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Thoracic discectomy by posterior pedicle-sparing, transfacet approach with real-time intraoperative ultrasonography

Clinical article

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Object. Symptomatic thoracic disc herniations (TDHs) are relatively uncommon, and the technical challenges of resecting the offending disc are formidable due to the location of spinal cord that has relatively poor perfusion characteristics within a narrow canal. The majority of disc herniations are long-standing calcified discs that can be adherent to the ventral dura. Real-time intraoperative ultrasound (RIOUS) visualization of the spinal cord during the retraction and resection of the disc greatly enhances the safety and efficacy of disc resection. The authors have adopted the posterior laminectomy with pedicle-sparing transfacet approach with real-time ultrasound guidance in their practice, and they present the clinical outcome in their patients to illustrate the safety profile of this technique.

Methods. Sixteen consecutive patients undergoing operative management of TDHs were identified from the authors' database. All patients underwent microdiscectomy through a posterior transfacet pedicle-sparing approach under RIOUS. Outcomes and complications were retrospectively assessed in this patient series. Clinical records and pre- and postoperative imaging studies were scrutinized to assess levels and types of disc herniation, blood loss, surgical time, pre- and postoperative Nurick grades, Japanese Orthopaedic Association (JOA) scores, and complications.

Results. All patients had single-level symptomatic TDHs. The patients presented with symptoms including thoracic myelopathy, axial back pain, urinary symptoms, and thoracic radiculopathy. Thoracic disc herniations involved levels T2–3 to T12–L1. Discs were classified as central or paracentral, and as calcified or noncalcified. All discs were successfully removed with no incidence of neural injury or CSF leak. The mean estimated blood loss was 523 ml, and the mean surgical time was 159 minutes. Nurick grades improved on average from 3.3 to 1.6. The mean JOA scores improved from 5.7 to 8.3 out of 11. The mean Hirabayashi recovery rate of the JOA score was 57%. All patients reported improvement in symptoms compared with preoperative status except for 1 patient with an American Spinal Injury Association Grade A spinal cord injury prior to surgery. The average duration of follow-up was 10.5 months. One patient developed postoperative wound infection that required additional operative debridement and revision of hardware.

Conclusions. Thoracic discectomy via a posterior pedicle-sparing transfacet approach is an adequate method of managing herniations at any thoracic level. The safety of the operation is significantly enhanced by the use of real-time intraoperative ultrasonography.
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Key Words • **thoracic disc herniation** • **real-time intraoperative ultrasound** • **thoracic instrumented fusion** • **posterior transfacet pedicle-sparing approach**

Symptomatic thoracic disc herniation (TDH) is a relatively uncommon entity responsible for less than 0.15%–4% of all discectomies.[3,5,10,20,22,25,28] Despite this, patients can be severely debilitated due to radicular pain and/or myelopathy, and in rare circumstances they present with paraplegia. The technical challenges of resecting the offending disc is formidable due to the location of spinal cord that has relatively poor perfusion characteristics within a narrow canal,[25] and the majority of disc herniations are long-standing calcified discs that can be adherent to the ventral dura.

Historically, a posterior approach with laminectomy alone or with discectomy resulted in poor clinical outcome,[1,10,13,15,19] likely due to iatrogenic injury to the spinal cord during retraction. Subsequent advances in surgical

Abbreviations used in this paper: ASIA = American Spinal Injury Association; JOA = Japanese Orthopaedic Association; RIOUS = real-time intraoperative ultrasound; TDH = thoracic disc herniation.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

techniques have yielded a myriad of approaches from posterolateral to anterior with relatively improved neurological results. The main surgical corridors to the thoracic disc can be summarized as posterior (laminectomy, transpedicular, or transfacet pedicle-sparing), posterolateral (costotransversectomy), lateral (lateral thoracotomy, lateral extracavitary or mini-extracavitary), anterolateral (transthoracic or thoracoscopic approach), or anterior (transsternal procedure).[3,10,19,25] The major disadvantages of the posterolateral, lateral, and anterior approaches are that they require significant dissection of the chest wall, including rib resections or splitting of the sternum and/or entry into the pleural cavity.[6] Transthoracic approaches require significant retraction of the lungs, require postoperative pleural drains, and can result in significant postoperative wound pain.[19,25,29] Although minimally invasive approaches such as thoracoscopic procedures may decrease the exposure-related complications, visualization of the operative field can be difficult and significantly increases the level of difficulty for the adequate decompression[21,23] due to the long trajectory of surgical instruments and stereoscopic vision. Moreover, these approaches are infrequently used in the usual practice of spinal surgeons and require a steep learning curve.[8,21,23] Conversely, the posterior approach is a very common approach used by spinal surgeons and requires no rib resection, chest wall dissection, or entry into the thoracic cavity. Moreover, the same surgical approach can be used for all levels of the spine.

We submit that the poor results with the posterior approach in the historical literature are primarily due to the iatrogenic injury to the spinal cord as one cannot infer the degree of cord deformation by looking at the dura intraoperatively. Moreover, progressive kyphosis after violation of the posterior elements with inadequate decompression can cause further injury to the spinal cord.[17] We believe that real-time intraoperative ultrasound (RIOUS) visualization of the spinal cord during the retraction and resection of the disc greatly enhances the safety and efficacy of disc resection. One can be certain of the degree of spinal cord (not just the dura) deformation during any retraction. Moreover, the surgeon can be confident on the extent of decompression using the RIOUS at the conclusion of the operation. We have adopted the posterior laminectomy with pedicle-sparing transfacet approach with real-time ultrasound guidance in our practice and present the clinical outcome in our patients to illustrate the safety profile of this technique.

Methods

Patient Population

Sixteen consecutive patients (between January 2007 and July 2012) who had TDHs with symptoms and neural compression on MRI were included. All patients underwent a posterior transfacet, pedicle-sparing corridor approach for thoracic discectomy. We used RIOUS in every case and supplemented the procedure with instrumented fusion of the index spinal level using 3D stereotactic navigation (Stryker Spine) to cannulate the pedicles. All patients had postoperative CT scans to assess the instrumentation and extent of decompression. Subsequent clinical follow-up comprised of clinical examination, documentation of complaints, and erect radiographs to assess alignment, instrumentation, and issues with fusion.

Surgical Technique

Patients were placed under general anesthesia with endotracheal intubation and were placed prone on a Jackson table (Mizuho OSI). The skin incision was marked with lateral C-arm fluoroscopy (Ziehm Vision FD vario 3D, Ziehm Imaging). The posterior elements were exposed in a standard subperiosteal fashion as far as the lateral aspect of the transverse process at the index level. Three-dimensional navigation registration was then performed, and the pedicle screws above and below the index disc were placed. Depending on the location of the disc (central or paracentral) and the extent of calcification, we supplemented the laminectomy with unilateral or bilateral facetectomies (Fig. 1A). The nerve root and lateral annulus were exposed with magnification under a microscope. Ultrasonography was then performed, using a hockey stick ultrasound transducer probe (Sector Scan Co.) with a 10- to 13.3-MHz B Mode setting (Aloka Co.) (Fig. 1B and C) to assess the morphology of the disc and the degree of compression of dura and spinal cord via the laminectomy corridor. The nature and degree of compression were clearly identifiable using RIOUS in every case and corresponded to the preoperative imaging (Fig. 2).

The posterolateral annulus was incised transforaminally, and the disc was resected to create a cavitation anterior to the central region where the herniated disc compresses the spinal cord. Once adequate space was created, an angled dissector or curette was used to dissect and push the herniated disc into the cavitation under RIOUS guidance (Fig. 1B). Real-time intraoperative ultrasound enabled the surgeon to visualize the spinal cord and the location of the dissector without direct line of

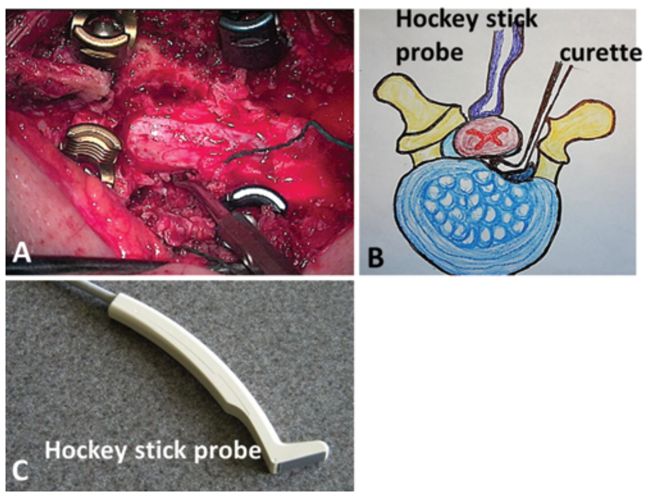

Fig. 1. A: Intraoperative view of the surgical field. Screw placement is followed by microdiscectomy under microscopic magnification. **B:** Scheme of the RIOUS-guided microdiscectomy. We place fine surgical instruments into the interface between spinal cord and disc herniation under direct visualization by putting the ultrasound hockey stick probe on the spinal cord gently. **C:** Photograph of the hockey stick probe.

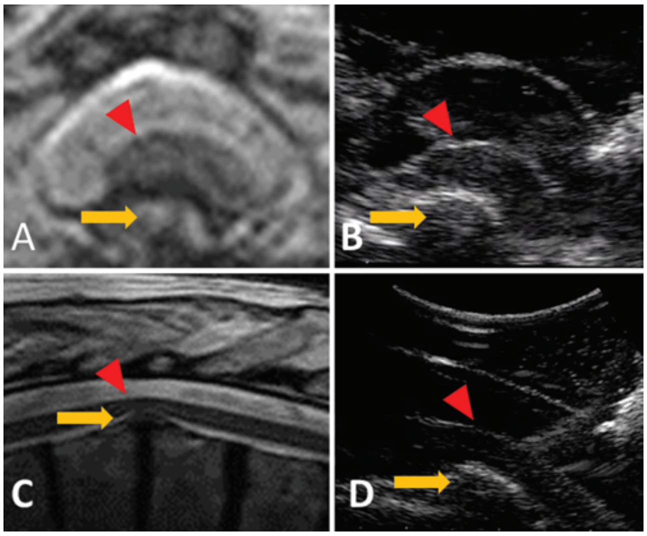

Fig. 2. Preoperative axial **(A)** and sagittal **(C)** T2-weighted MR images showing a TDH *(arrow)* compressing the spinal cord *(arrowhead)*. Axial **(B)** and sagittal **(D)** RIOUS views also demonstrate the disc herniation *(arrow)* and spinal cord *(arrowhead)* clearly. The RIOUS images correspond perfectly to the preoperative images.

sight, thus eliminating the need for significant retraction of the dura (Fig. 1B). This procedure was performed either unilaterally or bilaterally depending on the centrality, size, and nature of the herniated disc. At all times, the surgeon was able to view the status of the spinal cord using RIOUS, thus eliminating iatrogenic injury. At the conclusion of the discectomy, the degree of decompression was assessed by the RIOUS (Fig. 3). After decompression, pedicle screws were connected using titanium rods, and autogenous bone graft was placed in the lateral gutters to aid with bony fusion.

All patients underwent postoperative CT scanning within 24 hours to assess the instrumentation and adequacy of decompression (Fig. 4C). We also confirmed

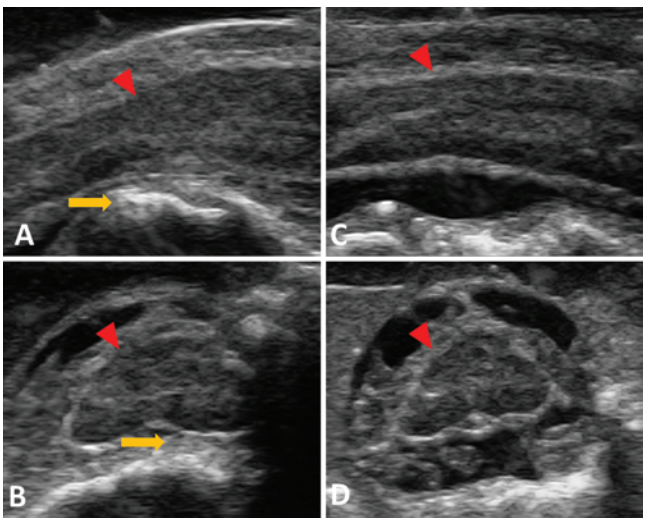

Fig. 3. Case 8. Sagittal **(A)** and axial **(B)** RIOUS views demonstrating spinal cord compression *(arrowhead)* due to TDH *(arrow)*. Sagittal **(C)** and axial **(D)** RIOUS views showing excellent decompression of the spinal cord *(arrowhead)* after microdiscectomy.

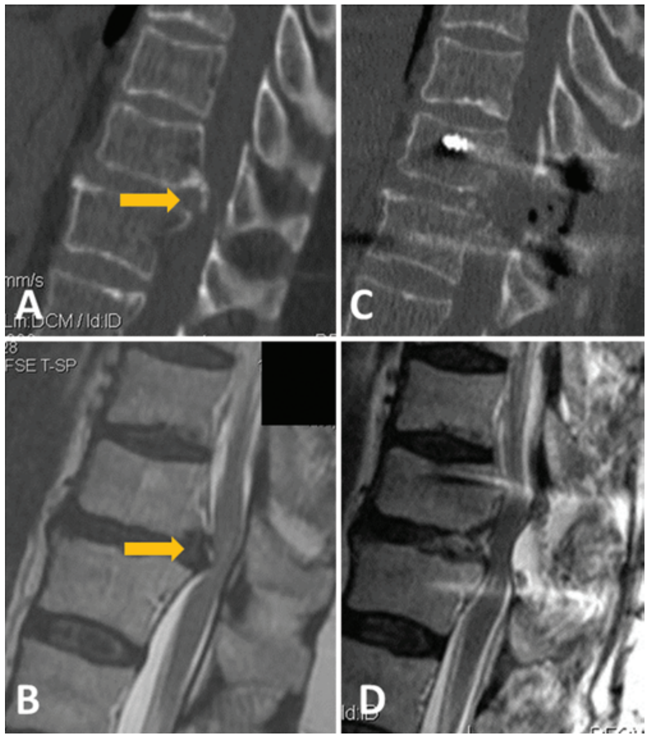

Fig. 4. Case 8. Preoperative CT scan **(A)** and sagittal T2-weighted MR image **(B)** showing a calcified disc herniation *(arrow)* compressing the spinal cord. The patient was referred to us with a 2-year history of thoracic myelopathy. Postoperative CT scan **(C)** and MR image **(D)** obtained on the day after surgery, revealing a well-decompressed spinal cord. The patient's symptoms improved from 2 to 1 (Nurick grade) and 7 to 9 (JOA score) with a Hirabayashi recovery rate of 50%.

sufficient decompression of spinal cord by referring to pre- and postoperative MRI (Fig. 4B and D).

Results

Clinical Results

Sixteen consecutive patients with symptomatic TDHs who underwent surgical decompression and instrumented fusion were included in this review (Table 1). Patients were followed up for an average duration of 10 months (range 5–48 months). The mean age of the patients was 49.5 years (range 32–71 years), and 6 were males.

Fifteen patients presented with clinical myelopathy with symptom duration ranging from 48 hours to 72 months. One patient (Case 15; Tables 1 and 2) presented with severe thoracic radiculopathy. Two patients (Cases 1 and 10; Tables 1 and 2) presented with acute onset of myelopathy and required emergency surgery.

All patients in this review had symptoms arising from single-level herniations, and 63% of the herniations were below T-9 (10 of 16 patients). Five patients (32%) had central disc herniations and 11 patients (68%) had paracentral herniations. Computed tomography evidence of partial calcification or complete calcification with and without osteophyte formation was found in 50% of herniated discs.

The average estimated blood loss was 523 ml (range

TABLE 1: Summary of 16 cases*

Case No.	Age (yrs), Sex	Symptom Duration	Level	Fusion	Concurrent Diseases	Preop Symptoms: Myelopathy	Preop Symptoms: Radiculopathy
1	43, M	NA	T11–12	T11–12	no	confined to bed rest, bilat leg weakness Grade 0, no sensation	no
2	51, F	2 yrs	T11–12	T11–12	no	loss of balance, spastic gait, bilat leg weakness Grade 3, bilat leg hypesthesia	no
3	52, M	6 mos	T10–11	T10–11	no	loss of balance, bilat leg weakness Grade 4, bilat leg numbness	no
4	53, F	20 mos	T11–12	T11–12	no	back pain, loss of balance, bilat leg weakness Grade 4	no
5	43, F	8 mos	T10–11	T10–11	no	loss of balance, spastic gait, bilat leg weakness Grade 4, bilat leg numbness, bladder dysfunction	no
6	59, F	4 mos	T2–3	T2–3	no	back pain, bilat dysesthesia below upper chest	no
7	45, M	3 yrs	T10–11	T10–11	no	loss of balance, spastic gait, bilat leg numbness, bladder dysfunction	abdominal dysesthesia
8	57, F	2 yrs	T10–11	T10–11	DM	loss of balance, spastic gait, bilat numbness below lower abdomen, bilat leg weakness Grade 4	no
9	71, M	7 mos	T12–L1	T12–L1	DM	bilat leg weakness Grade 4, bilat leg numbness	no
10	39, M	48 hrs	T6–7	T6–7	no	bilat leg weakness Grade 2, bilat leg numbness	no
11	43, F	10 yrs	T5–6	T5–7	no	bilat leg weakness Grade 4, bilat numbness below mid-abdomen	no
12	48, F	9 mos	T7–8	T7–8	no	loss of balance, spastic gait, bilat leg weakness Grade 4, bilat numbness below mid-abdomen, bladder dysfunction	chest pain
13	49, F	7 mos	T11–12	T11–12	no	loss of balance, spastic gait, bilat leg weakness Grade 4, bilat leg numbness, bladder dysfunction	no
14	50, F	72 mos	T9–10	T9–10	transverse myelitis, epidural lipomatosis	back pain, loss of balance, bilat leg weakness Grade 4, bilat leg numbness, below mid-abdomen numbness bilat, bladder dysfunction	no
15	32, M	48 mos	T8–9	T8–9	no	no	chest pain
16	55, F	6 wks	T5–6	T4–8	no	confined to wheelchair, bilat leg weakness Grade 2, bilat numbness below chest, no bladder function	no

* DM = diabetes mellitus; EBL = estimated blood loss; NA = not available; para = paracentral.

250–1000 ml), and the mean surgical time was 159 minutes (range 130–200 minutes). The percentage of cross-sectional area canal compromise as measured on axial imaging preoperatively was 45% on average (range 21%–67%) and postoperatively was 87% on average (range 72%–98%), which means a 193% expansion of the canal size from the preoperative state by the discectomy.

None of the patients had new neurological symptoms postoperatively, and all except 1 patient showed improvement in their preoperative neurological state. On average, the Nurick grade improved from 3.3 to 1.6, and the Japanese Orthopaedic Association (JOA) score improved from 5.7 to 8.3 from pre- to postoperative assessment. Two patients with a JOA score of 11 demonstrated complete resolution of radiculopathy and myelopathy postoperatively. One patient presented with ASIA Grade A injury after acute injury to the spinal cord (Case 1) and did not show any improvement postoperatively.

Complications

One patient (Case 10) developed deep wound infection approximately 2 months after surgery. This patient required repeat surgery for wound debridement and revision of hardware and long-term antibiotic therapy. At the 12-month follow-up, the patient demonstrated complete resolution of leg weakness (preoperative muscle power Grade 2 to muscle power Grade 5) and had ceased all antibiotics; radiographs demonstrated adequate alignment and stabilization. There were no other surgical complications in the remaining 15 patients. Importantly, despite 50% of the cases having calcified discs, no inadvertent dural tears were encountered with adequate decompression in all cases.

Illustrative Cases

Case 15. A 32-year-old man presented with a 2-year history of back pain spreading to the left flank. His chronic and unremitting thoracic radiculopathy was so severe particularly at night that it led to substantial sleep disturbance. He had no signs or symptoms of thoracic my-

TABLE 2: Clinical outcome of this study's 16 cases

Case No.	Nurick Grade Preop	Nurick Grade Final	JOA Score Preop	JOA Score Final	JOA Recovery Rate (%)	Op Time (mins)	EBL (ml)	ASIA Grade Preop	ASIA Grade Final	Calcification	Disc Location	Canal Compromise (%)	Removal Rate (%)	Surgical Complication	Follow-Up (mos)
1	5	5	0	0	0	180	600	A	A	no	central	55	89	no	5
2	4	2	5	8	50	160	500	D	D	no	para	43	90	no	6
3	3	1	6	10	80	140	400	D	E	no	para	54	80	no	48
4	3	1	7	10	75	150	1000	D	D	yes	para	52	95	no	10
5	3	1	7	9	50	160	700	D	D	no	para	44	88	no	12
6	2	1	9	10	50	180	500	D	D	no	para	25	72	no	8
7	2	1	8	10	67	160	400	D	E	yes	para	51	84	no	16
8	2	1	7	9	50	170	400	D	D	yes	central	45	88	no	8
9	4	2	6	9	60	150	800	D	D	no	para	42	80	no	7
10	5	2	2	9	78	180	600	C	D	no	central	31	75	infection, hardware revision	12
11	2	0	9	11	100	130	400	D	E	yes	para	42	98	no	6
12	3	1	7	9	50	150	500	D	D	no	para	21	87	no	10
13	4	1	5	8	50	140	250	D	D	yes	central	67	86	no	8
14	5	4	3	4	12	150	300	D	D	yes	central	38	90	no	6
15	1	0	9	11	100	150	300	E	E	yes	para	60	98	no	8
16	5	3	1	5	40	200	600	C	D	yes	para	45	90	no	6

elopathy. Thoracic spine MRI revealed a left-sided large disc bulge at T8–9 causing severe compression and distortion of the thoracic spinal cord and nerve root (Fig. 5C and D). Thoracic spine CT scans demonstrated a large calcified space-occupying lesion (Fig. 5A and B). Thoracic T8–9 foraminal compression of the T-8 nerve root was suspected as the cause of the patient's radiculopathy. Pedicle screws were inserted at T-8 and T-9 bilaterally with 3D navigation, followed by dorsal laminectomy of T-8 and T-9 and left-sided unilateral T8–9 facetectomy. We then used RIOUS, by which the large disc herniation was clearly visualized (Fig. 6A and B). We successfully removed the large calcified disc herniation with great caution taken to avoid movement or manipulation of the spinal cord under visualization using RIOUS (Fig. 6C and D). The immediate postoperative CT scans demonstrated excellent decompression of the ventral spinal cord (Fig. 5E and F), confirming what we had already demonstrated during the procedure with RIOUS. The patient's clinical course was uneventful, and his thoracic radiculopathy disappeared completely at 4 months of follow-up.

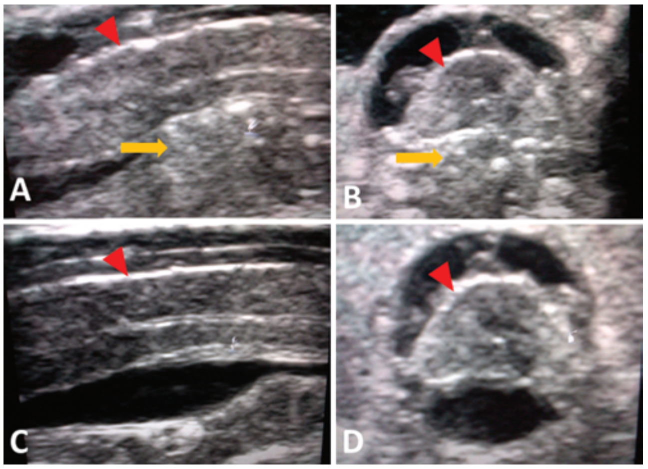

Fig. 6. Case 15. Sagittal **(A)** and axial **(B)** RIOUS views showing that the spinal cord *(arrowheads)* is deformed by compression from TDH *(arrows)* before repeat microdiscectomy. Sagittal **(C)** and axial **(D)** RIOUS views showing echo-free space in front of the spinal cord *(arrowhead)* clearly after microdiscectomy.

Case 16. A 55-year-old woman presented with a history of bilateral leg numbness and weakness, right greater than left, for 6 weeks. The patient had an acute deterioration of strength in the right leg with loss of bowel and bladder function within the past 24 hours, and she could not ambulate. On physical examination, she had Grade 2 power in the muscle groups of both legs. She had a T-6 sensory level. The patient had incomplete loss of bowel and bladder function with weak voluntary rectal contraction and reduced but present abnormal sensation at S-3, S-4, and S-5 to light touch and pinprick. Thoracic spine CT and MRI demonstrated a right-sided paracentral calcified disc protrusion with a left-sided caudal migrated disc herniation at T5–6 (Fig. 7A–D). Her thoracic spine was fused spontaneously at multilevel segments on thoracic spine CT, suggestive of ankylosing spondylitis (Fig. 7A). The sudden onset of neurological deterioration was deemed attributed to significant mechanical instability at

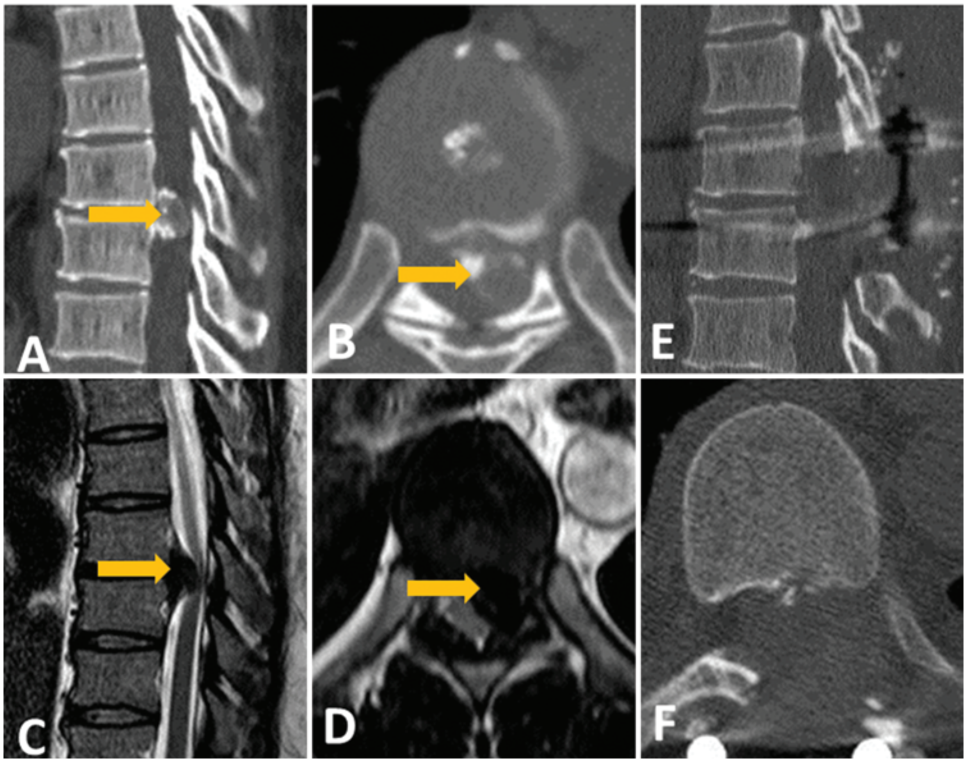

Fig. 5. Case 15. Preoperative CT scans **(A and B)** and MR images **(C and D)** showing a large calcified paracentral disc *(arrows)*. The patient complained of severe thoracic radiculopathy without thoracic myelopathy. The disc was successfully removed. The patient's radiculopathy completely disappeared at postoperative 4-month follow-up **(E and F)**.

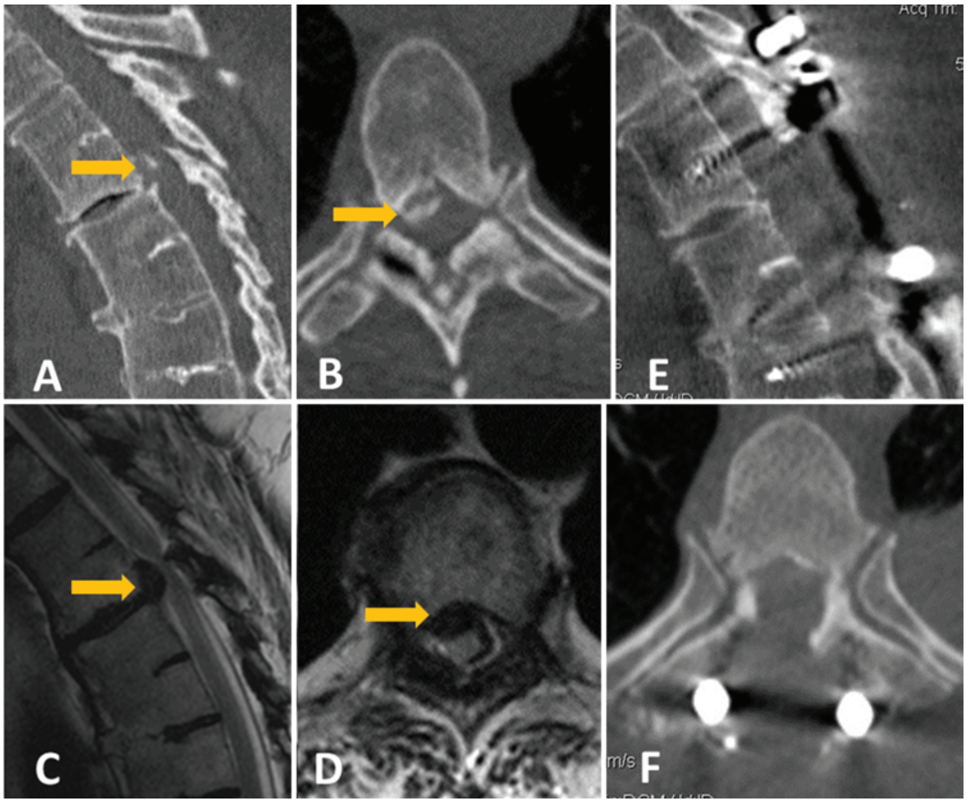

Fig. 7. Case 16. Preoperative CT scans **(A and B)** and MR images **(C and D)** showing a calcified paracentral disc at T5–6 *(arrows)*. The CT scans reveal multilevel spontaneous fusion, and there is a vacuum phenomenon at the T5–6 disc space and facet joint. T5–6 instability is presumed to contribute to forming a TDH. The patient demonstrated acute deterioration of neurological deficit, and emergency surgery was performed. Postoperative CT scans **(E and F)** showing that the disc was successfully removed.

T5–6 along with a TDH. Emergency surgical intervention was performed within 24 hours of the acute neurological deterioration. We performed T4–8 pedicle screw insertion under 3D navigation guidance, given the T5–6 instability accompanied by ankylosing spondylitis. This was followed by laminectomy and unilateral facetectomy at T5–6. A large disc herniation was identified on the right side and was subsequently successfully removed under RIOUS (Fig. 8). The postoperative course was uneventful with remarkable improvement of the sensory deficit and motor weakness. The immediate postoperative CT scans demonstrated complete decompression of the ventral spinal cord (Fig. 7E and F). The patient made a significant recovery in walking ability and was ambulating independently at 6-month follow-up.

Discussion

Symptomatic TDH is a relatively uncommon disease that can present with severe myelopathy or radiculopathy. Management options are usually limited to surgical decompression in symptomatic cases. Surgical techniques have evolved over time from posterior (laminectomy) alone to posterolateral, lateral, and anterior approaches with many variations. While the lateral and anterior approaches give access to the disc located ventrally in direct line of sight, these require a combination of significant

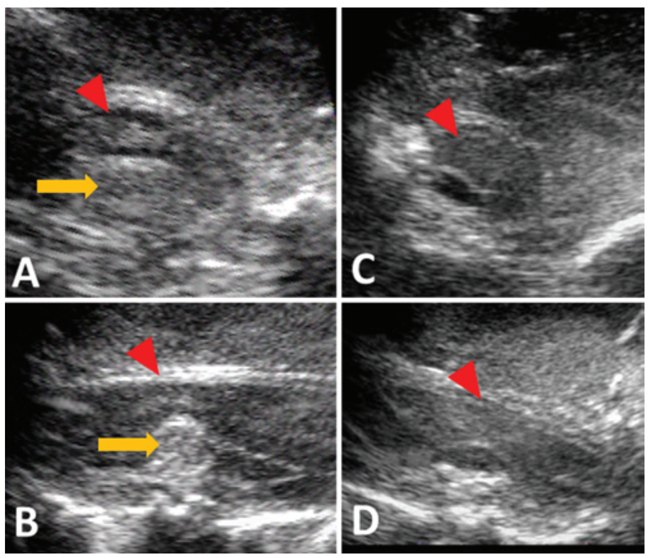

Fig. 8. Case 16. Axial **(A)** and sagittal **(B)** RIOUS views showing that the spinal cord *(arrowhead)* is squeezed and displaced by TDH *(arrow)* before microdiscectomy. Axial **(C)** and sagittal **(D)** RIOUS views showing that enough decompression of the spinal cord *(arrowhead)* is attained after microdiscectomy.

dissection of the chest wall and the diaphragm and rib resection and require thoracotomy or sternotomy depending on the location. The postoperative consequence of such extended approaches are not minimal[3,19,21,25,28,29] and are usually related to the approach.

We presented a cohort of 16 patients with 50% of patients having calcified discs at various levels in both central (32%) and paracentral (68%) locations in the thoracic spine. These patients were treated with a posterior pedicle-sparing transfacet resection of the disc using intraoperative ultrasound with instrumented fusion. Our results demonstrate the safety of the approach, with no deterioration in neurological status and a significant improvement in myelopathy and radiculopathy postoperatively.

The posterior pedicle-sparing transfacet approach has been described previously[3,4,12,19,26] and is a relatively familiar technique to most spine surgeons. Moreover, the use of intraoperative ultrasound to identify intradural pathology intraoperatively is well established.[7,9,11,16] However, the addition of the RIOUS for thoracic discectomy using the posterior approach is a unique combination that greatly enhances the safety of thoracic discectomy. The use of RIOUS enables resection of TDH at any level using the same surgical corridor, unlike the lateral and anterior approaches, which are restricted at some spinal levels due to the adjacent viscera. Using the same approach for a rare disease helps the surgeon to develop skills and expertise in a short amount of time, thus further reducing the learning curve–induced error.

Real-time intraoperative ultrasound is an extremely effective tool to visualize pathology in front of the spinal cord without manipulation of the thecal sac and spinal cord[14,18,24] and aid the surgeon. Intraoperative ultrasound has been described to assess the degree of decompression in cervical or thoracic ossification of the posterior longitudinal ligament or thoracolumbar burst fractures.[14,18,27] To our knowledge, there has been no report on application of intraoperative ultrasound for assessment in TDH operations. We believe that the addition of RIOUS is indispensible to thoracic discectomy using the posterior pedicle-sparing transfacet approach.

It is debatable whether an instrumented fusion is required with the pedicle-sparing transfacet approach. Previous reports using the same approach insisted that one should spare the lateral aspect of facet joint to avoid destabilization.[26] We submit that although the preservation of the lateral facet may avoid the need for instrumented fusion, removal of the entire facet gives a more oblique approach to the disc and allows manipulation of the instruments ventral to the spinal cord without any significant dural retraction. In our opinion, supplementation of instrumented fusion in the thoracic levels causes less morbidity than retraction of the spinal cord. Moreover, instrumented fusion helps prevent postoperative spinal instability associated with wide decompressions and potential axial back pain, especially with facetectomy and discectomy.[2,4]

The main limitation of our study is the small cohort of patients. When one considers the infrequent presentation of TDHs, our population contains a significant number of patients. Although our clinical follow-up is relatively short, we believe that to assess the safety of the procedure (detection of new neurological deficits or resolution of symptoms), this is an adequate length of follow-up. We do continue to accumulate experience and clinical follow-up of patients.

Conclusions

Thoracic discectomy via the posterior pedicle-sparing transfacet approach is an adequate method of managing herniations at any thoracic level. The safety of the operation is significantly enhanced by the use of RIOUS.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Nishimura, Tochigi, Ahn, Ginsberg. Acquisition of data: Nishimura, Ginsberg. Analysis and interpretation of data: Nishimura. Drafting the article: Nishimura. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Nishimura. Administrative/technical/material support: Ginsberg. Study supervision: Ginsberg.

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