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ORIGINAL RESEARCH

Endoscopic Revision Strategies and Outcomes for Recurrent L4/5 Disc Herniation After Percutaneous Endoscopic Transforaminal Discectomy

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Objective: We explore the endoscopic revision and surgical techniques for L4/5 recurrent disc herniation (rLDH) after percutaneous endoscopic transforaminal discectomy (PETD).

Methods: A retrospective study was conducted. From January 2016 to September 2022, 96 patients who underwent percutaneous endoscopic lumbar discectomy for L4/5 rLDH after PETD were enrolled in the study. Based on the revision approach, the patients were divided into PETD group (57 cases) and percutaneous endoscopic interlaminar discectomy (PEID) group (39 cases). Visual Analogue Scale (VAS) for back and leg pain, Oswestry Disability Index (ODI), and modified MacNab standard were recorded to evaluate the clinical outcomes.

Results: No significant differences were found in the demographic data and intraoperative blood loss between the two groups ($P>0.05$), but the time of operation and intraoperative X-ray fluoroscopy exposures in the PEID group were significantly less than that in the PETD group ($P<0.05$). The patients' postoperative clinical indexes gradually improved, and the VAS score, ODI index, and JOA score of the patients in both groups showed significant improvement compared with the preoperative period at the 1-week, 1-month, and 6-month postoperative follow-ups ($P < 0.05$). There was no serious complication observed during the follow-up.

Conclusion: For recurrent LDH after PETD of L4/5 segments, percutaneous endoscopic revision can achieve satisfactory results. Among them, PEID has a shorter operative and fluoroscopy time and allows avoidance of the scar that forms after the initial surgery, so it can be considered preferred when both procedures can remove the disk well. However, for some specific types of herniation, a detailed surgical strategy is required.

Keywords: endoscopic revision, recurrent lumbar disc herniation, percutaneous endoscopic lumbar discectomy

Introduction

In recent years, spinal endoscopic technique has developed rapidly and has become one of the most important procedures in spinal surgery. It makes the patient less traumatized and recovers faster and has been widely used in the treatment of all kinds of spinal degenerative diseases, especially lumbar disc herniation (LDH).[1,2] However, because the normal position of the disc is preserved, the possibility of recurrence exists after LDH. Studies have shown that patients with LDH treated with spinal endoscopic discectomy have a recurrence rate of up to 12.5%.[3,4] As recurrent patients continue to emerge, scholars in various countries have begun to explore the use of spinal endoscopic techniques in revision

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surgery. Junlong Wu et al[5] have demonstrated the efficacy and safety of percutaneous endoscopic techniques in revision surgery through a 36-month follow-up study of 94 patients who underwent percutaneous endoscopic revision.

For the definition of recurrence of lumbar disc herniation (rLDH), there are no clear criteria, but the basic criteria recognized are as follows: 1. A series of preoperative symptoms exist, such as low back and leg pain. 2. A pain-free period has elapsed after PELD. 3. The same segment of the disc herniates again and compresses the nerve root or dura mater and produces symptoms.[4,6–8]

The percutaneous endoscopic lumbar discectomy (PELD) mainly consists of two surgical modalities: percutaneous endoscopic transforaminal discectomy (PETD) and percutaneous endoscopic interlaminar discectomy (PEID). This study mainly focuses on the choice of these two procedures in the treatment of rLDH. There is no consensus on this issue because the original surgical approach may be interfered with by scarring and adhesions and destroyed bony structures, and avoidance of the original approach may result in poor removal of the disk. In the case of some specific herniations, the choice of revision procedure is similar to the strategy for the initial surgery, but the revision procedure is potentially more difficult and the risk of nerve injury is greater, making it even more important to choose the appropriate surgical approach for revision.

As L4/5 has no iliac crest occlusion on either side, this gives PEID enough space to deal with it. Meanwhile, its intervertebral plate gap is usually relatively large, which, together with the application of fully visualized trephine, significantly improves the efficiency of removing the vertebral plate,[9] which allows PEID to deal with its herniated discs as well. Therefore, based on the different types of rLDH, the revision strategy of L4/5 segments has a unique research value. Usually, for patients with normal L4/5 intervertebral foraminal conditions, PETD is more often used for the initial surgery; therefore, in order to control the variables and have a sufficient sample size, this study retrospectively analyzed 96 cases of postoperative recurrence of PEID at L4/5 segments and again used percutaneous endoscopic revision, in order to analyze the strategy of endoscopic revision with different types of recurrence and to evaluate the clinical efficacy.

Patient and Method

General Information

A retrospective study was conducted. From January 2016 to September 2022, a total of 96 patients were treated with PETD for LDH (L4/5) at our institution and underwent endoscopic surgery again for rLDH, including 60 males and 36 females; the mean age of the patients was 58.2 years old (23 ~ 78 years old); and the location of the recurrence was in the same segment (L4/5) for all patients. The patients were divided into PETD group (57 patients) and PEID group (39 patients) according to the revision approach.

Inclusion criteria: (1) The patient had been treated with PETD for LDH in the L4/5. Low back pain and lower extremity symptoms are significantly relieved after the initial surgery, and the pain is relieved for more than 2 weeks after the surgery. (2) MRI of lumbar spine after the initial operation showed that the herniated disc had been completely removed. (3) Low back pain and lower extremity neurologic symptoms reappeared again, and CT and MR findings of the lumbar spine were consistent with clinical symptoms and confirmed recurrent LDH (L4/5). (4) Patients failed to respond to conservative treatment (≥2 months). Exclusion criteria: (1) Patient's symptoms have not resolved after the initial surgery or have been in remission for less than 2 weeks. (2) Patient has undergone other spinal surgery (open surgery, MIS-TLIF, etc.) (3) In addition to rLDH at the L4/5, the patient has LDH at other segments, lumbar spinal stenosis, spinal fractures, lumbar spondylolisthesis, spinal infections, tumors, or other pathologies. (4) Nerve was damaged by the initial surgery and complications occurred after the surgery. (5) Incomplete postoperative follow-up or imaging data.

Revision Strategies and Surgical Techniques

For rLDH at L4/5, we prioritize PEID when both procedures can handle the pressor material well.

For special types of disc herniation, we performed a detailed classification, and the corresponding surgical approaches for each case are shown in Figure 1.

General anesthesia was the preferred method of anesthesia, and local anesthesia was used in 23 cases (8 of PEID and 15 of PETD) because the patients requested or could not tolerate general anesthesia.

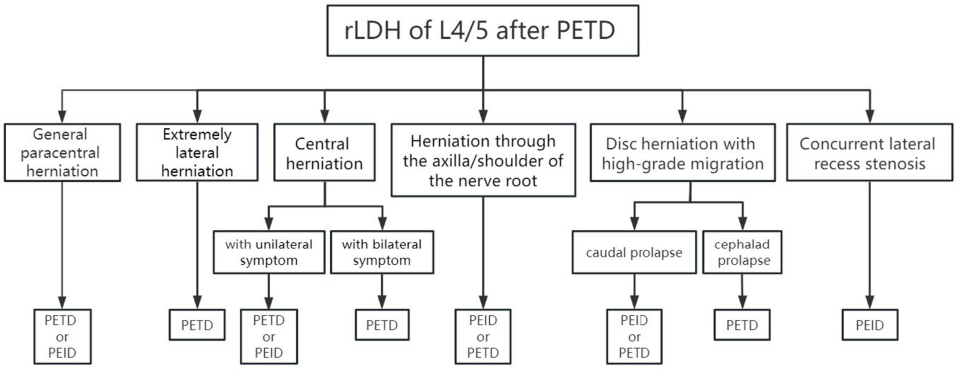

Figure 1 The endoscopic revision approach in patients of special herniations at L4/5.

After anesthesia was completed, the patient was placed in a prone position with the chest and iliac area being padded, and a C-arm machine was used to fluoroscopically position the patient to confirm that the surgical segments were correct, then the skin was routinely disinfected and a sterile cavity towel was laid out.

PETD

Determine the midpoint level of the surgical intervertebral space, and the intersection of this level with the posterior median line is the puncture target point. Using this target point as a reference, the puncture point is approximately 9–11 cm lateral along the horizontal line of the midpoint of the intervertebral space and 2–3 cm lateral to the cephalad as the puncture point, and the direction of puncture is the line between the puncture point and the target point. A puncture needle was used to reach the articular process of L4/5 in the direction of the puncture, and the skin was incised for approximately 8 mm centered on the puncture point (the direction of the incision was perpendicular to the long axis of the body). Then, the dilatation guide rod was placed in a stepwise fashion, and the muscle on the surface of the articular process was bluntly stripped. Finally, the U trocar is placed and the angle and position of the trocar is determined to be satisfactory by fluoroscopy with the C-arm machine. A T-cannula was placed, and the endoscope and RF electrodes were attached. After cleaning the soft tissues and exposing the bony anatomical structures, the residual articular process structures were again identified and confirmed. Then, a visual circular saw is placed to enlarge and shape the intervertebral foramen starting from the tip of the superior articular process (If bony structures cannot be identified, the number of fluoroscopies can be increased to ensure accurate localization). Then, expose the nerve root. This procedure tends to cause a lot of bleeding due to the massive destruction of scar tissue, which needs to be promptly stopped by using radiofrequency electrocautery to keep the microscopic field of view clear. Subsequently, the nerve roots and spinal cord were carefully isolated to reveal the herniated disc. The first surgery often creates adhesions here, and problems such as difficulty in distinguishing tissue structures can be encountered, so the process of separating the nerve from the disc must be done carefully to avoid damaging the nerve. Finally, the fibrous ring was incised and the protruding nucleus pulposus was removed, confirming that the nerve root compression was relieved and ending the procedure.

PEID

For revision after PETD, the procedure of PEID is almost identical to that used for non-revision. We used the bony structure at the outer upper edge of the L4/5 intervertebral plate gap (the outer lower edge of vertebral plate of L4) as the puncture point and marked it on the skin. The incision is approximately 8 mm (the direction of the incision is perpendicular to the long axis of the body). The guide rod is then placed vertically on the medial margin of the inferior articular process and the dilatation guide rod is placed in steps, and finally the U-shaped trocar is placed, and fluoroscopy with the C-arm machine determines that the trocar is satisfactorily positioned. A T-cannula was placed and the endoscope and RF electrodes were attached. The muscle, fat, and other tissues were cleaned up endoscopically, and the symbols of the bony structures were further identified, and the vertebral plate or articular process was appropriately resected to reveal the ligamentum flavum. The ligamentum flavum was removed layer by layer using the endoscopic vertebral plate biting

forceps to expose the dural sac and nerve roots. Rotate the U-T trocar and push away the nerve root and spinal cord to reveal the protruding disc. After grasping and removing the nucleus pulposus and adequately clearing the L4/5 intervertebral space, the nerve root was re-explored to determine nerve root laxity and satisfactory expansion of the dural sac.

Postoperative Management

All patients rested in bed after surgery with cardiac monitoring and oxygen via nasal cannula. Methylprednisolone and mannitol were routinely applied to anti-inflammatory and anti-swelling treatments for 1–2 days after the operation, while the patient was observed for the sensation and activity of both lower limbs. On the second postoperative day, patients were allowed to wear protective gear to move around on the ground, while observing the incision for redness, swelling, and oozing. All patients had lumbar X-rays, CTs, and MRIs reviewed before discharge and wore a brace for approximately 8 weeks after surgery. Patients are encouraged to strengthen their functional exercises after surgery to speed up the recovery of the low back muscles, and they should also avoid heavy labor and prolonged sitting and standing.

Postoperative Follow-Up and Outcome Evaluation Indicators

Postoperative follow-up and outcome evaluation indexes mainly include perioperative indexes, clinical outcome evaluation indexes, and imaging assessment.

Perioperative indicators include length of surgery, intraoperative bleeding, intraoperative fluoroscopy time, and perioperative complications. The amount of intraoperative bleeding was roughly estimated by collecting the total amount of effluent flushed out throughout the procedure (also includes fluid absorbed by intraoperative gauze, except urine) and subtracting the total amount of incoming fluid used intraoperatively (except for fluids imported into the body).

Clinical efficacy evaluation indexes mainly include low back pain VAS score, leg pain VAS score, ODI index, and JOA score. The patients' postoperative functional recovery was evaluated by the above indexes at preoperative and postoperative 1 week, 1 month, 6 months, and 12 months, respectively, and the excellent rate of the patients at 1 year postoperatively was also evaluated by using the modified MacNab scoring scale. Patients underwent lumbar spine X-ray, three-dimensional CT and MRI scans during the postoperative follow-up cycle to evaluate imaging changes.

Statistical Methods

SPSS 24.0 (IBM Inc., USA) statistical software was used to analyze the data. The normality test was performed on the measurement data, and the measurement data satisfying normal distribution were expressed as mean ± standard deviation (±S), and the *t*–test was used to test the differences between the two groups; the X^2 test was used to compare the counting data of the two groups; and the paired *t*-test was used to test the differences in the VAS scores, ODI, and JOA scores of the two groups before and after the treatment. $P < 0.05$ (bilateral) was considered a statistically significant difference.

Result

General clinical data

There were no statistically significant differences between the two groups in terms of age, gender, BMI, height, and weight (P>0.05), as shown in Table 1.

There was no statistically significant difference in intraoperative blood loss between the two groups (P>0.05), but patients in the PETD group had significantly more operative time (81.3±7.4 vs 60.2±7.9, P=0.026) and fluoroscopy time (10.6±3.8 vs 4.6±2.6, P=0.001) than patients in the PEID group, as shown in Table 2.

Clinical outcomes

There was no statistically significant difference between the two groups in terms of low back pain VAS scores, leg pain VAS scores, ODI, and JOA scores at each preoperative and postoperative follow-up time point (P>0.05). The symptoms of the patients gradually improved after the operation, and all the clinical efficacy evaluation indexes of the patients in the two groups were significantly improved compared with the preoperative period at the follow-up visits of 1 week, 1

Table 1 Demographic Data of Patients

	PETD Group (n=57)	PEID Group (n=39)	P value
Sex (M/F)	36/21	24/15	0.872
Age (year)	59.3±14.2	56.7±12.9	0.631
BMI (kg/m^2)	26.7±5.2	27.6±3.3	0.883
Height (cm)	168.5±7.5	167.3±4.7	0.733
Weight (kg)	74.8±12.6	76.1±13.5	0.683

Abbreviations: PETD, percutaneous endoscopic transforaminal discectomy; PEID, percutaneous endoscopic interlaminar discectomy.

Table 2 Perioperative Indicators

	PETD Group (n=57)	PEID Group (n=39)	P value
Blood loss (mL)	17.2±7.7	14.7±8.4	0.257
Operative time (min)	81.3±7.4	60.2±7.9	0.026
Intraoperative fluoroscopy time (sec)	10.6±3.8	4.6±2.6	0.001

Abbreviations: PETD, percutaneous endoscopic transforaminal discectomy; PEID, percutaneous endoscopic interlaminar discectomy.

month, and 6 months after the operation, and the differences were statistically significant ($P < 0.05$). According to the modified MacNab grading scale, the PETD group had an excellent rate of 93.3% and the PEID group had an excellent rate of 90.9%. Comparison of the excellent rate between the two groups, the difference was not statistically significant ($P>0.05$). (Table 3, and Figure 2.)

Postoperative complication

No intraoperative surgery-related complications such as dural tears and nerve and vascular injuries occurred in both groups. No spinal cord-like hypertension or loss of muscle strength was observed in patients after surgery, and the incisions healed well. No recurrence cases were observed during the follow-up period, and no related complications were observed.

Discussion

From January 2016 to September 2022, a total of approximately 3075 L4/5 segment PETD procedures were performed at our institution, of which 96 patients experienced postoperative recurrence, with an approximate recurrence rate of 3.12%. Usually, the segments of L4/5 are free of the iliac crest on either side, giving the PELD a great deal of room to maneuver. While it generally has a large intervertebral plate gap, together with that application of fully visualized trephine, it has significantly improved the efficiency of percutaneous endoscopic management of the vertebral plate,[9] which allows PEID to deal with its disc herniation as well. The results of the above comparison of surgery-related indexes between the two groups of patients showed that when reoperation was performed for recurrence after PETD, the operation time and fluoroscopy time of PEID were significantly shorter than that of PETD. In addition to the surgical technique itself, scarring and adhesions have a significant impact on reoperation after PETD.[7] Therefore, when both surgeries are able to remove the herniated disc, PEID is preferred to avoid scarring, reduce the risk of nerve damage, and avoid intraoperative disorientation due to the lack of typical bony markings, and the procedure and difficulty are similar to the initial surgery. Earlier studies by Ruetten et al have confirmed this opinion.[10]

However, there are some specific types of herniations that require us to carefully evaluate preoperatively with imaging information in order to achieve a good removal of the herniated disc. Revision with percutaneous endoscopy in these cases is somewhat similar to the strategy used for the initial procedure, but the revision procedure is more

Table 3 Preoperative, Follow-Up VAS, ODI, JOA Scores and Modified MacNab of Patients

	Time	PETD Group (n=57)	PEID Group (n=39)	P value		Time	PETD Group (n=57)	PEID Group (n=39)	P value
VAS scores (back pain)	Preoperative	6.2±1.7	5.6±1.2	0.125	ODI scores	Preoperative	53.9±8.7	53.3±8.1	0.869
	Post-1 week	4.1±1.3[a]	3.8±0.7 [a]	0.295		Post-1 week	17.3±7.1 [a]	15.7±6.6 [a]	0.277
	Post-1 month	2.3±1.1[a]	2.0±0.8 [a]	0.091		Post-1 month	11.9±6.1 [a]	11.5±5.3 [a]	0.703
	Post-6 months	1.5±0.8 [a]	1.1±0.6 [a]	0.201		Post-6 months	7.0±3.9 [a]	6.3±4.6 [a]	0.431
	Post-12 months	1.2±0.7 [a]	0.9±0.5 [a]	0.322		Post-12 months	6.5±3.7 [a]	6.0±5.1 [a]	0.665
VAS scores (leg pain)	Preoperative	6.9±1.5	6.1±1.3	0.134	JOA scores	Preoperative	11.7±3.4	11.6±4.3	0.875
	Post-1 week	4.1±1.6 [a]	4.0±1.7 [a]	0.758		Post-1 week	17.6±3.9 [a]	18.1±3.1 [a]	0.508
	Post-1 month	2.2±0.8 [a]	2.0±1.0 [a]	0.672		Post-1 month	21.7±4.2 [a]	21.9±5.1 [a]	0.759
	Post-6 months	1.0±0.7 [a]	1.2±0.9 [a]	0.643		Post-6 months	25.6±2.8 [a]	24.9±3.7 [a]	0.437
	Post-12 months	0.9±0.5 [a]	1.0±0.7 [a]	0.783		Post-12 months	26.4±2.7 [a]	26.0±3.5 [a]	0.752
					Excellent and good rate		94.10%	92.70%	0.713

Notes: [a]Compared with preoperative value, the difference is statistically significant ($p < 0.05$). PETD: percutaneous endoscopic transforaminal discectomy; PEID: percutaneous endoscopic interlaminar discectomy.

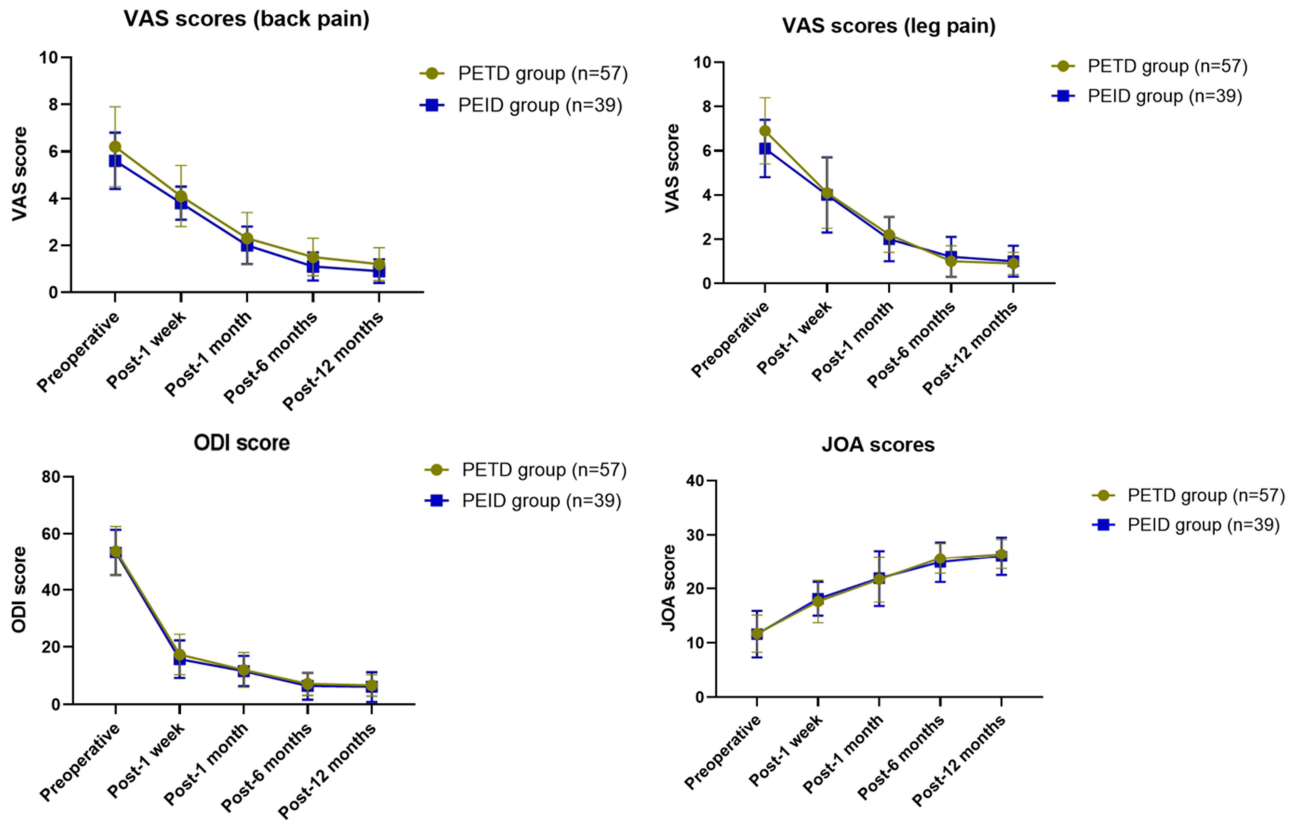

Figure 2 Postoperative follow-up.

difficult and the risk of potential nerve injury is greater, making it important to choose the appropriate procedure as well as to master the surgical technique at the time of revision.

Extremely Lateral Herniation Central Herniation or Lateral Recess Stenosis

In terms of the position of the herniated disc in the horizontal plane in relation to the spinal canal, special attention needs to be paid to extremely lateral and central herniations and lateral recess stenosis. As for extremely lateral herniation: The surgeon must deal with it by PETD, the skin incision is shorter from the posterior dorsal midline and usually does not require shaping of the articular process, but care must be taken to avoid injury to the nerve roots and blood vessels. For central herniation with bilateral leg symptoms: It is recommended to perform PETD with small-diameter endoscopes such as TESSYS and Isee and enter through the intervertebral foramen on the more symptomatic side and decompress bilaterally through the ventral aspect of the spinal cord (Figure 3). The surgeon needs to increase the distance from the skin incision to the midline to approximately 10–12 cm; approach as parallel to the intervertebral space as possible; remove the bone layer by layer on the dorsal side of the intervertebral foramina as needed (ISEE's visualization circular saw allows for this procedure to be done efficiently and safely); decompression is required to the ventral side of the contralateral nerve root; and the posterior longitudinal ligament could be resected if necessary, but care must be taken to avoid injury to the contralateral nerve root and dural sac. For central herniation with unilateral leg symptoms: Chao Shi et al have demonstrated that PEID can treat this type of intervertebral disc well,[11] and can avoid scars, thus effectively reducing the difficulty and risk of surgery. For herniation with lateral recess stenosis: In Ahn's study,[12] PETD was useful for recurrent disc herniation in selected cases, but was successful in only 33.3% of patients with concomitant lateral recess stenosis. While in FEID, the inner part of the articular process and the lower edge of the lamina can provide a relatively normal window to expose the nerve root and avoid being interfered with by scarring,[7] so that the herniation can be excised well after partial laminectomy is performed as needed (Figure.4).

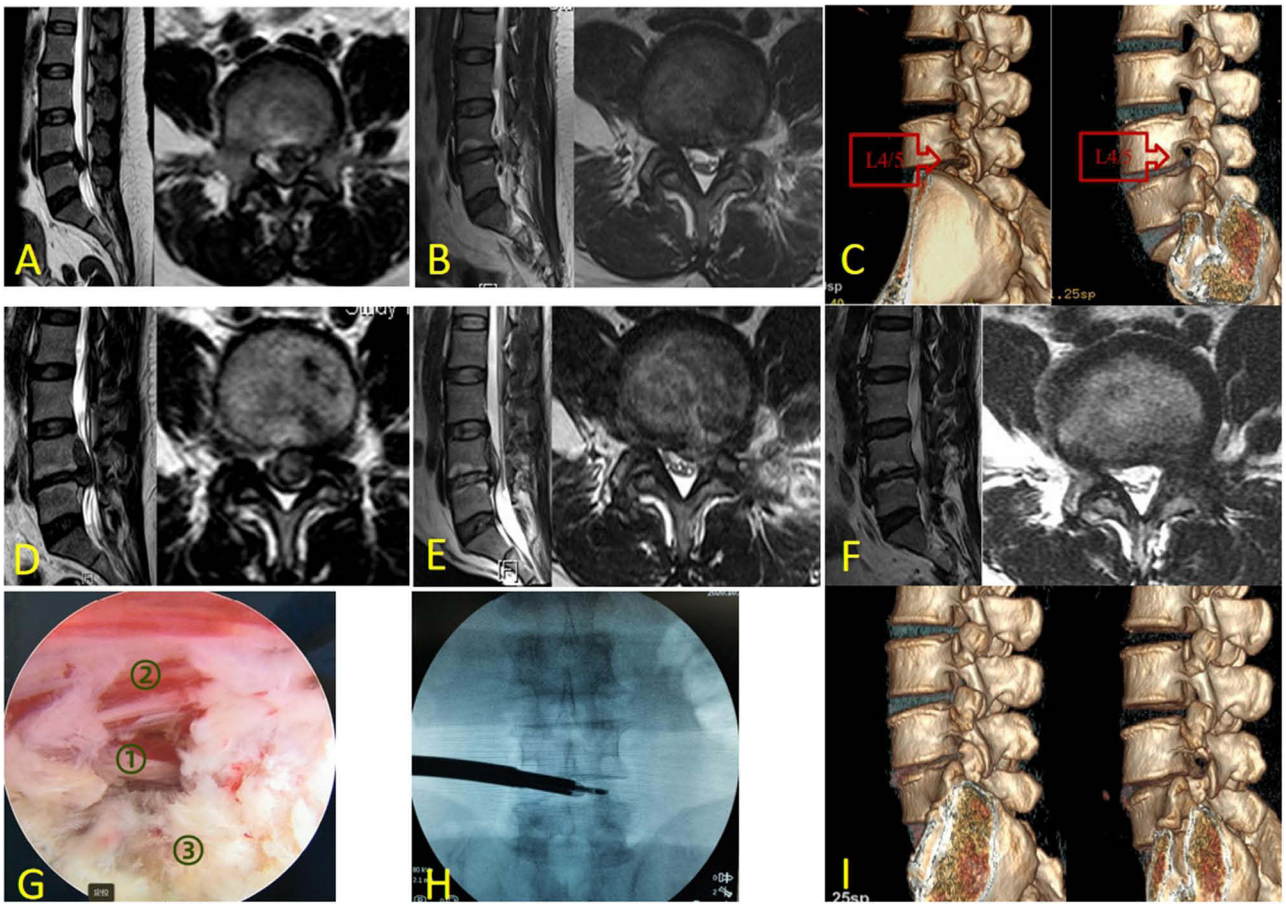

Figure 3 A 42-year-old female presented for the first time with "low back pain with pain in the left lower extremity", and the lumbar MR showed a disc herniation at L45 **(A)**. PETD was taken and the subsequent MR showed effective removal of the herniated disc **(B)** and **(C)** shows the removal of the articular process in the first operation. One year later, the patient presented with "low back pain with bilateral lower extremity numbness", and the lumbar MR showed a large central herniation at L4/5 with cephalad prolapse **(D)**. PETD was taken again, and **(G)**showed that the resection of the herniated disc reached all the way to the contralateral nerve root during the operation (① the contralateral nerve root, ② the ventral side of the spinal cord, ③ the residual disc). (**H**)is an intraoperative fluoroscopic image of the working channel, which shows that the grasping forcep has reached the position of the contralateral nerve root. **(E** and **F)** are lumbar MR at postoperative day 1 and 6 months, respectively. (**I)** shows that revision surgery removes the articular process to a greater extent, but still preserves part of the joint.

Large Protrusions of Prolapse

In terms of the position of the herniated disc in the sagittal position in relation to the spinal canal, the large herniation that prolapses cephalad or caudad needs to be treated differently. Toward the caudal side prolapse accompanied by lateral recess stenosis we have discussed above (Figure.4). For caudolateral prolapse with narrow base: With PETD, the main body of the herniation cannot be detected to determine if there is any residue. PEID with larger diameter endoscopes such as the Delta can easily and completely remove the herniation by thinning the lamina with an endoscopic grinding drill, followed by efficiently removing parts of the lamina with a vertebral plate biting forceps to fully reveal the dorsal aspect of the herniation. Prolapse toward the caudal side accompanied by wide-base protrusion is preferred to PEID to avoid the original approach if there are no other special circumstances. Only when the degree of prolapse is large enough to pick up into the inferior border of the vertebral body, the operator will need to perform PETD with a small-diameter endoscope (eg, TESSYS), increasing the head tilt of the endoscope and shaping the base of the articular process, while preparing to perform PEID of the inferior intervertebral space. For herniations that subluxate to the side of the head, we have proven through practice that PETD can remove the herniation well. The operator needs to perform PETD with a small-diameter endoscope (eg, TESSYS and Isee) with a small head tilt angle, shaped at the tip of the superior articular process and operated on a superior portion of the intervertebral foramen (Figure 3).

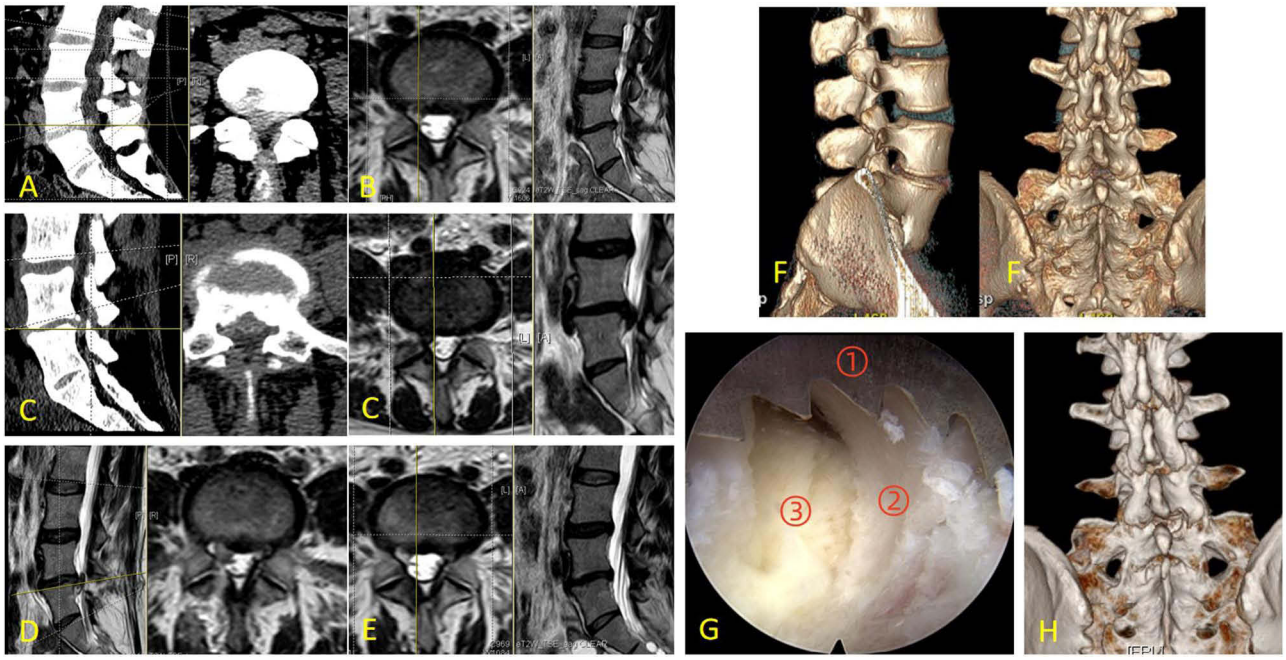

Figure 4 A 37-year-old woman's first visit to the doctor was for "low back pain with numbness and pain in the right lower limb", and the lumbar CT showed a disc herniation in the L4/5 **(A)**, which was treated with PETD, and the follow-up MR showed that the herniated disc had been removed **(B)**. The patient had a recurrence after 3 years, complaining of low back pain with bilateral lower limbs pain, and the lumbar CT and MR showed a disc herniation at L4/5 with lateral socket stenosis **(C)**. PEID was used for revision, and **(G)** shows that part of the intraoperative lamina was resected with a visualized circular saw ((① the serration of circular saw, ② the vertebral plate, ③ the ligamentum flavum). **(D** and **E)** are postoperative MR on the first day and at 6 months, respectively, showing that the surgery was successful in removing the herniated disc. And **(F–H)** show the vertebral plates before and after revision.

Herniations Located in the Axillary and Shoulder Regions of the Nerve Root

In terms of the location of the herniated disc in relation to the nerve root, special attention needs to be paid to herniations located in the axillary and shoulder regions of the nerve root. For this type of herniation, PEID works well to remove it and effectively avoid scarring from the original surgical path. Chao Shi et al utilized PEID to select an axillary approach for axillary-type herniation and a shoulder approach for shoulder-type herniation, removing part of the lamina as needed and obtaining good results.[11]

Conclusion

For rLDH at L4/5 after PETD, percutaneous endoscopic revision can achieve satisfactory results. Choosing the right procedure based on the type of disc herniation can effectively reduce the difficulty and risk of surgery. The PEID revision has less operative time and fluoroscopy time than PETD and allows avoidance of the scar that forms after the initial procedure, so PEID may be considered preferred when both procedures can remove the herniated disc well. In addition to this, the herniation of some special cases requires a carefully designed surgical program to ensure the success of the procedure. However, for some special disc herniations, the surgical strategy needs to be designed carefully to ensure the success of the surgery. In addition, the surgeon should develop a rational plan for endoscopic revision based on other special individual factors, combined with his or her own proficiency in the procedure.

Ethics Approval and Consent to Participate

All procedures were approved by the ethics committee of the Affiliated Hospital of Qingdao University (approval number: QYFY WZLL 28214). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was received from all patients and/or their legal guardian(s) before the operation.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors of this manuscript declare no relationships and conflicts of interest with any companies, whose products or services may be related to the subject matter of the article.

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