Journal of Orthopaedic Translation 24 (2020) 32–38

Contents lists available at ScienceDirect

Journal of Orthopaedic Translation

journal homepage: www.journals.elsevier.com/journal-of-orthopaedic-translation

Original Article

Analysis of the morphometric change in the uncinate process of the cervical spondylosis patients: A study of radiological anatomy

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ARTICLE INFO

Keywords:
Cervical spine
Cervical spondylosis
Intervertebral foramen decompression
Transverse foramen
Uncinate process

ABSTRACT

Purpose: Although there are many researches that focus on the relationship between the vertebral artery and uncinate process (UP), there were no publications concerning difference in the dimensions of the UP between the normal spine and degenerative spine, especially in Chinese patient. The purpose of this study is to determine the anatomic parameters that can be used as a guide for the procedure in intervertebral foramen decompression and for analysis of the morphometric change in the UP of the cervical spondylosis patients.

Methods: Forty patients from January 2016 to January 2019 were enrolled in this study. Three-dimensional computed tomography scans of the cervical spine were performed. The patients were subdivided into two groups which were nondegenerative cervical spine group (20 cases) and degenerative cervical spine group (20 cases). Six parameters concerning the height, width and angle of the UP were measured.

Results: In nondegenerative group, the average pedicle width was 3.63 mm–5.91 mm from C3 to C7. The average width of safe UP resection will be 3.06 mm at C3, 3.12 mm at C4, 3.28 mm at C5, 2.74 mm at C6 and 2.01 mm at C7. The average safe depth will be 6.04 mm at C3, 6.52 mm at C4, 7.61 mm at C5, 6.07 mm at C6 and 5.09 mm at C7. There are statistic difference between degenerative group and nondegenerative group, especially in the parameter minimum height of UP, maximum height of UP, medial border's distance of UP and later border's distance of UP.

Conclusion: In this retrospective study, our results suggest that for the Chinese patients who suffered from cervical spondylosis could be performed intervertebral foraminotomy decompression by resecting part of the UP. The safe range within the spinal canal was up to 6.73 mm of width between inferior vertebral endplate and superior vertebral endplate in the intervertebral space and up to 5.09 mm of depth from medial border of the UP to the lateral side atC3 to C7 without interfering the spinal nerve root and vertebral artery.

The translational potential of this article: Our study found the safe margin to perform intervertebral foramen decompression to the UP for the cervical spondylosis patients. This may help to improve safeness of the surgical procedure and provide data for future robotic surgery.

Introduction

Vertebral artery and nerve root injury is a catastrophic complication that can occur during the process in the anterior decompression of the cervical foramen [1,2]. None of the studies provide the most important information about the location of the vertebral artery and the height of the uncinate process (UP) which needs to be resected to achieve adequate decompression of the intervertebral foramen. The aim of the present study is to analyse the anatomic parameters between the various structures near the intervertebral foramen and the transverse foramen both in the normal person and the cervical spondylotic myelopathy patients. The morphologic dimensions of the UP were investigated in the Chinese population.

Materials and methods

This study was approved by the review board of the first affiliated hospital of Sun Yat-sen University in China. It was a retrospective

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https://doi.org/10.1016/j.jot.2020.03.011
Received 22 September 2019; Accepted 23 March 2020
Available online 18 April 2020

radiologic study of 40 patients (nationality: China, ethnic Han) who were enrolled from January 2016 to January 2019. These patients were subdivided into two groups. Group 1 is nondegenerative group which is selected from the patients who had not suffered from the cervical spine nondegenerative disease, such as benign thyroid gland disease, etc. There were 20 patients included in Group 1 (9 female patients and 11 male patients). The mean age of patients was 43.1 ± 11.3 years (range, 37–55 years). The mean height of the patients was 162.2 ± 13.5 cm. The mean body mass index (BMI) was 21.3 ± 2.5 kg/m^2.

Group 2 is degenerative group which selected from the patients who suffered from cervical spondylotic myelopathy without severe cervical spine osteophyte, vertebral artery malformation, transverse foramen stenosis and malformation of the cervical spine. We excluded patients with a previous history of spinal trauma or any operations for trauma, infection or tumour. There were 20 patients included in Group 2 (9 male patients and 11 female patients). The mean age of patients was 46.7 ± 14.8 years (range, 32–60 years). The mean height of the patients was 160.9 ± 14.7 cm. The mean BMI was 20.9 ± 3.8. All the patients in Group 2 were treated with laminoplasty.

They had undergone three-dimensional computed tomography of the cervical spine as part of routine check for the disease.

To measure the structure involved in the foraminal decompression, we drew several lines to measure the different distances between them. On the axial view, we drew a line bisecting the vertebral body to identify the midpoints of the anterior and posterior cortices. From the midpoints of the anterior cortex of the vertebral, we drew lines to the medial and lateral cortices of the pedicle from C3 to C7.

We measured the distance between the midline of vertebral body and the medial cortex of the pedicle. The medial border's distance of UP was named A. The distance from the midline of cervical vertebral body to the lateral pedicle cortex which we called it later border's distance of UP was named B (Figure 1).

We measured the height of the UP bilaterally from C3 to C7 on two coronal CT views of the cervical spine; the first view was at the level of the posterior cortex of the vertebral body and the second view was at the midportion of the vertebral body. These two views represent the minimal and maximal heights of the UP from the cranial cortex of the pedicles.

Minimum height of UP which was named parameter C was defined as the vertical distance between upper border of the vertebral body and the minimum height point of the UP (Figure 2).

Maximum height of UP which was named parameter D was defined as the vertical distance between upper border of the vertebral body and the maximum height point of the UP (Figure 3).

The medial border's distance of pedicle which was named parameter E was defined as the distance between the midline of vertebral body and the medial border of the UP at the superior vertebral endplate level. The lateral border's distance of pedicle which was named parameter F was defined as the distance between the midline of vertebral body and the lateral border of the UP at the superior vertebral endplate level (Figure 4).

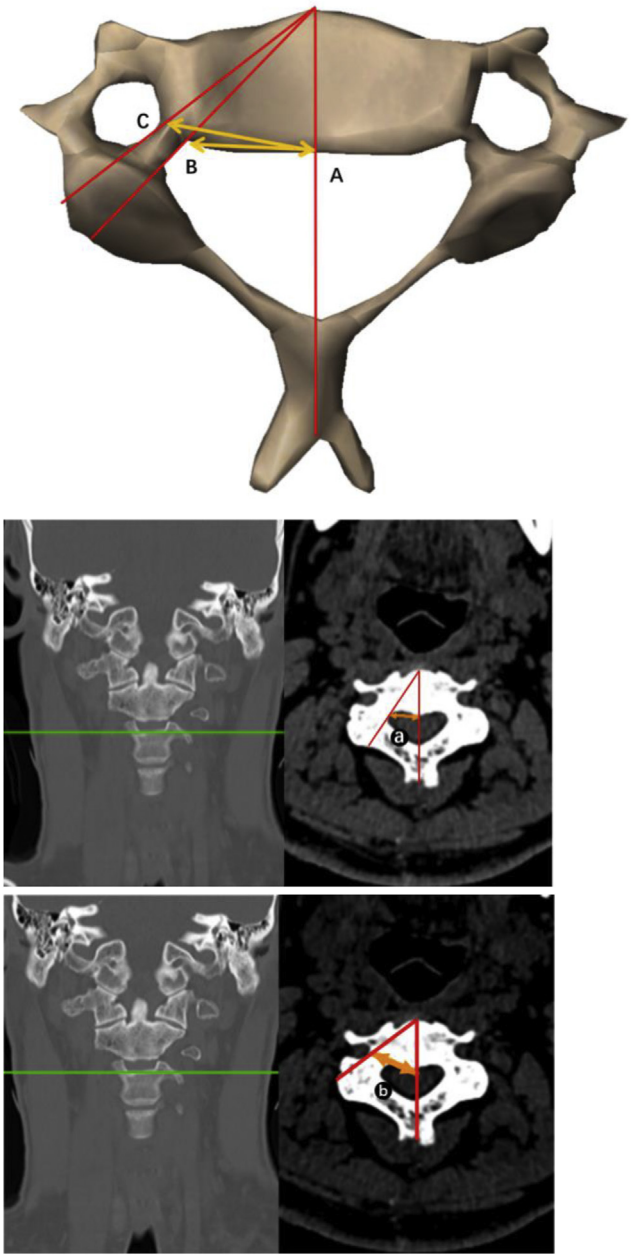

Figure 1. The axial view of a cervical vertebra demonstrating the parameter A and B. The distance a (AB) was defined as the distance from the midline of cervical vertebral body to the medial pedicle cortex. The distance b (AC) was defined as the distance from the midline of cervical vertebral body to the lateral pedicle cortex.

Statistical analysis

Mean and standard deviation were calculated and compared for continuous variables. Comparison of parameters between non-degenerative group and degenerated group was performed using independent-sample *t* tests, such as parameters from A to F and also for the parameter B-A, D-C, F-E. All the measurements performed by two independent observers were compared. P-values less than 0.05 were considered statistically significant. SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Comparison of the baseline characteristics between the overall patients revealed that there was no statistical difference in male to female ratio, the age composition and BMI between the nondegenerative group and degenerative group.

The distance between the midline of vertebral body and the medial cortex of the pedicle was named A. The right side was named AR. The left side was named AL. The parameter a gradually increased from C3 to C6 and decreased at C7. There was statistical difference between two groups at C3 and C4 for AR and C5 for AL. (Figure 5).

The distance from the midline of cervical vertebral body to the lateral pedicle cortex was named B. The parameter on the right side was named BR. The parameter on the left side was named BL. The parameter B gradually increased from C3 to C7. There was statistical difference in the parameter B on both right and left sides between Group 1 and Group 2 at C4 ($P < 0.05$) (Figure 5).

The width of pedicle will be the parameter B-A. In Group1, we

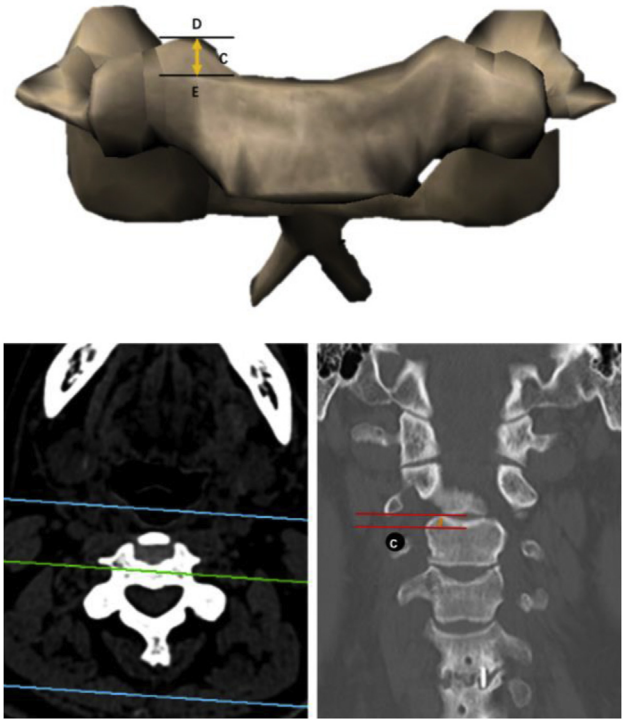

Figure 2. The axial and coronal view of a cervical vertebra demonstrating the parameter C. The distance c (DE) was defined as the vertical distance between upper border of the vertebral body and the minimum height point of the uncinate process.

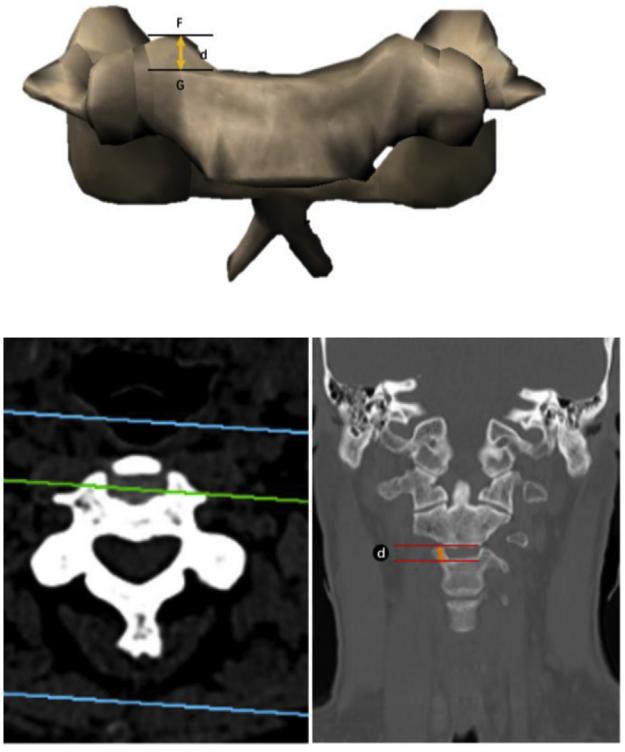

Figure 3. The axial and coronal view of a cervical vertebral demonstrating the parameter D. The distance d (FG) was defined as the vertical distance between upper border of the vertebral body and the maximum height point of the uncinate process.

calculate the normal pedicle width. The pedicle width was 4.81 ± 0.56 mm at C3, 4.4 ± 0.45 mm at C4, 3.63 ± 0.72 mm at C5, 3.85 ± 0.58 mm at C6 and 5.91 ± 0.99 mm at C7. The width of pedicle reached its maximal point at C7 and its minimal point at C5. There were significant statistical differences between two groups in parameter BR-AR and BL-AL at C4 level (Figure 6).

The vertical distance between upper border of the vertebral body and the minimum height point of the UP was named parameter C. The parameter on the right side was named CR. The parameter on the left side was named CL. There were statistical differences in CR and CL between the two groups at C3, C4, C5, C6 and C7 (Figure 5).

The vertical distance between upper border of the vertebral body and the maximum height point of the UP was named parameter D. The parameter on the right side was named DR. The parameter on the left side was named DL. There was statistical difference between two groups in parameter D at C3, C4 and C5 (Figure 5).

The width of safe margin when we perform Foramen decompression will be parameter D-C. In Group1, we calculate the parameter D-C. We found that the width of safe UP resection was 3.06 ± 0.32 mm at C3, 3.12 ± 0.57 mm at C4, 3.28 ± 0.68 mm at C5, 2.74 ± 0.43 mm at C6 and 2.01 ± 0.50 mm at C7. The width of safe margin reached its maximal point at C5 and its minimal point at C7. There was significant statistical difference between two groups in the parameter DR-CR at C5 level and for the parameter DL-CL at C4, C5 level (Figure 6).

The distance between the midline of vertebral body and the medial border of the UP at the superior vertebral endplate level was named E. The parameter on the right side was named ER. The parameter on the left side was named EL. There was statistical difference in ER and EL between the two groups at C3, C4, C5, C6 and C7 level (Figure 5).

The distance between the midline of vertebral body and the lateral border of the UP was named F. The parameter on the right side was named FR. The parameter on the left side was named FL. For the parameter FR, there was statistical difference at C4, C5, C6 and C7. For the parameter FL, there was statistical difference at C5. The distance between the midline of vertebral body and the lateral border of the UP gradually increased from C3 to C7 (Figure 5).

In the procedure of Foramen decompression, we often used lamina rongeur to resect the UP according to the path from parameter E to F. So, the distance F-E will be the safe depth when we performed the foramina decompression from medial part of vertebral body to the lateral side. In Group1, we calculate the normal distance F-E. The safe depth will be 6.04 ± 0.31 mm at C3, 6.52 ± 0.58 mm at C4, 7.61 ± 0.46 mm at C5, 6.07 ± 0.63 mm at C6 and 5.09 ± 0.64 mm at C7. There was statistical difference between two groups for the parameter FR-ER and FL-EL at C3, C4, C5, C6 and C7 level (Figure 6).

The *t* test was performed between Group 1 and Group 2. The parameters' value and statistical significance were shown in Table 1.

We found that there were statistic differences between the two groups in AR at the level of C3 and C4; AL at the level of C5; BR at the level of C4; BL at the level of C4; CR at the level of C3–C7; CL at the level of C3–C7; DR at the level of C3–C5; DL at the level of C3–C5; ER at the level of C3–C7; EL at the level of C3–C7; FR at the level of C4–C7 and FL at the level of C5.

There was symmetric statistical difference in both right and left sides in the parameter C at the level of C3–C7, D at the level of C3–C5 and E at the level of C3–C7. The results were shown in Table 1.

Discussion

Cervical spondylosis is one of the most common diseases among the elderly population.

The typical symptoms may include pain, numbness and weakness of the shoulders and arms, and some patients may also suffer from weakness of legs and arms. The patients may have trouble in keeping balance while walking. Surgical treatment is necessary while nonsurgical treatment cannot help the patients achieve satisfactory alleviation with nonsurgical

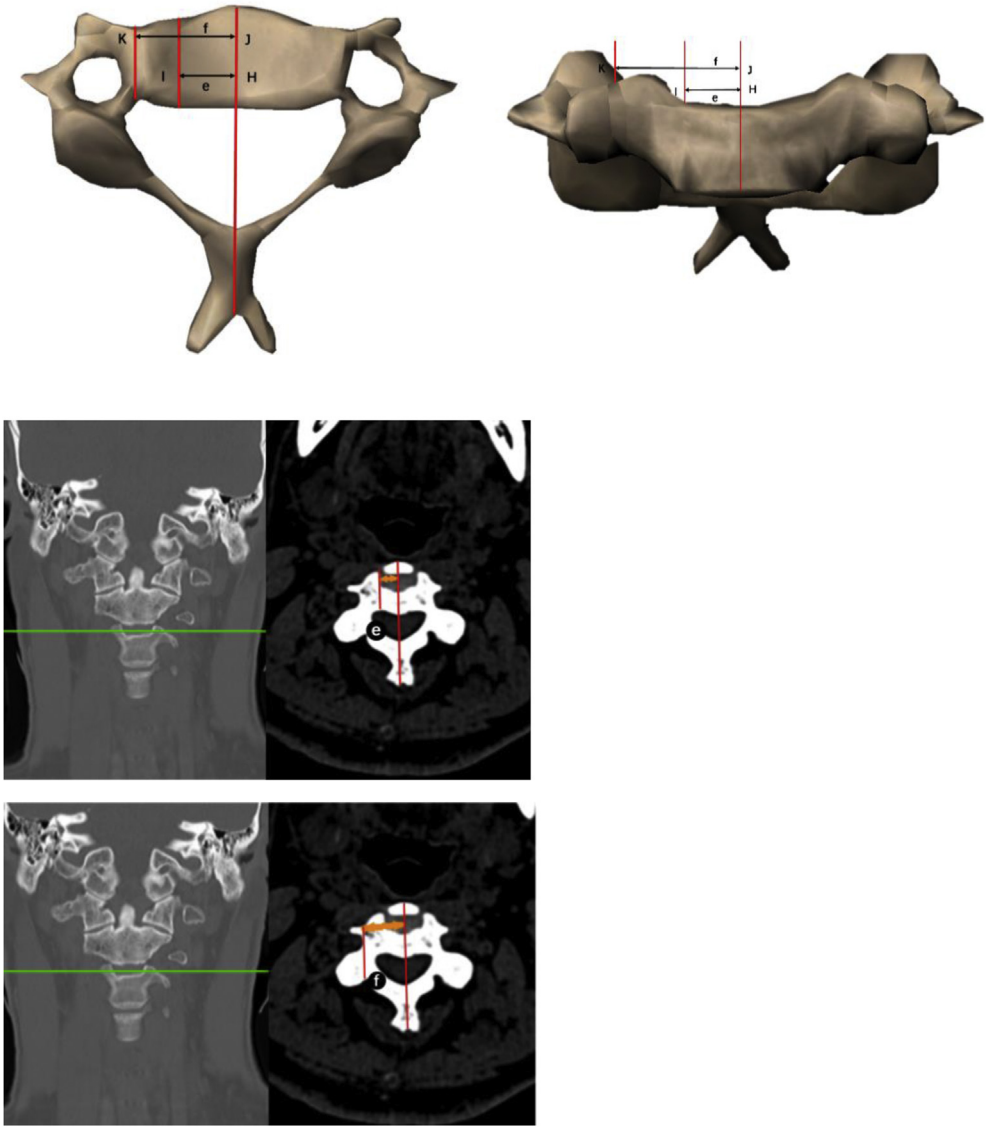

Figure 4. The axial and coronal view of a cervical vertebra demonstrating the parameter E and F. The distance e (IH) was defined as the distance between the midline of vertebral body and the medial border of the uncinate process. The distance f (KJ) was defined as the distance between the midline of vertebral body and the lateral border of the uncinate process.

treatment [3]. Among the surgical treatment of cervical spondylosis, anterior cervical discectomy and fusion has been widely used and have proven to be a safe and effective method. However, its complication during the surgery has drawn a great attention [4]. Especially the injury to the vertebral artery, which is at risk during the procedure of foraminal decompression, can result in catastrophic consequences such as massive bleeding, cerebellar or brain stem infarction or even death. The UP which forms the uncovertebral articulation is common sites for osteoarthritic changes. The osteophytic spurring from the UPs project laterally and thus can impinge on anatomical structures which include the spinal nerve root, vertebral artery, radicular artery, cervical spinal cord and cervical sympathetic trunk, etc [5]. The resection of the part of the UP is crucial in the foraminal decompression.

In 1834, Rathke [6,7]defined the UP as a bony protuberance that extends from posterior margin of vertebral body. In 1858, Von Luschka [6,7] introduced the description of uncovertebral joint between the UP and vertebra. The UP existed in the vertebra from C3 to T2 [8]. The UP could stabilise the vertebra by limiting lateral flexion and posterior translation. The UP also bears the load from the vertebral above.

Patients with cervical radiculopathy may have narrow neural foramen because of osteophyte accumulation or hypertrophy of the uncovertebral joints. For those patients suffered from neural foraminal stenosis, uncinate resection performed with ACDF could achieve better outcome. In the case of myelopathy, decompression between both UPs is sufficient; however, in case of radiculopathy, more lateral decompression is required to decompress the neural foramen. This may put the nerve root and vertebral artery near the UP at great risk.

Many researches have focused on the anatomical features of the UP. However, the studies did not provide the information regarding the location the vertebral artery, the height and width of the UP and the difference between the normal people and the patients who suffered from degenerative cervical spondylosis. The purpose of this study is to describe the anatomical features of the UP and its relationship to the adjacent vertebrae as well as to be used as a guide for the decompression of the foramen.

We found that the distance between the midline of the vertebral body and the medial cortex of the pedicle 9.82 mm at C3, 10.80 mm at C4, 12.18 mm at C5, 12.35 mm at C6, 10.94 mm at C7 in group 1. The distance increased from C3 to C6, reached its max point at C6 level, and it decreased at C7 level. Compared with the patients suffered from cervical

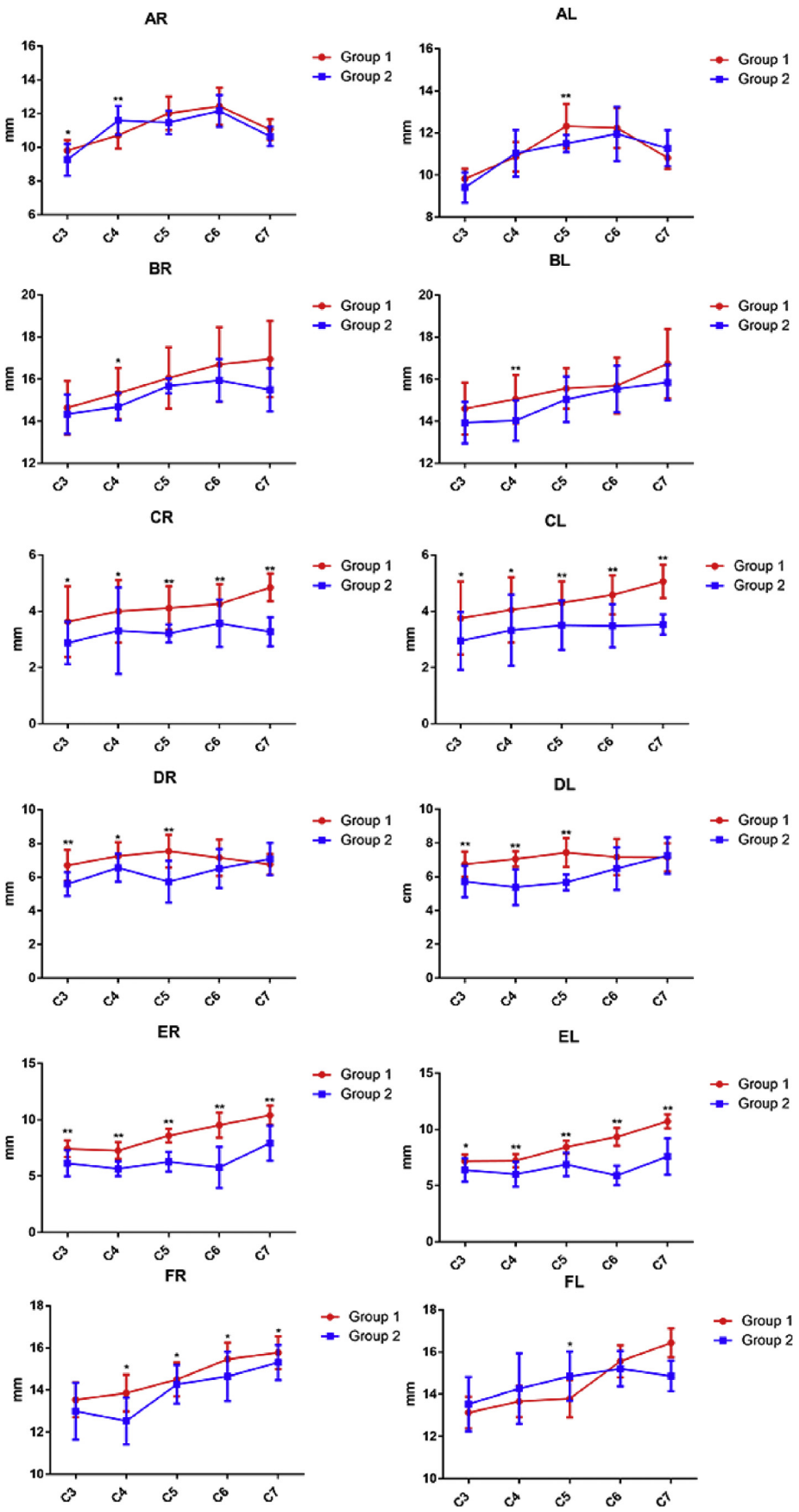

Figure 5. Parameter A, B, C, D, E, F change pattern at different cervical spine level. * means there was statistical difference between two groups $p < 0.05$. ** means there was statistical difference between two groups $p < 0.01$. Figure 5: we found that the parameters AR and AL were gradually increase from C3 to C5 and reach their maximal point at C6. There was a little decrease at C7. Group 1 and Group 2 showed the same trend. The parameters BR and BL increased from C3 to C7. The two groups showed in same trend except for parameter BR in group 2 at C7 showed little decrease.In Group 1, the parameter CR and CL increased from C3 to C7. But in group 2, the parameter CR and CL was gradually increased from C3 to C6 and slightly decreased at C7 level. In group1, the parameters DR and DL reach their maximal point at C5. In group 2, the DR and DL reached their maximal point C7. The parameters ER and EL gradually increase from C3 to C7 in group 1. In group 2, we found that ER and EL gradually increased at C5, little decrease at C6 and reach it maximal point at C7. The parameter FR and FL were gradually increased from C3 to C7 and reach its maximal point at C7 except for the FR in group 2 which showed little decreased at C7.

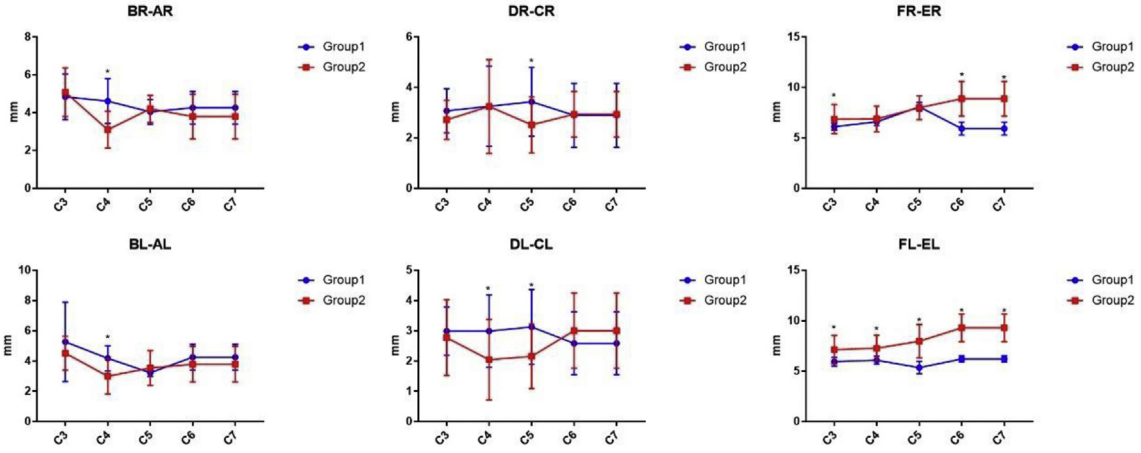

Figure 6. Parameter B-A, D-C, F-E change pattern at different cervical spine level. *means there was statistical difference between two groups $p < 0.05$. There was statistical difference between two groups in the parameter BR-AR and BL-AL at C4 level; parameter DR-CR at C5 level; parameter DL-CL at C4 and C5 level; parameter FR-ER at C3, C6 and C7 level; parameter FL-EL at C3 to C7 level.

spondylosis myelopathy in group 2. This distance in bilateral sides had statistically significant difference at C5 level.

The distance from the midline of cervical vertebral body to the lateral pedicle cortex was 14.63 mm at C3, 15.20 mm at C4, 15.81 mm at C5, 16.20 mm at C6 and 16.85 mm at C7. This distance gradually increased from C3 to C7 and reaches its maximum point at C7 level. This distance at C4 had statistically significant difference between the two groups. The data were higher in group 1 than in group 2.

The vertical distance between upper border of the vertebral body and the minimum height point of the UP was 3.69 mm at C3 level, 4.03 mm at C4 level, 4.21 mm at C5 level, 4.42 mm at C6 level and 4.95 mm at C7 level. This distance gradually increased from C3 to C7 and reaches its maximum point at C7 level. There was statistic difference between two groups at C3, C4, C5, C6 and C7 level.

The vertical distance between upper border of the vertebral body and the maximum height point of the UP was 6.73 mm at C3, 7.15 mm at C4, 7.49 mm at C5, 7.16 mm at C6 and 6.96 mm at C7. In Group 1, the vertical distance between upper border of the vertebral body and the maximum height point of the UP gradually increased from C3 to C5. The parameter reached its maximum point at C5 level and slightly decreased at C6 and C7. In Group 2, the parameter D gradually increased from C5 to C7. The maximum level was at C7 level. There was statistical difference between C3, C4 and C5 between the two groups.

Tubbs et al. [9] found that the height of the UP was 5–6 mm at the C4-6 levels, making the anterolateral window for decompression of the neural [7]foramen determinable by the height and width of the UP, and this is comparable to the findings of Lu et al. These authors also found that the UPs were significantly taller at C4–C6 levels which is consistent with our conclusion in the nondegenerative group. In addition, height of UPs was reported in 10 studies, indicating an increasing pattern from C3 to lower cervical spines. Moreover, four of 10 studies revealed shorter UPs of C7 compared with those of the adjacent C6 [15]. We speculate that the factor of degeneration may play an important role in the height change pattern of UPs.

The distance between the midline of vertebral body and the medial border of the UP at the superior vertebral endplate level was 7.30 mm at C3 level, 7.25 mm at C4 level, 7.04 mm at C5 level, 9.45 mm at C6 level and 10.57 mm at C7 level. The distance gradually increased from C3 to

Table 1
Comparison of different parameters' value between nondegenerative group and degenerative group.

Parameter	Group	C3	*p*	C4	*p*	C5	*p*	C6	*p*	C7	*p*
AR(mm)	1	9.81 ± 0.63	0.03 #	10.72 ± 0.79	<0.01 #	12.02 ± 0.99	0.053	12.44 ± 1.11	0.39	11.06 ± 0.61	0.39
	2	9.26 ± 0.94		11.60 ± 0.86		11.48 ± 0.69		12.15 ± 0.94		10.66 ± 0.57	
AL(mm)	1	9.82 ± 0.47	0.88	10.87 ± 0.70	0.57	12.33 ± 1.06	<0.01 #	12.25 ± 0.95	0.42	10.82 ± 0.54	0.42
	2	9.41 ± 0.72		11.04 ± 1.11		11.50 ± 0.41		11.96 ± 1.29		11.28 ± 0.86	
BR(mm)	1	14.65 ± 1.28	0.39	15.33 ± 1.22	0.04 #	16.06 ± 1.46	0.26	16.70 ± 1.77	0.11	16.96 ± 1.81	0.11
	2	14.34 ± 0.94		14.69 ± 0.65		15.68 ± 0.35		15.95 ± 1.01		15.50 ± 1.03	
BL(mm)	1	14.61 ± 1.23	0.67	15.06 ± 1.15	<0.01 #	15.56 ± 0.97	0.12	15.70 ± 1.34	0.68	16.74 ± 1.65	0.68
	2	13.94 ± 0.99		14.04 ± 0.96		15.05 ± 1.08		15.54 ± 1.11		15.85 ± 0.85	
CR(mm)	1	3.63 ± 1.26	0.03 #	4.00 ± 1.11	0.03 #	4.11 ± 0.78	<0.01 #	4.26 ± 0.70	<0.01 #	4.84 ± 0.49	<0.01 #
	2	2.88 ± 0.76		3.31 ± 1.54		3.21 ± 0.32		3.57 ± 0.84		3.27 ± 0.52	
CL(mm)	1	3.75 ± 1.30	0.04 #	4.06 ± 1.16	0.02 #	4.31 ± 0.75	<0.01 #	4.58 ± 0.70	<0.01 #	5.06 ± 0.59	<0.01 #
	2	2.95 ± 1.03		3.33 ± 1.26		3.51 ± 0.88		3.48 ± 0.77		3.53 ± 0.36	
DR(mm)	1	6.70 ± 0.93	<0.01 #	7.25 ± 0.82	0.01 #	7.54 ± 0.97	<0.01 #	7.15 ± 1.08	0.08	6.76 ± 0.62	0.08
	2	5.59 ± 0.71		6.55 ± 0.84		5.73 ± 1.25		6.51 ± 1.16		7.08 ± 0.96	
DL(mm)	1	6.75 ± 0.74	<0.01 #	7.05 ± 0.46	<0.01 #	7.44 ± 0.85	<0.01 #	7.17 ± 1.07	0.07	7.15 ± 0.84	0.07
	2	5.72 ± 0.93		5.38 ± 1.06		5.67 ± 0.46		6.49 ± 1.26		7.26 ± 1.08	
ER(mm)	1	7.43 ± 0.74	<0.01 #	7.27 ± 0.75	<0.01 #	8.60 ± 0.62	<0.01 #	9.54 ± 1.12	<0.01 #	10.41 ± 0.85	<0.01 #
	2	6.14 ± 1.16		5.66 ± 0.67		6.28 ± 0.88		5.78 ± 1.84		7.93 ± 1.56	
EL(mm)	1	7.18 ± 0.59	0.01 #	7.23 ± 0.59	<0.01 #	8.44 ± 0.58	<0.01 #	9.35 ± 0.81	<0.01 #	10.72 ± 0.63	<0.01 #
	2	6.40 ± 1.04		6.02 ± 1.10		6.88 ± 1.04		5.91 ± 0.87		7.59 ± 1.61	
FR(mm)	1	13.54 ± 0.82	0.13	13.86 ± 0.88	0.01 #	14.50 ± 0.81	0.03 #	15.46 ± 0.79	0.01 #	15.78 ± 0.78	0.01 #
	2	13.00 ± 1.36		12.53 ± 1.11		14.27 ± 0.92		14.65 ± 1.17		15.31 ± 0.84	
FL(mm)	1	13.14 ± 0.75	0.24	13.67 ± 0.74	0.15	13.80 ± 0.88	<0.01 #	15.57 ± 0.76	0.16	16.44 ± 0.69	0.17
	2	13.54 ± 1.29		14.27 ± 1.67		14.86 ± 1.17		15.21 ± 0.84		14.87 ± 0.73	

means there was statistical difference between two groups.

C7. The mean value is higher in group1 than in group2. There was statistical difference between the two groups at each level from C3 to C7.

The distance between the midline of vertebral body and the lateral border of the UP was 13.34 mm at C3, 13.77 mm at C4, 14.65 mm at C5, 15.52 mm at C6 and 15.66 mm at C7. The distance gradually increased from C3 to C7. There was no statistic difference between two groups bilateral sides at each level.

Yilmazlar et al. [10] attributed the increased width of the UP at C5 to spondylosis secondary to the increased cervical segmental motion at this level. The height and width of UPs display a gradually increasing pattern from C3 to C6. However, after C6, we observed a decreasing pattern. This is quite expectable, as these protuberances are not observed after T1 [11]. After C6, we see a decline in the morphometric values of UPs because of relative downsizing.

We found an asymmetry in some of UPs's parameters between bilateral sides, and we suppose that this phenomenon may be attributed to the asymmetrical degeneration of bilateral UPs [5,12]. In general, the comparison of UPs's parameters indicated that Chinese patients had smaller dimensions of cervical vertebrae compared with the other population [13,14].

For the patients who suffered cervical spondylotic myelopathy, the distance between the UP and the medial border of the transverse foramen is narrower than that of a healthy person. The UP becomes larger and flatter as individuals get older, losing its sharp and bony characteristics. Tubbs et. did not regarded the UP as synovial joints. Instead of that, he regarded it as a product of the formation of fibrocartilage and new bone because of reactive osteogenesis and degeneration. The UP and inferior border of upper cervical vertebral body forms the uncovertebral joints. The uncovertebral joints are in a lifetime development from a rudimentary joint up to a mature joint and eventually degenerate. The uncinate osteophytes forms when the uncovertebral joints degenerate, causing compression effect in nerve root or vertebral artery.

There are some strengths in our study. First, to the best of our knowledge, this is the first study gauging the morphology of Chinese patients cervical uncovertebral joints and UP based on 3D reconstructions. Second, compared with the studies before, the researchers always use the cadaver to measure the parameters of UP and morphology. The data and conclusion may not be as accurate as that done in CT measurement of living persons. Third, in our present study, we compared the anatomical changes between the UP in normal cervical spine and that in the patients suffered from cervical spondylotic myelopathy.

This study had several limitations. It was retrospective study, and the sample size may be insufficient. Second, the patients selected for the degenerative group was the patients suffered from one typical disease. Selection bias may have influenced the conclusion. Finally, age and gender may play an important role in the UP degeneration. Owing to the small size sample, we could not analyse these factors in each group.

Conclusion

This study suggested that in most cases of Chinese patients, one can resect part of UP to complete foraminotomy within the spinal canal up to 6.73 mm of width between inferior vertebral endplate and superior vertebral endplate in the intervertebral space and up to 5.09 mm of depth from medial border of the UP to the lateral side at C3 to C7 without interfering the spinal nerve root and vertebral artery. It is recommended that the surgeon should pay great attention to the preoperative CT scan and careful operation during the surgery.

Author contributions statement

Each of the coauthors has involved in the design of the study, data analyses, interpretation of data and writing of the manuscript. All authors have read and approved the final submitted manuscript.

Conflict of Interest

There is no conflict of interest to declare.

Acknowledgement

This study was funded by following fundings: Sun Yat-sen University, China, Grant numbers: 80000-18843410; National Natural Science Foundation of China, China, Grant numbers: 81772293, 81772302; Department of Science and Technology of Guangdong Province, China, Grant numbers: 2019A030317003.

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