Effect of intercavernous sinus drainage pattern on exactness of bilateral inferior petrosal sinus sampling results in foretell the area of Cushing’s disease tumors

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Research Article

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Abstract

Background

Cushing's disease (CD) is originated from immoderatedischarge of adrenocorticotropic hormone (ACTH) from tumor cells, which leads to adrenal cortical hyperplasia and excessive glucocorticoid secretion, resulting in disordered metabolism of various substances, and hypercortisolism. The purpose of this research was to assess the effect of the intercavernous sinus drainage pattern on ability of bilateral inferior petrosal sinus sampling (BIPSS) to predict tumor location in patients with CD.

Methods

The clinical data of 50 patients with CD who experienced BIPSS in the Department of Neurosurgery of the First Affiliated Hospital of Zhengzhou University between August 2018 and April 2022 were retrospectively analyzed. Data included the patients' basic preoperative clinical data, preoperative dynamic contrast-enhanced MRI of the pituitary gland, BIPSS results, grading of the intercavernous sinus drainage pattern, and intraoperative determination of tumor location. A chi-square test was performed to evaluate the correlates with the actual tumor lateralization during transsphenoidal surgery in both symmetric and asymmetric intercavernous sinus drainage patterns. In the asymmetric drainage pattern, a chi-square goodness-of-fit test was conducted for two classified variables: whether the mean nondominant side/peripheral ACTH ratio was greater than 1, and whether the tumor was located on the nondominant side. The mean nondominant side/peripheral ACTH ratio was defined as $\alpha$.

Results

BIPSS results showed that the right side of the intercavernous sinus drainage pattern was much more likely to be the dominant side [21 cases (42.0%)] than the left side [11 cases (22.0%)]. In symmetric drainage patterns, BIPSS prediction of tumor lateralization was largely related to intraoperative tumor location ($p < 0.001$). In asymmetric drainage patterns, tumor lateralization was related to $\alpha$ ($p = 0.034$). The tumor was located on the nondominant side when $\alpha$ was greater than 1 and on the dominant side when $\alpha$ was less than 1.

Conclusion

The intercavernous sinus drainage pattern influences the accuracy of BIPSS for prediction of tumor location in Cushing's disease. The combination of intercavernous sinus drainage pattern and the comparison of nondominant IPSS with the peripheral ACTH gradient can be used for accurate prediction of tumor location CD.
1 Introduction

Pituitary microadenomas that secreted adrenocorticotropic hormone (ACTH), also known as Cushing's disease (CD), are the most common cause of Cushing's syndrome and can lead to a range of severe symptoms due to elevated cortisol levels in the blood\[^1\]. Inferior petrosal sinus sampling (IPSS) tests are used to distinguish Cushing's disease from ectopic ACTH syndrome\[^2\]. CD is diagnosed when ACTH levels in the inferior petrosal sinus (IPS) exceed those in the peripheral blood sample\[^3\].

After desmopressin stimulation, bilateral inferior petrosal sinus sampling (BIPSS) has been reported to have a 96% susceptibility and a 100% specificity for detecting CD\^[4, 5, 6]\^, and it is safe and reliable\[^7\]. However, its ability to predict tumor lateralization is limited, and it has been suggested that this may be related to BIPSS operator experience, excessive differences in bilateral catheter entry position during blood sampling, and parasellar venous variation\[^8\]. Therefore, relying on IPSS results to select the side for resection in MRI-negative microadenomas is very risky. In our experience, after excluding factors such as asymmetric operation and catheter entry location, we have found that cavernous sinus drainage to the contralateral side is very common, especially in the left cavernous sinus. Thus, we speculate that IPSS lateralization is influenced by the intercavernous sinus drainage pattern, which in turn affects the reliability of IPSS for localization of CD.

In the present research, we analyzed 50 patients' data meeting the inclusion criteria retrospectively, analyzed the imaging and laboratory indicators of patients during BIPSS, and graded their intercavernous sinus drainage patterns. These results were compared to the actual tumor location confirmed intraoperatively during transsphenoidal surgery to assess the effect of the intercavernous sinus drainage pattern on the accuracy of BIPSS results in predicting tumor location.

2 Materials And Methods

2.1 Clinical data

During August 2018 and April 2022, we collected and analyzed clinical data of CD that experienced BIPSS at Zhengzhou University's First Affiliated Hospital, Department of Neurosurgery. The inclusion criteria were: (1) diagnosis of CD confirmed by examinations prior to transsphenoidal surgery (preoperative early morning blood cortisol, low-dose dexamethasone suppression test, high-dose dexamethasone suppression test) and postoperative pathology \[^1\]; (2) administration of BIPSS to support the diagnosis of CD; (3) and no history of adjuvant therapy prior to surgery. The exclusion criteria were: (1) failure of BIPSS; (2) large discrepancy in bilateral catheter entry positions into the inferior petrosal sinus (catheter position corresponding to the connection between the horizontal and vertical parts of the inferior petrosal sinus); (3) history of previous intra- and parasellar surgery and presence of other sellar lesions. All patients were evaluated by a team of specialists including interventional neurologists, endocrinologists, and neurosurgeons. We followed the Declaration of Helsinki and obtained approval from the Zhengzhou
University First Affiliated Hospital Institutional Review Board (IRB no.: 2019-KY-176). Clinical data are detailed in Table 1.

Table 1
The clinical data of patients with Cushing’s disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>33 (66.0%)</td>
</tr>
<tr>
<td>Male</td>
<td>17 (34.0%)</td>
</tr>
<tr>
<td>Age</td>
<td>42.5 (17–70)</td>
</tr>
<tr>
<td>IPSS lateralization</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>29 (58.0%)</td>
</tr>
<tr>
<td>Symmetric</td>
<td>2 (4.0%)</td>
</tr>
<tr>
<td>Left</td>
<td>19 (38.0%)</td>
</tr>
<tr>
<td>Venous drainage pattern</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>21 (42.0%)</td>
</tr>
<tr>
<td>Symmetric</td>
<td>18 (36.0%)</td>
</tr>
<tr>
<td>Left</td>
<td>11 (22.0%)</td>
</tr>
<tr>
<td>Transphenoidal surgery lateralization</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>27 (54.0%)</td>
</tr>
<tr>
<td>Symmetric</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Left</td>
<td>22 (44.0%)</td>
</tr>
<tr>
<td>ACTH mean value (ug/l)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>220.8 (51.1, 540.9)</td>
</tr>
<tr>
<td>Left</td>
<td>100.8 (77.5, 588.7)</td>
</tr>
<tr>
<td>Peripheral mean</td>
<td>58.4 (36.4, 85.2)</td>
</tr>
</tbody>
</table>

2.2 BIPSS procedure

BIPSS was performed as before reported[^9]. Briefly, the patients with CD were on a digital subtraction angiography operating table in the supine position with cardiac monitoring, and the left and right groin were routinely disinfected and draped. After local anesthesia, the bilateral femoral veins were punctured
using a modified Seldinger method. Then, after successful placement of the 5F and 7F 11 cm venous sheaths via guidewires, 10 ml of heparin saline was flushed laterally and two 5F vertebral catheters were guided through the superior vena cava into the bilateral internal jugular veins (IJV), respectively, with hydrophilic guidewires. Afterwards, two 0.01800 microcatheters were introduced into the bilateral IPS via 0.01400 microguidewires. Observation of intercavernous venous drainage pattern by superselective contrast injection into bilateral IPSs. Then 10 µg DDAVP was injected intravenously and samples were collected from both the right and left IPSs and the periphery of the 7F venous sheath at -3, 0, 3, 10 and 15 minutes. The collected samples were refrigerated and immediately sent to the laboratory for testing of serum ACTH and prolactin levels.

2.3 Grading of intercavernous sinus drainage pattern

Intercavernous sinus drainage patterns have previously been identified through superselective venography\[^9,10\]; however, its ability to predict tumor lateralization is limited\[^8\]. In the present study, the intercavernous sinus drainage pattern was further refined and classified into four grades based on whether the ipsilateral and contralateral cavernous sinuses were filled with contrast medium. Contrast medium filling of the ipsilateral cavernous sinus after injection of superselective contrast only was defined as intercavernous sinus drainage pattern grade I (complete ipsilateral drainage). Contrast medium filling of the ipsilateral cavernous sinus that crossed the midline through an intercavernous coronal vein after injection but does not indicate the contralateral cavernous sinus or inferior petrosal sinus was defined as grade II (mild contralateral drainage). Contrast medium filling of the ipsilateral cavernous sinus that crossed the midline through an intercavernous coronal vein after injection but does not indicate the contralateral cavernous sinus or inferior petrosal sinus unclearly was defined as grade III (moderate contralateral drainage). Contrast medium filling of the ipsilateral cavernous sinus that crossed the midline through an intercavernous coronal vein after injection and indicates the contralateral cavernous sinus and inferior petrosal sinus very clearly was defined as grade IV (severe contralateral drainage) (Fig. 1). If the ipsilateral grade was higher than the contralateral grade, the contralateral side was considered the dominant side of drainage. If the ipsilateral grade was lower than the contralateral grade, the ipsilateral side was considered the dominant side of drainage. If the ipsilateral and contralateral grades were the same, the drainage was considered symmetrical (Fig. 1).

2.4 BIPSS for diagnosis of Cushing's disease and prediction of tumor laterality

Left and right IPS samples and peripheral venous blood were collected for ACTH and PRL assays. Diagnostic indicators of CD: IPS to peripheral blood mean ACTH gradient ratio > 2, IPS to peripheral blood mean ACTH gradient ratio > 3 after desmopressin stimulation\[^11\]. A tumor was considered lateralized if the intergradient difference between the two sides was greater than 1.4:1\[^12\], and considered intermediate (left of center or right of center) if the gradients on the two sides were similar and the intergradient difference was less than 1.4:1. The side with the higher mean ACTH level was considered the dominant side and the side with the lower level was considered the nondominant side.
2.5 Tumor lateralization determination during transsphenoidal surgery

Tumor lateralization was determined based on intraoperative observation of the location of the tumor center combined with postoperative pathological findings. The tumor center that deviates from the midline is classified as left or right, and the tumor center that is exactly in line with the midline is defined as centered[9].

2.6 Statistics

SPSS 21.0 software was used for statistical analysis of data. Continuous variables are expressed as mean ± standard deviation or median (interquartile range) and categorical variables are expressed as number of cases (percentage). Groups were compared pairwise using Fisher’s exact test and the chi-square goodness-of-fit test. Differences with p < 0.05 were considered statistically significant.

3 Results

3.1 Clinical characteristics

In the analysis of the clinical data of 67 patients highly suspected of having Cushing’s disease who underwent BIPSS, 17 cases were excluded. This included two cases in which the comparison of central and peripheral indicators of IPSS did not meet the diagnostic criteria, four cases in which stored postoperative imaging data of IPSS were lost, five cases in which one side of the IPS could not be entered for blood sampling to be performed, and six cases in which the difference in the catheter position for blood sampling between the two sides was too large. Finally, 50 patients were included in the final analysis. There were 17 male (34.0%) and 33 female (66.0%) cases ranging in age between 17–70 years with a mean age of 42.5 years. IPSS revealed 29 cases (58.0%) on the right side, 19 cases (38.0%) on the left side, and two cases (4.0%) in the middle. Transsphenoidal surgery revealed 27 cases (54.0%) of tumors on the right side, 22 cases (44.0%) on the left side, and one cases (2.0%) in the center (Table 1).

3.2 Characterization of intercavernous sinus drainage patterns

In terms of intercavernous sinus drainage patterns, there were 21 cases (42.0%) with a dominant right side, 11 cases (22.0%) with a dominant left side, and 18 cases (36.0%) with symmetric drainage (Table 1). The left cavernous sinus drained to the contralateral side (grade II–IV) in 86.0% of cases, with grade II in 10.0%, grade III in 32.0%, and grade IV in 44.0% of cases. The right cavernous sinus drained to the contralateral side (grade II–IV) in 70.0% of cases, with grade II in 18.0%, grade III in 16.0%, and grade IV in 36.0% of cases. The intercavernous venous drainage (VD) pattern on the right side (42%) was much more likely to be dominant than that on the left side (22%); the right side was usually the dominant side (Table 1).

3.3 Correlation between asymmetric drainage patterns and tumor location
In asymmetric drainage patterns, the mean nondominant side/peripheral ACTH ratio was > 1 in 22 cases, and the intraoperative tumor location was on the nondominant side in all 22 cases. The mean nondominant side/peripheral ACTH ratio was < 1 in 10 cases, and the intraoperative tumor location was on the dominant side in all 10 cases. The chi-square goodness-of-fit test was performed for the two categorical variables, namely whether the mean nondominant side/peripheral ACTH ratio was greater than 1 and whether the tumor was located on the nondominant side. The results showed that the intraoperative tumor location was significantly correlated with the mean ratio of the nondominant side and peripheral ACTH (p < 0.05). The tumor was located on the nondominant side when the mean nondominant side/peripheral ACTH ratio was > 1 and on the dominant side when the mean nondominant side/peripheral ACTH ratio was < 1 (Table 2). IPSS results showed that the mean nondominant side/peripheral ACTH was > 1, and the tumor was observed in the nondominant side during surgery (Fig. 2).

<table>
<thead>
<tr>
<th>Name</th>
<th>Actual-frequency</th>
<th>Actual ratio</th>
<th>$\chi^2$</th>
<th>$p$</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>No</td>
<td>10</td>
<td>31.25%</td>
<td>4.500</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>22</td>
<td>68.75%</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>No</td>
<td>10</td>
<td>31.25%</td>
<td>4.500</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>22</td>
<td>68.75%</td>
<td></td>
</tr>
</tbody>
</table>

whether the mean nondominant side/peripheral ACTH ratio was greater than 1 was defined as $A$. whether the tumor was located on the nondominant side was defined as $B$.

### 3.4 Correlation between symmetric drainage patterns and tumor location

In symmetric drainage patterns, IPSS indicated the right side in 12 patients (66.7%), the left side in five patients (27.8%), and intermediate lateralization in patients (5.5%). The lateralization predicted by IPSS was highly consistent with intraoperative tumor location determined during transsphenoidal surgery (17/18, 94.4%), and the chi-square test indicated significant correlation between IPSS-predicted tumor lateralization and intraoperative tumor location (p < 0.05) (Table 3). IPSS results suggested that tumors tended to be on the right side, and tumors were observed to be on the right side during surgery (Fig. 3).
Table 3
Results of the chi-square test in 18 patients with symmetrical drainage patterns

<table>
<thead>
<tr>
<th>Transphenoidal surgery lateralization</th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td>Symmetric</td>
<td></td>
</tr>
<tr>
<td>IPSS</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Right</td>
<td>1</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Symmetric</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

4 Discussion

In the present research, we analyzed the reasons for the inability of BIPSS to accurately predict tumor laterality by assessing the drainage pattern of the intercavernous sinus veins. We found that IPSS prediction of lateralization depended strongly on the intercavernous sinus drainage pattern, and that IPSS lateralization was generally the same as the location determined intraoperatively when the intercavernous sinus drainage pattern was symmetric. When the intercavernous sinus drainage pattern was asymmetric, IPSS combined with comparison of the nondominant and peripheral ACTH can be used to predict the tumor location determined during transsphenoidal surgery.

As CD has a high mortality rate and a number of serious complications, timely diagnosis and optimal treatment are crucial to enhance patient outcomes[1,13,14]. In regards to Cushing's disease, surgery is recommended for the surgical removal of ACTH-secreting pituitary adenomas[15,16]. Magnetic resonance imaging is commonly used to detect these adenomas[17]. Unfortunately, Cushing's disease is largely caused by microadenomas, making surgery a significant challenge for treatment[18,19]. Therefore, a precise preoperative diagnosis of tumor location is key to successfully treating Cushing's disease.

BIPSS is considered the gold standard for differentiating between pituitary and ectopic sources of ACTH hypersecretion, but it cannot be used for diagnosing the location[20,21]. We believe this may be influenced by factors such as the intercavernous sinus drainage pattern and the significant variation in intraoperative catheter placement. In the present research, We evaluated the pattern of intercavernous sinus venous drainage during IPSS by venography at almost identical left and right catheter locations, and tumor lateralization was assessed through IPSS, compared with tumor lateralization results from intraoperative observation, and confirmed by pathological diagnosis. We found that IPSS lateralization could not accurately predict tumor location with respect to intercavernous sinus drainage pattern.

Previous studies have shown that IPSS results are inaccurate for predicting tumor lateralization due to factors such as intracranial venous system flow patterns[22,23]. A retrospective study of 30 patients by Sun et al. found that cavernous sinus sampling results were not associated with intraoperative tumor lateralization findings[24]. Factors such as asymmetric or dysplastic IPS anatomy and excessive
differences in bilateral ductal entry locations have been suggested to influence the incorrect prediction of tumor lateralization\(^{[21, 25]}\). In a 2003 retrospective study, Lefournier et al. assessed the effect of different catheter locations on predicting tumor lateralization. Overall, IPSS accurately predicted adenoma lateralization in 57% of patients. The accuracy was 86% for both catheters localized in the IPS and 50% for both catheters localized in the cavernous sinus. IPSS has been shown to be more accurate if cavernous sinus venous outflows are symmetrical\(^{[25]}\). Wind et al. suggested that false-positive results could also be caused by a mixture of intercavernous veins or the presence of a dominant side of cavernous sinus venous drainage\(^{[4]}\). The present study also confirmed that IPSS results were influenced by intercavernous cavernous sinus drainage after rigorous screening for dysplastic IPS anatomy and asymmetric catheter placement. In recent years, in a retrospective study of CD by Ghorbani et al. found that the dominant side of the parasternal venous drainage was associated with IPSS lateralization. However, IPSS lateralization did not have any significant correlation with intraoperative lateralization. Therefore, they concluded that the outcome of IPSS lateralization depended on the dominant side of parasternal venous drainage and was not related to intraoperative lateralization. Their criteria for determining the dominant side of intercavernous sinus VD were as follows: If the contrast fills the cavernous sinus ipsilaterally and crosses the midline through the intercavernous coronary vein to reveal the contralateral cavernous sinus or subcavernous sinus after superselective contrast injection, the VD pattern is considered contralateral and symmetric or dominant. If the contrast fills the cavernous sinus ipsilaterally only, the injected ipsilateral side is considered to be the dominant side of the paracavernous VD\(^{[9]}\).

We carefully graded previous studies of intercavernous sinus drainage patterns and found that IPSS lateralization in CD is decided by the intercavernous sinus drainage pattern rather than tumor location. When intercavernous sinus drainage is symmetrical, IPSS accurately predicted the actual tumor lateralization. With asymmetric drainage, the nondominant side/peripheral ACTH ratio was also accurate for predicting the actual tumor lateralization. This finding allowed for clear determination of tumor location by IPSS prior to transsphenoidal surgery.

As a diagnostic test, BIPSS is now utilized when biochemical tests and MRI results are inconclusive in suspected CD patients\(^{[26, 27, 28]}\). Thus, our findings can help localize pituitary adenomas in patients in whom microadenomas cannot be identified on MRI, help to guide intraoperative exploration to determine the location of the tumor, reduce damage to normal pituitary tissue, and reduce the incidence of postoperative complications such as hypopituitarism and cerebrospinal fluid leakage. Of course, it is also notable that although obtaining dynamic sequences immediately after contrast injection can improve the sensitivity of pituitary contrast-enhanced MRI slightly\(^{[29, 30]}\), it has not been confirmed that this can improve the success rate of microadenoma detection. We also found that the intercavernous sinus drainage pattern influenced the changes in ACTH gradients in both sides of the IPS. Rarely have previous studies evaluated and discussed the role of intercavernous sinus drainage patterns assessed by bilateral superselective venography and their association with IPSS lateralization findings.
There are some shortcomings in the present study that warrant mention. First, this was a single-center retrospective study with a small number of cases, and a multi-center, large sample, prospective study is needed to validate our results. Second, there is a lack of grading criteria for intercavernous sinus drainage patterns. The present study combines previous grading methods to refine the grading of intercavernous sinus drainage patterns, but its accuracy must be further verified by clinicians.

5 Conclusion

The intercavernous sinus drainage pattern influences the accuracy of BIPSS for prediction of tumor location in Cushing’s disease. The combination of intercavernous sinus drainage pattern and the comparison of nondominant IPSS with the peripheral ACTH gradient can be used for accurate prediction of tumor location in patients with CD.

Declarations

Data Availability Statement

In this article, the authors provide the raw data supporting their conclusions without undue reservation.

Ethics statement

Informed consent was given by the Declaration of Helsinki and under approval from The First Affiliated Hospital of Zhengzhou University (IRB no: 2019-KY-176).

Conflict of Interest

A conflict of interest regarding this manuscript is not declared by the authors.

Author Contributions

HNJ, JJB, and DMY designed the project, analyzed the data, and drafted the manuscript. XYL, XQZ and SQM performed the experiments and downloaded the data. YS downloaded and collated the data.

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References


**Figures**
Figure 1

Grading of intercavernous sinus drainage patterns.

A. Grade I intercavernous sinus drainage pattern. Contrast medium fills the ipsilateral cavernous sinus only after injection with superselective contrast. B. Grade II intercavernous sinus drainage pattern. Contrast medium fills the ipsilateral cavernous sinus and crosses the midline through an intercavernous coronal vein after injection but does not indicate the contralateral cavernous sinus or inferior petrosal
sinus. C. Grade III intercavernous sinus drainage pattern. Contrast medium fills the ipsilateral cavernous sinus and crosses the midline through an intercavernous coronal vein after injection but indicates the contralateral cavernous sinus or inferior petrosal sinus unclearly. D. Grade IV intercavernous sinus drainage pattern. Contrast medium fills the ipsilateral cavernous sinus and crosses the midline through an intercavernous coronal vein after injection and indicates the contralateral cavernous sinus and inferior petrosal sinus very clearly.

Figure 2

Asymmetric drainage pattern.

A–H show determination of actual tumor lateralization in cases of asymmetric intercavernous sinus drainage patterns. Based on the intercavernous sinus drainage pattern grading criteria, A shows grade I on the right side and B shows grade IV on the left side, so the right side is the dominant side. C shows preoperative coronal dynamic contrast-enhanced MRI (no obvious abnormalities in the sellar region). Since the mean IPSS of nondominant (left) side/peripheral ACTH ratio is > 1, the intraoperative tumor is judged to be on the left side. D shows the intraoperative tumor location (left side). E shows grade IV on the right side and F–G show the preoperative coronal dynamic contrast-enhanced MRI (tumor is seen on the right side). Since the mean IPSS of the nondominant (right) side/peripheral ACTH ratio is > 1, the intraoperative tumor is judged to be on the right side. H shows the intraoperative tumor location (right side).
Figure 3

Symmetric drainage pattern.

A–D show determination of actual tumor lateralization in cases of symmetric intercavernous sinus drainage patterns. Based on the intercavernous sinus drainage pattern grading criteria, A shows grade IV on the right side and B shows grade IV on the left side, so the drainage pattern is symmetric drainage. C shows the preoperative coronal dynamic contrast-enhanced MRI (no obvious abnormalities in the sellar region). Based on IPSS results, the intraoperative tumor is judged to be on the right side. D shows the intraoperative tumor location (right side).