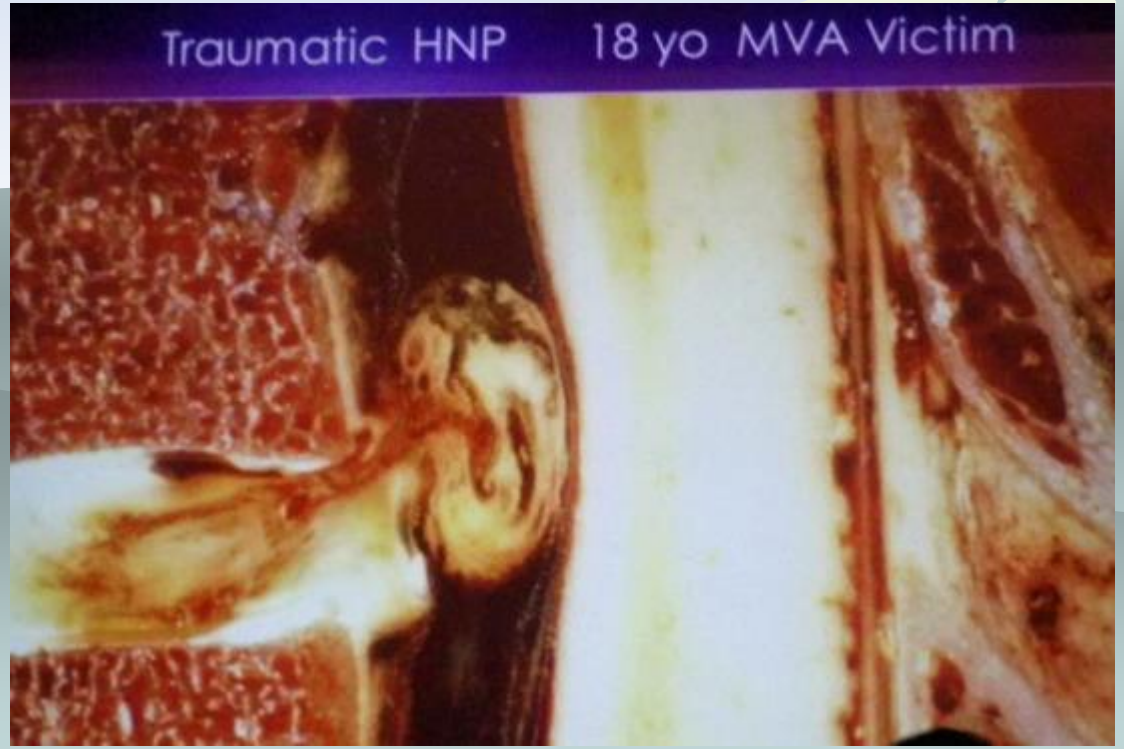
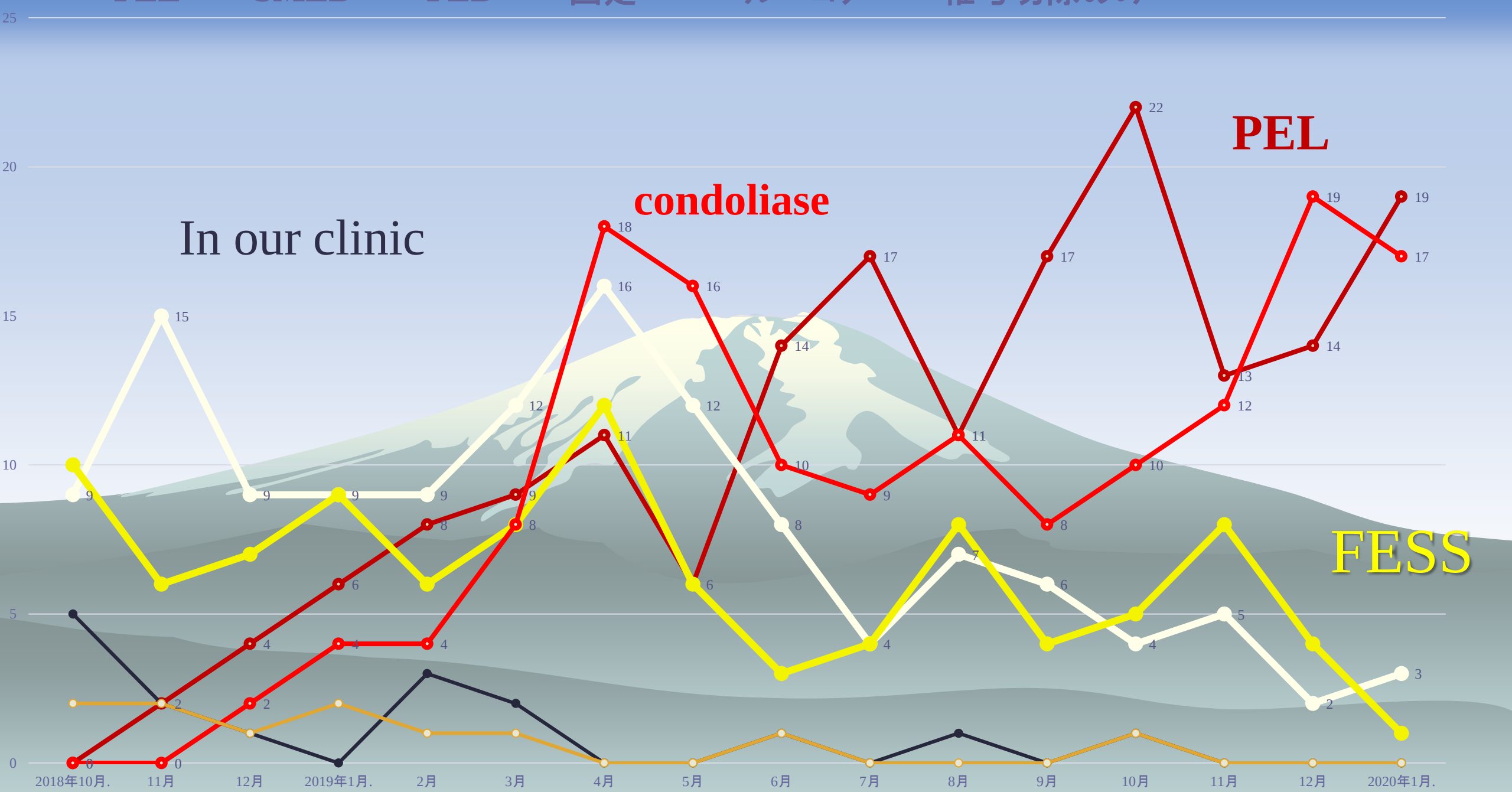
Injection therapy in the intervertebral disk by the condoliase



Meiryukai Akira Dezawa

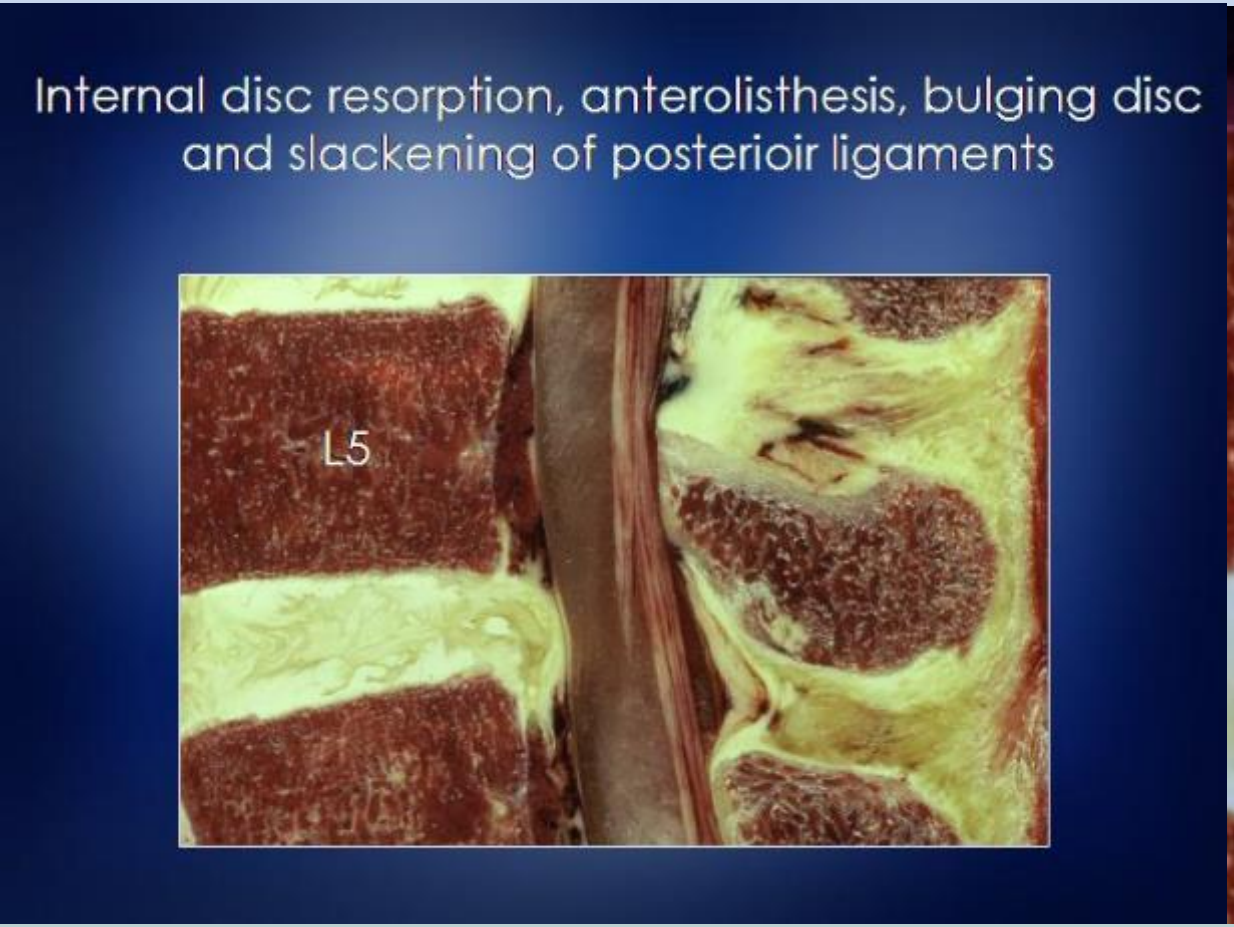

In our clinic
condoliase
PEL
FESS
25
20
15
10
5
0
2018年10月.
11月
12月
2019年1月.
2月
3月
4月
5月
6月
7月
8月
9月
10月
11月
12月
2020年1月.

The cases of FESS surgery **15/180 (8.3%)**

- The symptom was improved, but wants to raise QOL more — 3cases
- Herniation combined with SCS — 2
- Overlook the lateral recess stenosis — 1
- Stimulate ganglion(POD) — 1
- Others — 8

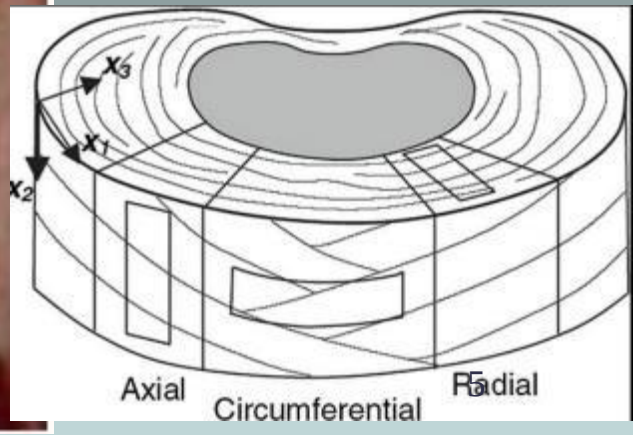
Sub ligament

transligament

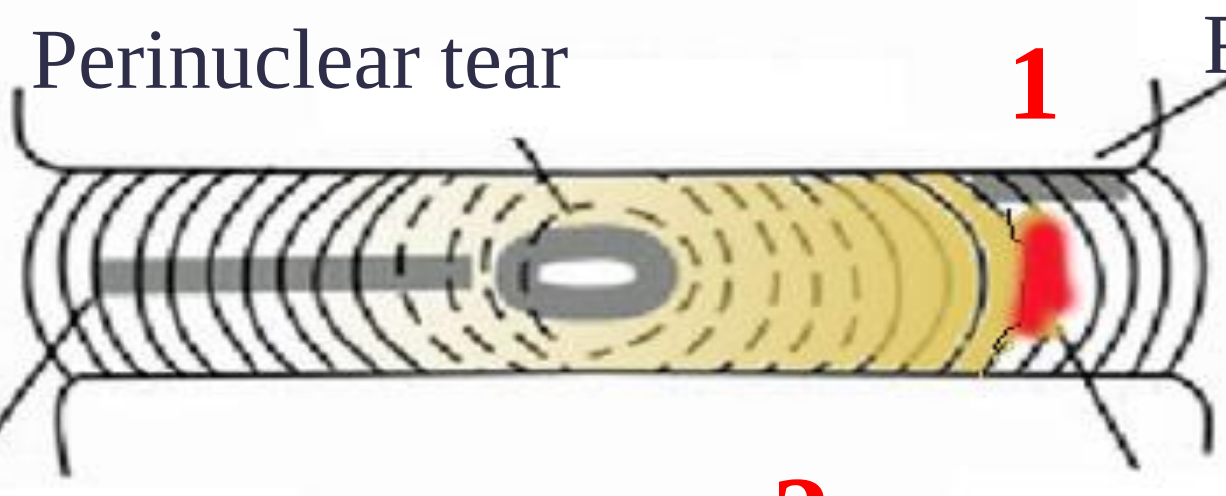


By courtesy of Raushning

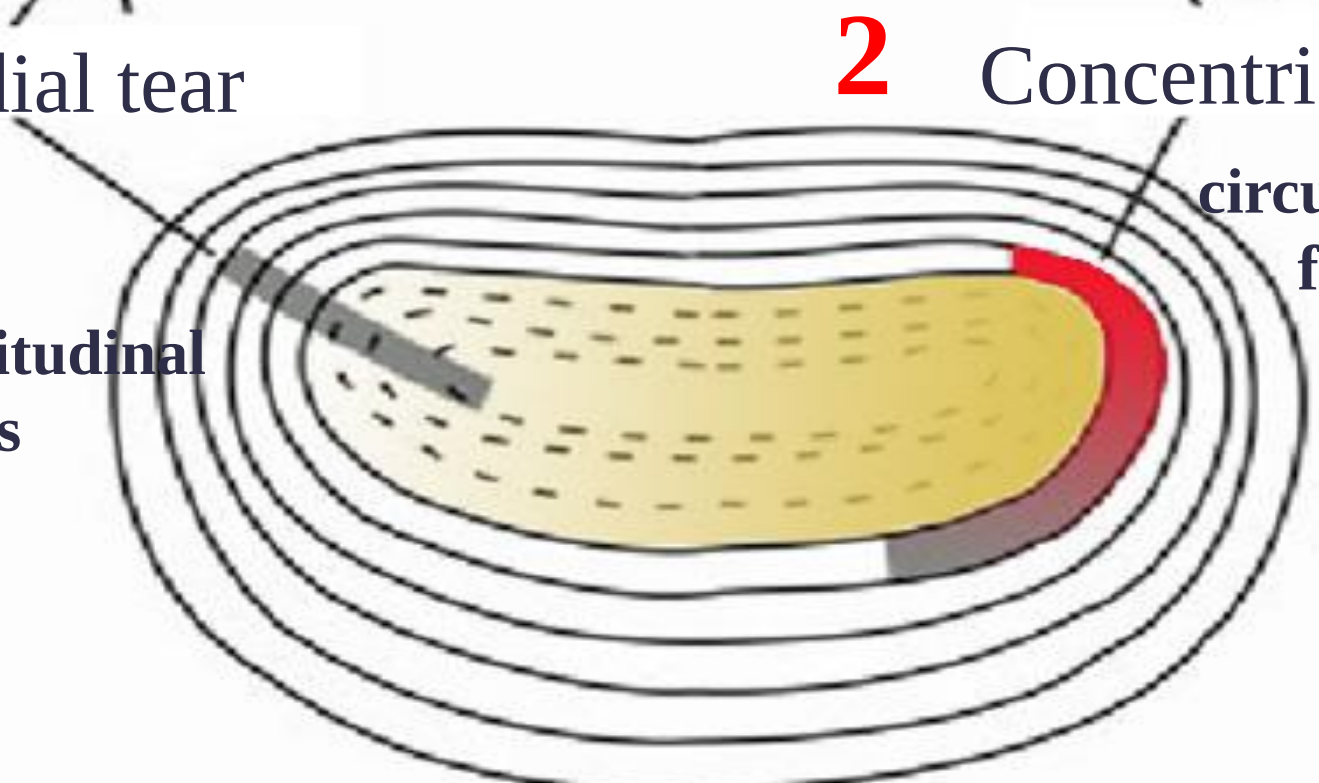

© Rauschning

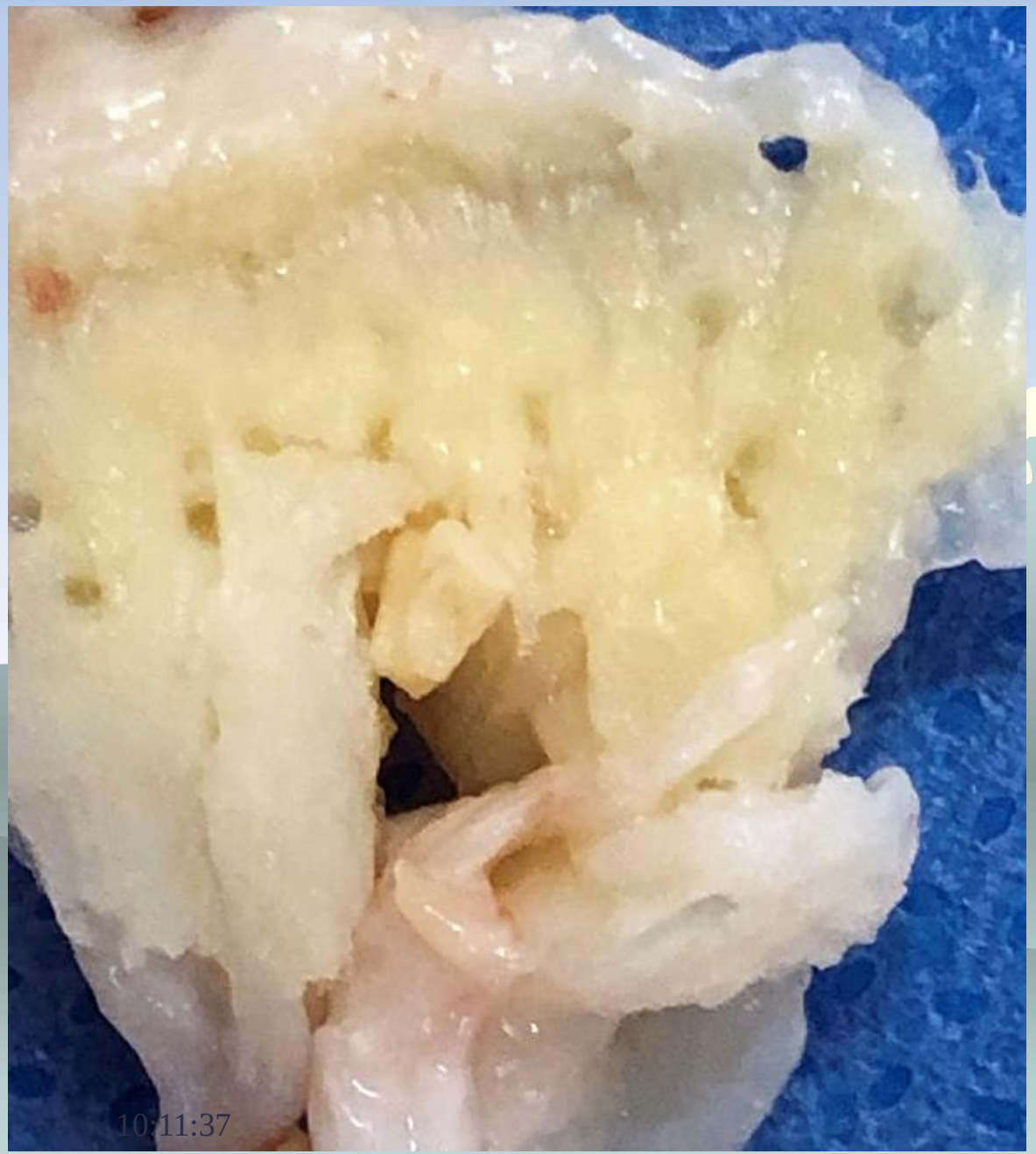

x_3
x_1
x_2
Axial
Circumferential
Radial

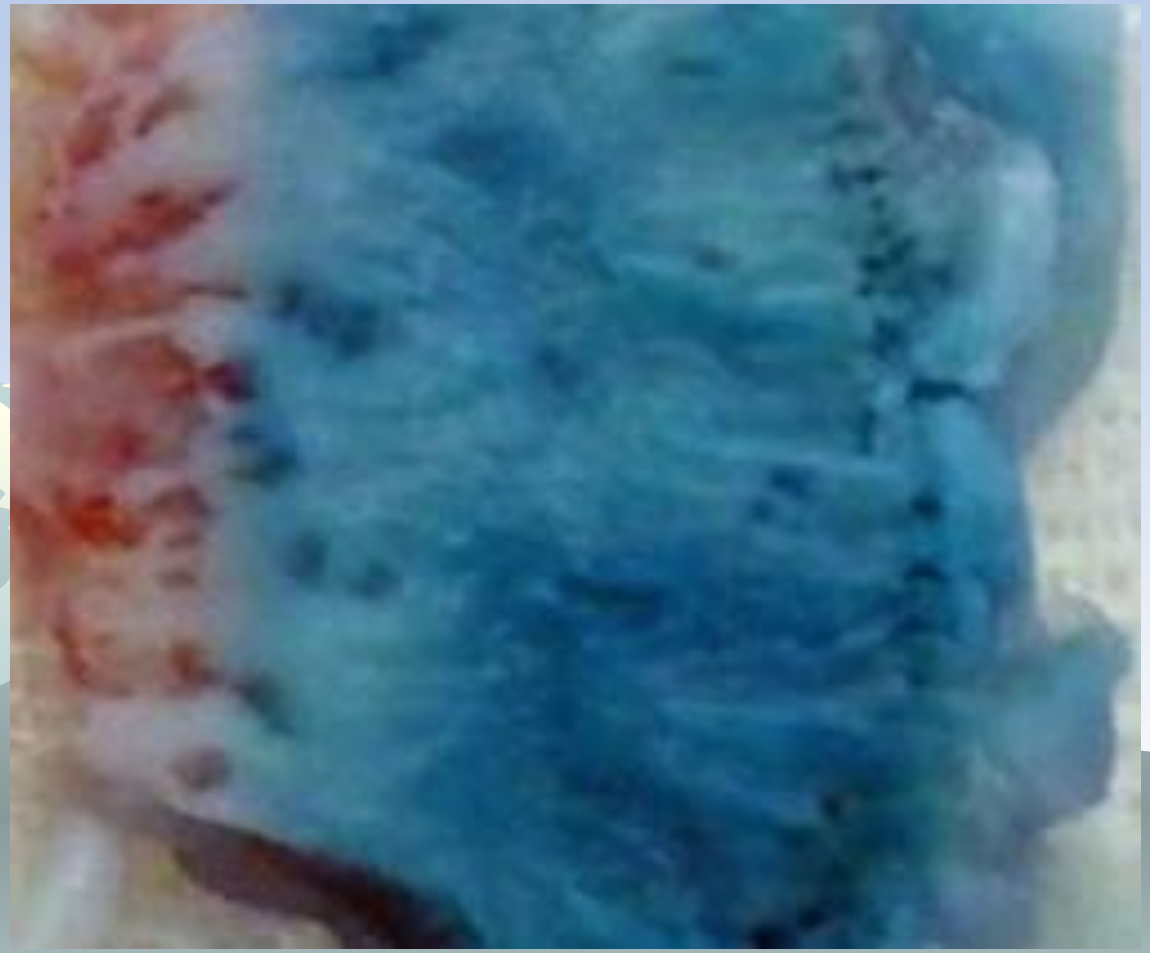
Classification of tears of the intervertebral disc

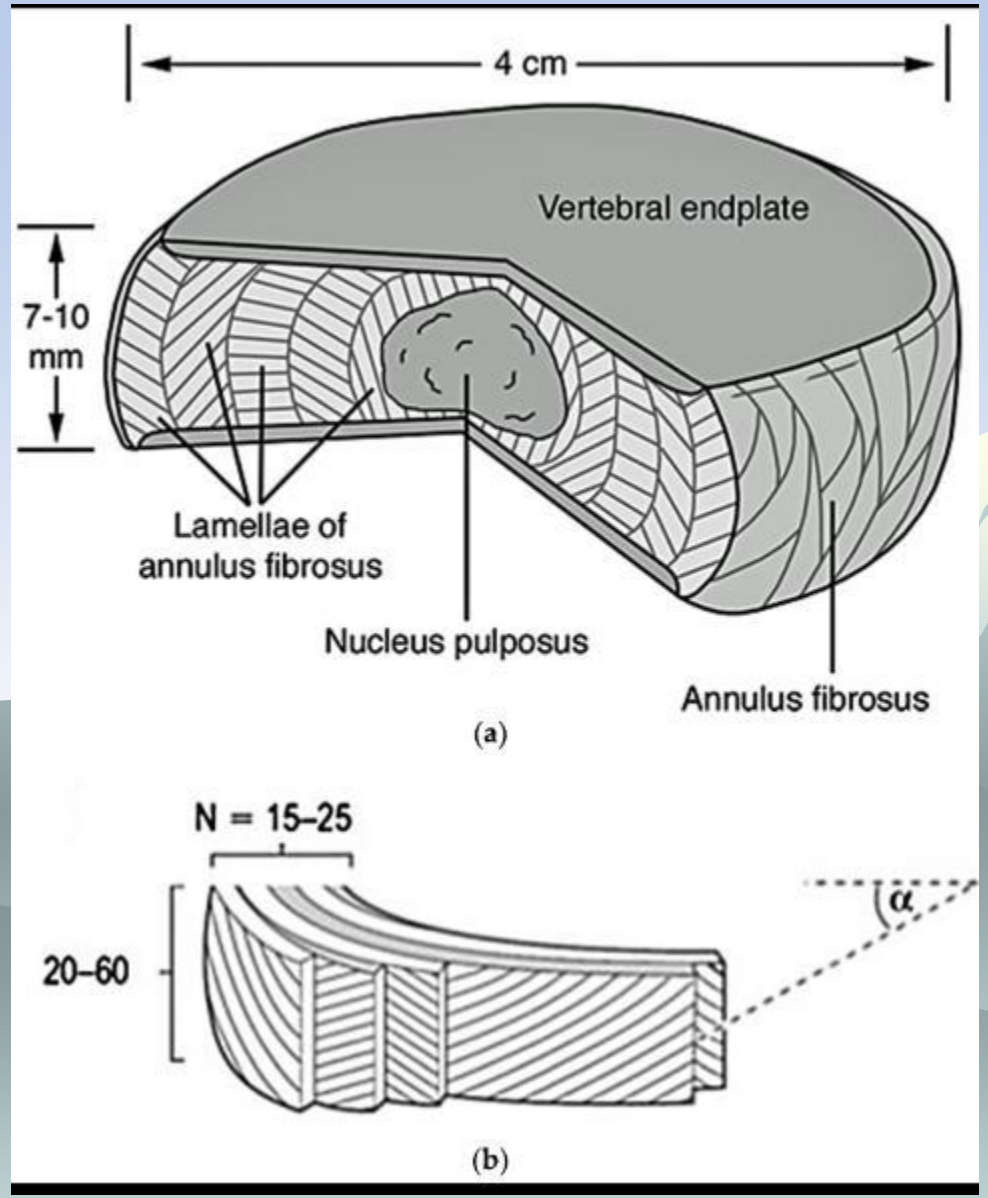


10% superior rim lesion
27% inferior

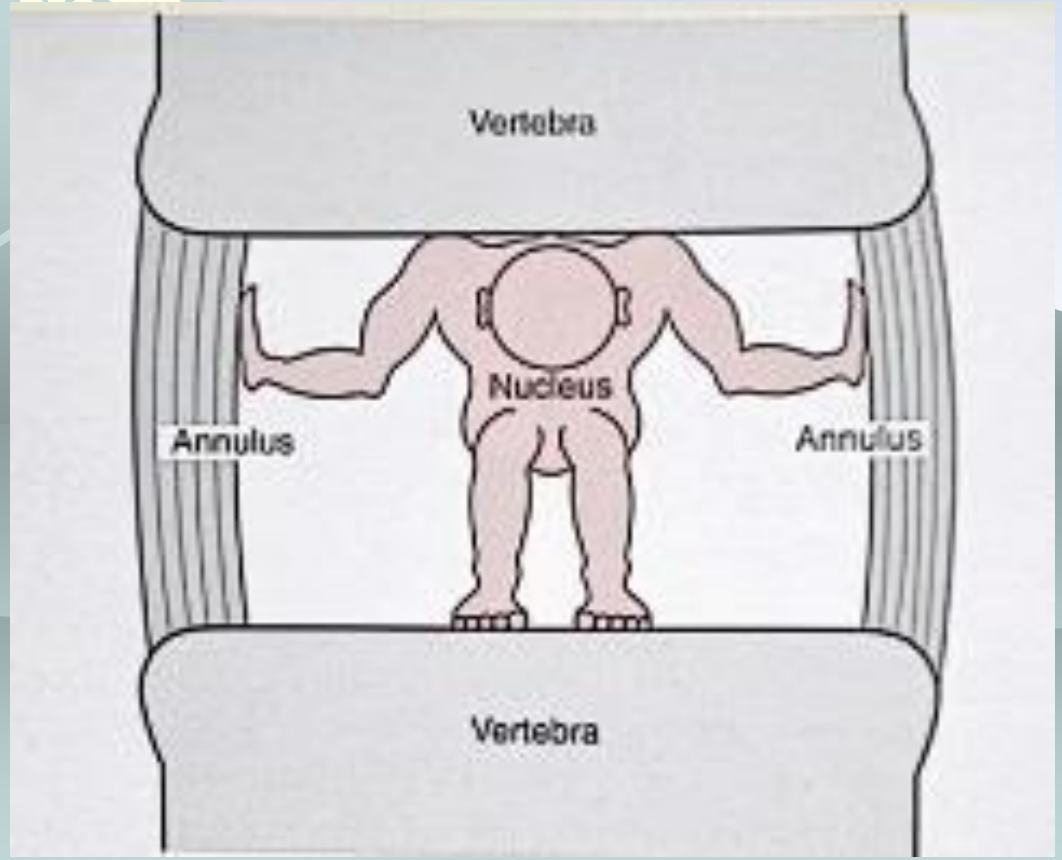








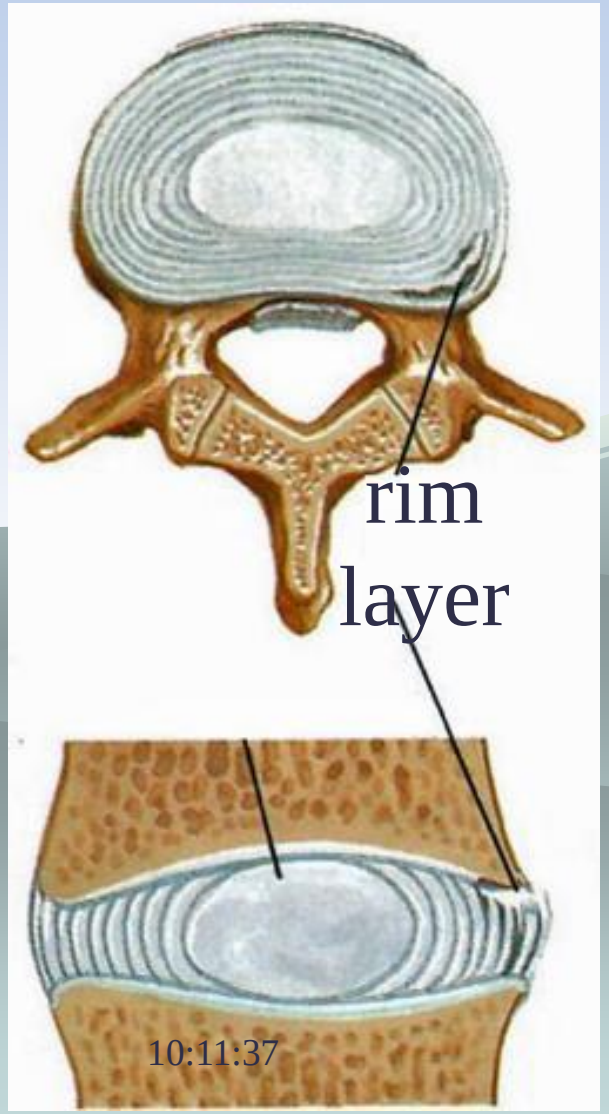
- Collagen 10-25 laminar structure
- Front side is thick、rear is thin
- 30 inclination from a plane
- most outer layer is Sharpey fiber
- depths touch it with the cartilage end plate

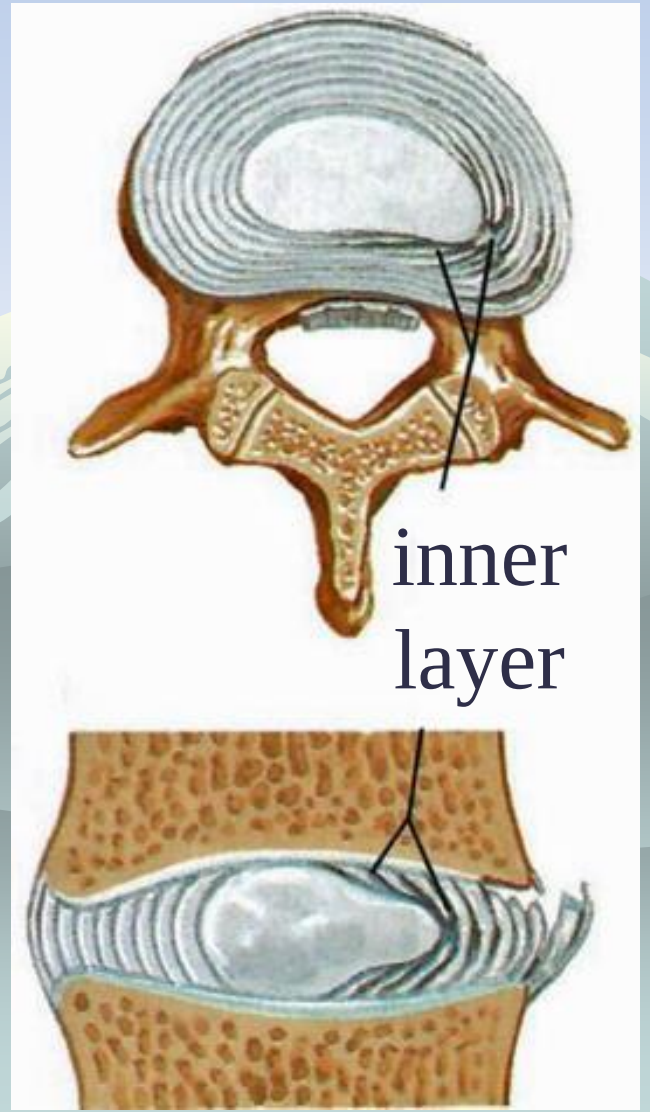


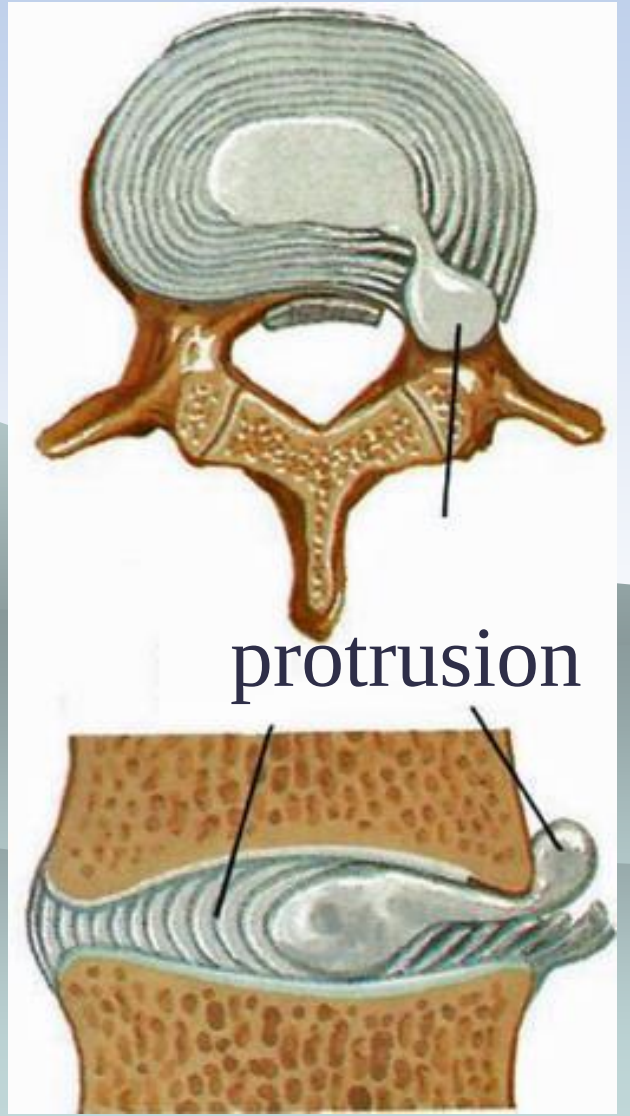
Marginal injury

Weakening and
tear of inner layer

Protrusion

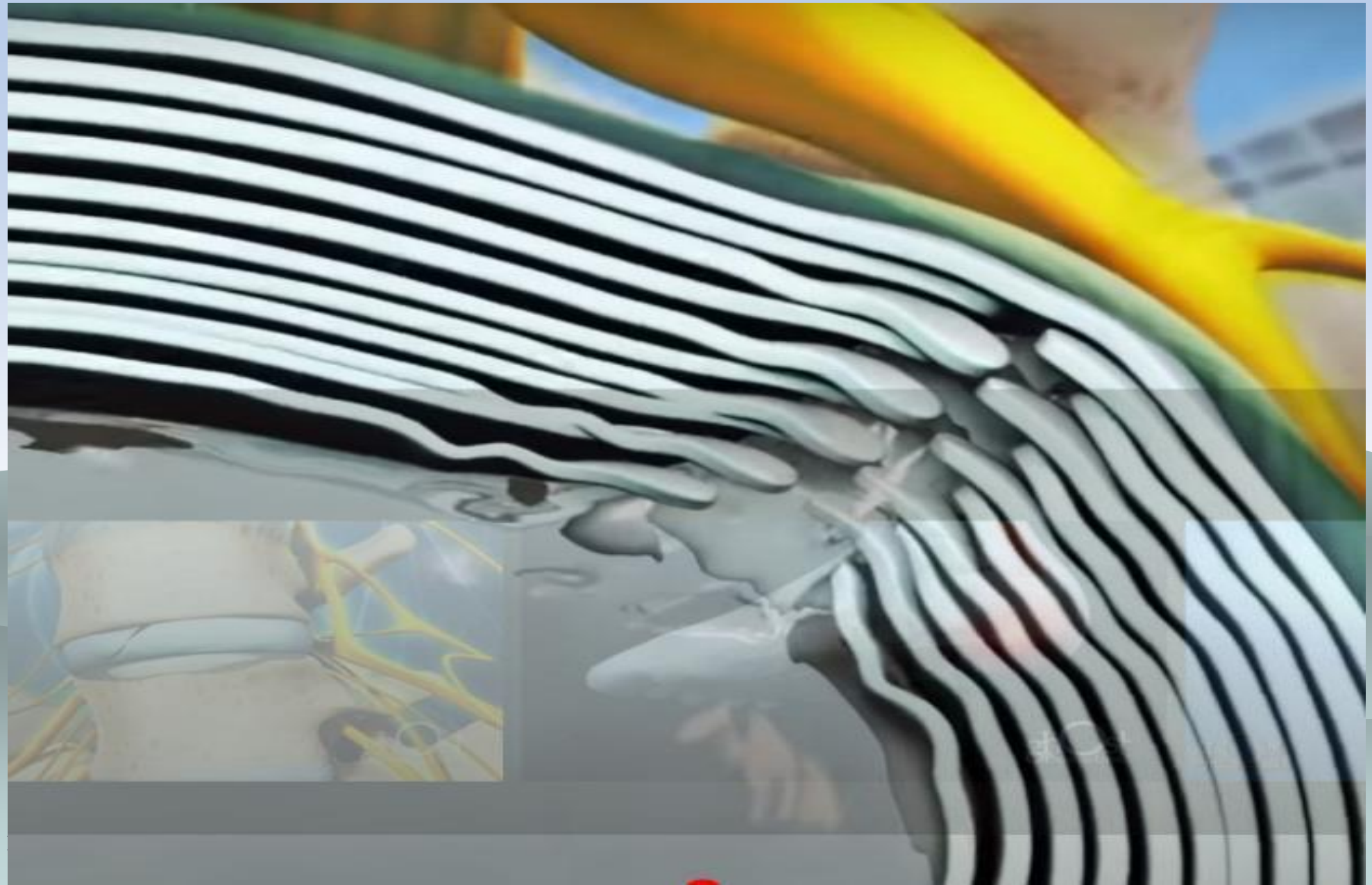




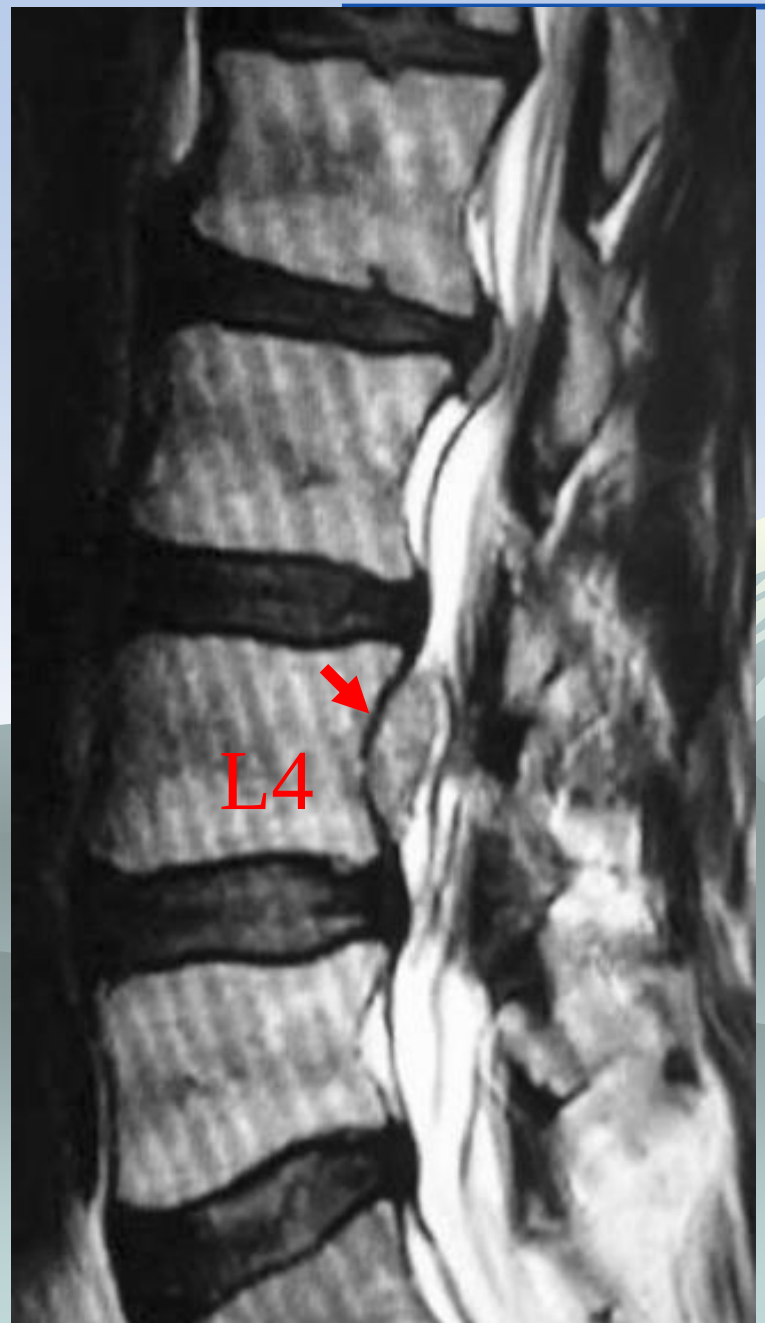


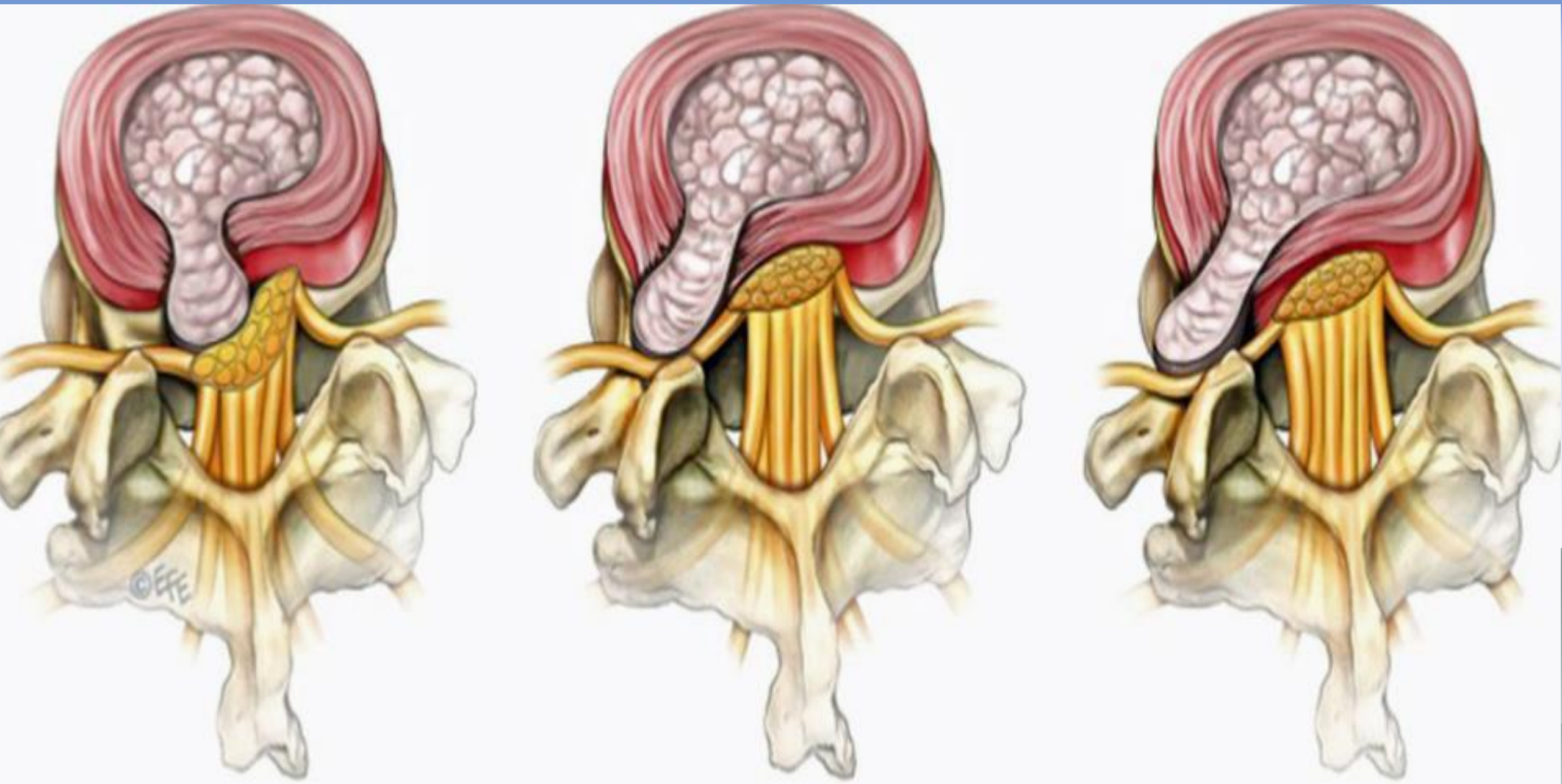
10:11:37

delamination



Mechanism of cranial migration





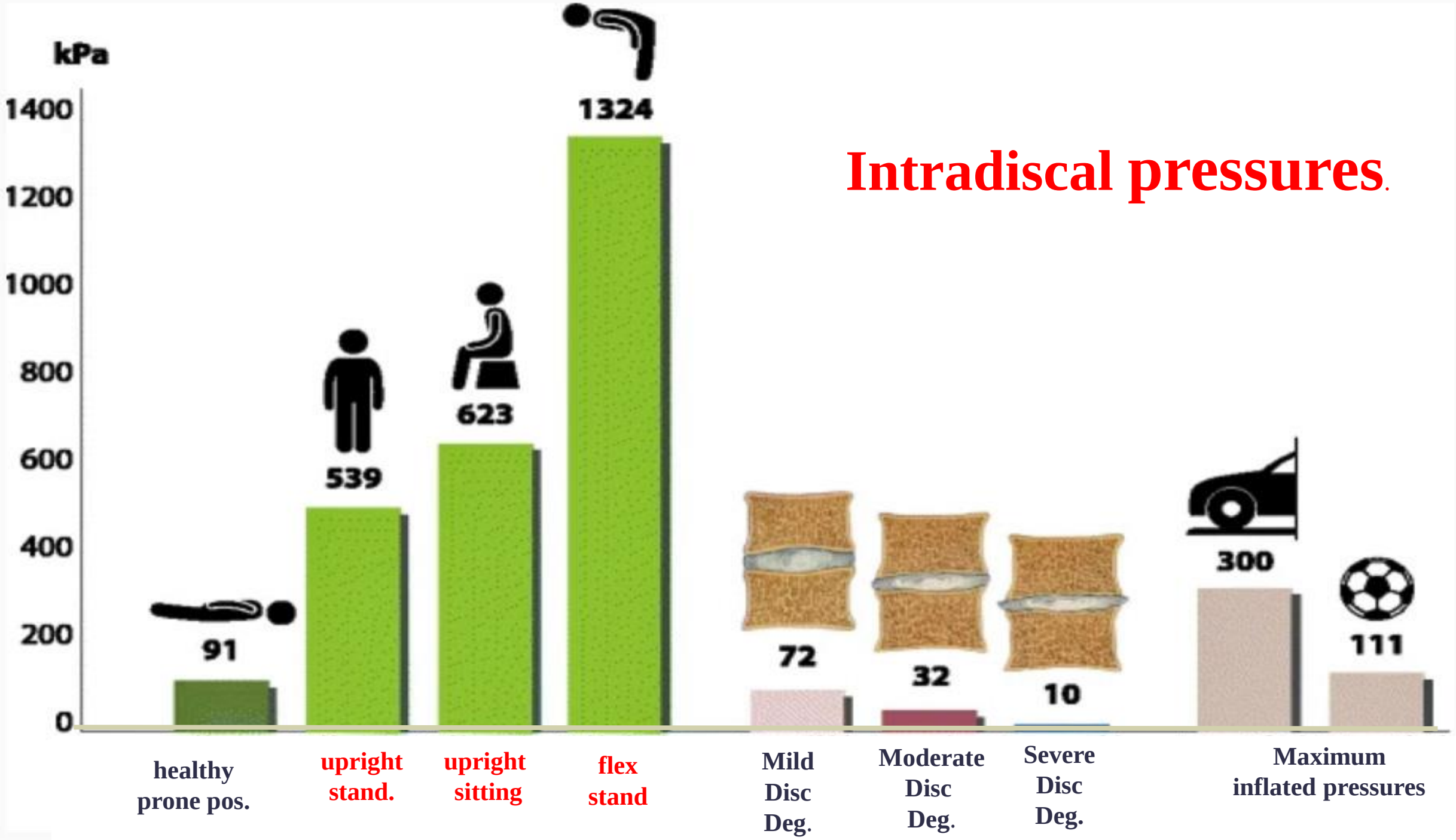
(I) Median or paramedian

(II) Foraminal

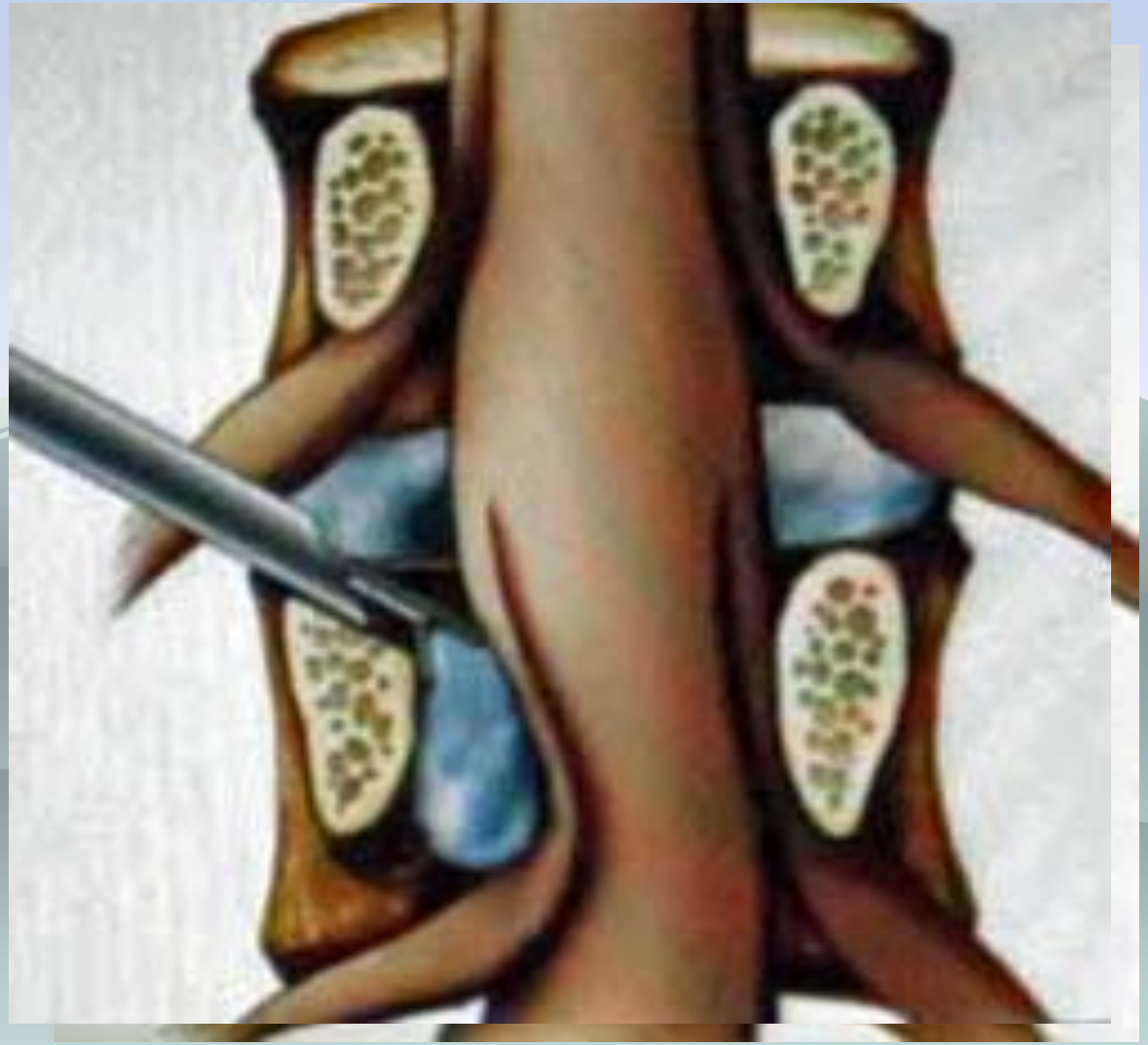
(III) Extraforaminal

神経根
下椎体椎弓根靱帯
上椎体椎弓根靱帯
黄色靱帯
上横椎管孔内靱帯
下椎体横突起靱帯
中横椎管孔内靱帯
下横椎管孔内靱帯

Intradiscal pressures.



Oblique pediculectomy to caudal migration hidden zone approach



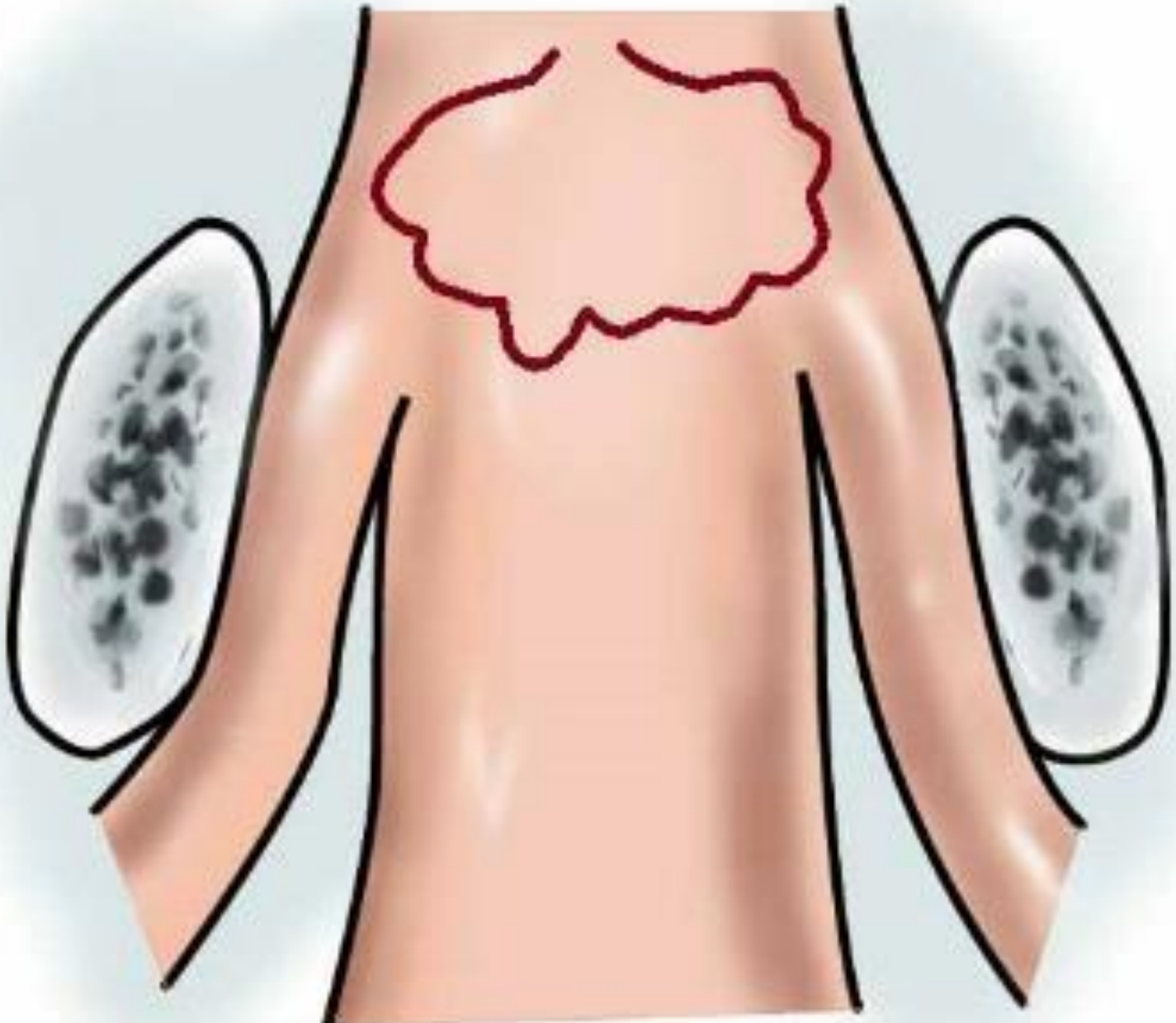
history of the hernial disk extraction

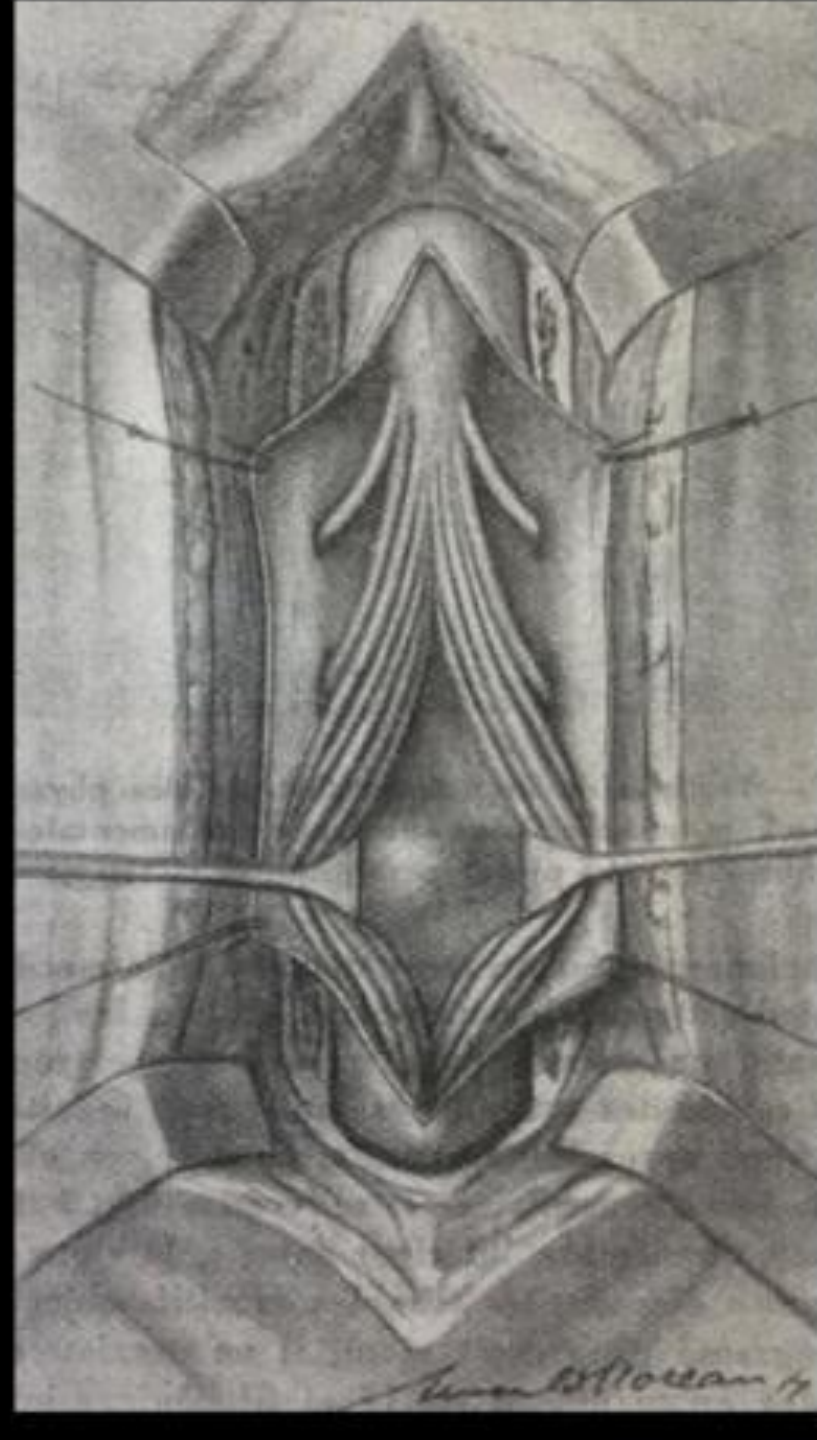
- 1700 Cotugno and Kocher
- 1919 [illegible] and Cushing enchondroma
- 1934
- 1938 [illegible]xtradur[illegible]
- 1932 [illegible]t Yoic[illegible] sciatica is
- 1977 [illegible]rologic[illegible] surgery
- 1970 [illegible]many p[illegible]ation would improve without surgical intervention.
- 1977 Casper microdiscectomy

Joseph Barr in 1964
In a special TALK to the Orthopaedic club of San Diego said: "He is sorry to see so many failure back surgery".

He said; "we must find another technique to remove a few grams innocent tissue of herniated disc which gives so pain relieve to the patient with a fewer IATROGENIC complications (Jonathon Cohen, 1986).

We dedicate this technique (UED) to the memory of Joseph Barr





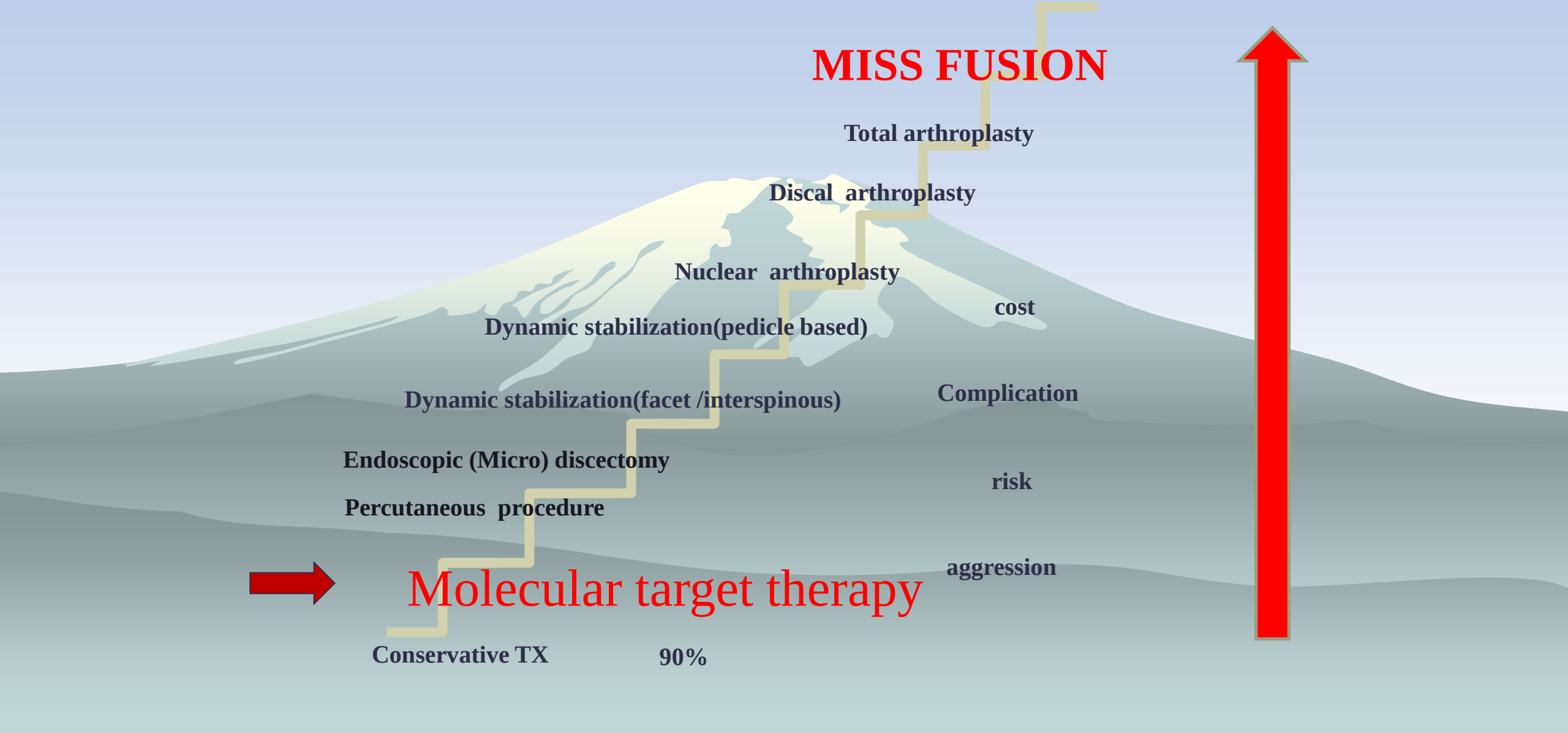
history of the hernial disk extraction

- 1700 Cotugno and KocherMacEwen, Krause, Taylor, Dandy, and Cushing, enchondroma
- 1919 Goldthwaite
- 1934 Mixter and Barr
- 1938 Love described the intralaminar, extradural approach.
- 1932 Surgery of the assistant professor at Yoichi Azuma (Kyushu University)sciatica is successful
- 1977 Yasargil University of Zurich neurological surgery Father of the microsurgery
- 1970 Weber and Hakelius, showed that many patients with lumbar disc herniation would improve without surgical intervention.
- 1977 Casper microdiscectomy

Automated Percutaneous Lumbar Discectomy (APLD)

Automated percutaneous lumbar discectomy (also referred to as Percutaneous Nuclectomy) was introduced by Gary Onik in 1985 as a means of providing a more safe mechanical means of physically debulking the interior of a disc.

misTX of Lumbar surgery



endoscopy lumbar spine surgery minimally

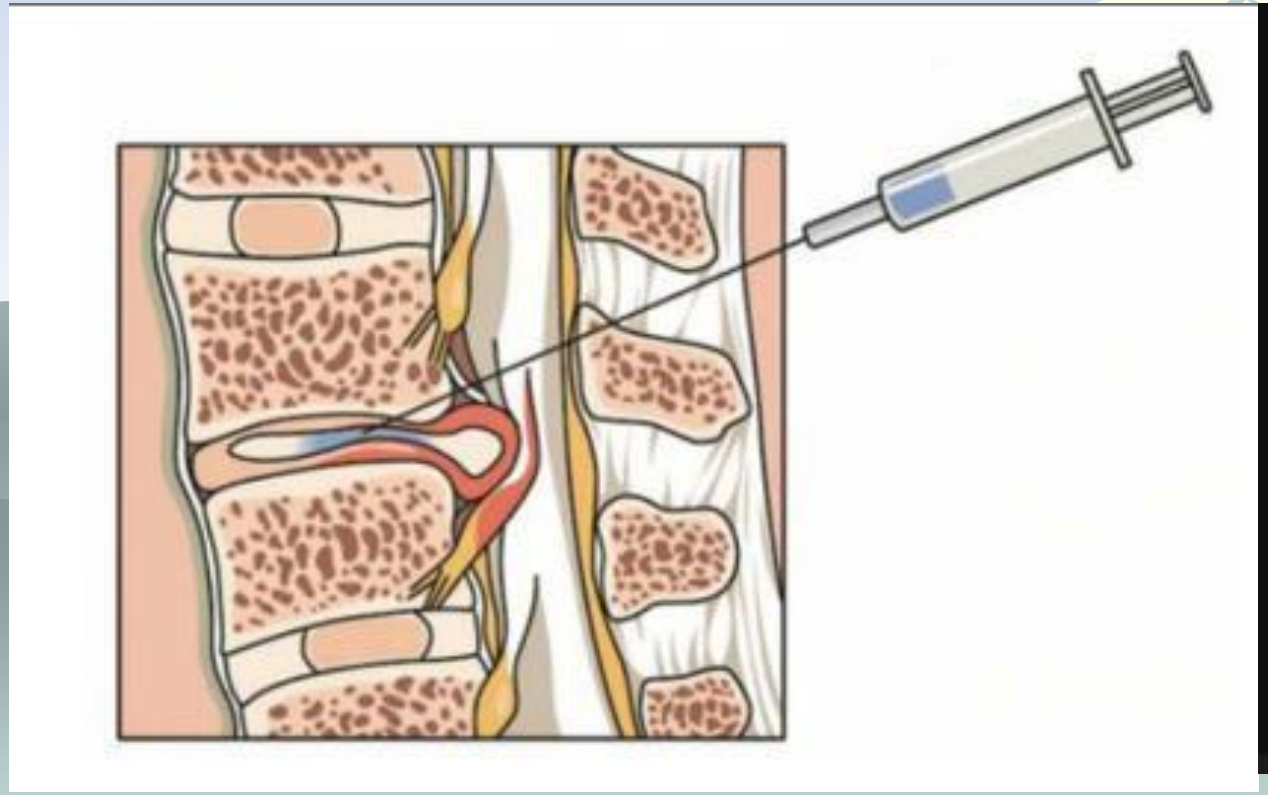
sprout cradle establishment seedtime maturation

	1995–2000	2000–2005	2005–2010	2010–2015
	Laparo	laparo thoraco	MED	PELD-Full endo
前方腰	.210.237.238.207.208.212.214.215.216.	182.176.172.184.187.188.189.192.193.	120.118.91.126.131.137	.61.26.25
	217.218.223.224.225.227.228.231.235.236	194.195.196.198.199.200.203.204.205.206		
MED		150.152.159.160.166.179.1	*79.80.85.89.92.93.94.96.97.98.100*101.102.105.106.112.	29.18.16.31.35.36.37.42.*48.53.55.56*60.65.76.77.78
			113.116.121.122.130.132.137.140.143.145.147.148..	
PED	230.229241	151.155.169.	82.83.84.86.87.88.104.110.111.114.117.119.123.	1.2.3.4.5.6.7.8.9.12.14.17.19.20.22.24.27.40.41.43.44.
			124.125.129.133.135.136.141.142.	45.46.47.49.51.52.57.58.59.62.63.67.68.69.71.72.73.74
前方胸	213.209	153.165.168.177.178.185.186.197.	99.90.81.103.127.134.139.146.	33.32.13.54.64
ppts		180.171	157	.23.1.30
review		183.161	0.115	11
video etc		190	138neuroscopy	21
micro			109	34
arthoscopic	.232.222.219.234	202	95	66

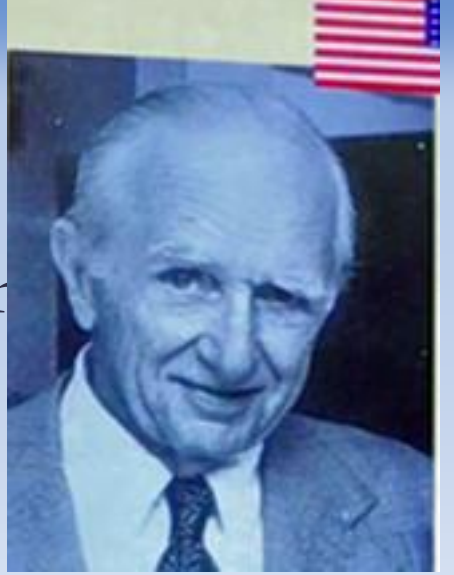
Molecular target therapy

1）steroid injection therapy in the intervertebral disk（SIDT)

2）Chemonucleolysis



Chymopapain(CP)

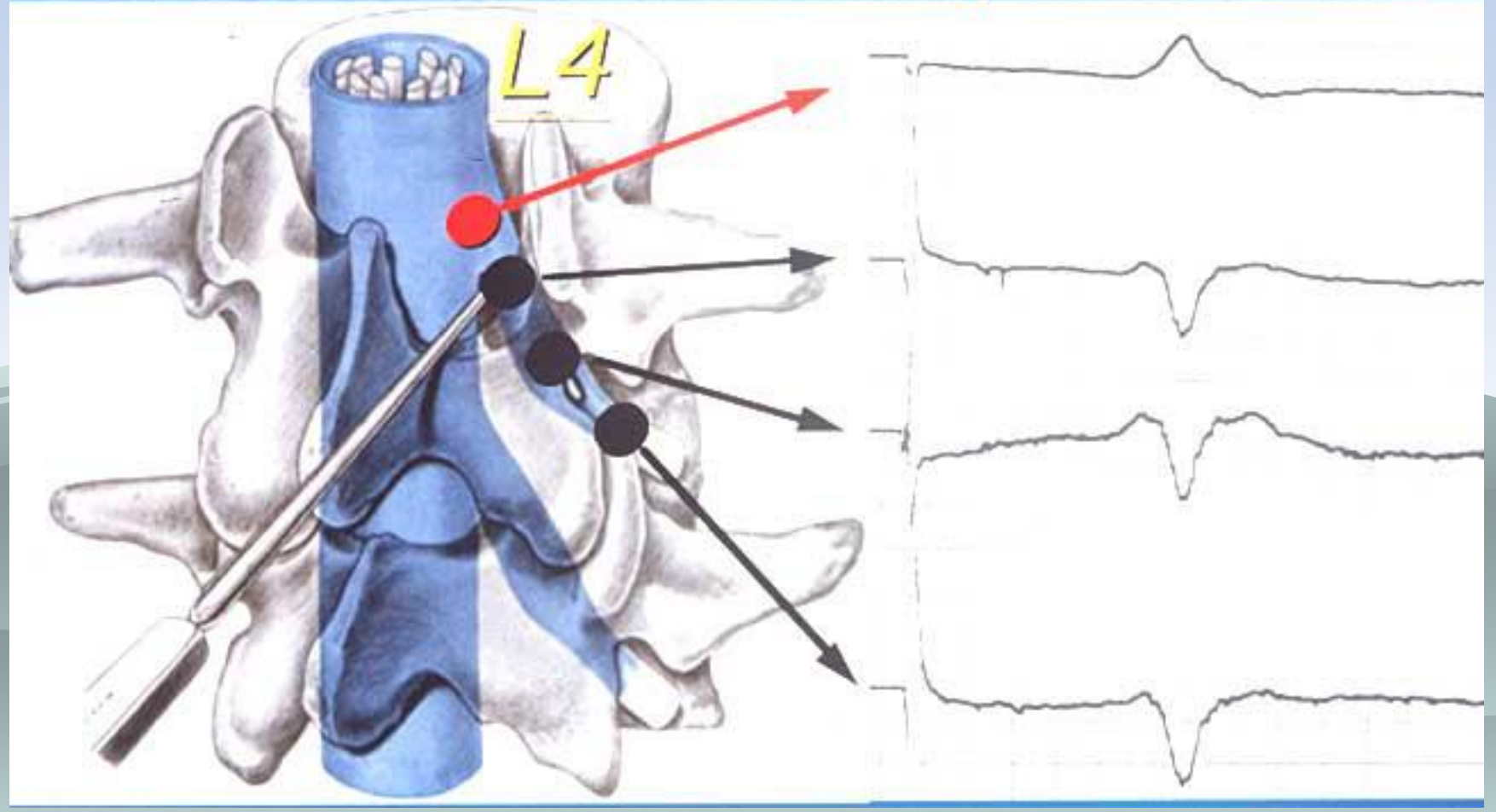


- 1941 Jansen Balls isolate it from the fruit of the papaya
- 1956 Thomas broken down cartilage cells with the CP in the ear
- 1956 Feffer steroid injection therapy in the intervertebral disk
- 1963 Smith Inject CP in intervertebral disk of rabbits
- 1964 Smith Ten clinical outcomes
- 1968 Yamagata extract chondroitinase ABC from ProteusVulgaris
- 1969 Sussman collagenase(nucleolysin)
- 1976 FDA A double-blind study does not show efficacy
- 1982 FDA Approval
- 1984 Japanese IDT society
- 1987 IITS(International Intradiscal Therapy Society)
- 2003 EU suspend CP

Trasylol, hyaluronidase, ozone, keratanase

Root action potential

Rt.peroneal N.stim.



Nerve conduction velocity(m/sec)

◆ Vehicle(n=6)	41	-
◆ CondroitinaseABC (n=6)	53	ns
◆ Chymopapain(n=3）	5	p＜0.05

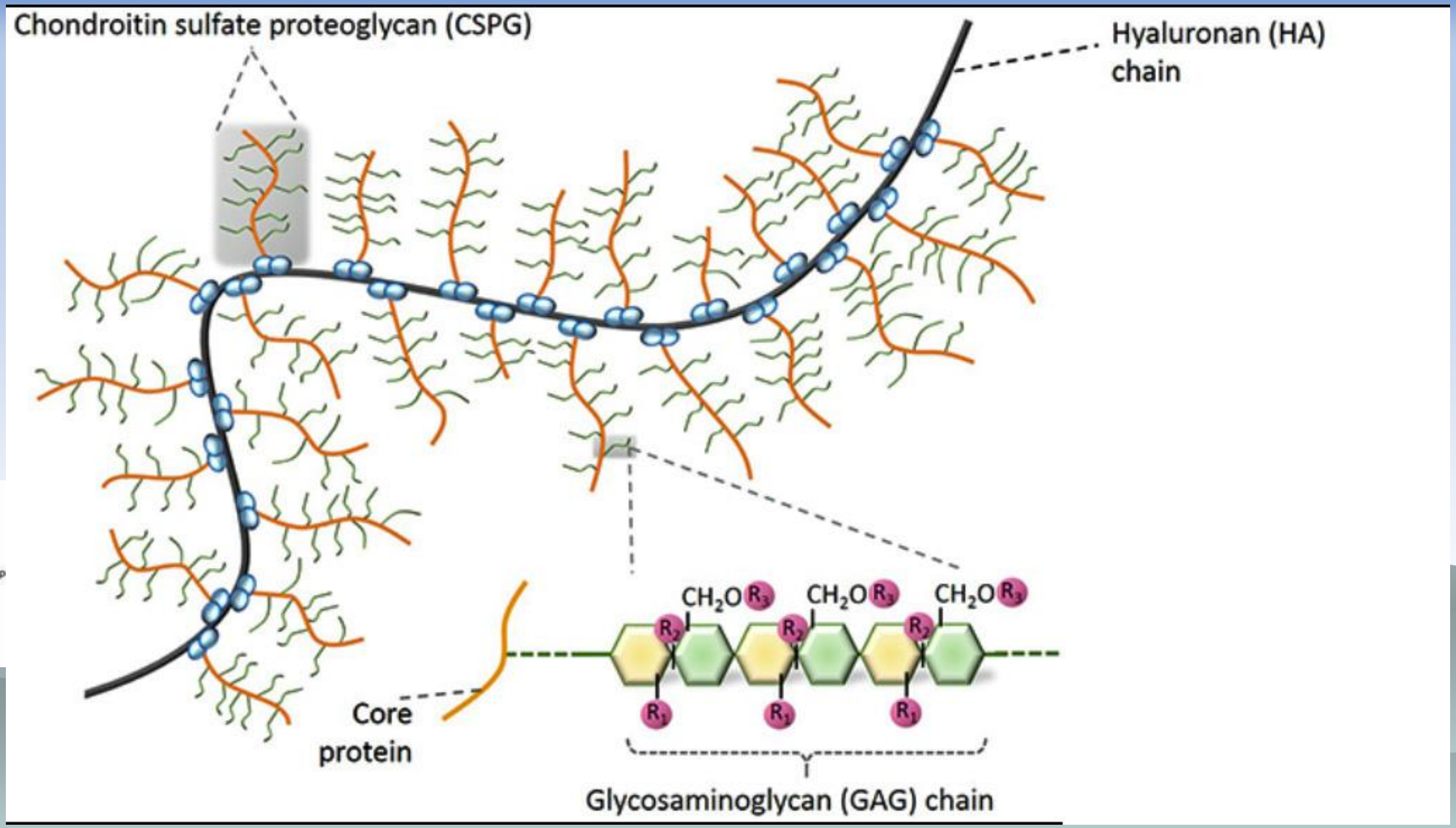
Olmarker Spine21:1996

Complications of CP(13500：1982-1991FDA)

- 0.5%Anaphylaxis (seven patients die 0.019%)
- 24cases infection
- 32 bleeding
- 12 paraplegia（Problem of the needle tip side）
  Haag(1999) late T8 myelopathy
- Subarachnoid hemorrhage due to the dural injury
- Cerebral hemorrhage

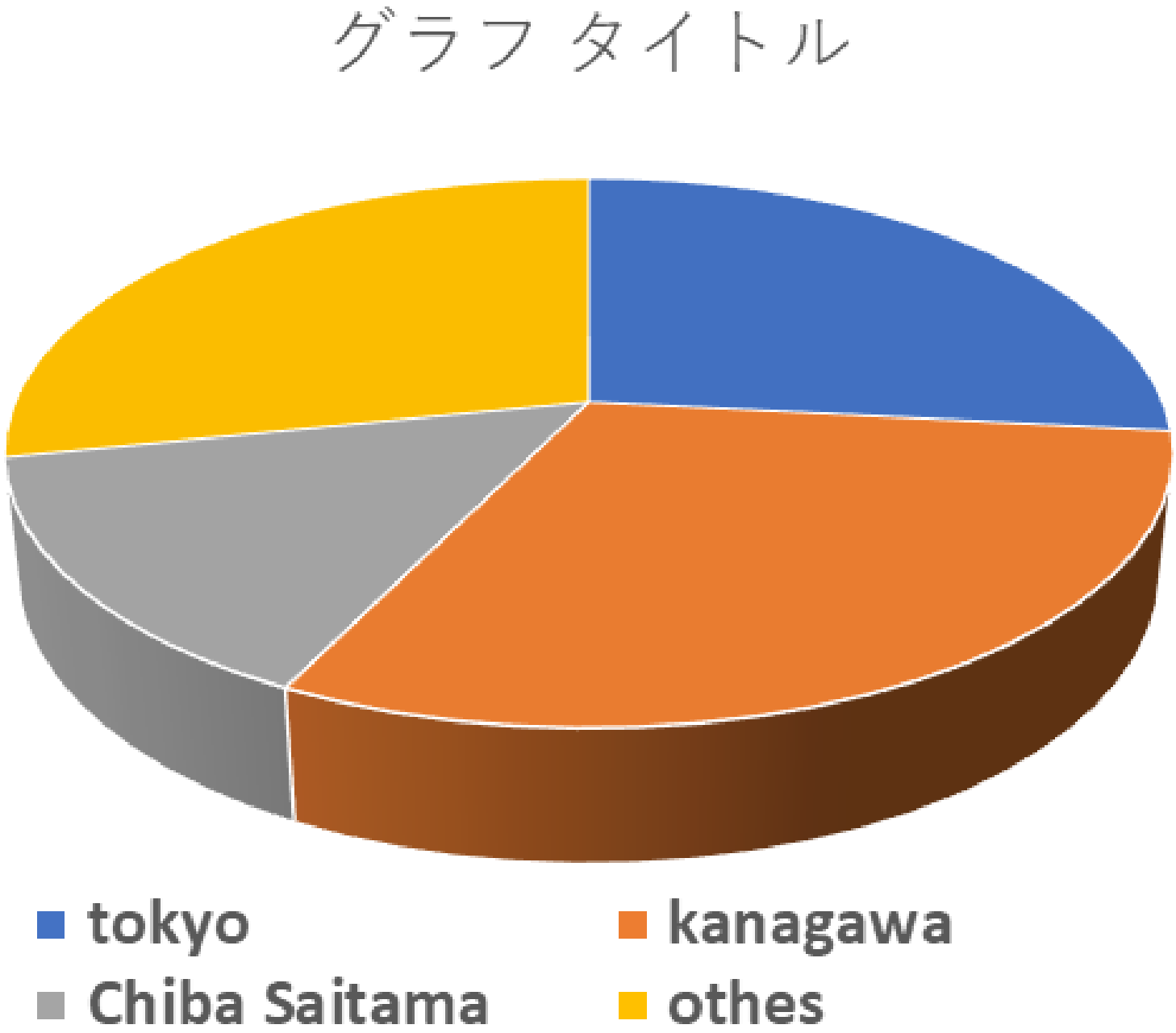
Clin Orthop Relat Res1993.122

Problems in adaptation and the procedure

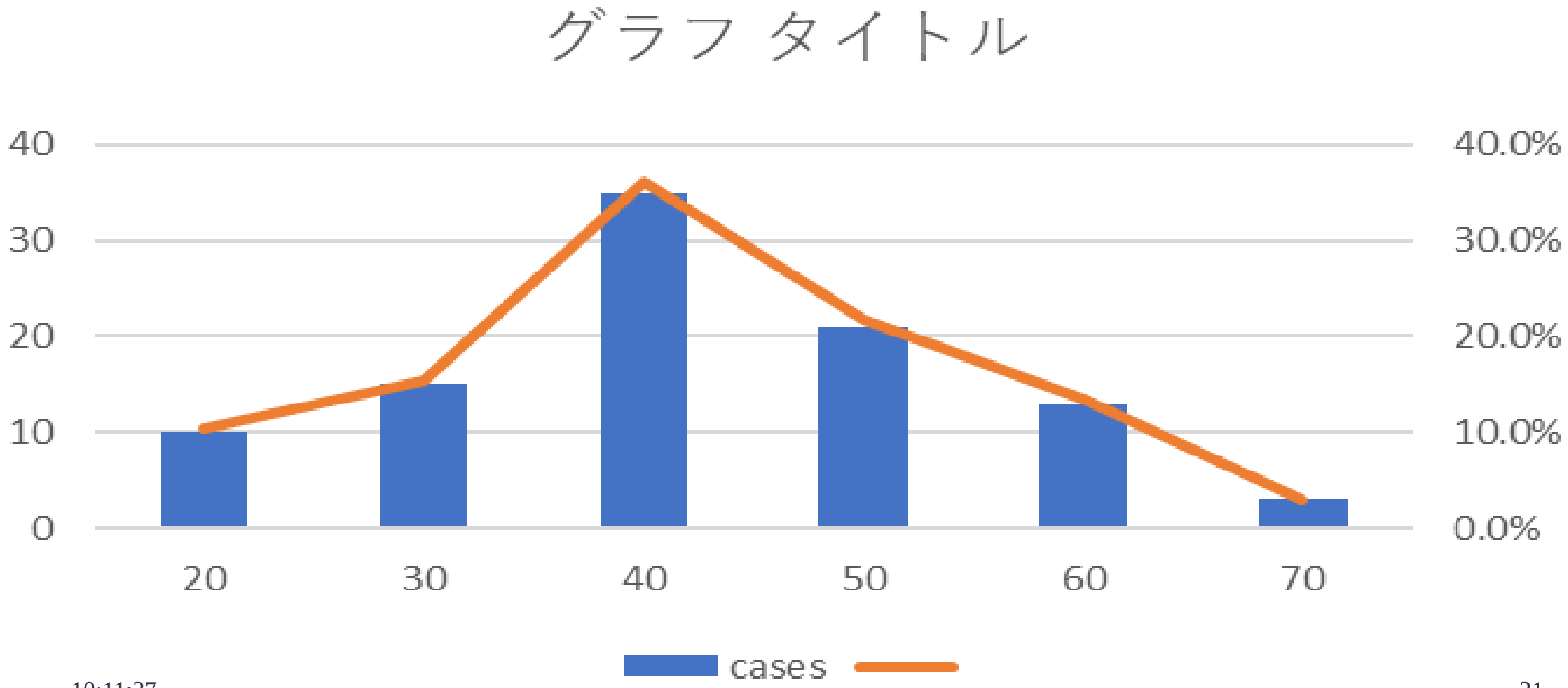

Chondroitin sulfate proteoglycan (CSPG)
Hyaluronan (HA) chain
Core protein
Glycosaminoglycan (GAG) chain

The cases of FESS surgery **15/180 (8.3%)**

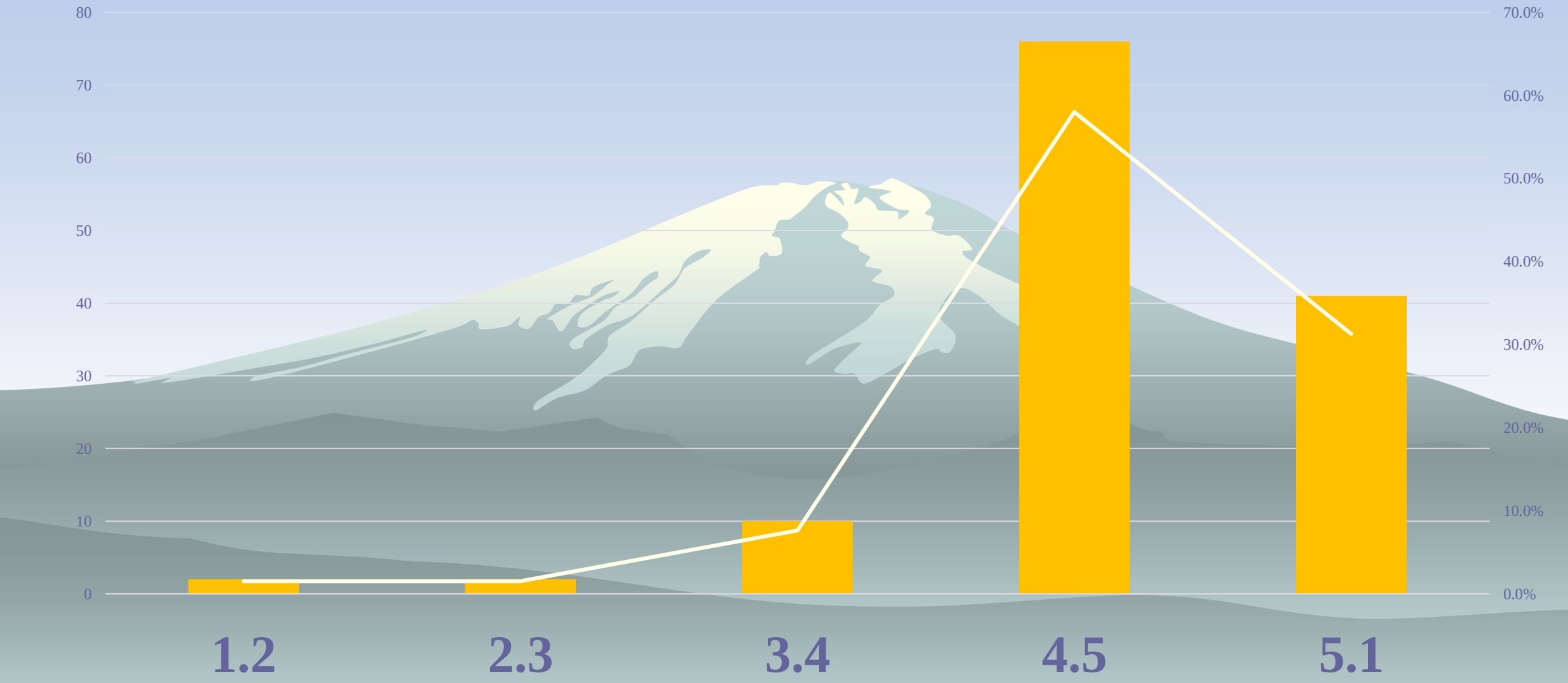
- The symptom was improved, but wants to raise QOL more — 3cases
- Herniation combined with SCS — 2
- Overlook the lateral recess stenosis — 1
- Stimulate ganglion(POD) — 1
- Others — 8


グラフ タイトル
tokyo
kanagawa
Chiba Saitama
othes

Condoliase patients in our clinic (2018,12-2020.3)



Cases at level



A grading system of intervertebral disk degeneration

Grade I	Disc has a uniform high signal in the nucleus on T2.	
Grade II	Central horizontal line of low signal intensity.	
Grade III	High intensity in the central part of the nucleus with lower intensity in the peripheral regions of the nucleus.	
Grade IV	Low signal intensity centrally and blurring of the distinction between nucleus and annulus.	
Grade V	Homogeneous low signal with no distinction between nucleus and annulus.	

Pfirmann

0

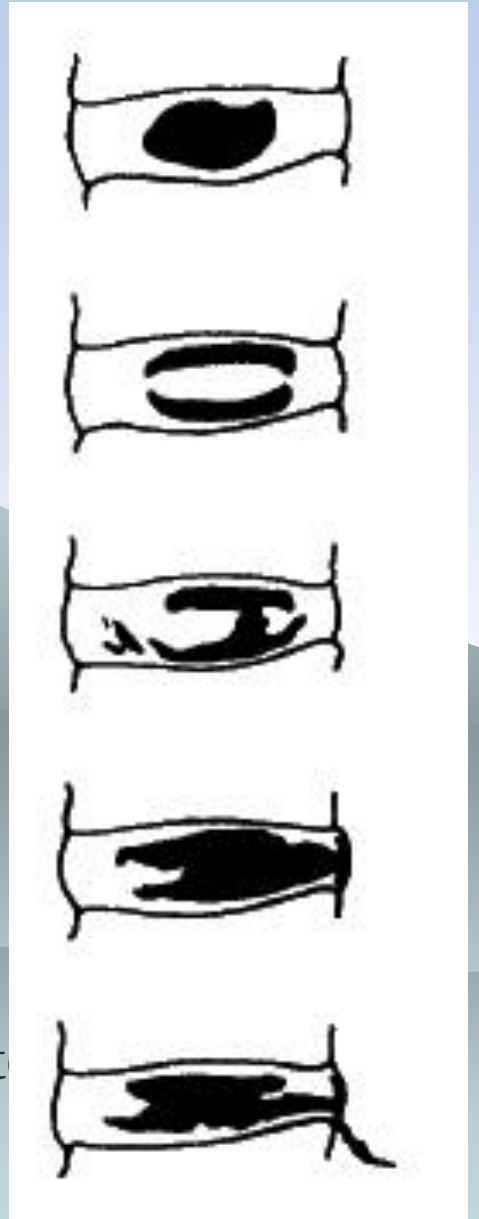
3

37

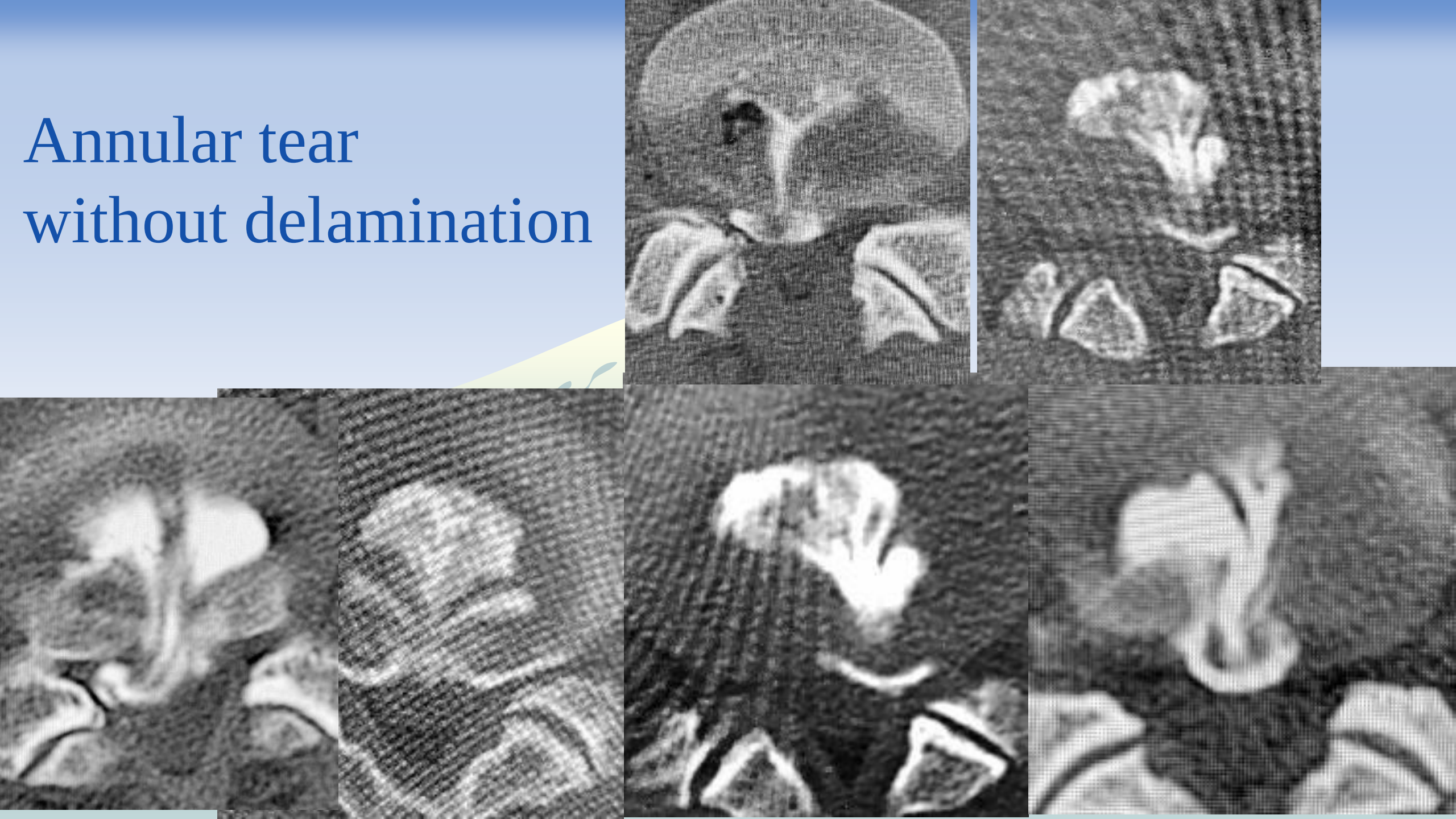
140

Discogram type stage of disc degeneration

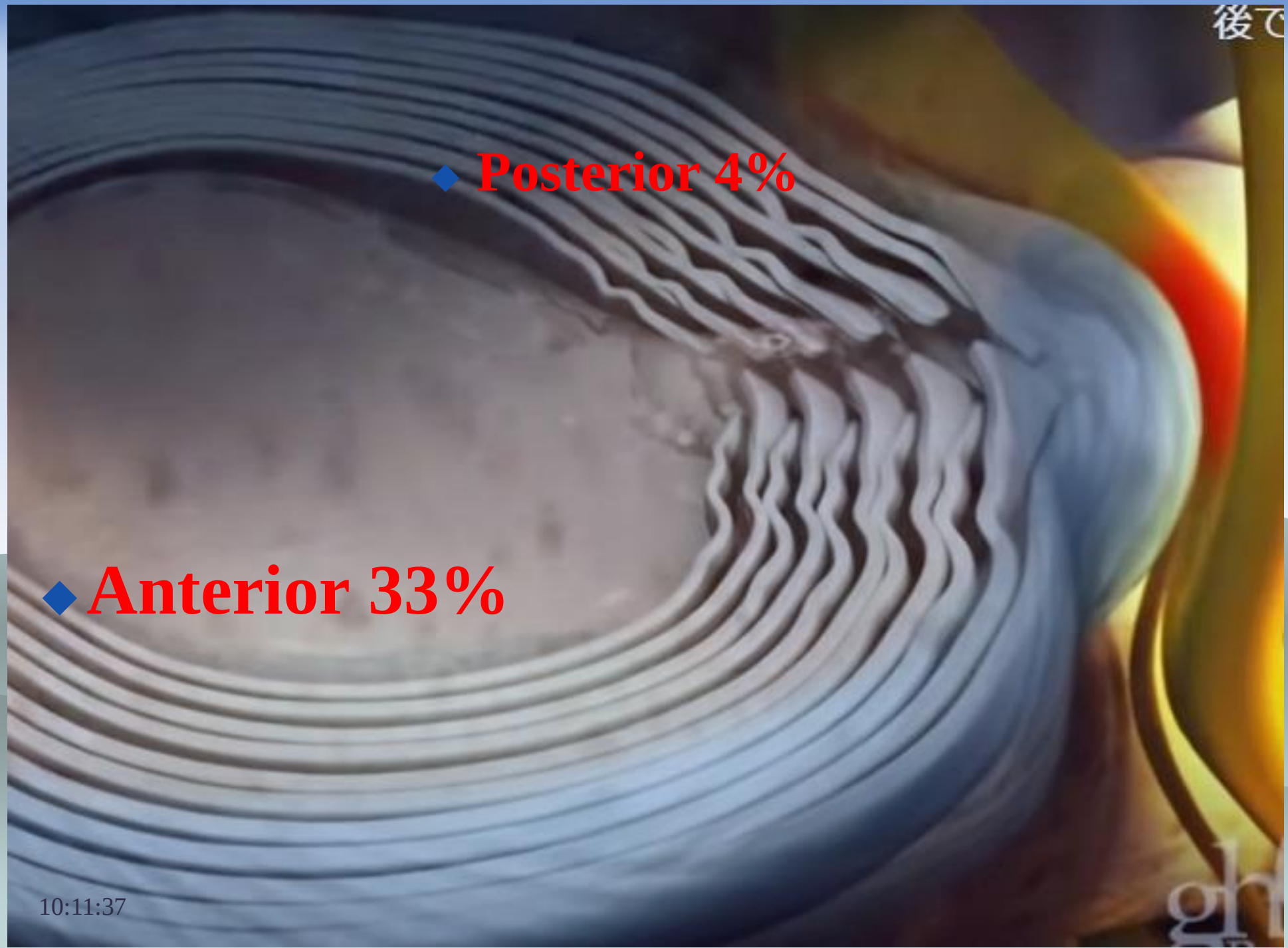
- **Cottonball** — no signs of degeneration soft white amorphous nucleus — 0
- **Lobular** — mature disc with nucleus starting to coalesce fibrous lumps — 0
- **Irregular** — degenerated disc with fissures and cleft in the nucleus and inner annulus — 9
- **Fissured** — degenerated disc with radial fissure leading to outer edge of annulus — 45
- **Ruptured** — Disc has a complete radial fissure that allow fluid t escape. can be any state of degeneration. — 126



Annular tear without delamination



delamination



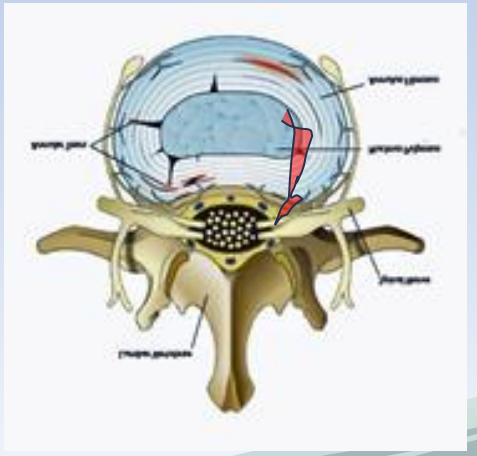
- Posterior 4%
- Anterior 33%

HIZ 6w

Aprill C, Bogduk N : High- intensity zone : a diagnostic sign of painful lumbar disc on magnetic resonance imaging. Br J Radiol 65 : 361-369, 1992

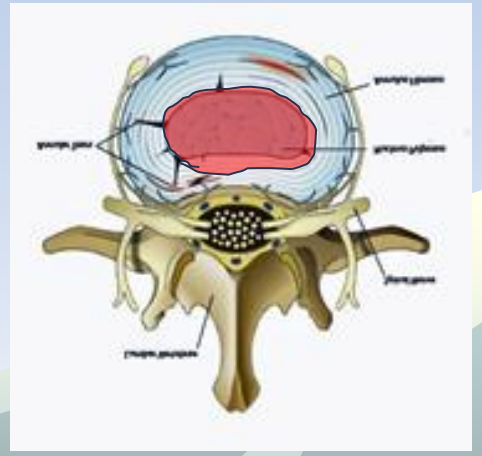
Annular tear with delamination

Type of DiscoCT



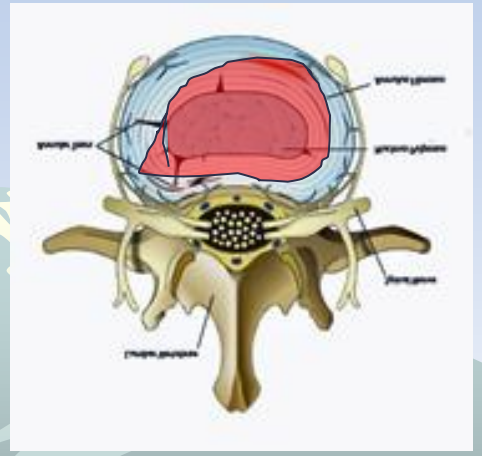
Type1

Annular tear



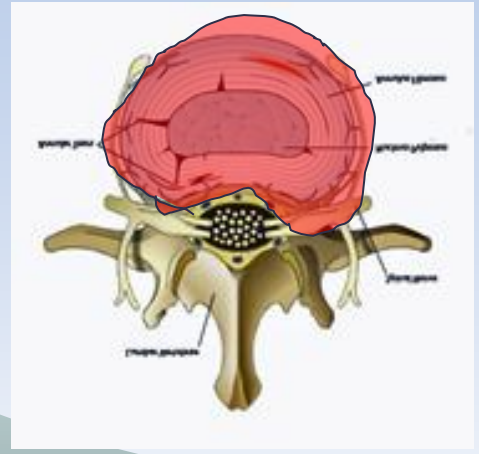
2

deg of nucleus



3-1

mild deg of annulus



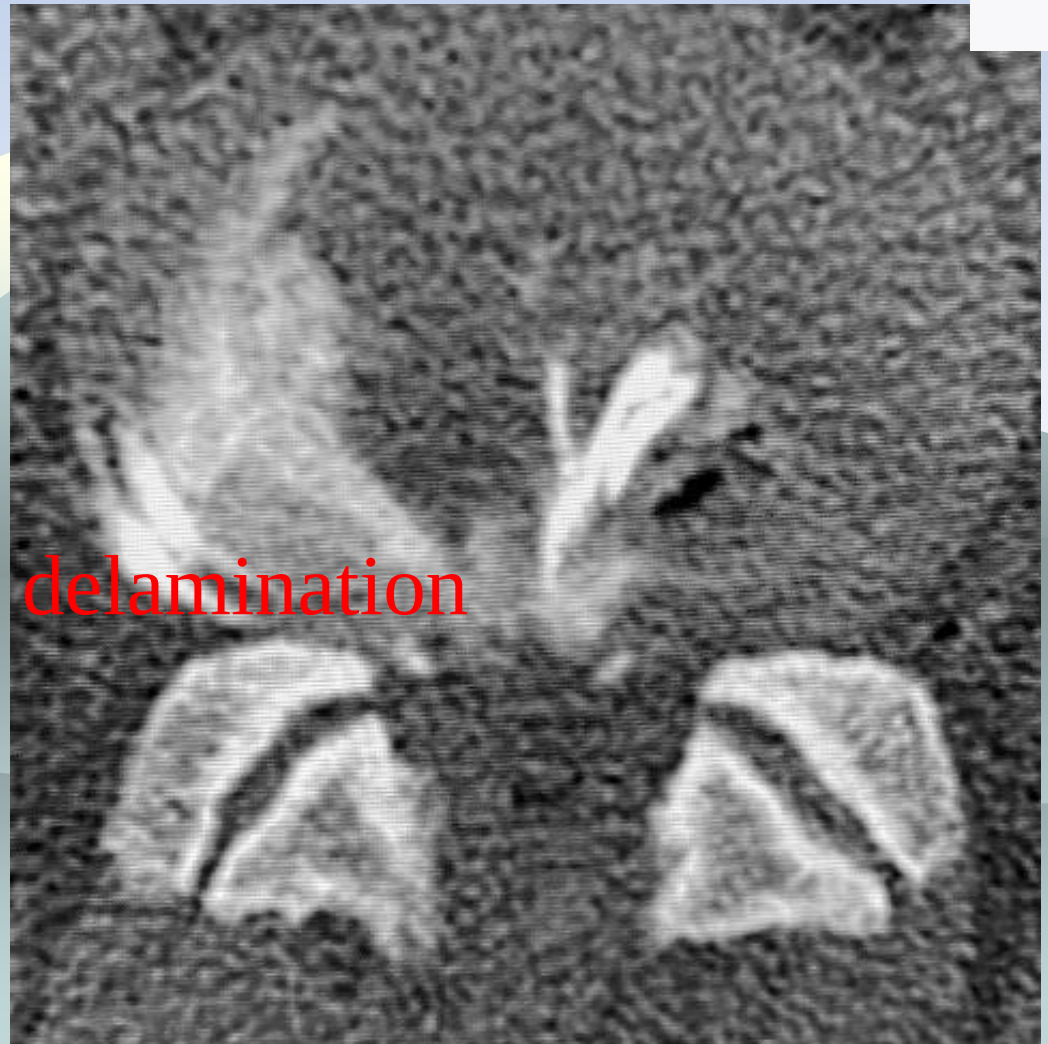
3-2

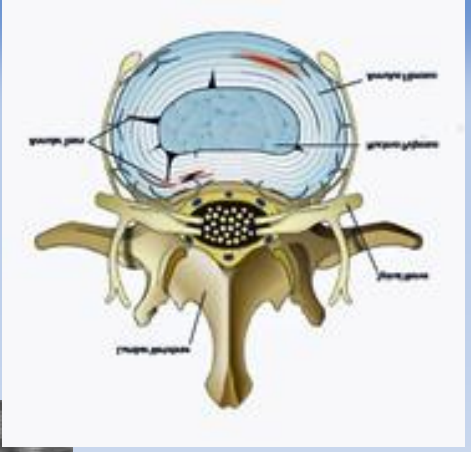
severe deg of annulus

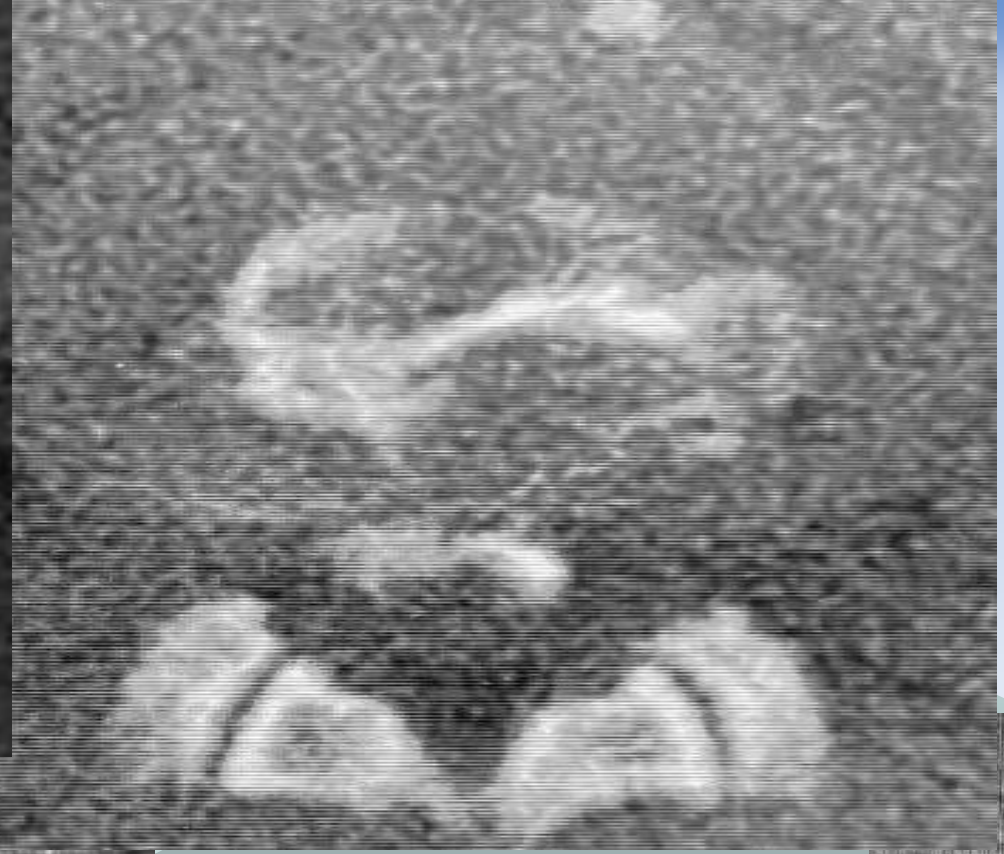
type1

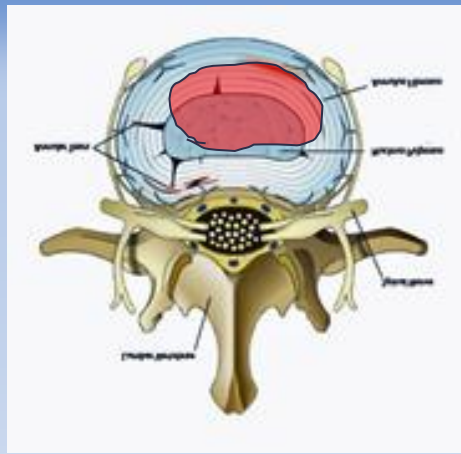
◎

✖ type3-1



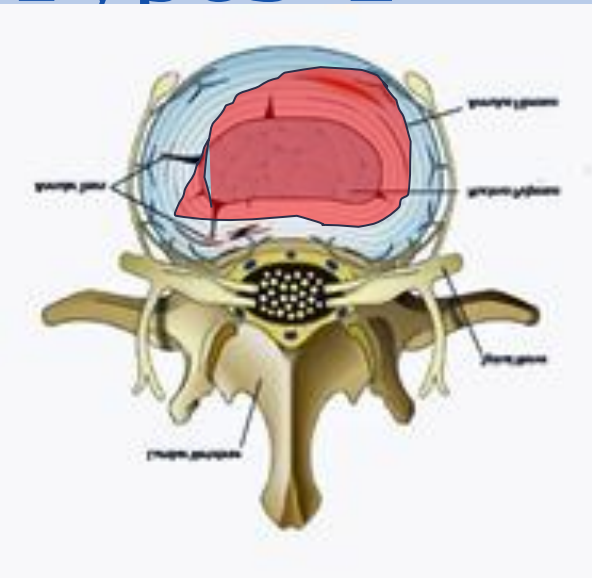


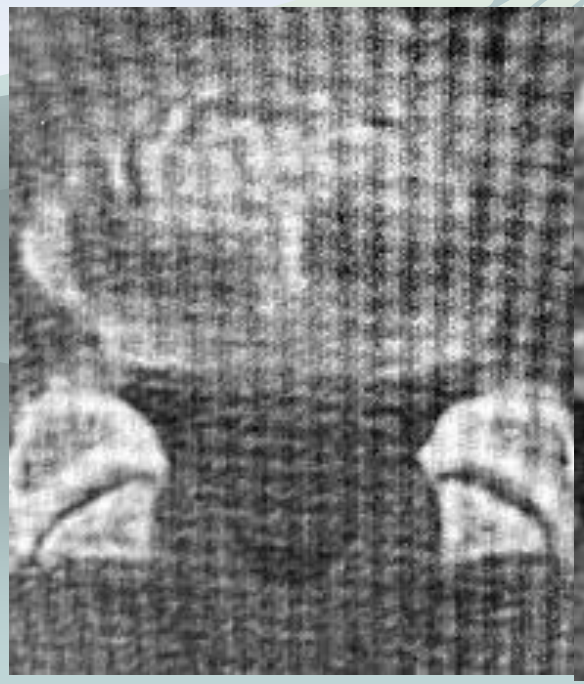




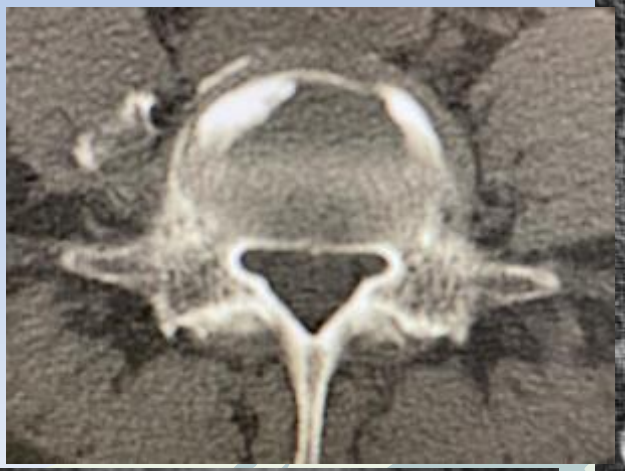
Type2

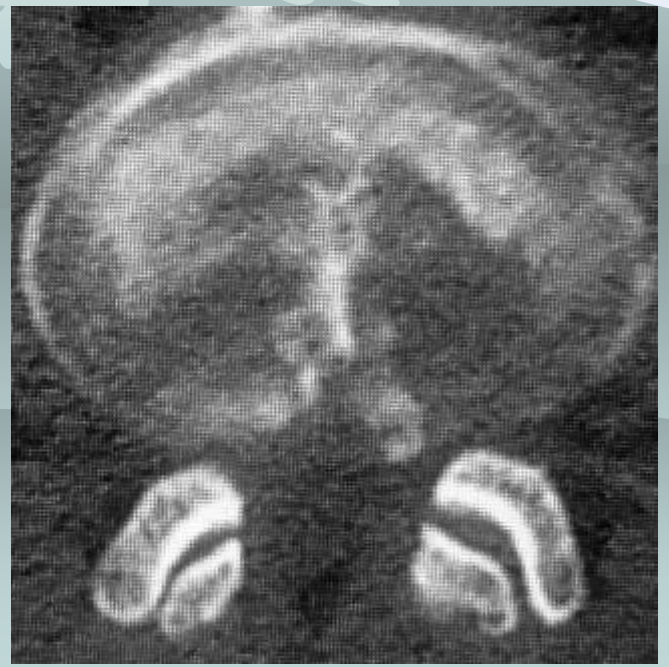
Type3-1

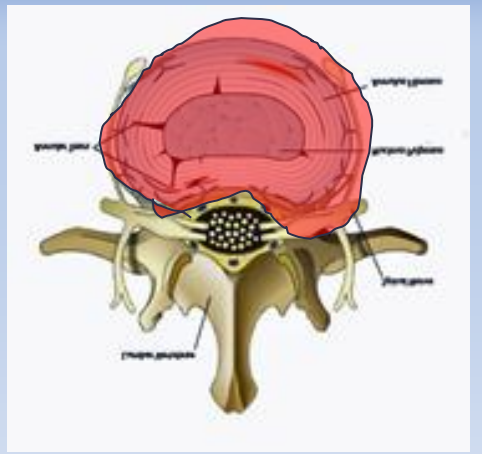




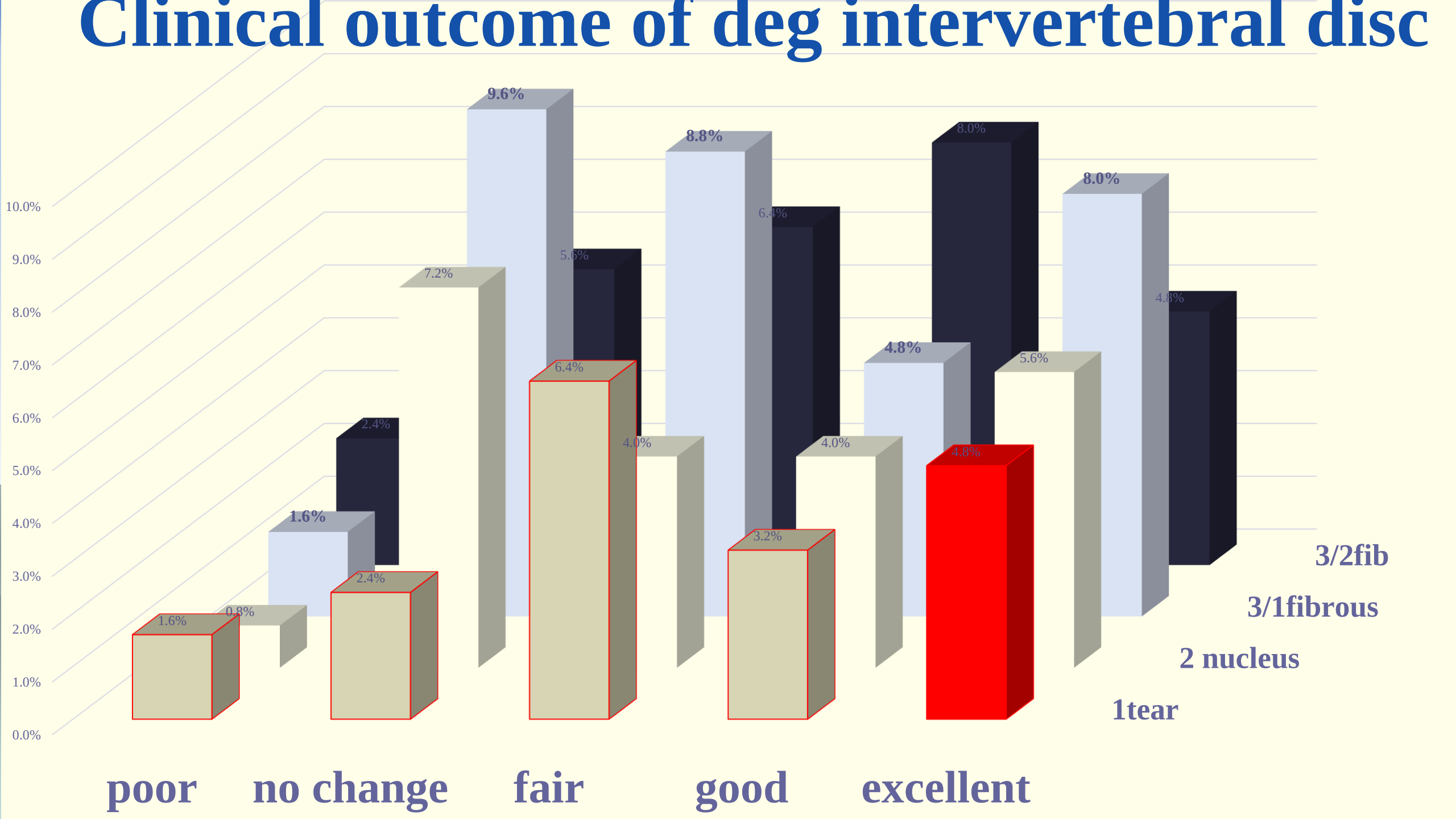
Type 3-2



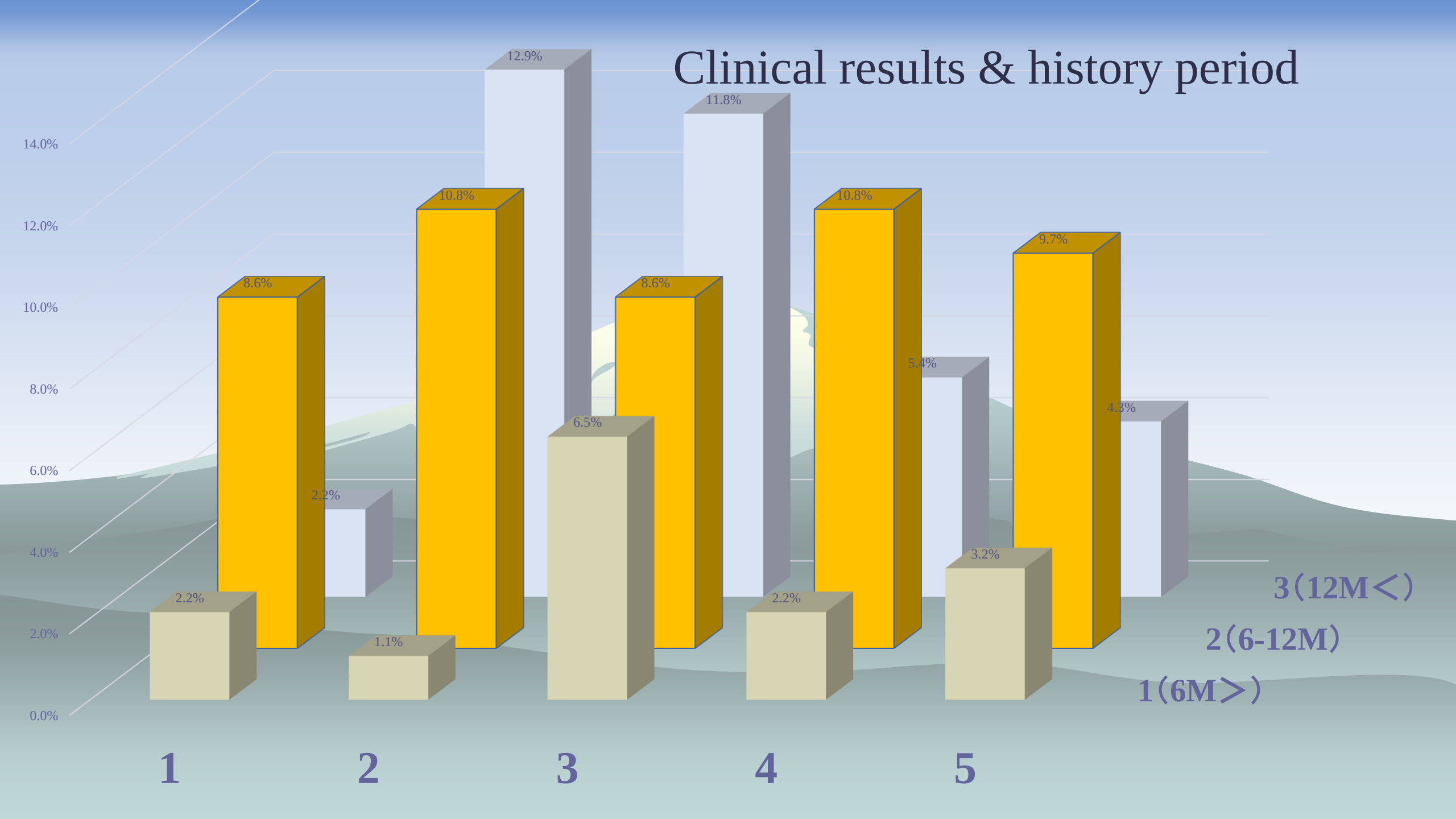




Clinical outcome of deg intervertebral disc



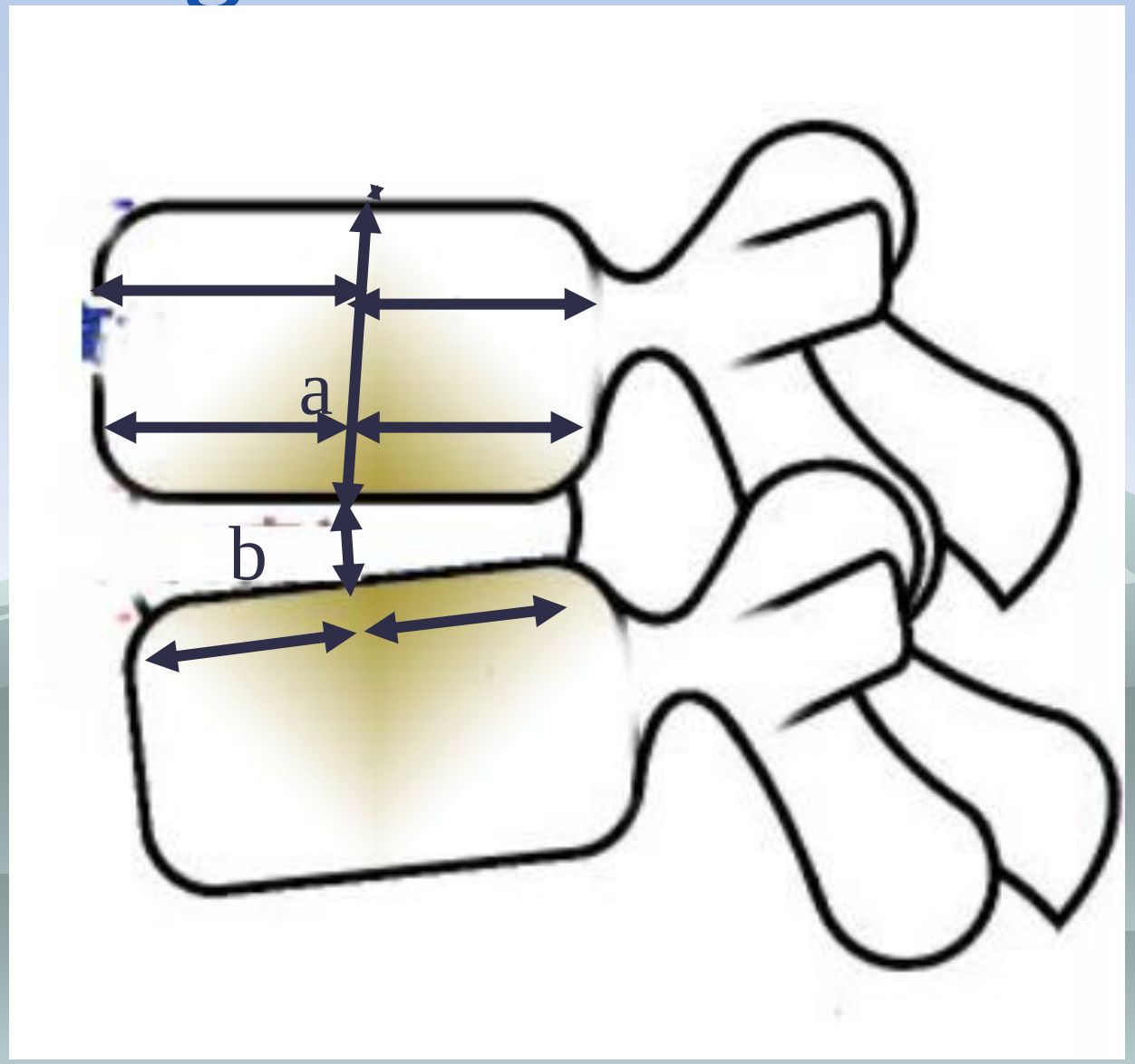
Clinical results & history period



Q1

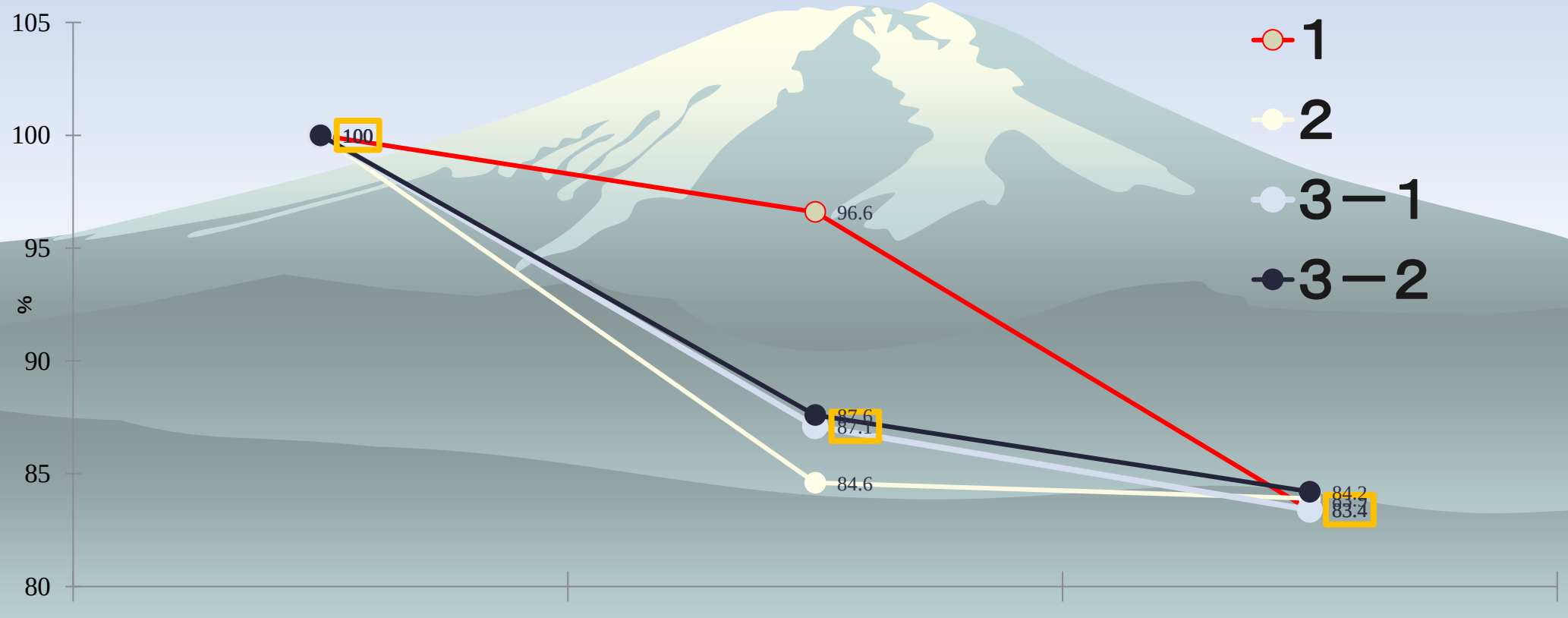
Is a change of the disc height connected with degeneration degree of the intervertebral disk?

Disc height ratio b/a



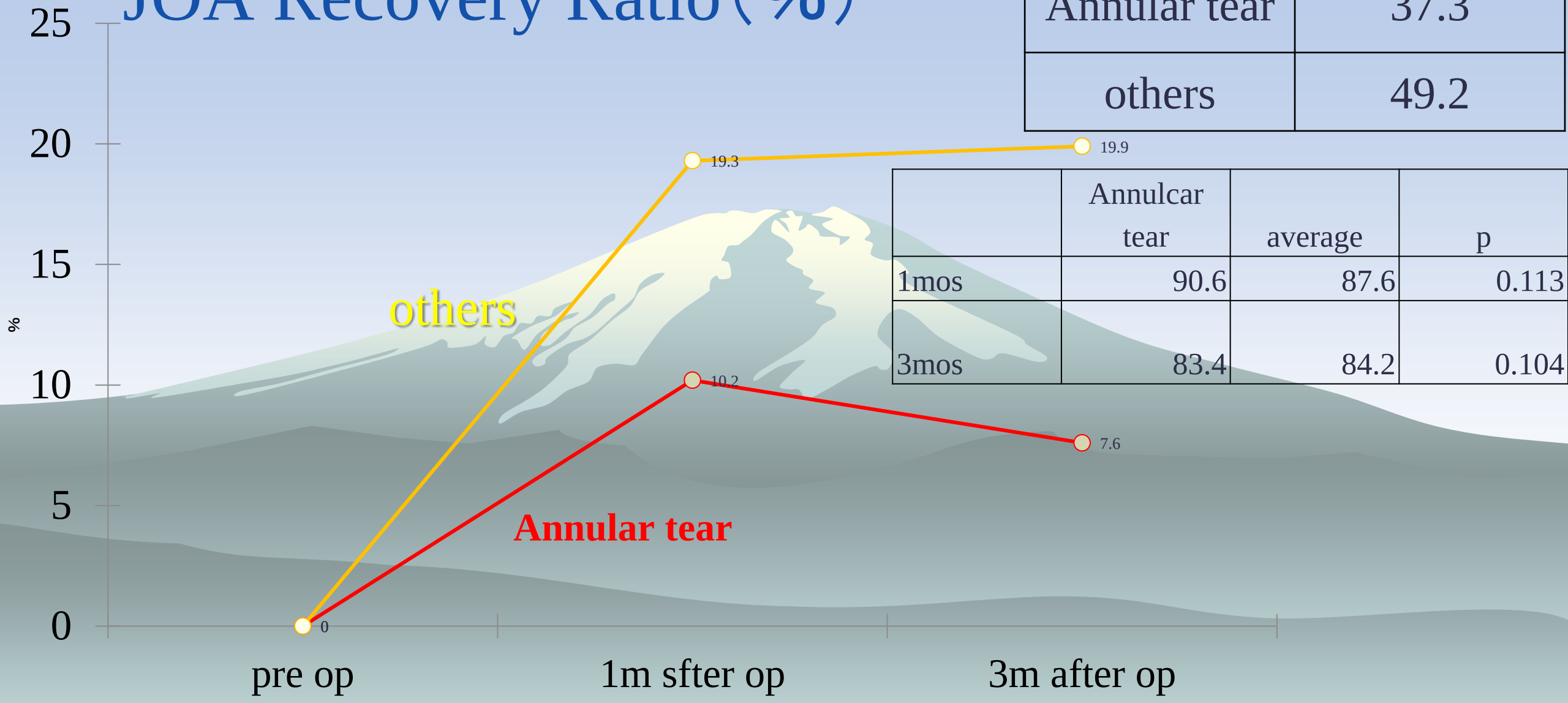
Three engineers measure three times and make the average

Temporal changes of disc height with CT classification



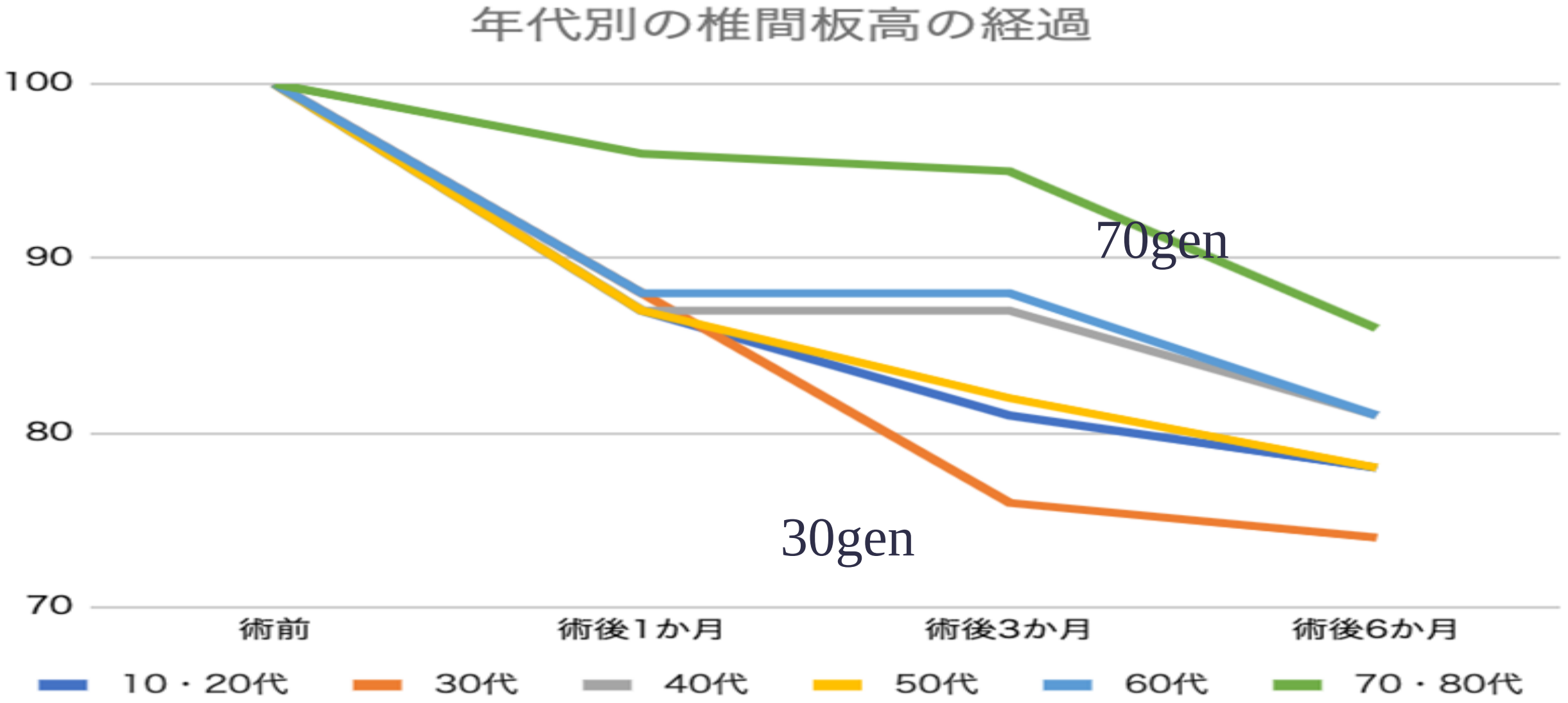
JOA Recovery Ratio（%）

	Mean age
Annular tear	37.3
others	49.2



	Annulcar tear	average	p
1mos	90.6	87.6	0.113
3mos	83.4	84.2	0.104

Temporal changes of disc height with age

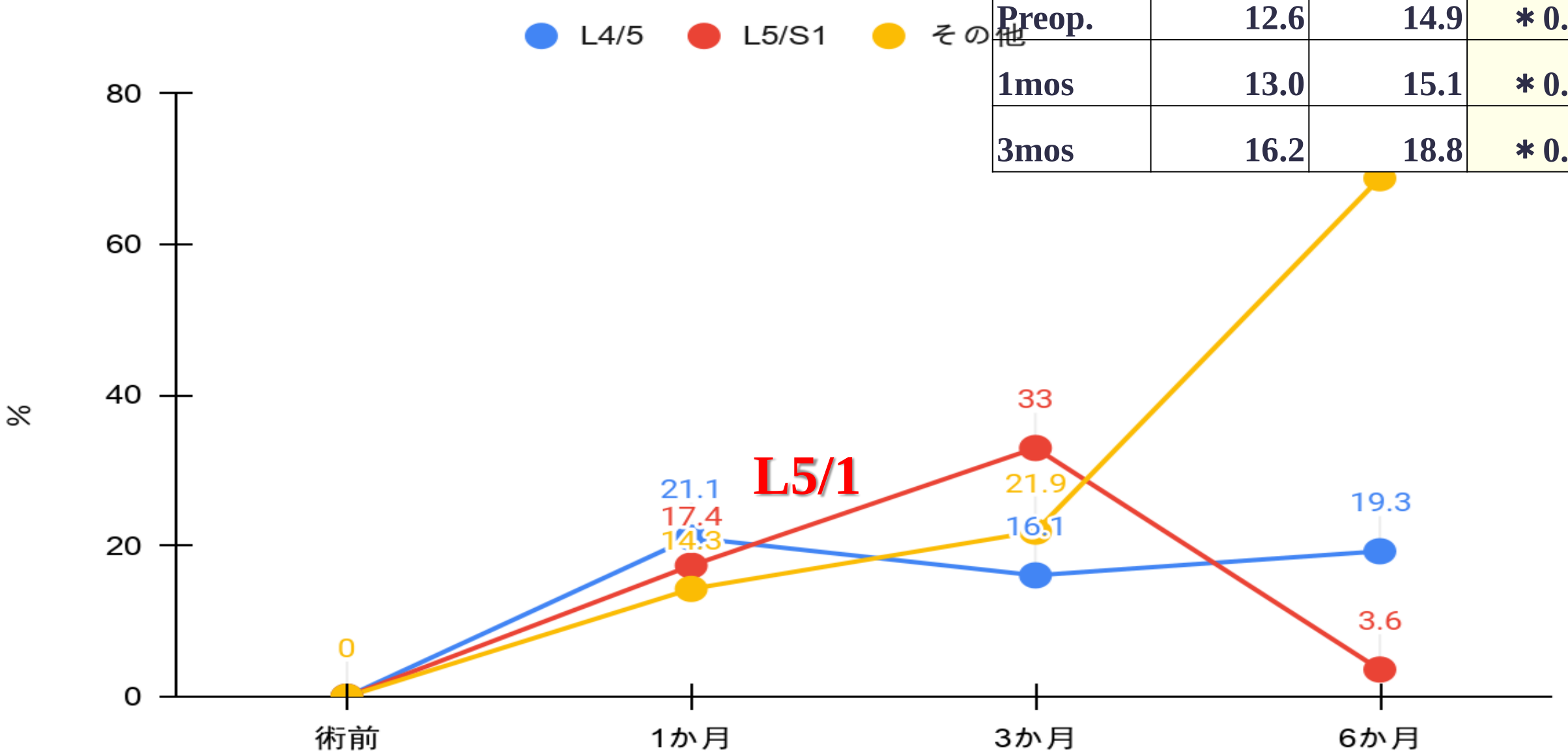


Q2

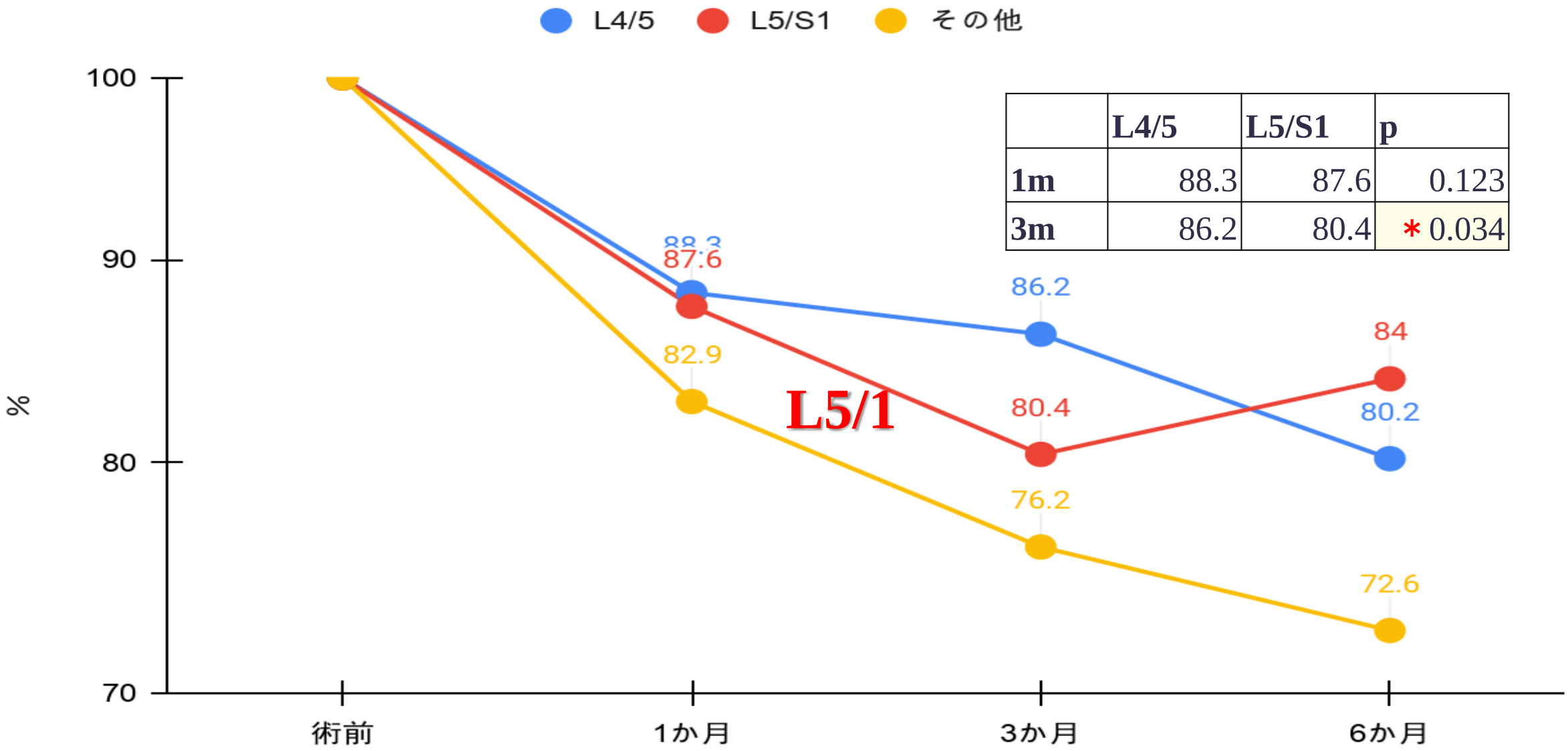
Did the difference of the clinical outcome result from a disc level?

JOA Recovery Ratio（%）

	L4/5	L5/S1	p
Preop.	12.6	14.9	＊0.012
1mos	13.0	15.1	＊0.048
3mos	16.2	18.8	＊0.037



Change of disc height with levels（%）



	L4/5	L5/S1	p
1m	88.3	87.6	0.123
3m	86.2	80.4	* 0.034

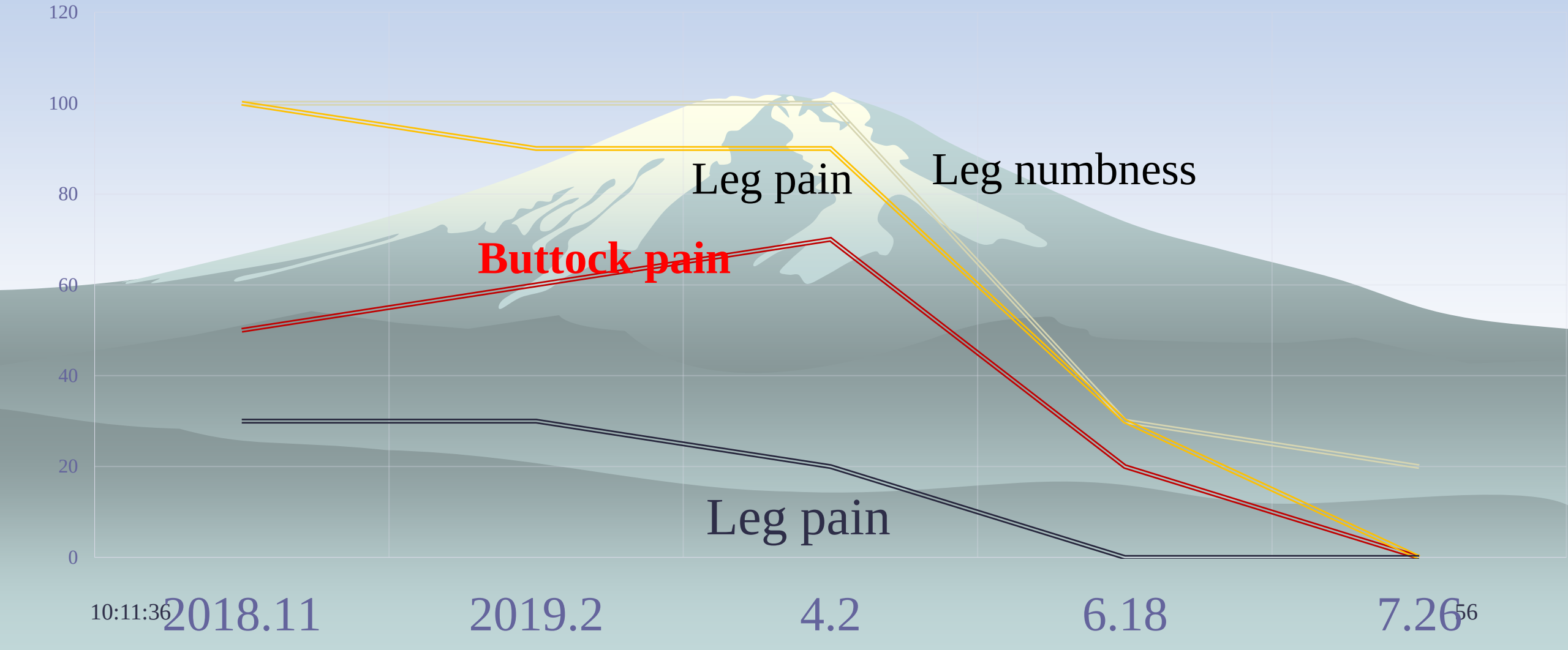
Case #30

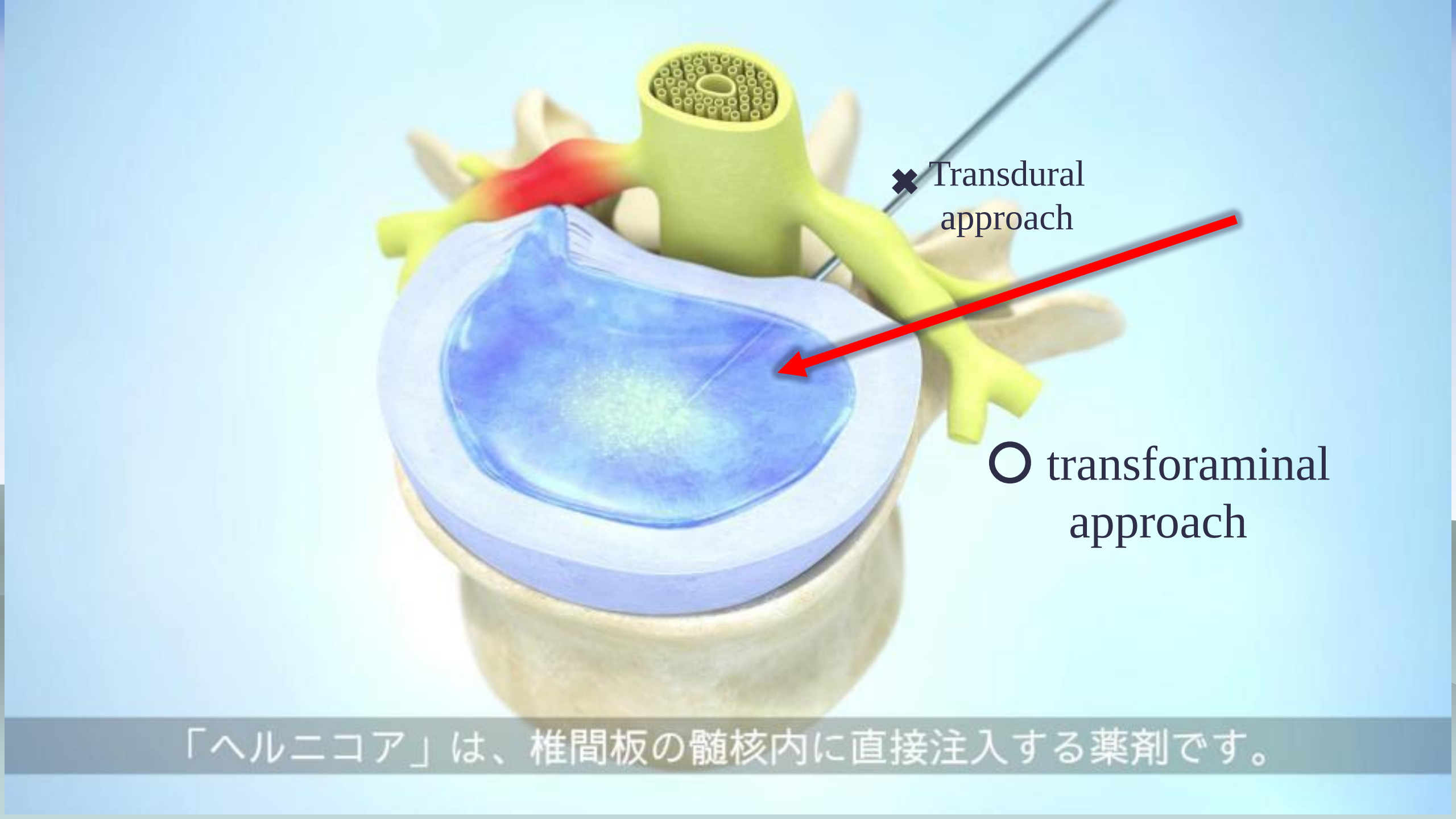
44y female low back pain and leg pain for 2y

Adviser counselor

- **2018.11** outpatient with sever lowback &leg pain
- **2019.2** right s1 nerve root block effect
- **2019.4.2** condoliase
- **2019.4.23** return to work
- **2019.7.26** complete recovery other than the desensitization of the right leg

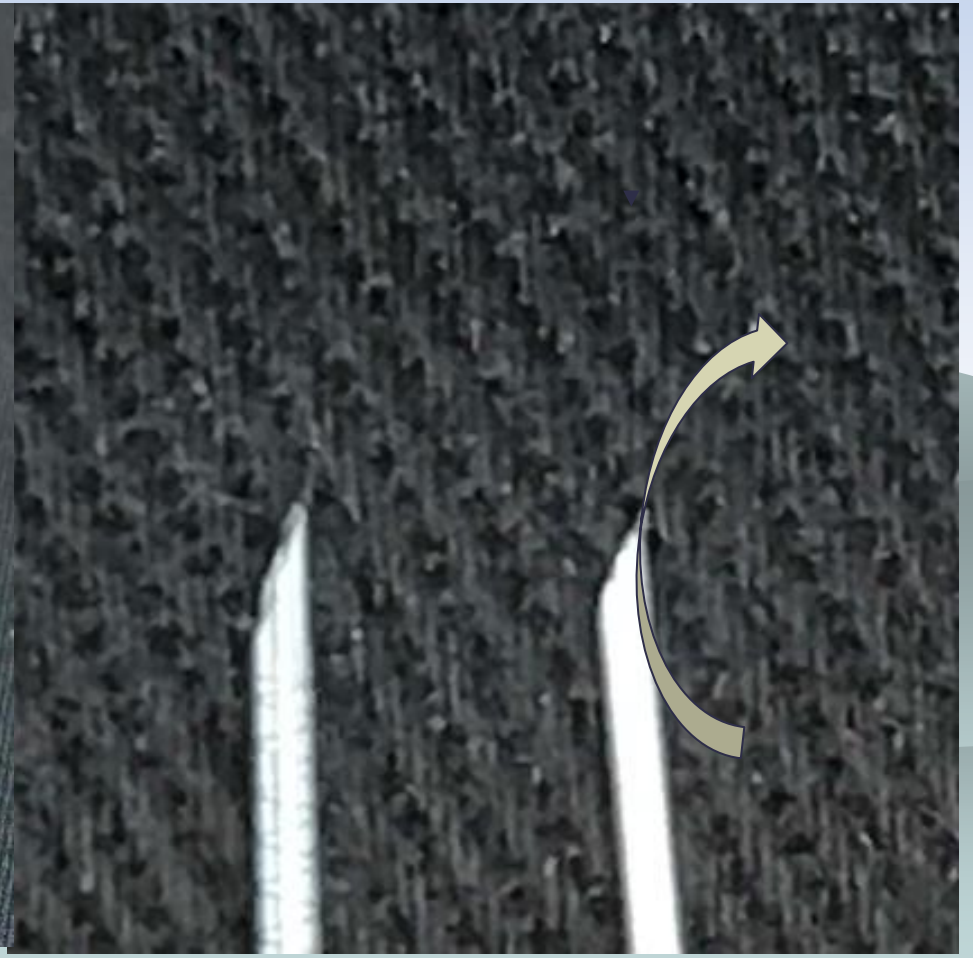
Case #30 2019.4.20 condoliase





「ヘルニコア」は、椎間板の髄核内に直接注入する薬剤です。

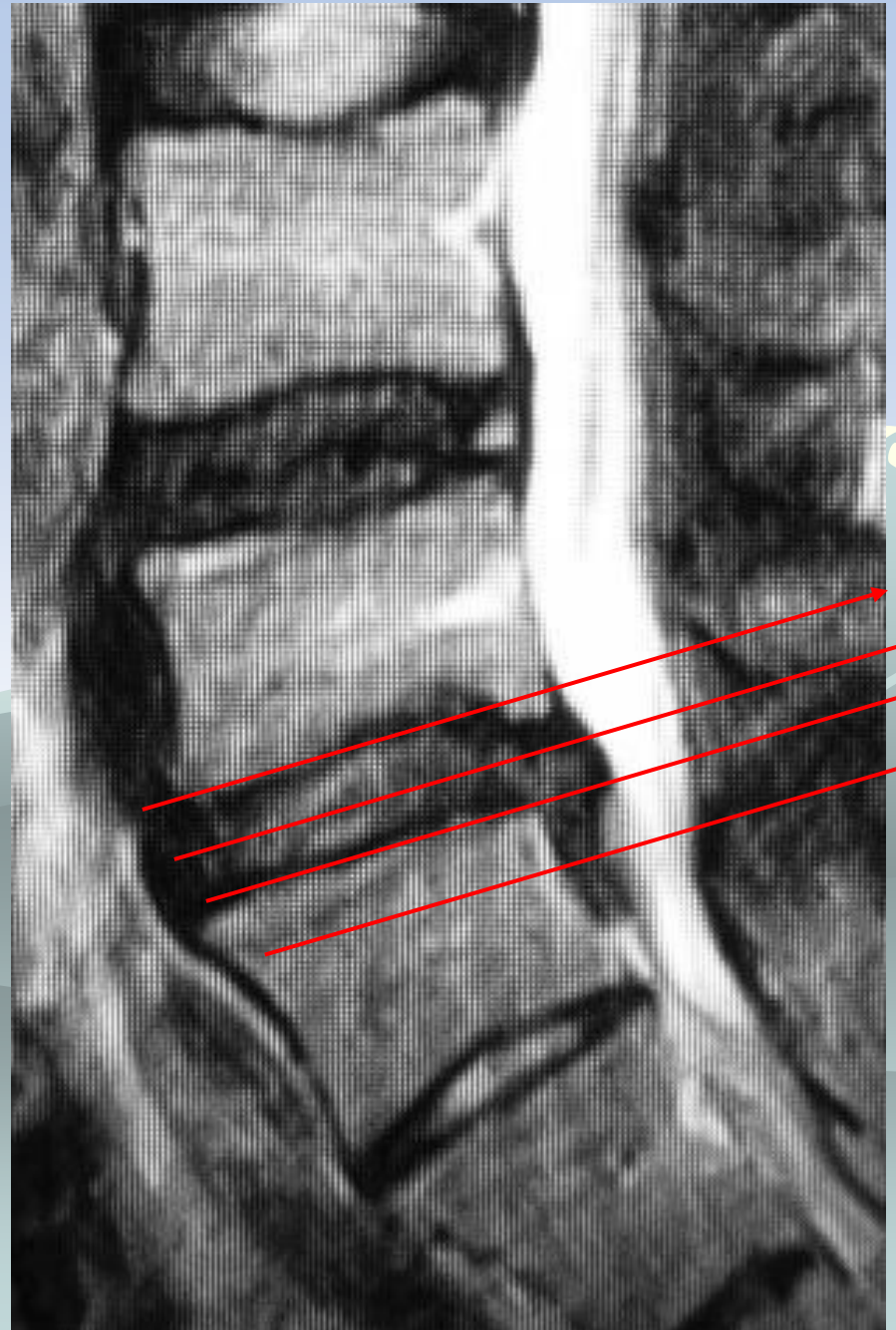

94.9 mm
L-UPR



Q3

Is there the case to be improved remarkably on the several days after a condoliase injection?

4/180 CASES (1.4%)



Upper endplate

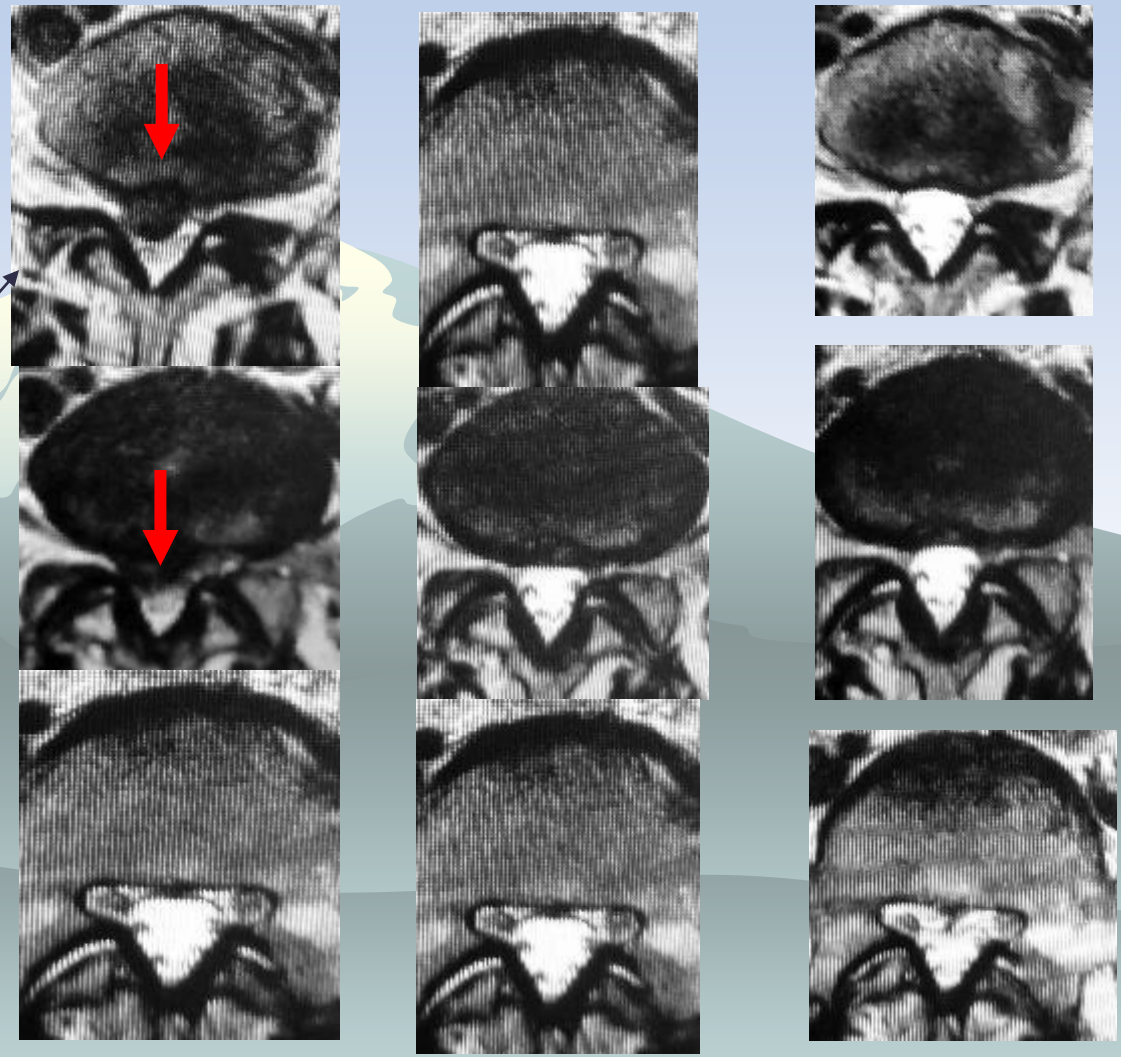
Low endplate

10:11:38

Case30 FS disappear in 1M

2019.4.2

2019.2.13 5.27 7.22



Case #134

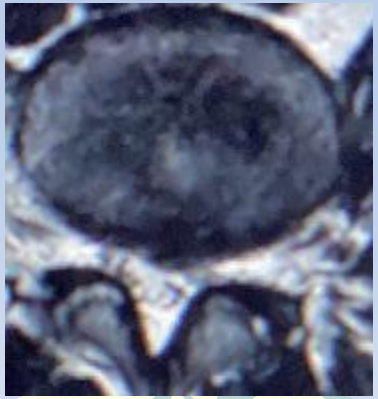
KY

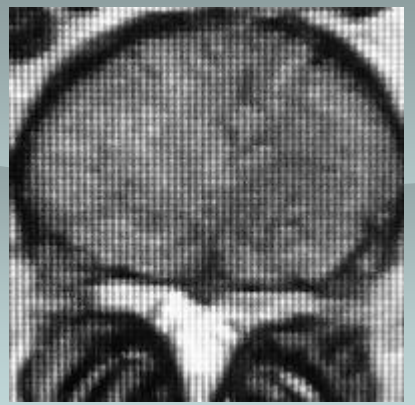
remitted in a suppository

every day seven months

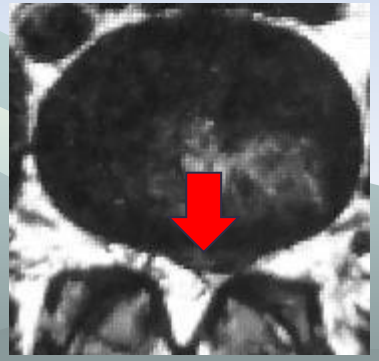
from the use infusion next day

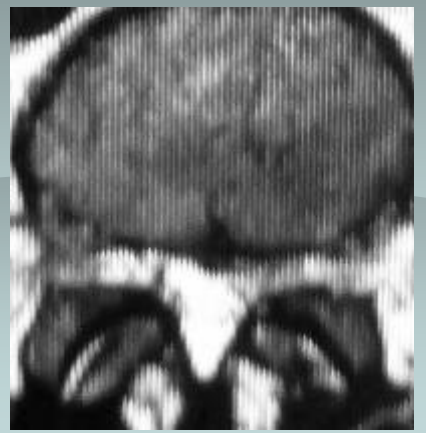
2019.6.18





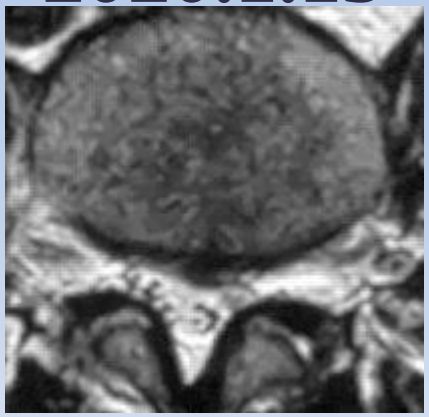
10.13

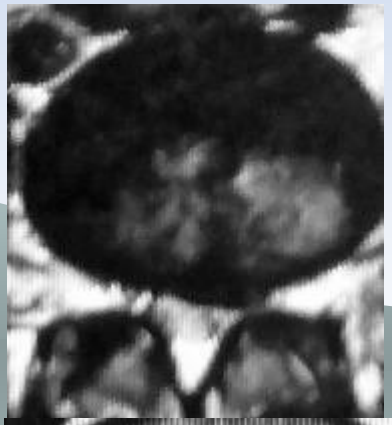




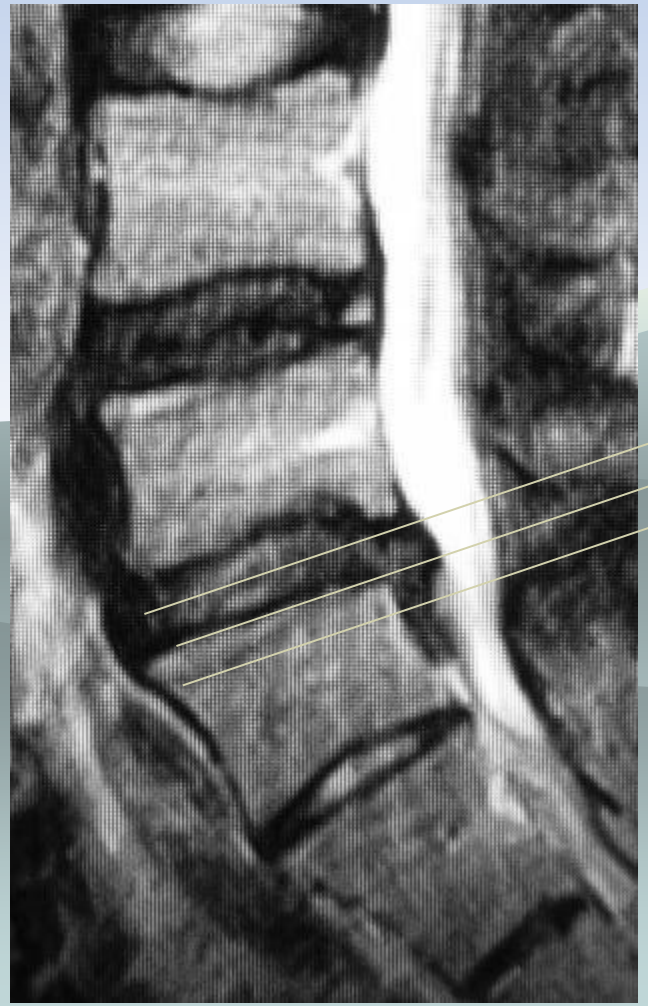
2020.1.7

2020.1.15



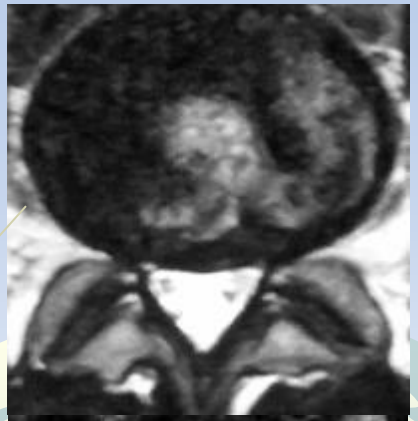


case# 50
37y male
Continuous mig.

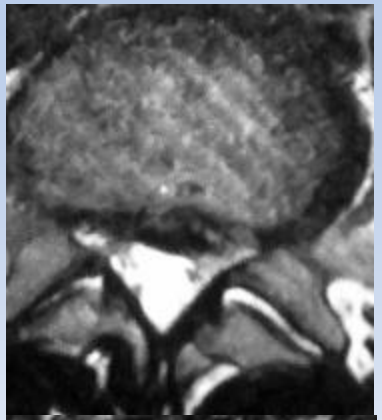


19.5.31Condoliase

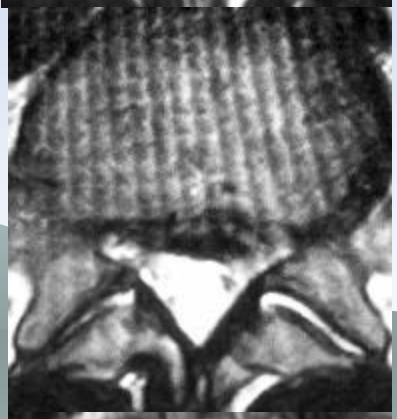
19.4.9



19.9.28



20.2.12



Mechanical effect

- ① alkaline effect anti-inflammatory effect
- ②cellular pain mediator
- ③ polymerizing effect
- ④ local control of autoimmune reaction

Q4.

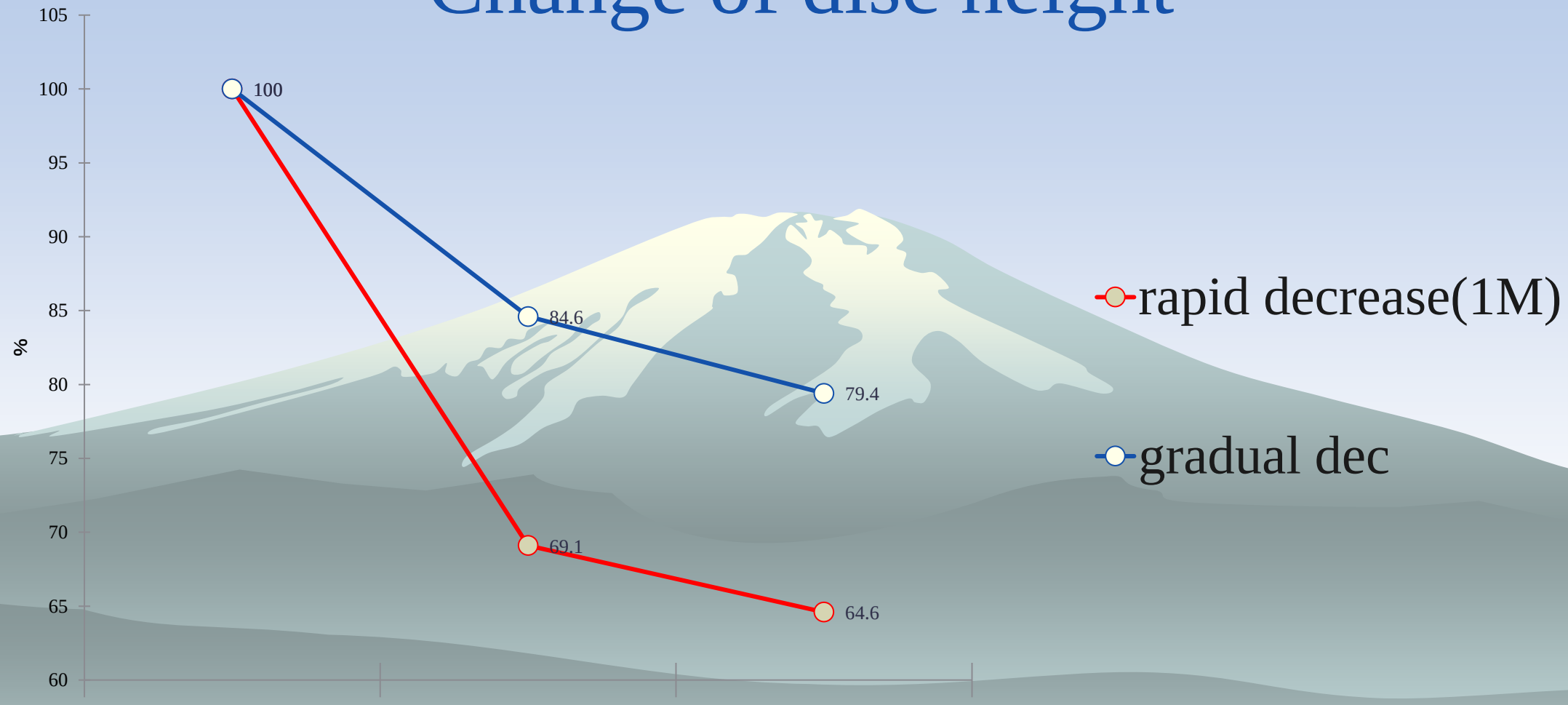
How is the results of the case that disc height decreases rapidly?

A,

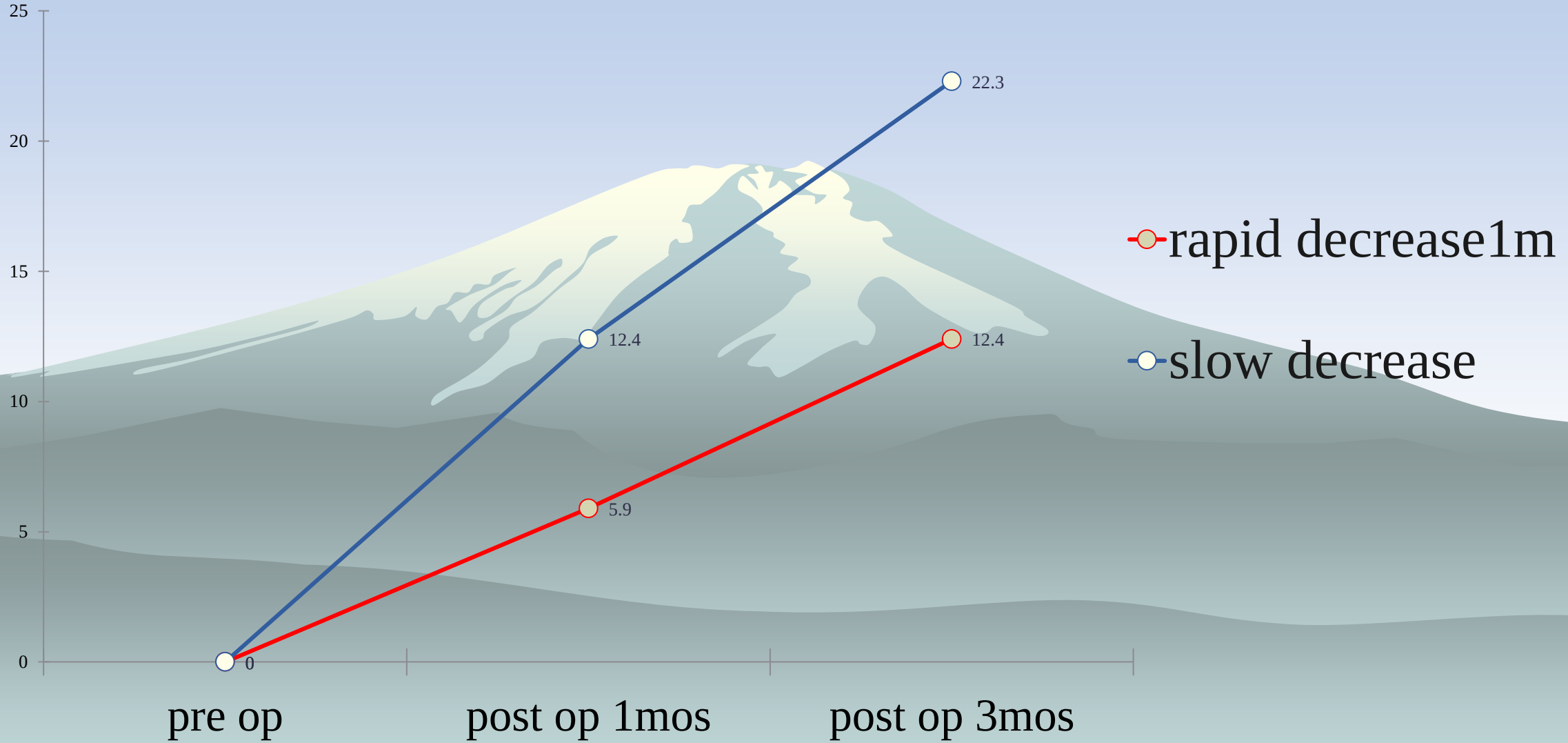
The clinical outcome of the case to decrease rapidly of disc height is not good.

The case with disc height gradually decreases tends to have good results

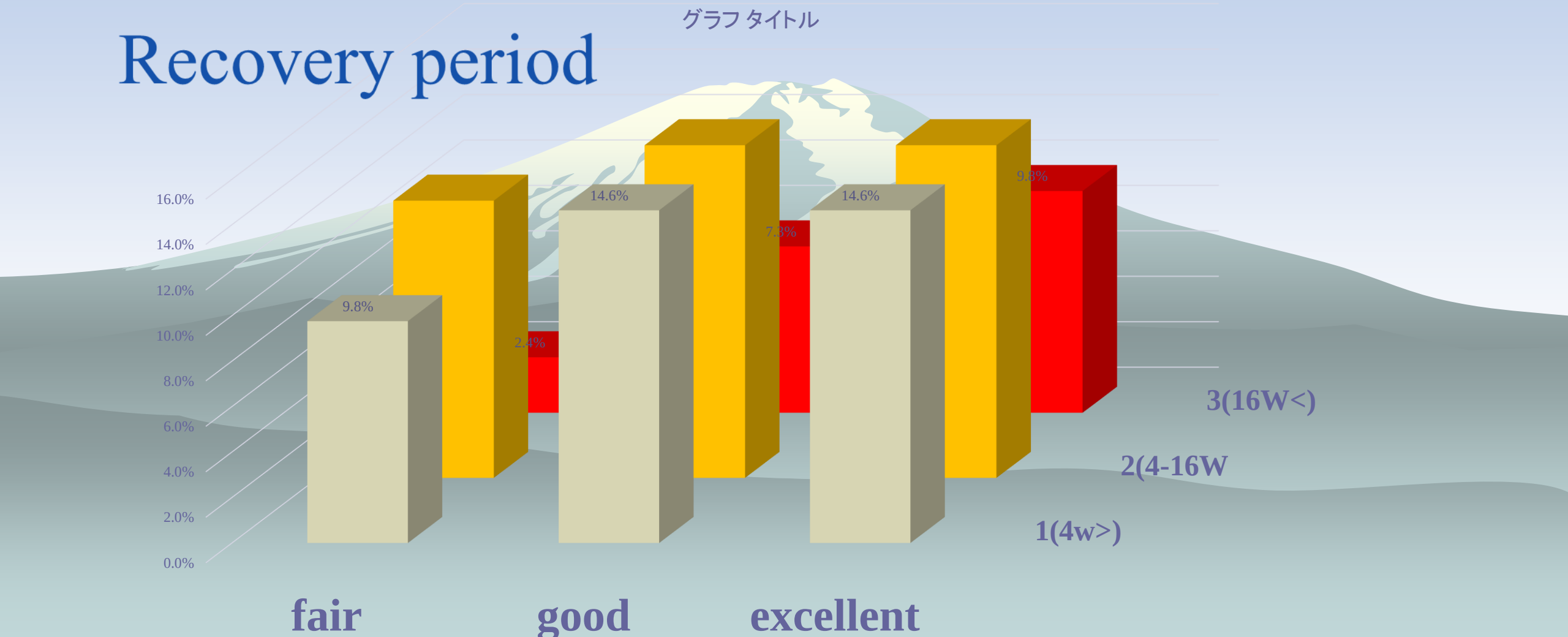
Change of disc height



JOA Recovery Ratio（%）



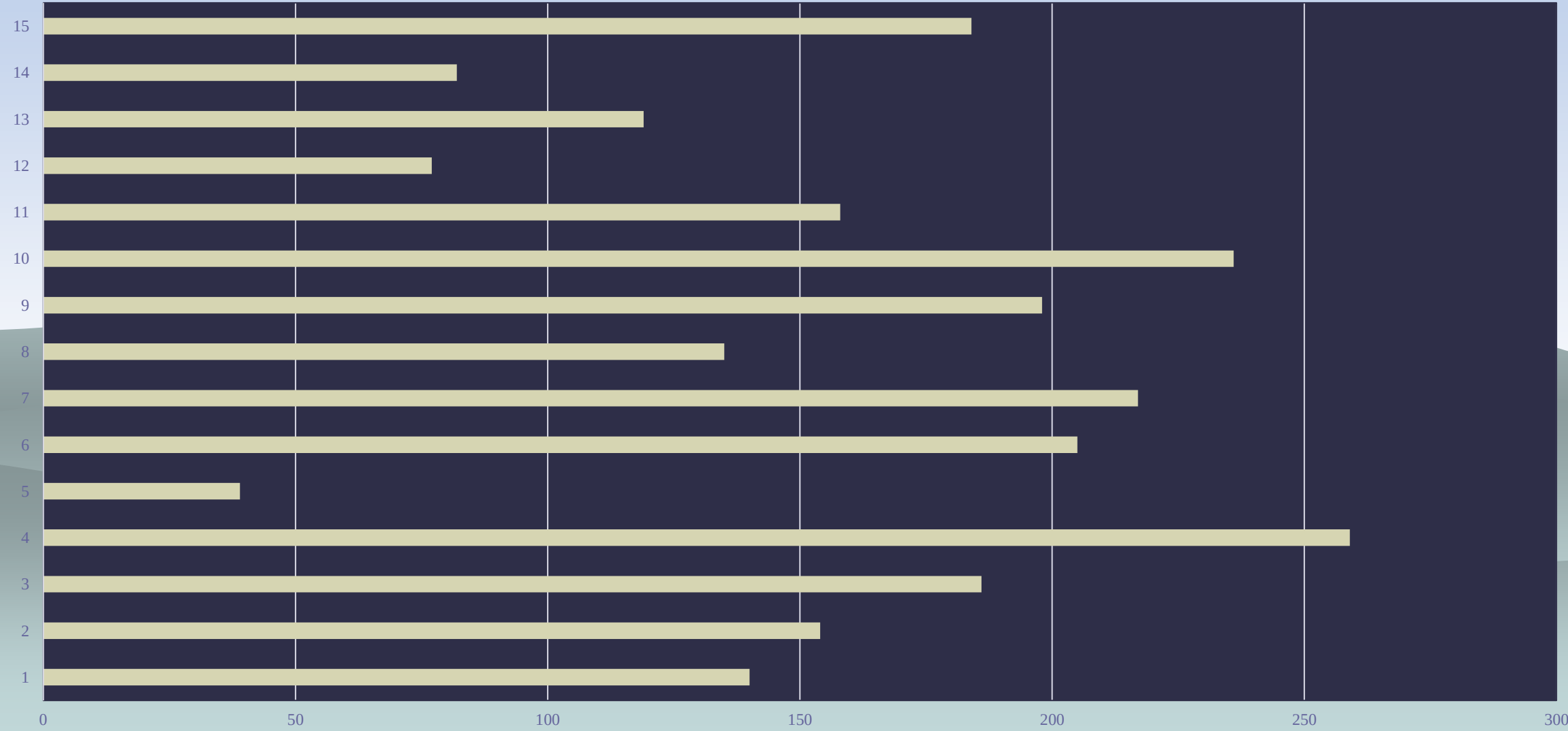
Q5 How Long Should You Wait Before Surgery?
The Timing FESS Surgery



The cases of FESS surgery **15/180 (8.3%)**

159.4days(23w)

period between condoliase inj. and FESS

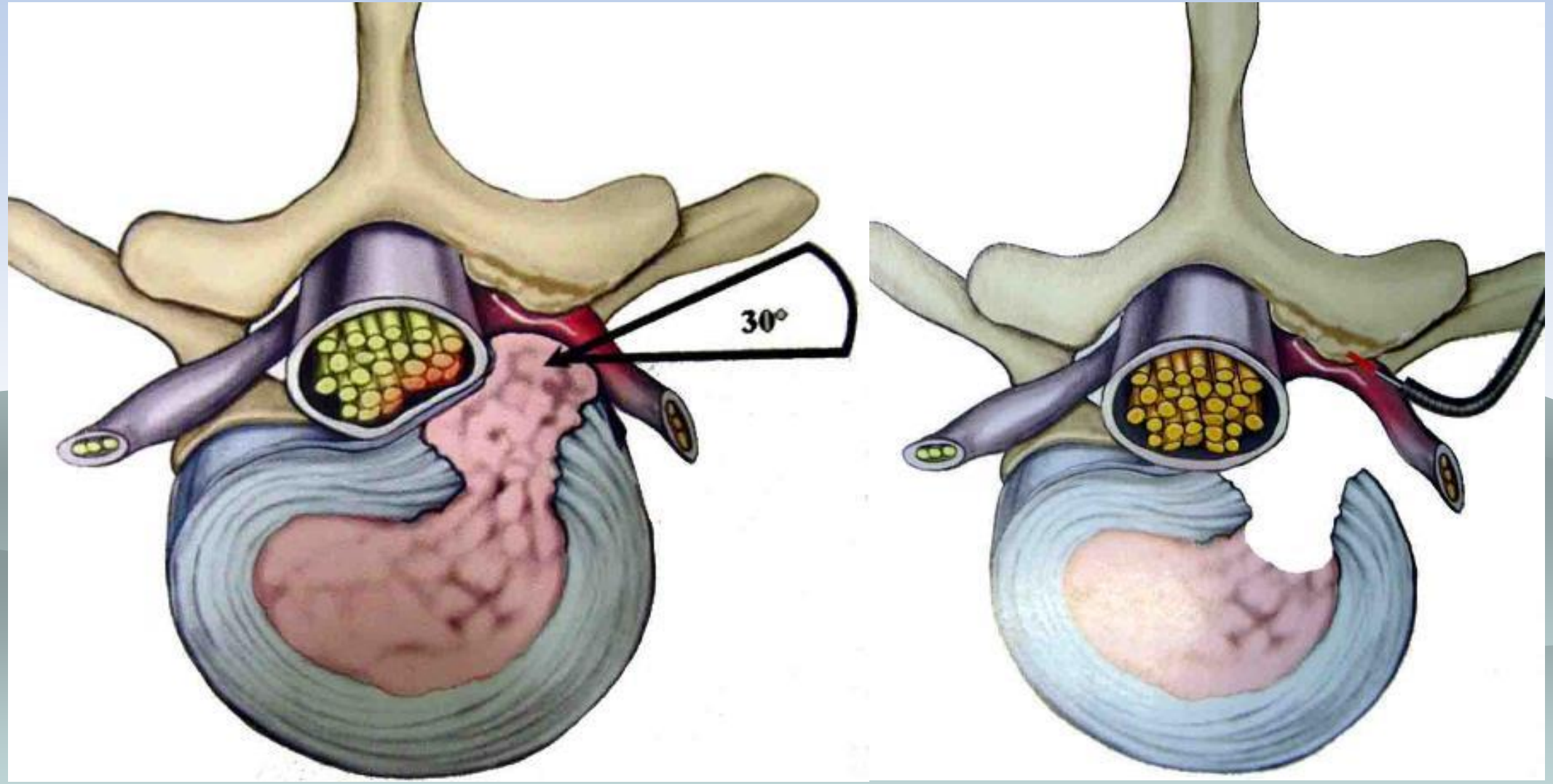


The cases of FESS surgery **15/180 (8.3%)**

- The symptom was improved, but wants to raise QOL more — 3cases
- Herniation combined with SCS — 2
- Overlook the lateral recess stenosis — 1
- Stimulate ganglion(POD) — 1
- Others — 8

Hand down outside in

Inside -out



Q6

How much is the frequency of complications?

Complications 8/180(4.5%)

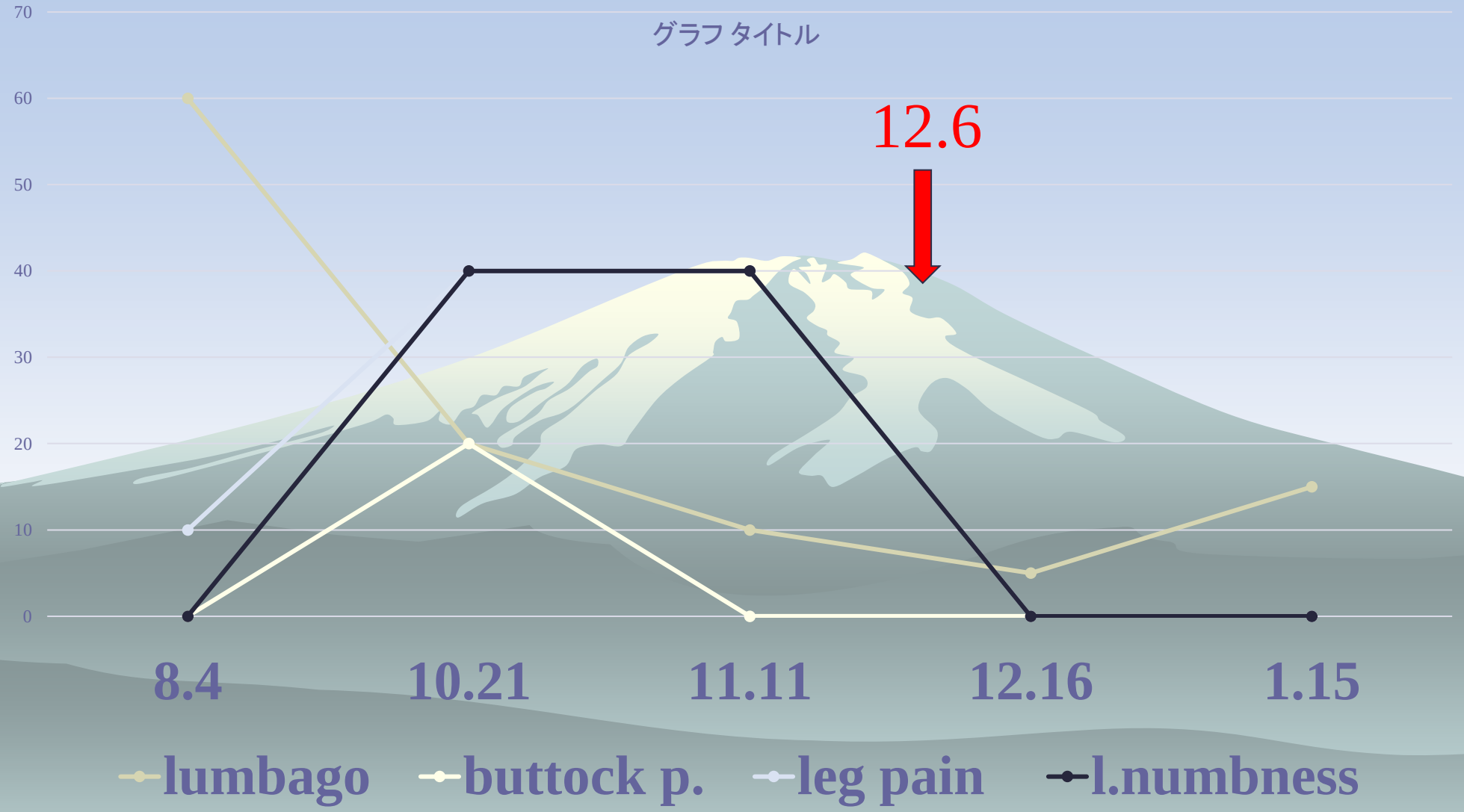
Eruption 5/180 (2.8%)

Pain of eyes 1/180 (0.6%)

OPE日	出現/h	消失/d	発熱	かゆみ	腹痛	頭痛	発赤	MRI画像	CTパターン	成績
2019/04/14	48	14						不変	3-2	3
2019/07/23	48	7		●		●		不変	3-2	5
2019/9/3	24	10	●					縮小	2	4
2019/10/11	48	10						縮小	3-1	4
2019/10/19	48	7		●	●			縮小	3-1	5
2019/12/01	48	7		●			●	不変	3-2	4
2020/2/4	24	5						不変	3-1	5

Case#115 MN 50y

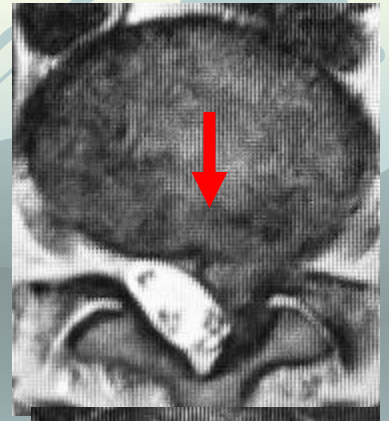
2019.12.6 condoliase　eye pain after inj



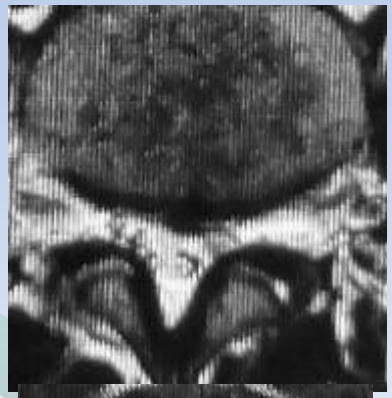
Case#115 MN 50y
Eye pain

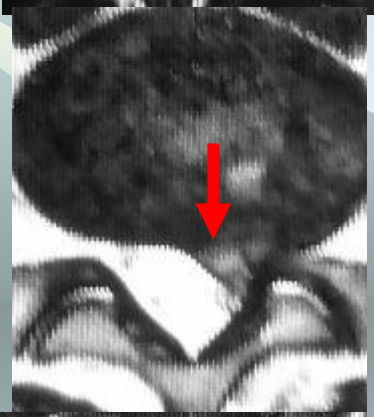
12.6

2019.5.4



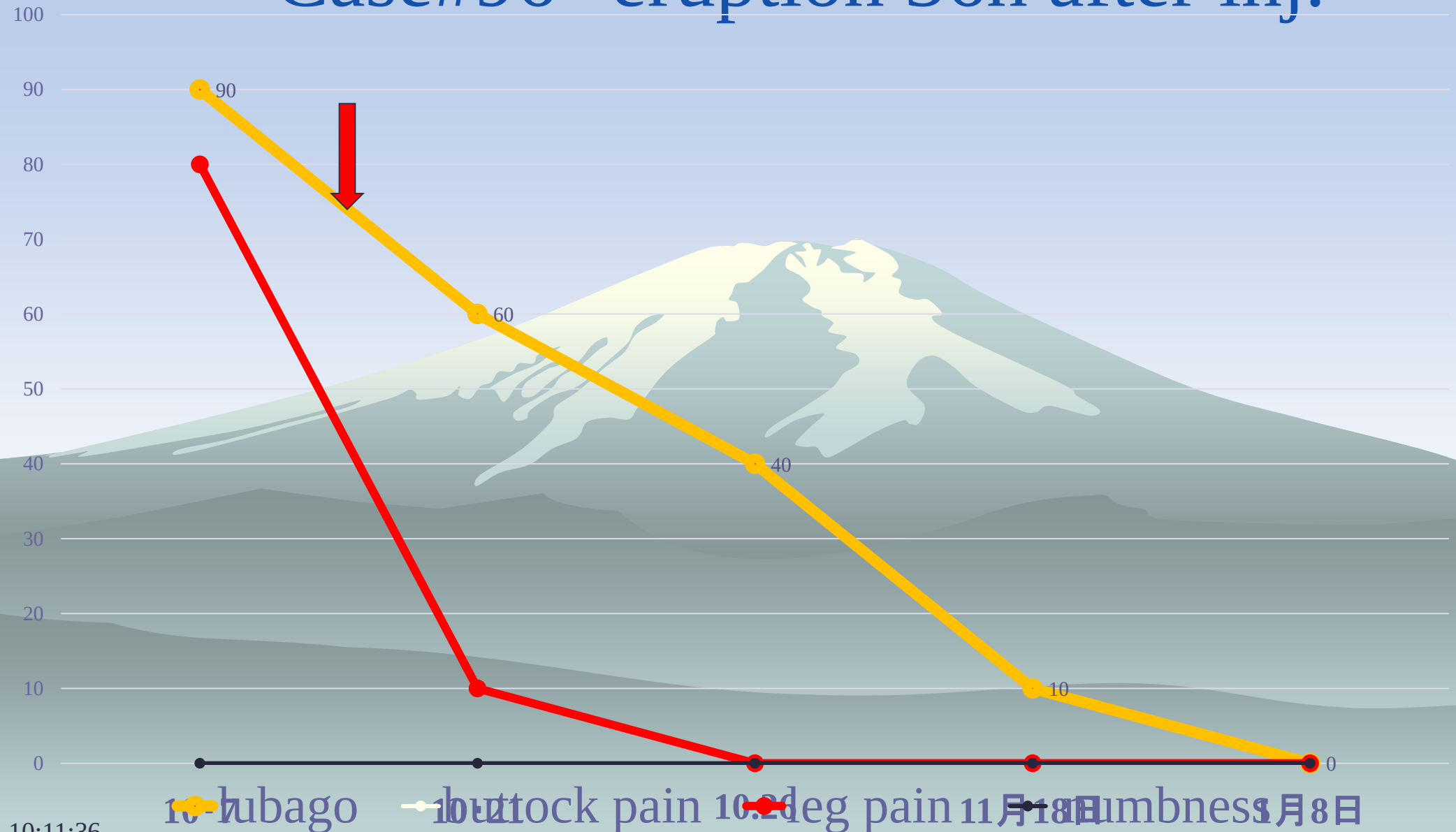
2019.10.21





2020.1.15

Case#96 eruption 36h after inj.

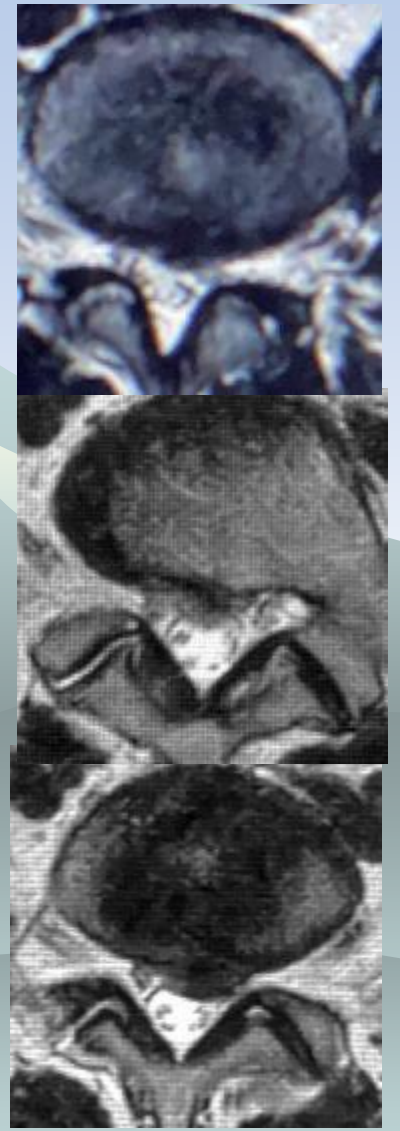


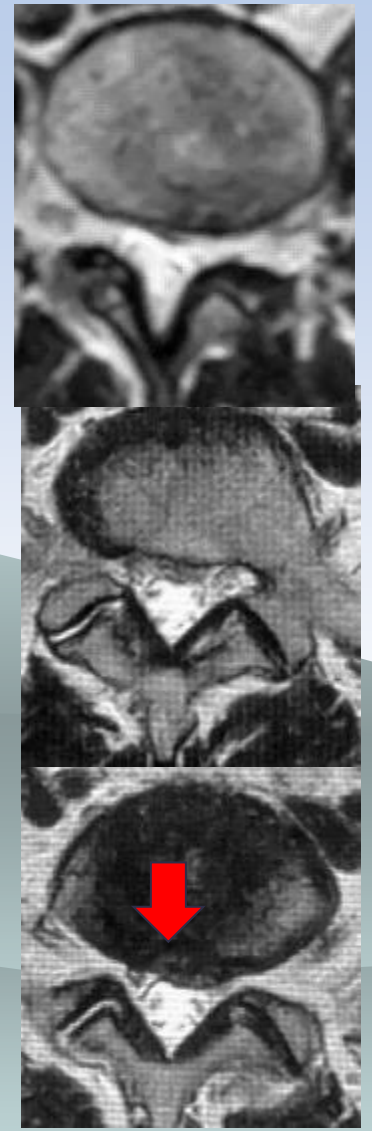
Case#96 NN 44y eruption recovered in 3mos

10-19

2019.9.30 11.18 2020.1.8

L5/1



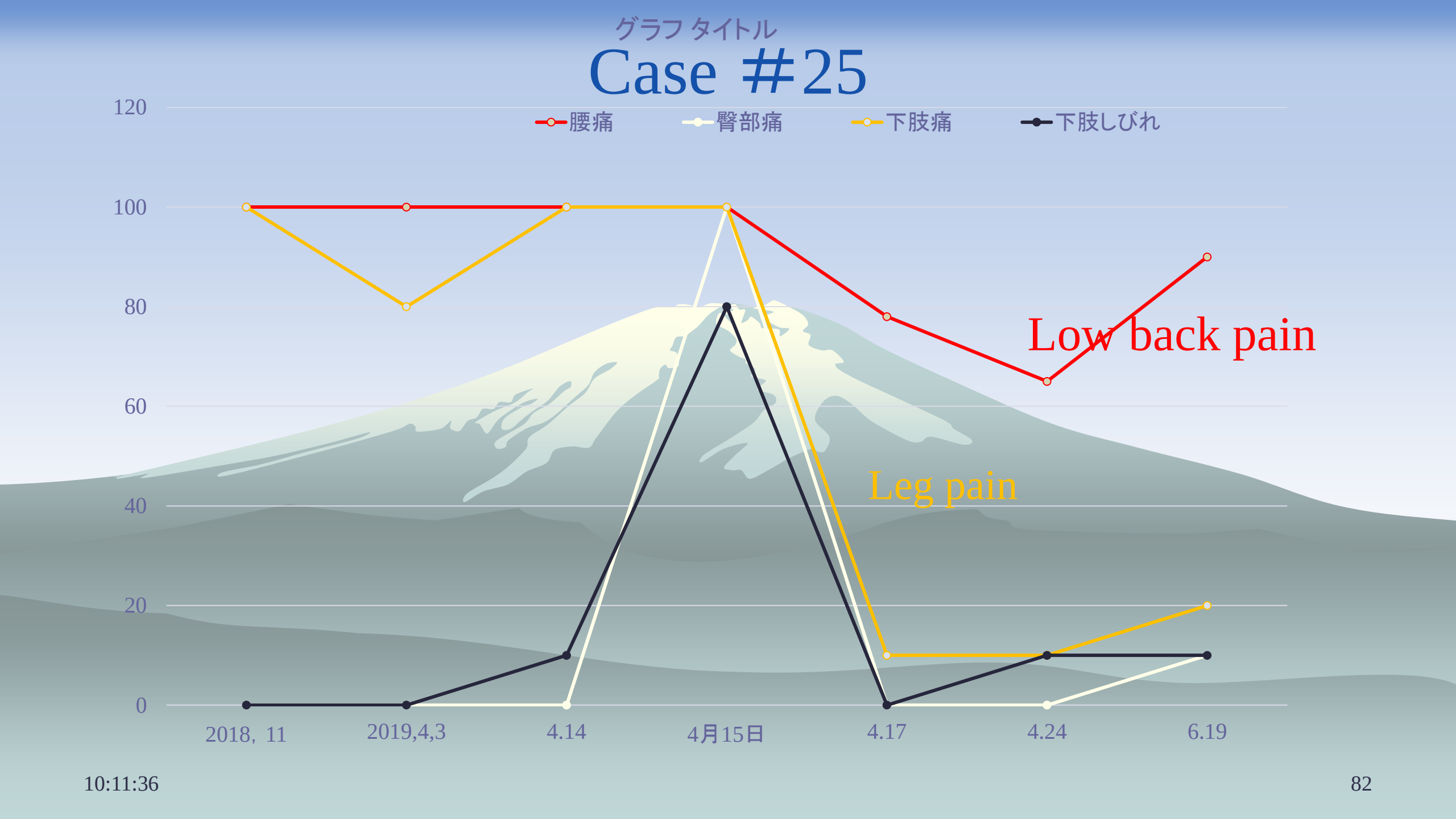


Case#25 77y female

- **2018 11** **Pain & numbness of bilateral leg to have trouble of for four years**
- **L5 nerve root block was effective**
- **2019.4.14pm2** **Condoliase was administrated**
- **4.15 midnight** **exacerbation of low back pain at18h after administration of condoliase**
- **4.16** **Eruption onset**

  Low back apina leg pain numness100/100 for 1week

Case #25

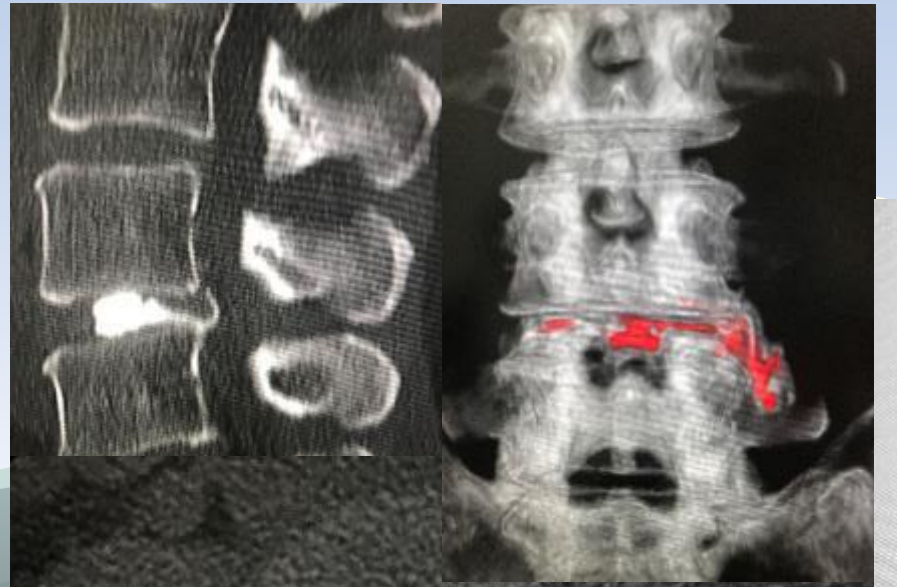

グラフ タイトル
120
100
80
60
40
20
0
腰痛
臀部痛
下肢痛
下肢しびれ
2018，11
2019,4,3
4.14
4月15日
4.17
4.24
6.19
Low back pain
Leg pain

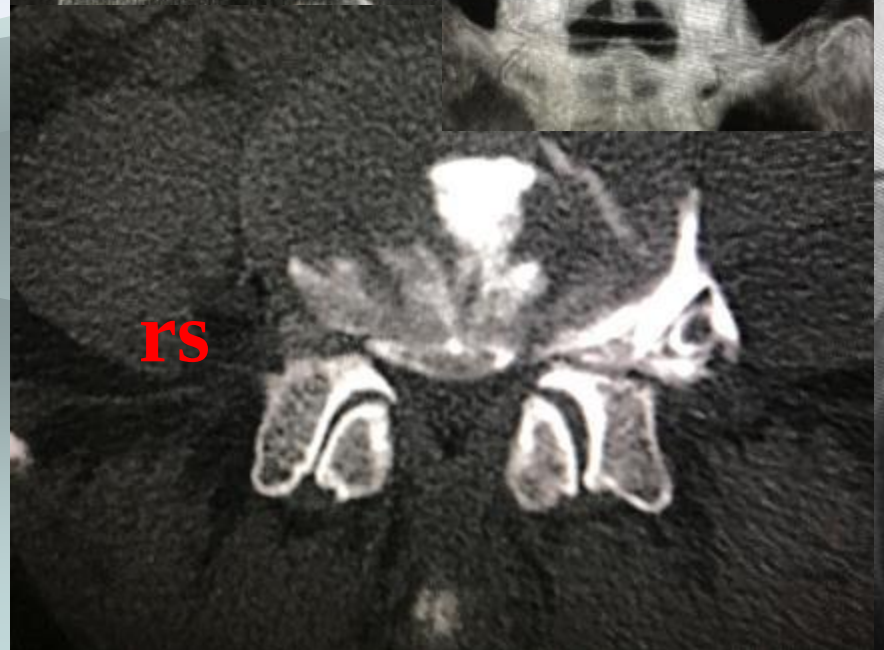
Case no25 Erythema multiforme type

- **DLST(drug induced lymphocyte stimulation test (-)**

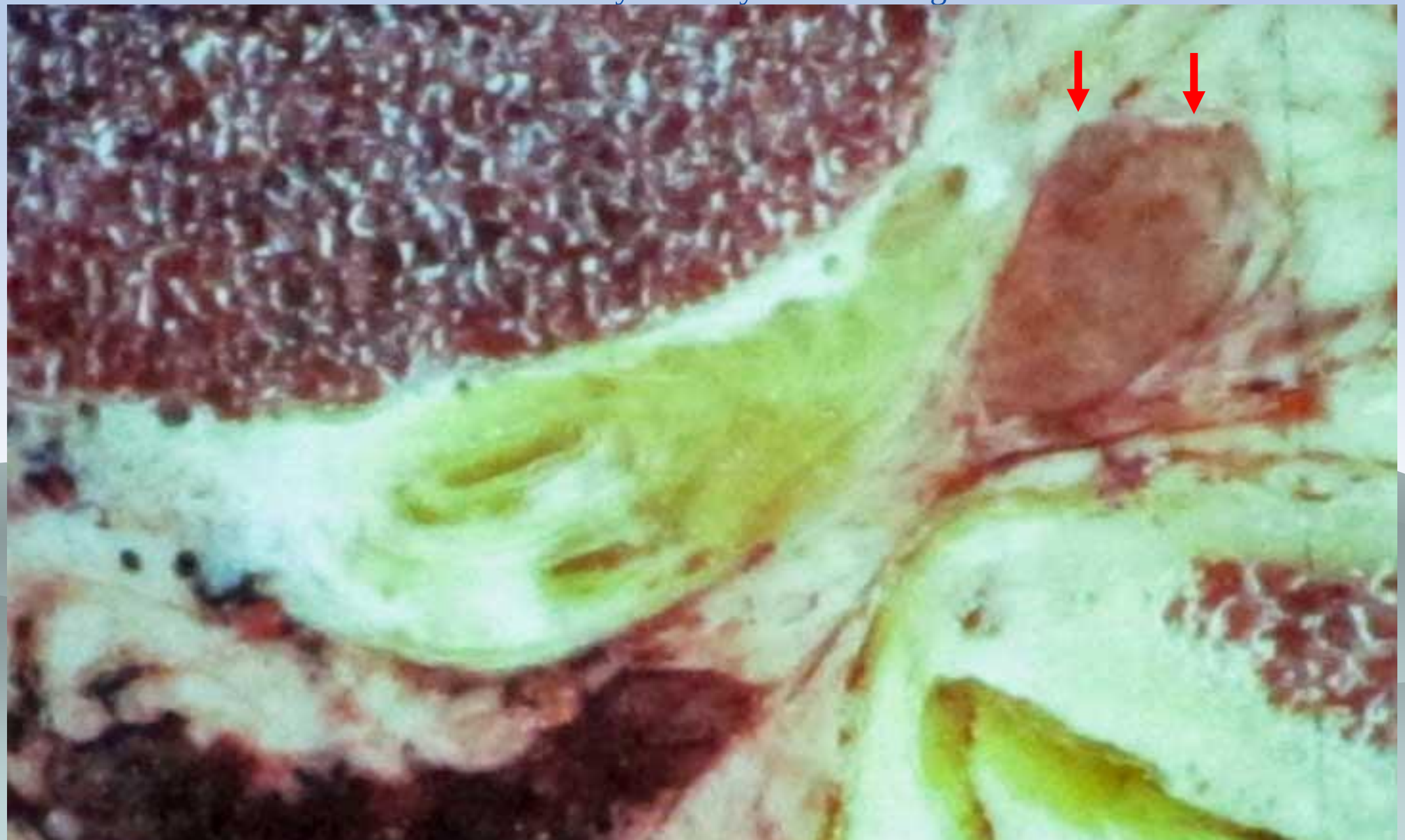
Case＃82 43f ganglion(POD)

VAS lumbago 80-90
Numbness50-100（r－l）
Leg pain10-100(r-l)





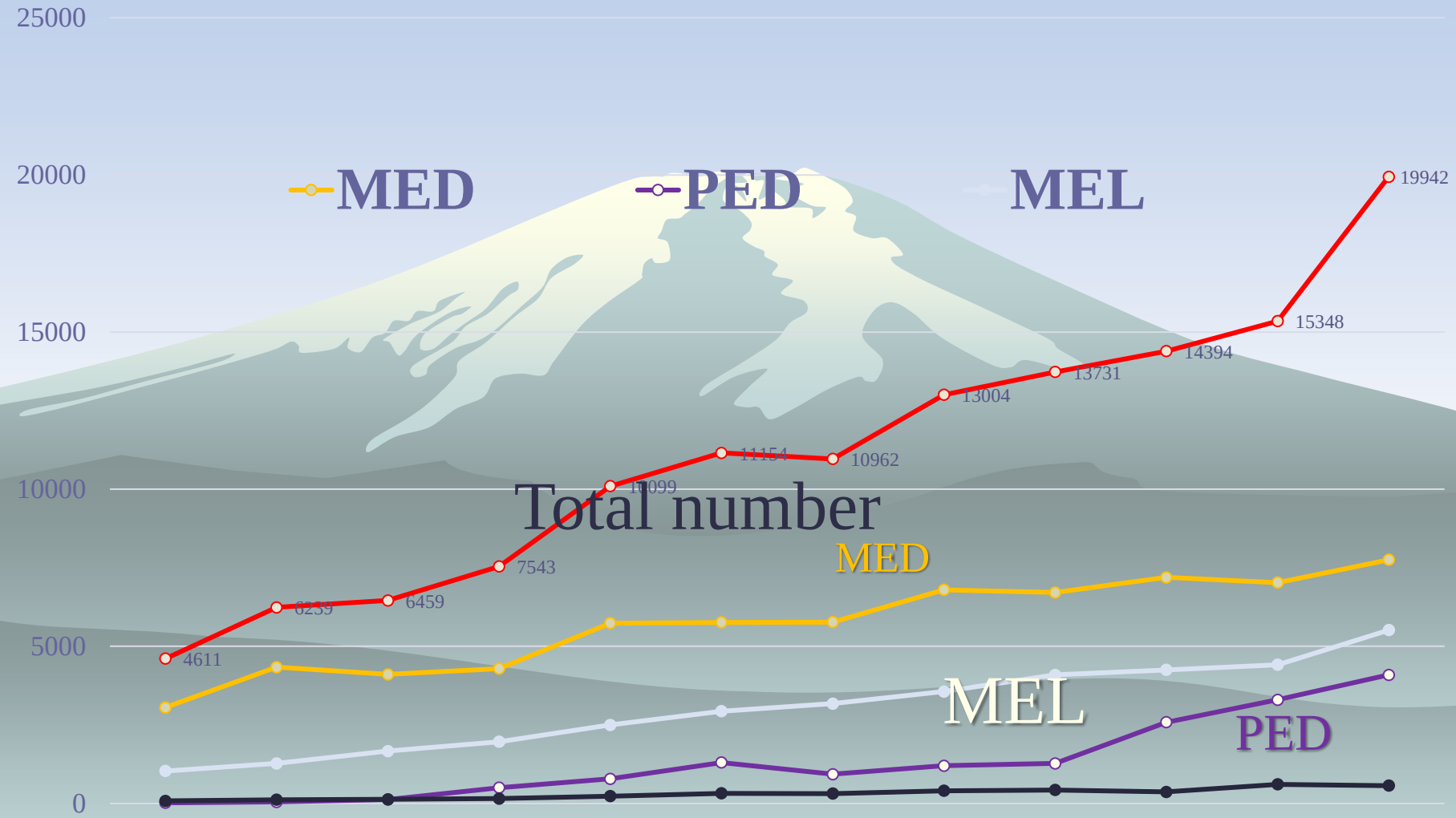
By courtesy of Raushning



Number of endoscopic surgery

グラフ タイトル

In a nationwide survey over 100.000 MISS cases for decade



4complications

- **Dural tear** MEL>MED>cervical>PELD ·PEL

  2.92 1.37 0.47 0.24

- **SEH** MEL ＞cervical ＞ MED ＞PELD ·PEL

  0.48 0.32 0.13 0.13

- **Infections** cervical > MEL>MED>PELD ·PEL

  0.23 0.05 0.04 0.03

- **Nerve injury** PELD ·PEL >cervical > MEL> MED

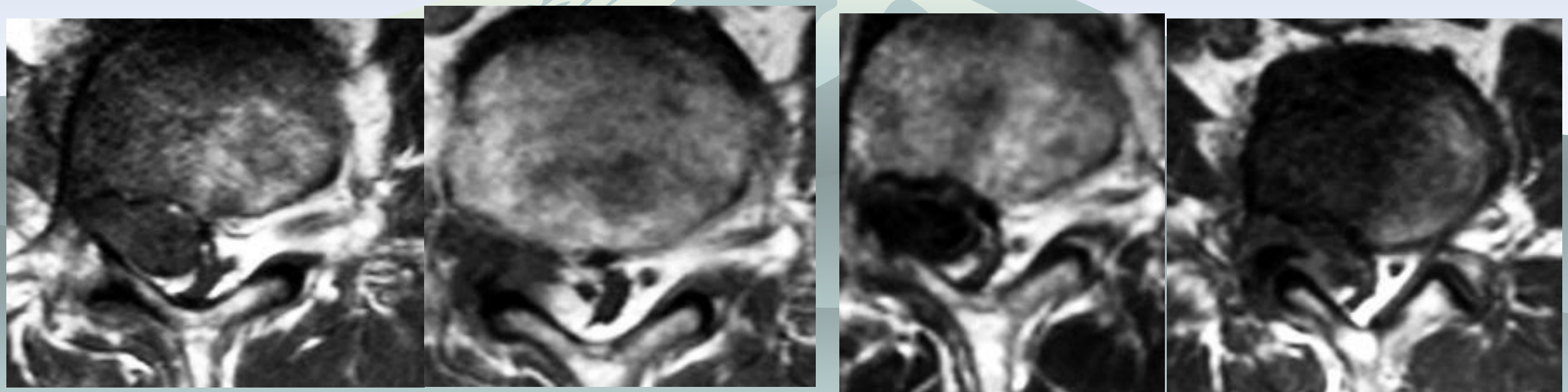
  0.47 0.23 0.14 0.13

Guidelines on endoscopic lumber herniated disc extraction

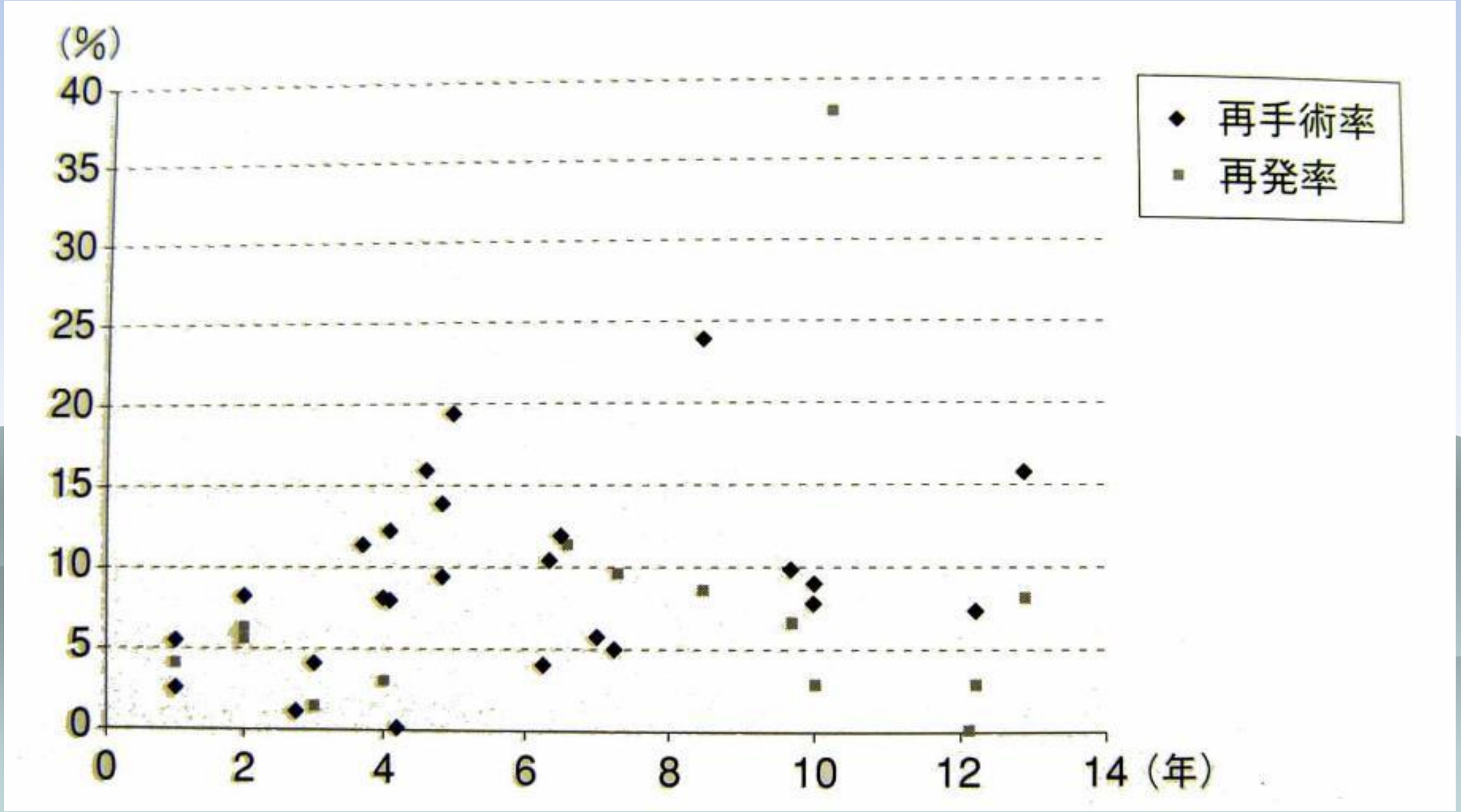
- Indication
- Clinical results
- Complications
- Invasiveness
- Reherniation Prognosis

Reherniation at L4/5 52y M

L4/5 MED Reherniation3y later PELD



Reherniation open procedure



reseach question

Rate of recurrence and the results

1. The endoscopic (MED, PELD) extraction is possible for recurrent hernia. The results good or more gain 90% of results from 81.4 in evaluation criteria of Macnab.

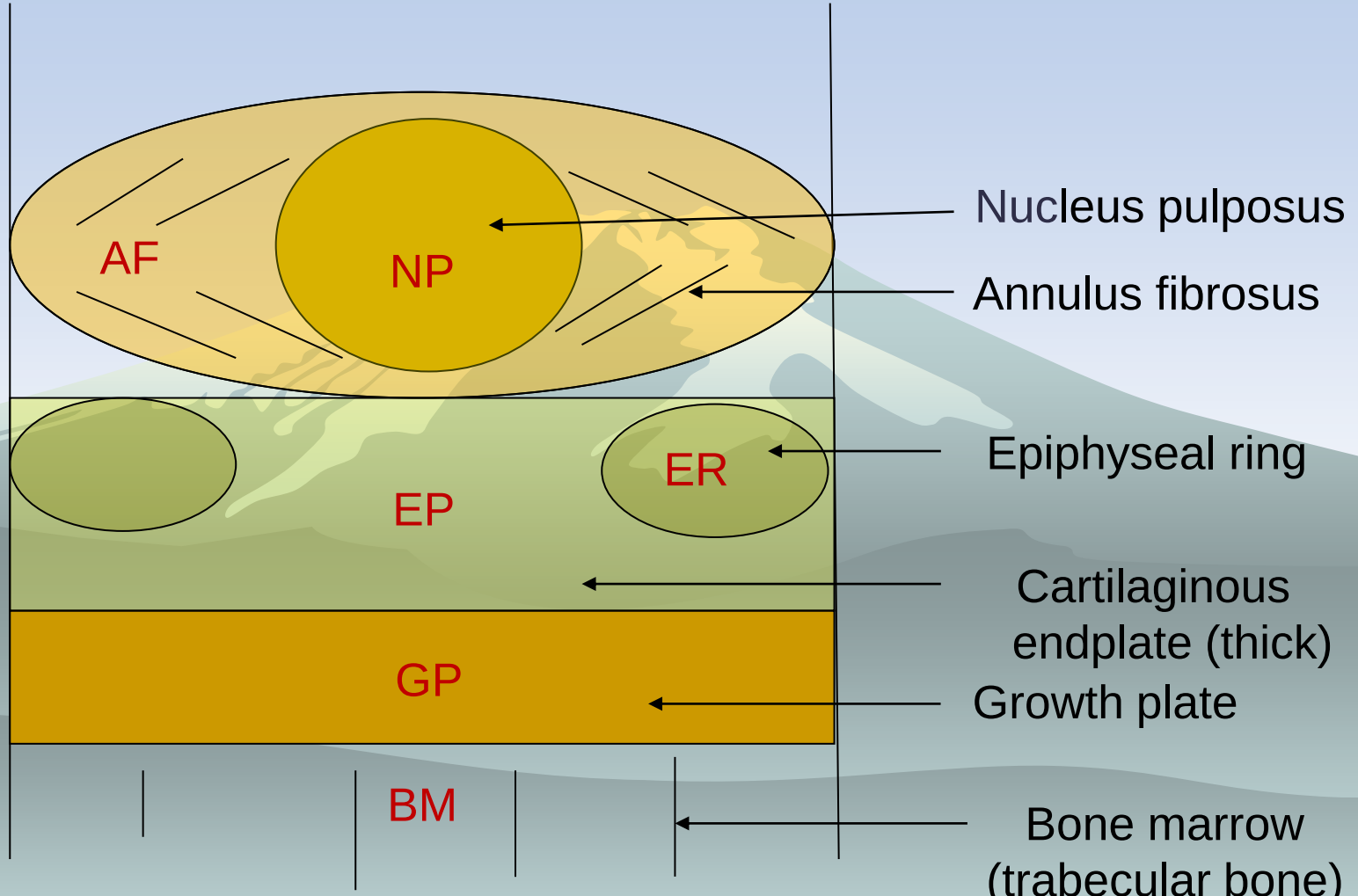
2. There is a randomized, controlled comparison report that the Chymopapain combination group decreased a recurrence from 6.9 in 1.9%. by the follow-up of two years in the PELD method

Q8
DID YOU CONDUCT EFFECT MEASUREMENT OF THE CONDOLIASE TREATMENT?

We examine the configuration of the nucleus pulposus tissue after the condoliase exposure

We investigate whether the resolution of the chondroitin sulfate was accomplished by a histopathological method

Diagram of the normal intervertebral disc structure



Data on file at Seikagaku corporation

Case #37

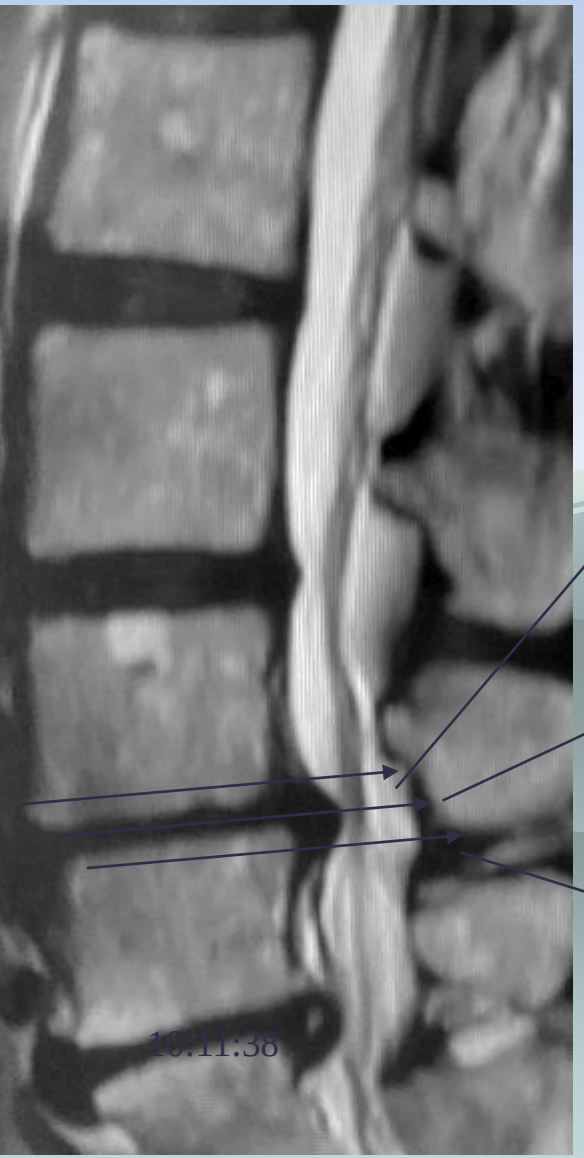
- 63y female　central herniation at L4/5level（Subligamentous　extrusion）
- Chief comp　　:leg pain low back pain
- Disease period:　15mos
- administere the condoliase:　　2019/5/7
- FESS surgery　　2019/10/8

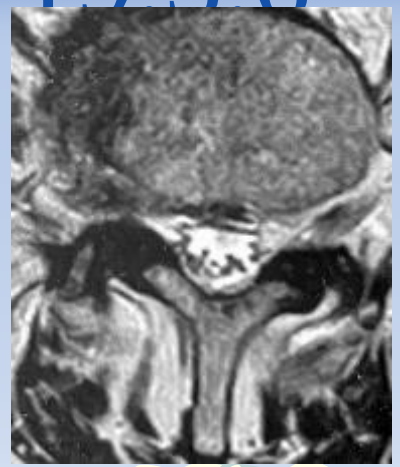
（Clinical examination）

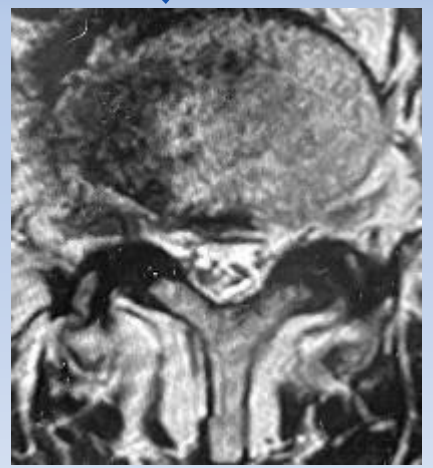
- Modic　　: Type I
- Disco CT　　: Type3-2（deg. Severe）
- Disc height　　:　no change
- Leg pain　　: Pain of lower extremities reappears in 1week after administration of condoliase

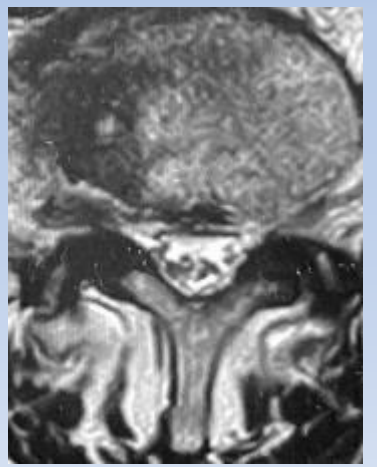
19.3.6 (5/7) 19.9.11 19.9.30

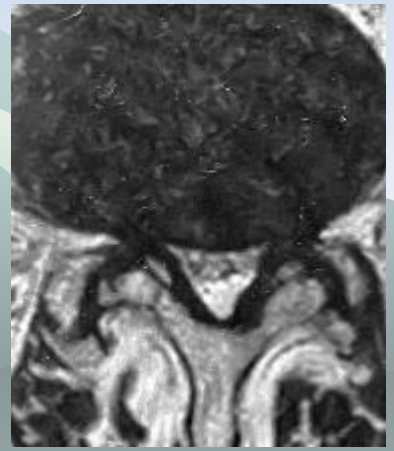
Case #37 63f

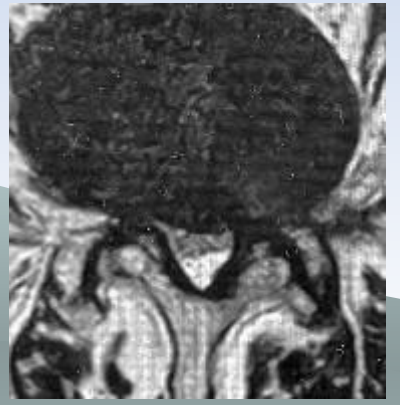


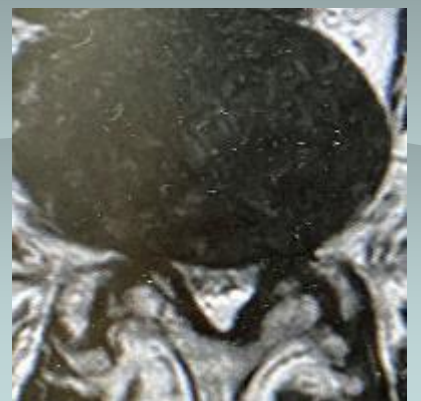


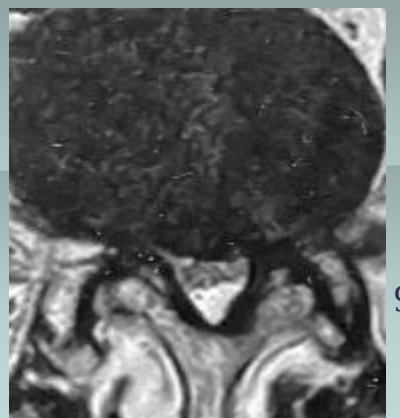




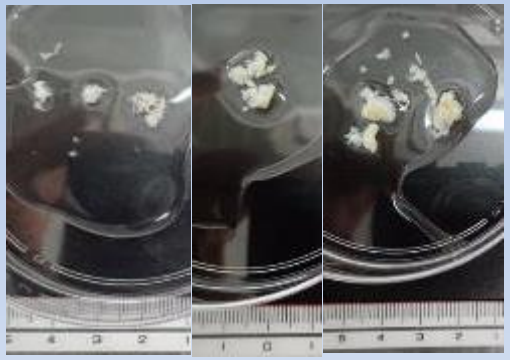








Method



- Sample, human lumbar disc
- Staining - morphology

  Hematoxylin and Eosin stain **(H&E)**

  Safranin O stain (SO) **Masson's trichrome stain (MT)**

  Toluidine blue stain (TB)

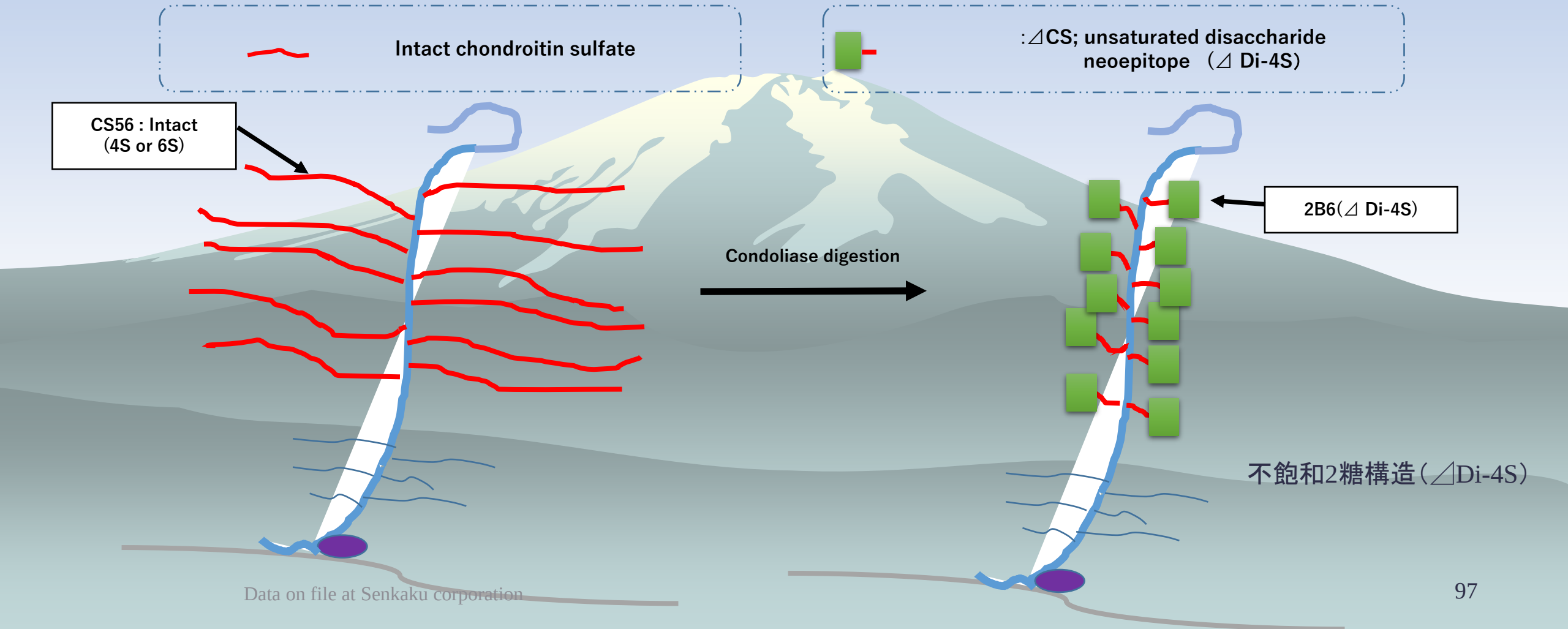
  - confirmation of degradation of chondroitin sulfate proteoglycans (CS-PGs) by HERNICORE

    CS-PGs detection; antibody CS56

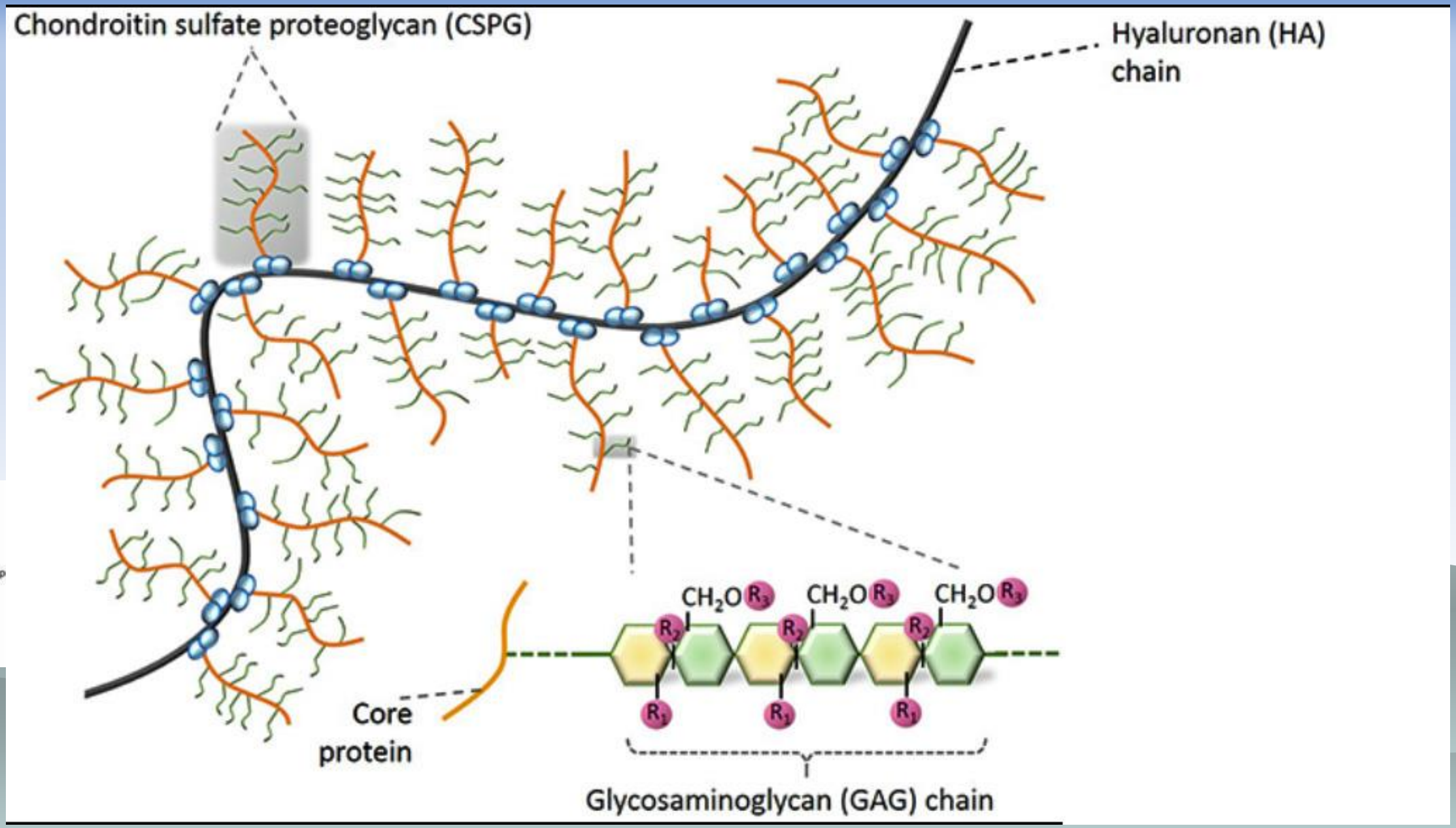
    CS-PGs degradation product detection; antibody 2B6

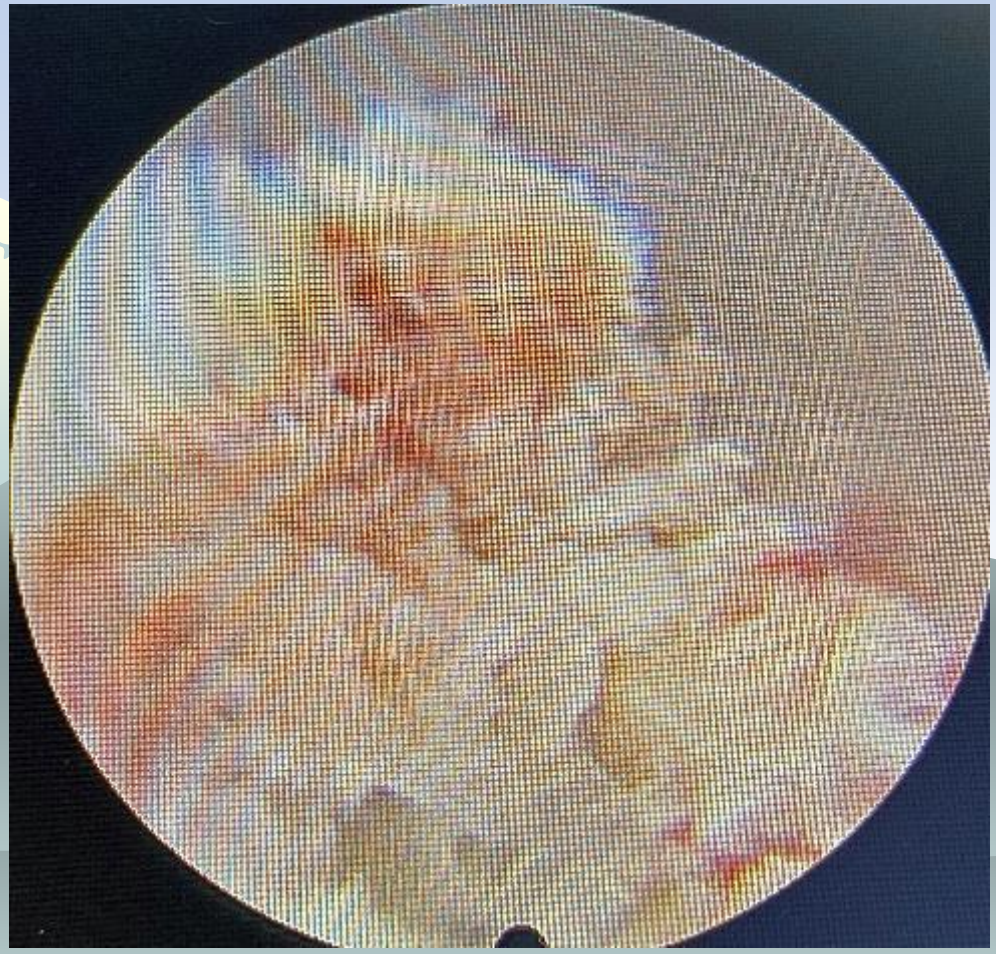
antibody 2B6

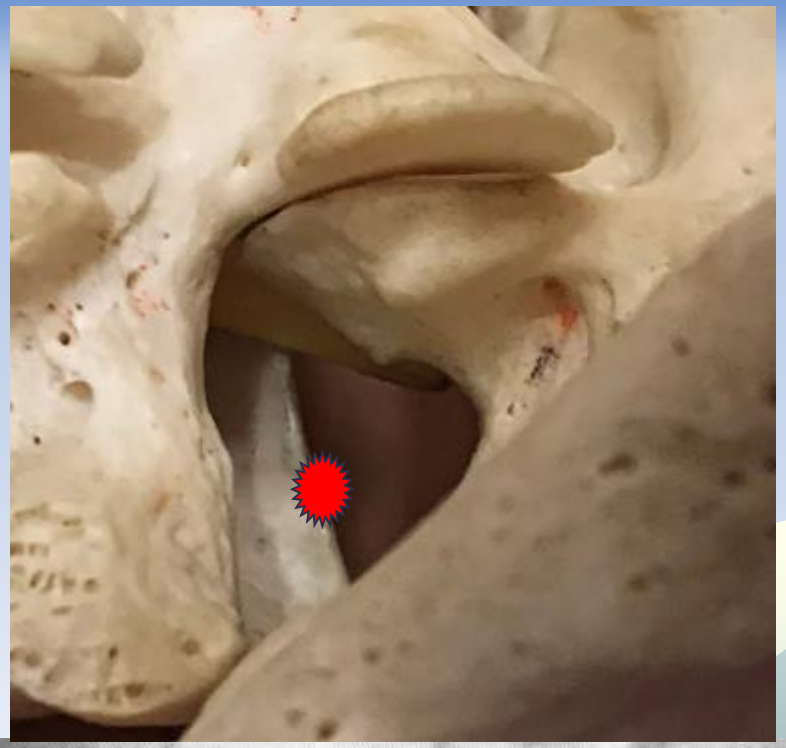
- Monoclonal antibody 2B6 is produced using chondrotinase ABC digestive products of CS-PGs as antigens, and recognizes the 4-sulfated **unsaturated disaccharide neoepitope (⊿Di-4S)** which is **a specific limited degradation cleavage surface (Stub).**

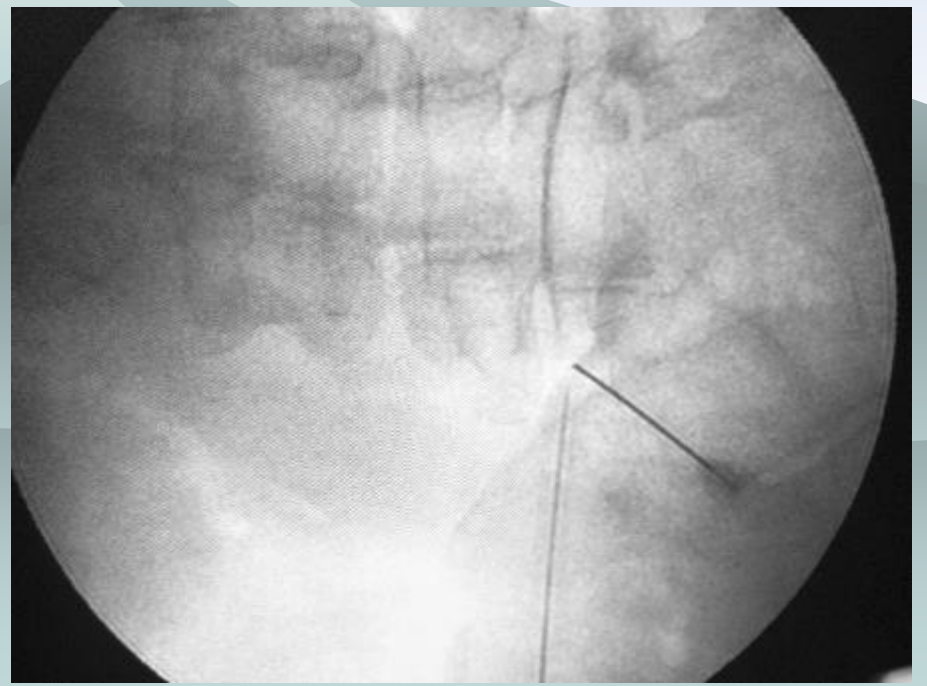


Data on file at Senkaku corporation


Chondroitin sulfate proteoglycan (CSPG)
Hyaluronan (HA) chain
Core protein
Glycosaminoglycan (GAG) chain



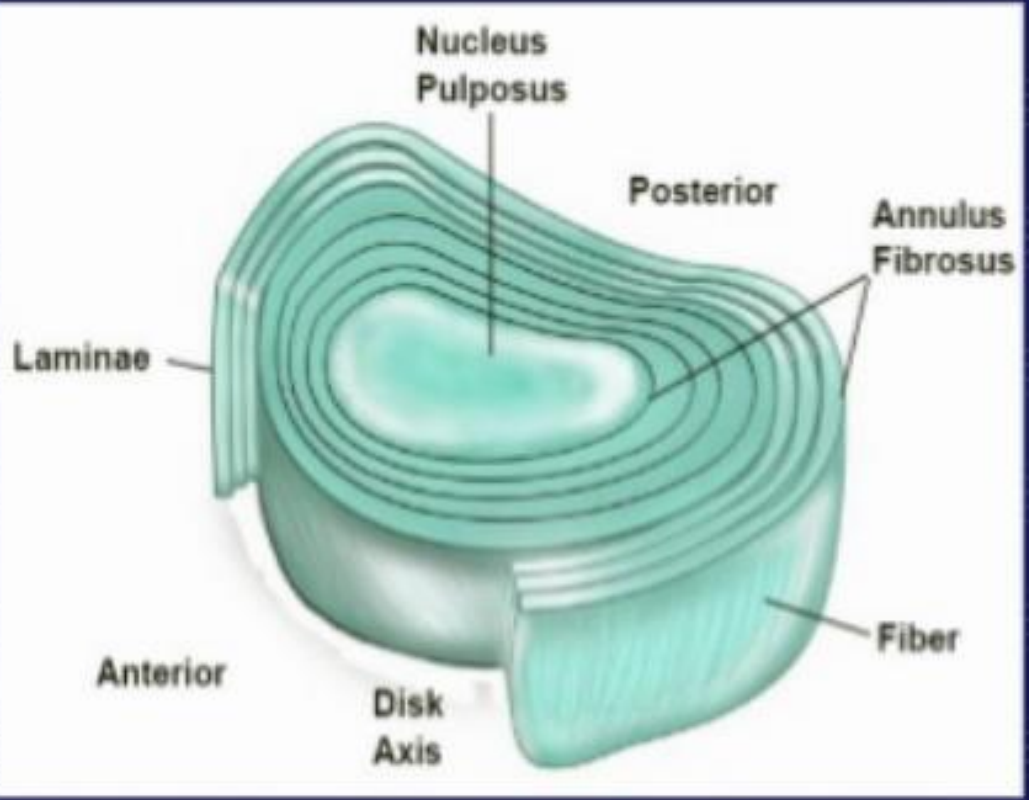


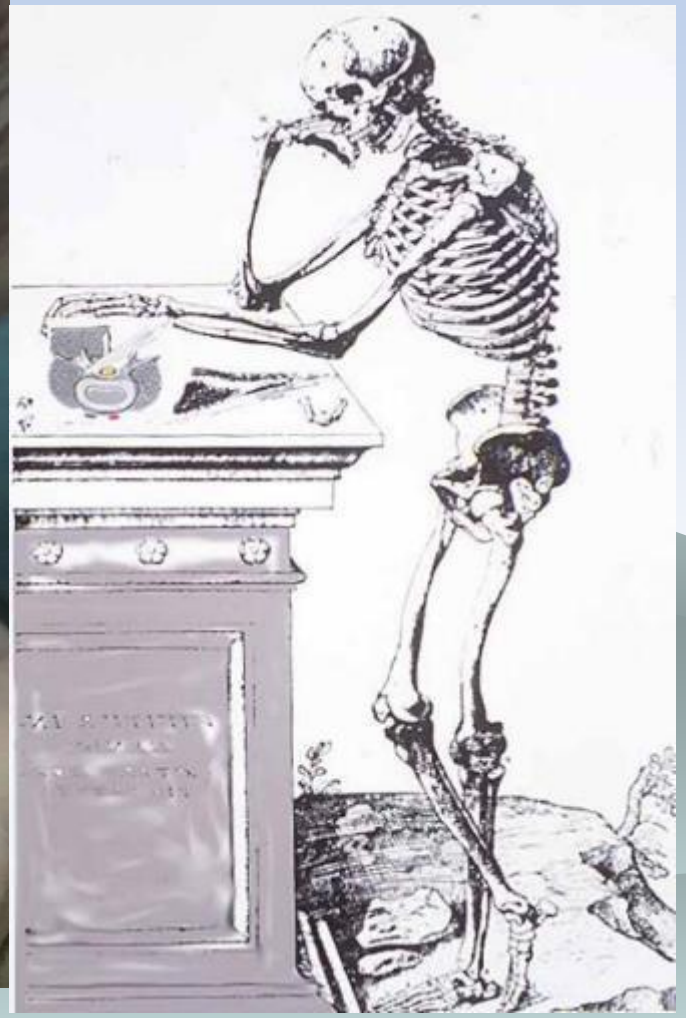


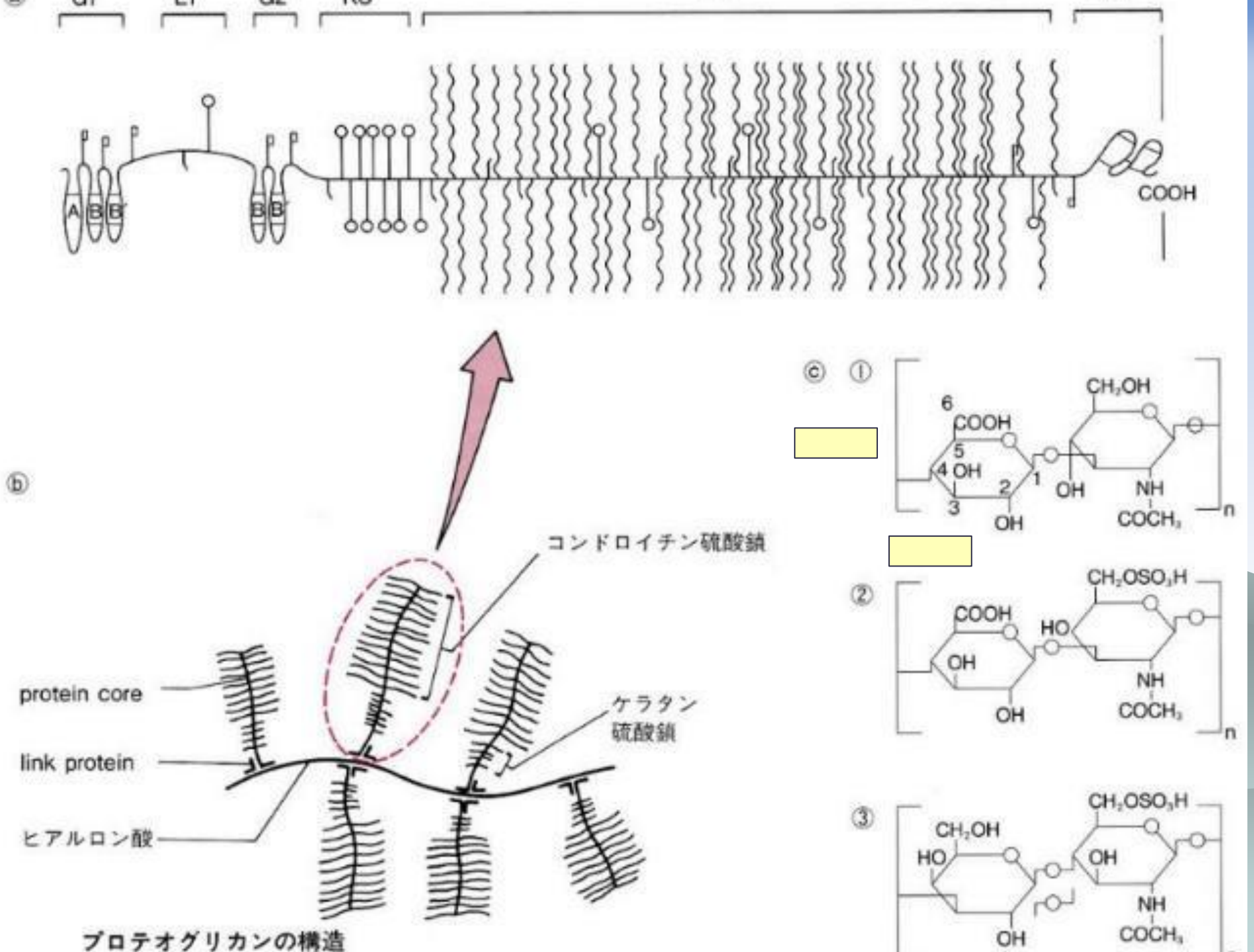
Kinematics

The Intervertebral Disc

- Primary articulation
- Viscoelastic
- Absorbs energy
- Major constraint to motion
- Limited fatigue tolerance
- Nucleus
  - 90% H_2O
  - Type II collagen and proteoglycans
- Annulus
  - ≈90 type I collagen sheets at 30°







プロテオグリカンの構造