bilateral inferior petrosal sinus sampling; c/p gradient = central/peripheral gradient; DAP = dose area product; DSA = digital subtraction angiography; FT = fluoroscopy time; MRI = magnetic resonance imaging
ACTH = Adrenocorticotropes Hormon; BIPSS = Sinus-petrosus-Blutentnahme; c/p Gradient = Zentraler/peripherer Gradient; DAP = Dosisflächenprodukt; DSA = Digitale Subtraktionsangiografie; FT = Durchleuchtungszeit; MRI = Magnetresonanztomografie

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▶ **Table 3** Clinical course of patients with ectopic ATCH source.

▶ **Tab 3** Klinischer Verlauf der Patienten mit ektoper ACTH-Quelle.

Patient	Sex	Age	Pituitary adenoma in MRI	BIPSS indicating ectopic ACTH source	Imaging-based tumor localization in PET-CT	Histological analysis	Therapy
1	m	46	no	yes	–		bilateral adrenalectomy
2	m	45	no	yes	–	malignant peritoneal mesothelioma	bilateral adrenalectomy
3	f	74	yes	yes	–		bilateral adrenalectomy
4	f	68	no	yes	pancreas	pancreatic NET	left-sided pancreatic resection
5	f	41	no	yes	lung	pulmonary carcinoid tumor	bilateral adrenalectomy + pulmonary lobectomy
6	m	57	yes	yes	lung	pulmonary carcinoid tumor	pulmonary lobectomy
7	m	65	no	yes	–		medical treatment
8	f	48	no	yes	–		medical treatment
9	m	50	yes	yes	pancreas and lung	pancreatic NET with solitary pulmonary metastasis	bilateral adrenalectomy
10	f	66	yes	yes	–		medical treatment
11	m	51	no	yes	–		medical treatment + bilateral adrenalectomy
12	f	59	no	yes	lung	pulmonary carcinoid tumor	bilateral adrenalectomy
13	f	20	no	yes	lung	pulmonary carcinoid tumor	pulmonary lobectomy

ACTH = adrenocorticotropin hormone; BIPSS = bilateral inferior petrosal sinus sampling; MRI = magnetic resonance imaging; NET = neuroendocrine tumor; PET-CT = positron emission tomography–computed tomography
ACTH = Adrenocorticotropes Hormon; BIPSS = Sinus-petrosus-Blutentnahme; MRI = Magnetresonanztomografie; NET = Neuroendokriner Tumor; PET-CT = Positronen-Emissions-Tomografie-Computertomografie

to both technical causes as well as anatomical variants of the venous drainage pattern [16, 23]. Furthermore, the lateralization pattern in BIPSS may not only be influenced by the location of the adenoma, but also by inter-individual cavernous sinus venous drainage patterns [24]. Therefore, the usefulness of the procedures in determining the lateralization of the pituitary adenoma for preoperative navigation remains controversial [25, 26]. Different parasellar venous drainage patterns have been described by Miller et al. [27]. Type 1 and 2 comprise symmetrical bilateral sinuses. Type 3 describes a unilateral hypoplastic or plexiform inferior petrosal sinus and in type 4, a connection with the ipsilateral internal jugular vein is not present. While complete type 4 anatomy necessitates an aberrant sampling route, e. g., from the external jugular vein, type 3 carries a special risk for misinterpretation of the results. In this scenario, the hypoplastic sinus might be visualized by ipsilateral contrast administration. However, venous blood sampling from the cavernous sinus might be impossible. No data is available yet on the incidence of the different variants.

As a demanding fluoroscopy-guided procedure, the radiation exposure that may contribute to stochastic effects has to be acknowledged. Because the primary onset of symptoms associated with CS often occurs in younger patients, attention should be paid to adequate management of radiation exposure. Despite the broad literature on the diagnostic outcome of BIPSS, our study is – to the best of our knowledge – the first that explicitly deals with the aspect of periprocedural radiation exposure. Even though we observed a significant correlation between patient habitus and overall DAP, fluoroscopy per se seems to be the most relevant factor for an increase in DAP values. Moreover, we found a considerable range of radiation doses due to fluoroscopy, which might reflect different degrees of difficulty during vessel cannulation.

Beside the standard portfolio of manufacturer-specific dose-saving tools, modifications of the default angiography settings can result in further relevant dose reductions [28]. Those adjustments might include the reduction of the frame rate for DSA and pulse rate for fluoroscopy, as well as the decrease of radiation exposure per frame on DSA images [29]. Although we found a field of view of 48 cm to be sufficient, the higher radiation exposure associated with a smaller field of view could be acceptable in some cases, especially when vessel cannulation is difficult in the presence of deviating variants [30]. Changes in the angulation of the X-ray tube might also be helpful in such a scenario. However, theoretically this would also lead to an increase in radiation dose [31].

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Another possibility of further dose reduction was not considered in our study. DSA series in our patients were obtained sequentially via unilateral contrast agent injection, resulting in a minimum of two series. Instead, the number of DSA series could be reduced by bilateral cannulation and simultaneous contrast administration. Additionally, even if it was our subjective impression that a fluoroscopic pulse rate of 7.5/s was adequate during BIPSS, it may be discussed whether a pulse rate of 4/s might be sufficient, at least to catheterize up to the level of the jugular vein. After that the pulse rate might be increased to 7.5/s for the cannulation of the inferior petrosal sinuses [32]. Certainly, those modifications must always be weighed against a possible degradation of image quality to ensure preserved procedural safety. When being compared to recent national diagnostic reference levels in Germany, the highest dose values obtained from our procedures can be roughly compared to those that are proposed for two intracranial thrombectomy procedures in acute ischemic stroke or three endovascular treatment procedures of intracranial aneurysms [33].

One might question the necessity of DSA acquisition during BIPSS. It is the authors' experience that verification of correct catheter placement during sampling is of utmost importance, and acquisition of DSA venography series is best suited to ensure this. Based on our data, we consider the DSA-related amount of radiation dose to be justified, considering the relevant diagnostic benefit. It can be discussed that, besides the high level of expertise of the performing examiner, DSA series prior to sampling also contribute at least in part to the comparatively high technical success rates.

Complications like venous thrombosis, subarachnoid hemorrhage, cerebral infarction, and nerve paralysis have been reported in the literature but are extremely rare [34, 35]. Due to the hypercoagulable state in the presence of overt CS, thromboembolic events and their potentially fatal outcome are particularly feared complications [36]. This may contribute to the fact that some centers perform BIPSS only under periprocedural heparinization [37, 38]. In our study cohort, however, we did not encounter any severe procedure-related complications leading to permanent sequelae. In particular, venous thrombosis was not observed despite the omission of heparinization throughout all procedures. One case of transient vasovagal syncope in a young patient during the procedure appeared to be severe, but fortunately did not result in any permanent sequelae. Our literature search regarding complications related to BIPSS did not reveal any other comparable cases. However, it may be hypothesized that mechanical irritation by the guidewire may have led to the development of this adverse event.

The presented study has some limitations. First, this study is retrospective, including a single-center and non-randomized study design. Because of the retrospective data acquisition, information regarding therapeutic management, histopathological results, and patient outcome after surgery could not be obtained in some cases. The diagnostic performance of BIPSS could, therefore, only be evaluated to a limited extent. Additionally, assumed lateralization could not sufficiently be confirmed due to the lack of surgical reports in some cases. Nevertheless, the single center nature of the study and the fact that BIPSS was performed by the same radiologist allow for very homogeneous results. Furthermore, we believe that our data may give further insight into this rare procedure, especially from a technical point of view. As another consequence of the retrospective study design, pituitary MRI studies were not standardized in terms of MRI protocols and readers, which might result in a deviating diagnostic value. Moreover, only the MRI results from the written reports were taken into consideration (i. e., no blinded reading of MRI scans was conducted for this study). This limitation may have also contributed to the low concordance between MRI and BIPSS results. Regarding the analysis of radiation exposure, only data routinely recorded by the system dosimeter was considered. In the future, it would be interesting to perform further dedicated dosimetry studies, for example by placing real-time dosimeters in the area of the patients' eye lenses, to be able to determine equivalent doses.

In conclusion, BIPSS including CRH stimulation is a useful, reliable, and safe interventional procedure contributing to the differentiation of pituitary and ectopic CS, especially when performed by experienced operators and in specialized centers. The amount of periprocedural radiation exposure is not negligible and is mainly affected by fluoroscopy during cannulation.

CLINICAL RELEVANCE OF THE STUDY

- Bilateral inferior petrosal sinus sampling facilitates the distinction between pituitary and ectopic Cushing's syndrome.
- The procedure can be accompanied by considerable radiation exposure.
- Radiation protection measures should aim at the reduction of dose from fluoroscopy.

Conflict of Interest

The authors declare that they have no conflict of interest.

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