The route of metastatic vertebral tumors extending to the adjacent vertebral body: A histological study

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Running Title

Vertical extension of spinal metastasis

Abstract

Background. Each vertebra can be regarded as a compartment surrounded by several anatomically characterized barriers. However, in some cases tumors extends beyond these barriers. The route of the vertical extension to the adjacent vertebrae is unclear. The extent of vertical extension of a metastatic spinal tumor is important in the preoperative decision regarding the cranio-caudal surgical margin. The objective of this study was to investigate the route of the vertical extension of metastatic vertebral tumors.

Methods. We examined 20 en bloc resected metastatic vertebral bodies where the tumors had extended outside the vertebral body. Five to eight sagittal sections including the pedicle, and the lateral and central parts of the PLL were prepared from each resected specimen. The sections were stained with haematoxylin and eosin, and elastica van Gieson. Histological examination focused on the routes of the vertical extension of the tumor at each barrier tissue and the degree of tumor extension along each route.

Results. Vertical extension of the tumor was observed at the ALL in 6 cases, at the central part of the PLL in 14 cases, at the lateral part of the PLL in 20 cases, at the cartilaginous endplate in 3 cases, and at the periosteum on the lateral side of vertebral body in 7 cases. The tumor had extended the farthest at the lateral part of PLL in 18 cases, at lateral side of the vertebral body in 1 case, and through the disc in 1 case.

Conclusions. Metastatic vertebral tumors most commonly extend vertically at the lateral part of the PLL. The lateral part of the PLL is raised by the tumor, which extends between the PLL and the posterior aspect of the disc.

Title

The route of metastatic vertebral tumors extending to the adjacent vertebral body: a histological study

Introduction

Metastatic tumors appear commonly in the spine, causing back pain and paralysis as a result of mechanical instability and direct compression of the spinal cord. Each vertebra can be regarded as a compartment surrounded by several anatomically characterized barriers.[1] Tomita et al developed and applied total en bloc spondylectomy (TES) for solitary metastatic and primary malignant vertebral tumors.[2,3,4] TES involves en bloc removal of the affected vertebra(e) in order to reduce local recurrence of vertebral tumors.[2,3,4] However, in some cases the tumor extends outside the barriers surrounding the vertebral compartment. Horizontal extension of a metastatic spinal tumor has been reported by Fujita[1]. However, the route of the vertical extension of tumors to adjacent vertebrae is unclear. It is important to determine the vertical extension of a metastatic vertebral tumor for preoperative decisions regarding the cranio-caudal surgical margin. The purpose of this study was to investigate the routes of the vertical extension of metastatic vertebral tumors by using histological analysis of resected specimens obtained by en bloc spondylectomy.

Materials and methods

We examined 20 cases of *en bloc* resected solitary metastatic vertebral tumors that had extended vertically outside of the vertebral body. This study was approved by our institutional review board. The tissue samples were obtained during total en bloc spondylectomies carried out from July 2005 to May 2007. Between one and three contiguous vertebral bodies were resected depending on the vertical extension in each case. The series included 11 men and 9 women with an average age of 55 years (range 34 to 77 years). The primary malignant tumors, the level of the metastatic lesions, and the number of resected vertebral bodies are described in Table 1.

Resected specimens were fixed in 10% buffered formalin. The specimens were cut into 5-mm-thick slabs in the sagittal plane using a BS-3000 cutting and grinding system (Exakt Apparatebau, Norderstedt, Germany). Thus, 5 to 8 sagittal serial sections including the pedicle, the lateral part of the posterior longitudinal ligament (PLL) and the central part of the PLL were prepared from each resected specimen. Macroscopic observation and radiography were conducted for each slab. The slabs were then decalcified in 20% formic acid solution for 2 days and embedded in paraffin wax.

Histological sections were then prepared by standard methods. The sections were stained with hematoxylin and eosin, and elastica van Gieson. Histologic examination focused on the following four issues.

1) ***The predicted region of seeding in the vertebral body and the region where the tumor is predicted to first extend outside of the vertebral body***

The region of seeding was predicted based on the shape of the tumor. After initial seeding, tumors appeared to grow in a concentric fashion until they reached a tissue barrier. At first, the sagittal section with the largest area of tumor was chosen from the 5-8 sections in each case. The vertebral body was divided into two regions, anterior and posterior, and the region with the larger area of tumor was chosen from the two regions. In the same way, the vertebral body was divided into three regions, upper, middle, and lower, and the region with the largest tumor area was chosen from the three regions. The crossover region was defined as the predicted region of seeding. Cases in which the entire vertebral body was already replaced by the tumor were excluded because of the difficulty in predicting the region of seeding under these circumstances.

The region where the tumor first extends outside the vertebral body was predicted as the midpoint between the most distal cranio and the most distal caudal extension (Figure 1).

2) Routes of vertical extension of the tumors

The vertebral body is contained within four major barriers. These are the anterior longitudinal ligament (ALL), the PLL, the periosteum on the lateral side of the vertebral body, and the cartilaginous endplate. The route of the vertical extension of a tumor is formed by breaking each barrier. Four routes, corresponding to each of the four barriers, exist. It was examined how tumors extend vertically along each route. Furthermore, the PLL is divided into two parts, a central part and a lateral part. In the central part, the PLL consists of two layers, a superficial and a deep layer. In the lateral part, the PLL consists of only a superficial layer.[5] We considered that the strength of the PLL as a barrier is different for each of the two layers: therefore, the central part and the lateral part were examined separately.

3) The degree of tumor extension along each route

The degree of tumor extension was assessed using a three-point grading system: G0, no vertical tumor extension; G1, vertical tumor extension to the level of the adjacent disc; G2, vertical tumor extension to the level of the adjacent vertebral body (Figure 2). In all routes, the route that allowed tumors to extend farthest in the vertical plane was examined.

4) Comparison of magnetic resonance imaging (MRI) with histological findings

The MRI estimation of the vertivcal extent of the tumor was compared with histological findings. Lesions were identified as areas of low signal on T1-weighted images with corresponding areas of high signal on T2-weighted images.

Results

1) ***The predicted region of seeding in the vertebral body and the region where the tumor is predicted to first extend outside of the vertebral body***

In 6 out of the 20 cases examined, the entire vertebral body had already been replaced by the tumor. In the remaining 14 cases, the sagittal section with the largest area of tumors was in the central part of PLL in 5 cases, the lateral part of PLL in 8 cases, and the pedicle in 1 case. The predicted region of seeding to the vertebral body was upper-posterior region in 5 cases, middle-posterior region in 8 cases, and lower-posterior region in 1 case (Figure 3).

In 13 out of 14 cases the tumor had extended outside the vertebral body at the lateral part of PLL. In the remaining 1 out of 14 cases the tumor had extended outside the vertebral body through the disc. In 13 cases where the tumor had extended outside the vertebral body at the lateral part of PLL, the part where the tumor was predicted to first extend outside the vertebral body was at middle third of the vertebral body in 12 cases and at the lower third of the vertebral body in 1 case. In 1 case where the tumor had extended outside the vertebral body through the disc, the part where the tumor was predicted to first extend outside the vertebral body firstly was at the lower third of the vertebral body.

2) Routes of vertical extension of the tumors

Vertical extension of a tumor was observed at the ALL in 6 out of 20 cases, at the central part of the PLL in 14 out of 20 cases, at the lateral part of the PLL in 20 out of 20 cases, at the cartilaginous endplate in 3 out of 20 cases, and at the periosteum on the lateral side of vertebral body in 7 out of 20 cases.

The PLL was raised by the tumor and the tumor extended between the PLL and the posterior aspect of the disc in all 20 cases. At the lateral part of the PLL the tumor extended vertically in all 20 cases, whereas at the central part of the PLL the tumor extended vertically in 14 cases (Figure 4). In addition, in one of the 20 cases there was a tumor thrombus within the anterior internal vertebral vein; this vein runs vertically on the posterior surface of the vertebral body at the lateral part of the PLL (Figure 5).

The ALL was raised by the tumor and the tumor extended between the ALL and the anterior aspect of the disc in 6 cases. These 6 cases were consistent in that the entire vertebral body was already replaced by the tumor on issue 1. In all 6 cases, the tumor had also extended vertically both at the PLL and at the periosteum on the lateral side of the vertebral body, and the vertebral body was observed to have collapsed (Figure 6). At the periosteum on the lateral side of vertebral body the tumor extended vertically in 7 cases. In 6 of the 7 cases the tumor extended vertically just beneath the periosteum. In the remaining case the tumor formed a large extraosseous mass on the lateral aspect of the body (Figure 7).

Although the tumor had extended to the cartilaginous endplate in all 20 cases, the tumor had invaded the disc through the cartilaginous endplate in 3 cases. In 2 of the 3 cases, an endplate fracture, caused by a vertebral collapse, was observed (Figure 8). In the remaining case, the central disc had disappeared and was displaced by granulation tissue as a result of the degenerative process (Figure 9). In these 3 cases, the cartilaginous endplate seems to have been destroyed by a degenerative process or fracture.

3) The degree of tumor extension along each route

The degree of tumor extension at each barrier tissue and the most vertically extending part of the tumor are indicated in Table 2. The vertical extension of a tumor at the ALL was graded as G1 (5 of 20 cases) or G2 (1 of 20 cases), at the central part of the PLL was graded as G1 (10 of 20 cases) or G2 (4 of 20 cases), at the lateral part of the PLL was graded as G1 (11 of 20 cases) or G2 (9 of 20 cases), at the cartilaginous endplate was graded as G1 (2 of 20 cases) or G2 (1 of 20 cases), and at the periosteum on the lateral side of vertebral body was graded as G1 (4 of 20 cases) or G2 (3 of 20 cases).

The tumor had extended the farthest at the lateral part of the PLL in 18 cases, at the lateral side of the vertebral body in 1 case, and through the disc in 1 case. Consequently, the tumor had extended the farthest in the vertical plane most frequently at the lateral part of the PLL.

4) Comparison of MRI with histological findings

In 19 out of 20 cases, comparison of the vertical extent of the tumor seen in MRI with the pathological specimens revealed similar findings (Figure 10). In one of the 20 cases, MRI overestimated the extent of tumor (Figure 11). While lesions were considered to indicate the presence of a tumor in MRI: histologically, edematous reaction zones were considered to indicate the presence of a tumor.

Discussion

The results of this study show that metastatic vertebral tumors most commonly extend vertically at the lateral part of the PLL. The reason tumors extend vertically at the PLL is that the dorsal region of the vertebral body is commonly the first site to be invaded by metastatic tumor cells.[1,6,7,8] This may be due to the presence of a large vertebral vein leading to Batson’s plexus, located posterior to the vertebral body.[9,10] Asdourian[6] postulated that the tumor cells enter the dorsal region of the vertebrae through the vertebral vein in a retrograde fashion. Our results also showed that the dorsal region between bilateral pedicles is the predicted region of seeding to the vertebral body. Although tumors may invade anywhere in the posterior vertebral body, the middle-posterior vertebral body tends to be the first region where the tumor extends outside the vertebral body. There are two possible reasons for this. One explanation of this fact is that there is a basivertebral vein in the middle-posterior vertebral body and that it leads the tumor to this part of the vertebral body.[11] The other explanation is that the main part of the PLL has an hourglass shape.[5] Therefore the middle portion of the PLL is the narrowest and weakest point. As a result, the middle portion of the PLL is easily raised by the tumor and the tumor extends vertically beneath the PLL.

The reason tumors extend further at the lateral part of the PLL than the central part of the PLL may lie in the difference between the two parts. As explained above, the central part of the PLL consists of two layers, a superficial and a deep layer, whereas the lateral part has only a superficial layer.[5] Consequently, the lateral part of the PLL is easily raised by the tumor and the tumor, which may extend vertically between the PLL and the posterior aspect of the disc (Figure 12). Notably, there was a tumor thrombus within the anterior internal vertebral vein in one case. In addition to direct tumor extension, hematogenous tumor extension may be a route by which tumors extend vertically. One or two large vertebral veins run horizontally through the center of the vertebral body and flow into the anterior internal vertebral vein lying on the lateral part of the PLL.[5,12-14] However, a tumor was found to have extended through this route in only one case in this study. This route is considered infrequent. Therefore, direct tumor extension is much more prevalent than hematogenous extension.

In all cases where the tumor had extended vertically at the ALL, the tumor had also extended vertically both at the PLL and at the periosteum on the lateral side of the vertebral body, and the vertebral body was observed to have collapsed. It seems that the vertebral body was replaced by the tumor leading to its subsequent collapse. This route at the ALL was observed only at an advanced stage. An explanation for this is that the ALL is more tightly attached to the vertebral body whereas the PLL is loosely attached to the vertebral body.[5,12] Another explanation is that the biomechanical strength of the ALL is approximately twice that of the PLL.[15]

Generally, the cartilaginous endplate serves as a strong barrier to tumor extension. [1] A number of investigators have demonstrated that the tissue constituting the cartilaginous endplate contains protease inhibitors and other substances that inhibit tumor vascularization.[16] The disc also serves as a strong barrier to tumor extension.[1,17] A number of possible explanations for this resistance have been proposed.[9,18,19] The most common one is that the disc is avascular, thus limiting exposure to metastatic cells. Another explanation is that the high pressure inside the disc acts as a mechanical barrier to tumor extension. However, in our study, the tumor had extended into the disc in 3 cases. In these 3 cases, the cartilaginous endplate seemed to have been destroyed by a degenerative process or fracture. With a degenerative process, neovascularization occurs. The cartilaginous tissue is gradually replaced by granulation tissue or bone.[20-22] Under these conditions the cartilaginous endplate did not play a role as a barrier, and thus did not inhibit the advance of the tumor into the disc.

Clinically, MRI is usually used for evaluation of the cranio-caudal range of metastatic vertebral tumors. Generally, edematous changes on MRI often suggest a greater rather than smaller involvement.[23] There is a possibility that MRI overestimated the extent of tumor in our findings. This is rarely of clinical importance because adequate surgical management of metastatic vertebral tumors requires a wide surgical margin beyond the reactive tissue. Surgeons tend to pay attention to the midsagittal plane of the spinal canal, where the relationship between metastatic vertebral tumors and the neural structures can be clearly evaluated. However, the results of this study show that the lateral part of the PLL is the major barrier to the farthest extension of metastatic vertebral tumors in the vertical plane. Therefore, it is important to use MRI to evaluate the vertical extension of the tumors at the lateral part of the PLL when making decisions regarding cranio-caudal surgical margin. In addition, it should be noted that the tumor may extend into a disc when a pathological fracture or degenerative change of the vertebral body is observed.

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Figure legends

Figure 1.

The region of seeding in the vertebral body and the part where the tumor first extends outside the vertebral body were predicted.

A : Anterior part of the vertebral body

P : Posterior part of the vertebral body

S : The predicted region of seeding in the vertebral body

F : The part where the tumor is predicted to first extend outside the vertebral body

Figure 2.

The degree of tumor extension was assessed using a three-point grading system: G0, no vertical tumor extension; G1, vertical tumor extension to the level of the disc; G2, vertical tumor extension to the level of the adjacent vertebral body.

Figure 3.

The predicted region of seeding in the vertebral body and the d part where the tumor is predicted to first extend outside the vertebral body firstly

A : Anterior part of the vertebral body

P : Posterior part of the vertebral body

F : The part where the tumor is predicted to first extend outside the vertebral body

* : 1 case where the tumor had extended outside the vertebral body through the disc is included in this number

Figure 4.

A: Photomicrograph showing tumor extension at the central part of the PLL.

B: Photomicrograph showing tumor extension at the lateral part of the PLL.

The tumor raised the PLL and extended between the PLL and the posterior portion of the disc. The tumor extended further at the lateral part of the PLL than at the central part of the PLL. Arrows indicate the PLL (hematoxylin and eosin) (Object×1). T, tumor; D, the intervertebral disc.

Figure 5.

There was a tumor thrombus within the anterior internal vertebral vein that ran vertically on the posterior surface of the vertebral body at the lateral part of the PLL. Arrows indicate blood vessel walls (elastica van Gieson) (×2).

Figure 6.

Photomicrograph and gross picture showing tumor extension at the ALL. The vertebral body was observed to have collapsed. The tumor extended between the ALL and the anterior aspect of the disc (hematoxylin and eosin)(Object×1). Arrows indicate the ALL. T, tumor; D, the intervertebral disc.

Figure 7.

Posterior aspect of the resected vertebrae. At the PLL, the tumor extended further at the lateral part of the PLL than at the central part of the PLL. The tumor extended the farthest at the lateral side of the vertebral bodies. T, tumor; P, pedicle.

Figure 8.

The continuity of the cartilaginous endplate was disrupted. The tumor extended into the disc from the split in the cartilaginous endplate (hematoxylin and eosin)(Object×2). T, tumor; D, the intervertebral disc.

Figure 9.

The tumor directly extended to an adjacent vertebral body through the intervertebral disc. The center of the disc disappeared and was replaced by a fibrous granulation tissue as a result of the degenerative process (hematoxylin and eosin) (×1). T, tumor; D, the intervertebral disc.

Figure 10.

A. MRI (T2-weighted image)

B. Pathological finding (hematoxylin and eosin) (×1)

MRI and the pathological findings were similar.

Figure 11.

A. MRI (T2-weighted image)

B. Pathological finding (hematoxylin and eosin) (×1). T, tumor; E, Edema.

While in the MRI, a lesion that was considered to be the tumor was shown, in the histology an edematous reaction zone was found.

Figure 12.

Schematic illustration and photomicrograph of the vertical extension of a tumor

A. The central part of the PLL consists of two layers, a superficial and a deep layer, whereas the lateral part has only a superficial layer. Therefore, the lateral part of the PLL is easily raised by the tumor.

B. At the lateral part of the PLL, the tumor extends vertically between the PLL and the posterior aspect of the disc.

C. Photomicrograph showing the vertical extension of the tumor at the lateral part of the PLL

Table 1.

case	age	sex	primary tumor (organ, histologic type)	level	No. of resected vertebral bodies
1.	57	F	thyroid, follicular carcinoma	T11	1+
2.	66	M	lung, adenocarcinoma	T11	1+
3.	34	F	mandible, osteosarcoma	T7	2+
4.	77	F	thyroid, follicular carcinoma	T7	1
5.	38	M	kidney, spindle cell carcinoma	T9	1+
6.	50	M	thyroid, follicular carcinoma	T4	1+
7.	58	F	breast, adenocarcinoma	T7	1+
8.	59	F	uterus, leiomyosarcoma	L1	3
9.	57	M	liver, hepatocellular carcinoma	L4	1
10.	53	F	breast, adenocarcinoma	T8	2+
11.	51	F	thyroid, follicular carcinoma	L3	2
12.	55	F	lung, adenocarcinoma	L1	1+
13.	54	M	thigh, liposarcoma	L3	2+
14.	46	M	kidney, clear cell carcinoma	L2	1
15.	62	M	kidney, clear cell carcinoma	T5	1+
16.	60	M	kidney, clear cell carcinoma	T6	1+
17.	57	F	lung, adenocarcinoma	T2	2+
18.	52	M	kidney, clear cell carcinoma	L1	2+
19.	58	M	kidney, clear cell carcinoma	T6	1+
20.	50	M	liver, hepatocellular carcinoma	T5	2+

+: resected specimen includes parts of the adjacent vertebra(e)

Table 2.

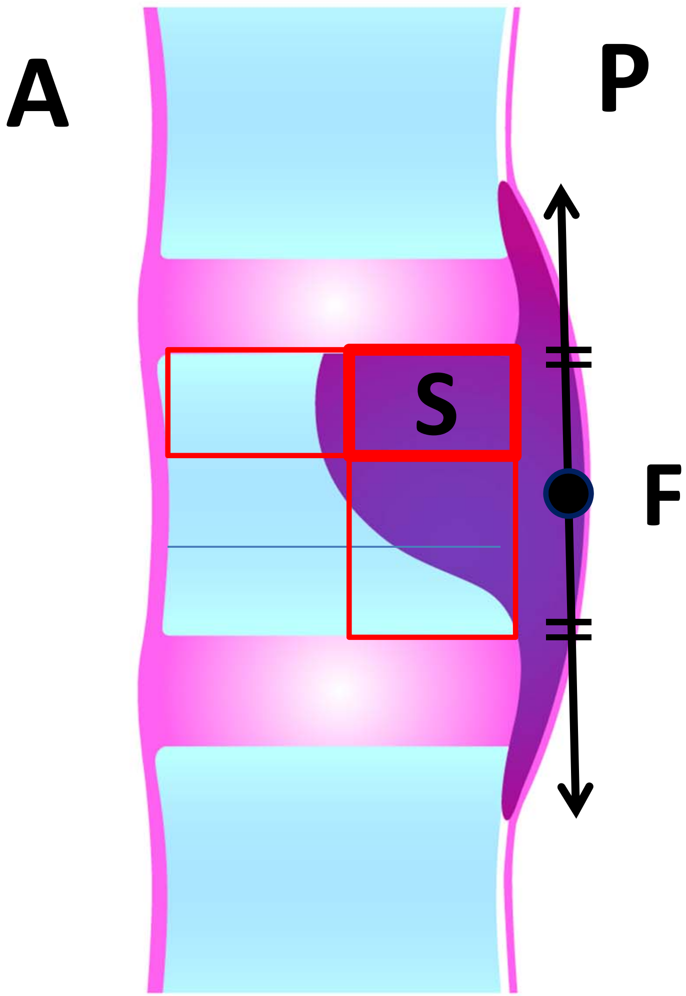
barrier / case	ALL	PLL (central)	PLL (lateral)	Cartilaginous endplate	Periosteum
1.	-	-	G1*	-	-
2.	-	G1	G2*	-	-
3.	-	G2	G2*	-	-
4.	-	G1	G1*	-	-
5.	-	G1	G1*	-	-
6.	G2	G2	G2*	G1	G2
7.	G1	G1	G1*	-	G1
8.	G1	G1	G1	-	G2*
9.	-	G1	G1*	-	-
10.	-	-	G1*	-	-
11.	-	-	G1	G2*	-
12.	-	G1	G1*	-	-
13.	-	G1	G2*	-	-
14.	-	-	G1*	-	-
15.	-	-	G2*	-	-
16.	-	G2	G2*	-	G1
17.	G1	G1	G2*	G1	G1
18.	G1	G2	G2*	-	G2
19.	-	-	G1*	-	-
20.	G1	G1	G2*	-	G1

- (G0): no vertical extension

G1: vertical extension to the level of the disc level

G2, vertical extension to the level of the adjacent vertebral body

* : the part where tumors extend farthest in the vertical plane



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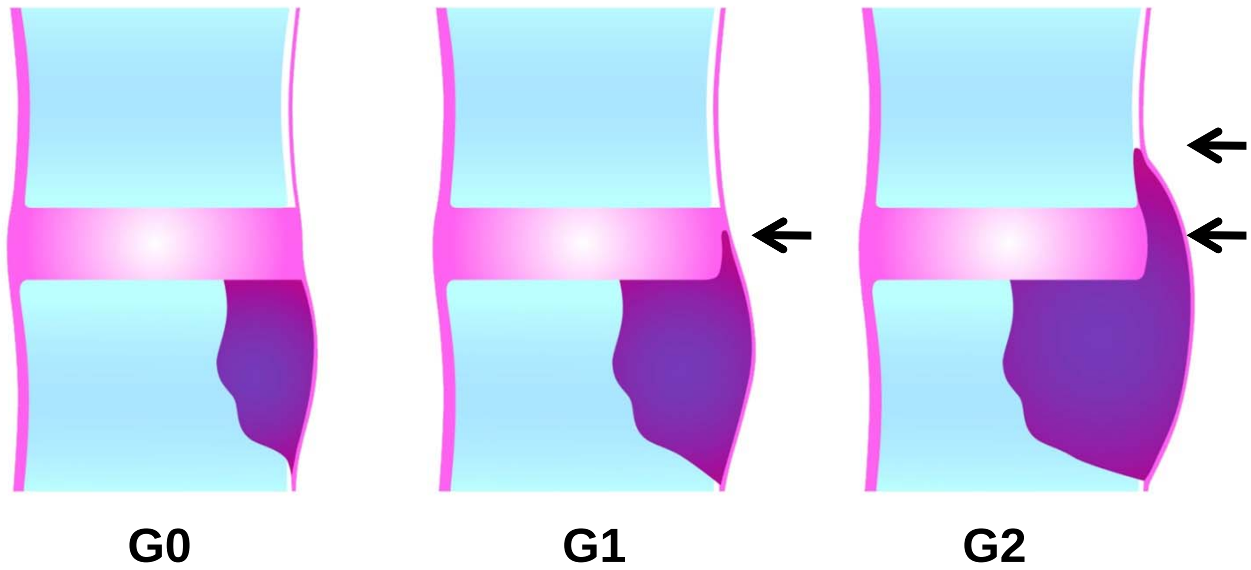

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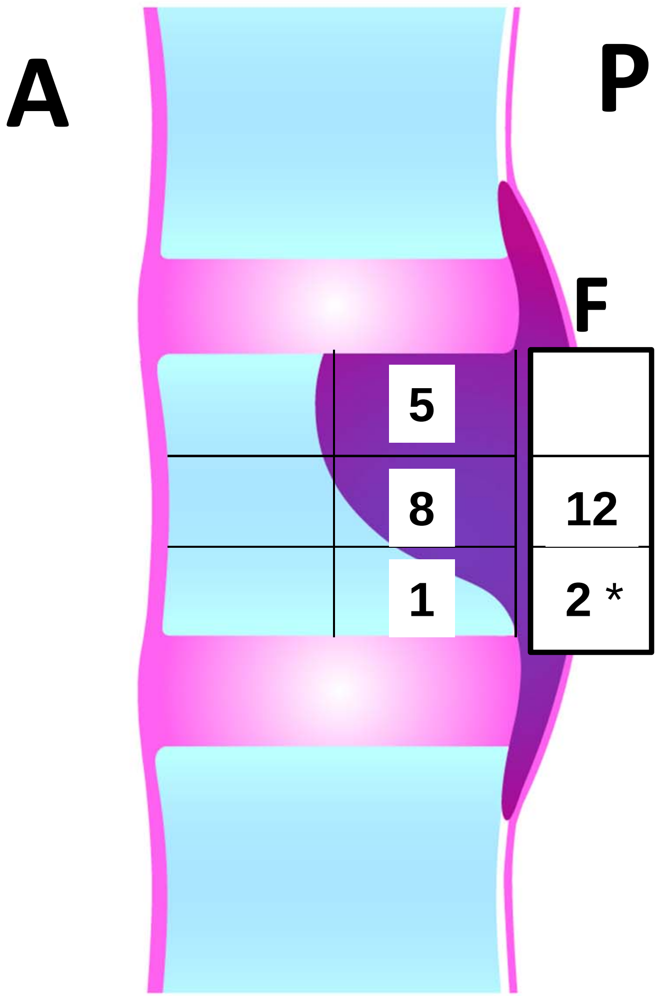

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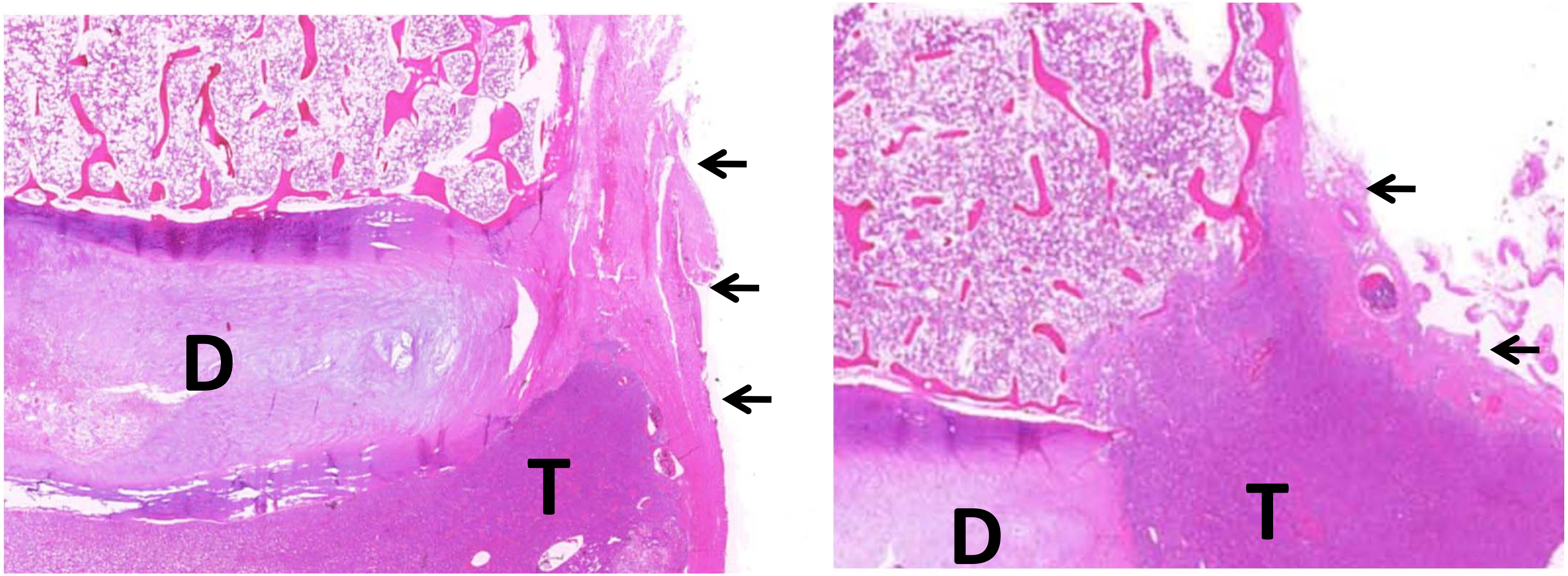

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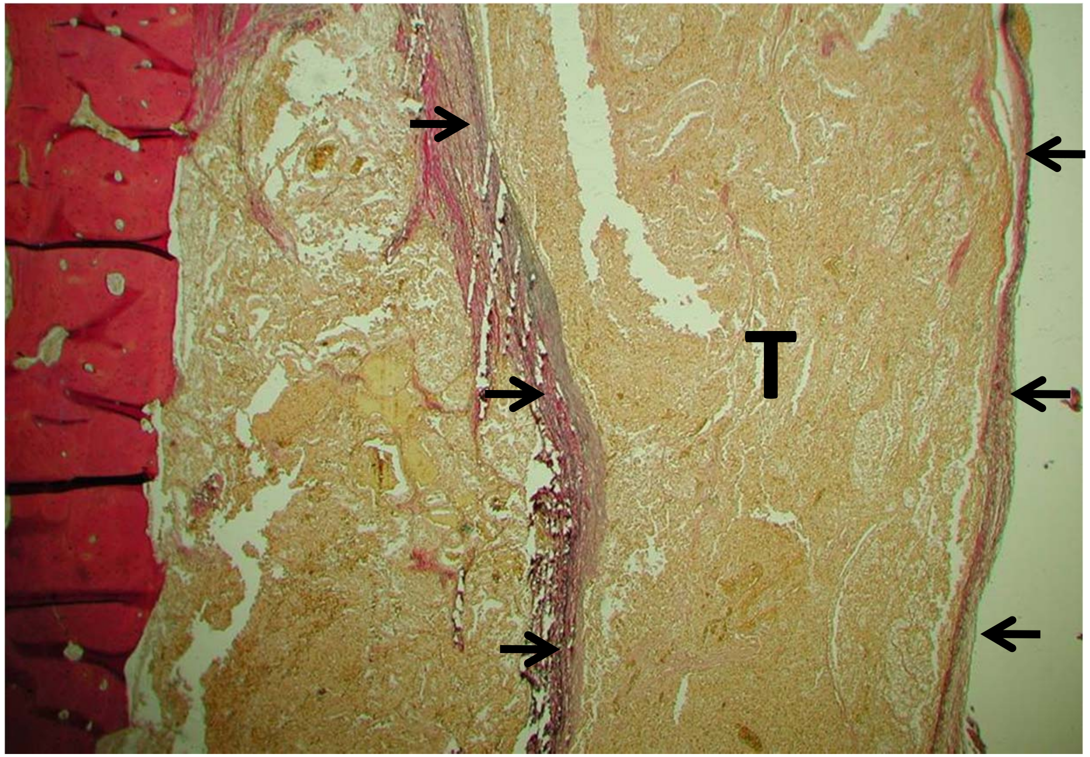
Figure 4.



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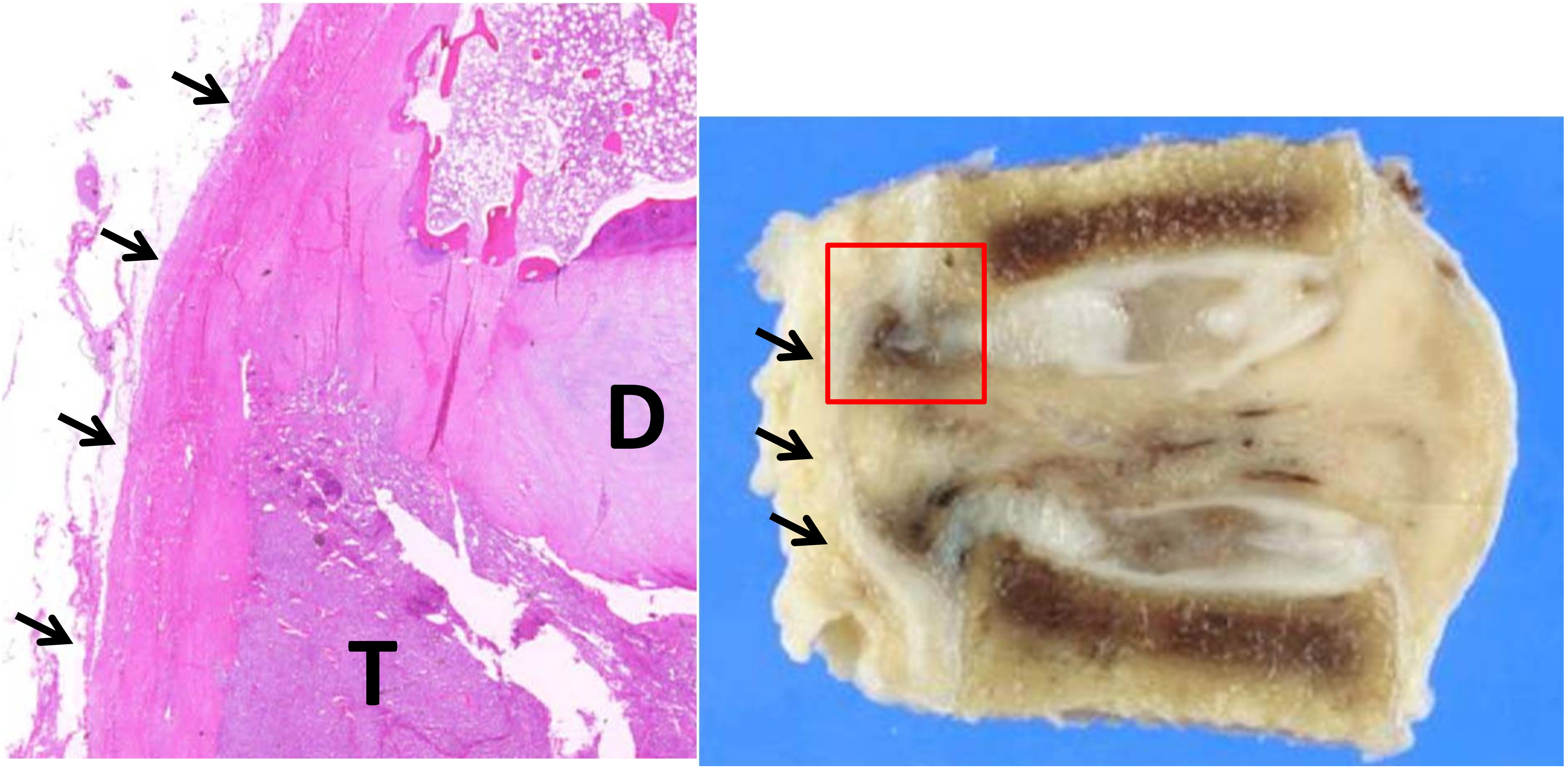

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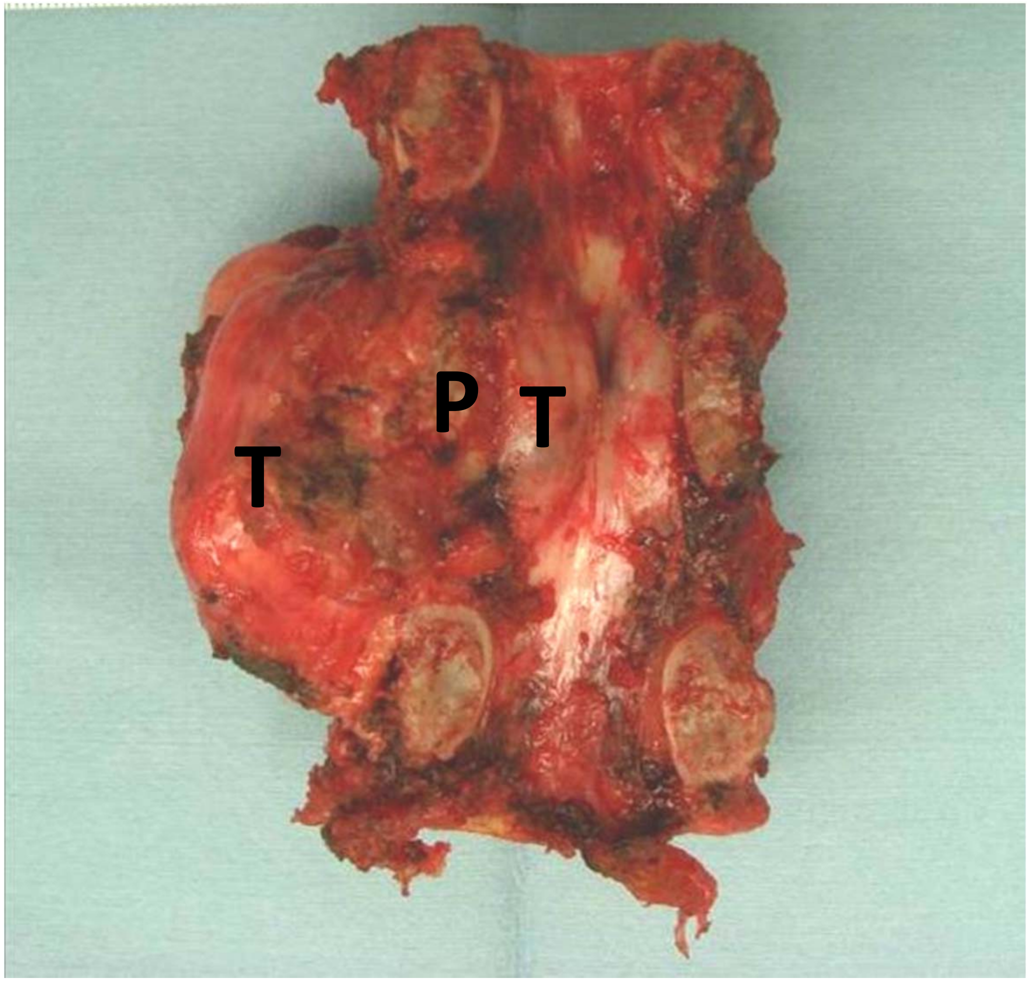

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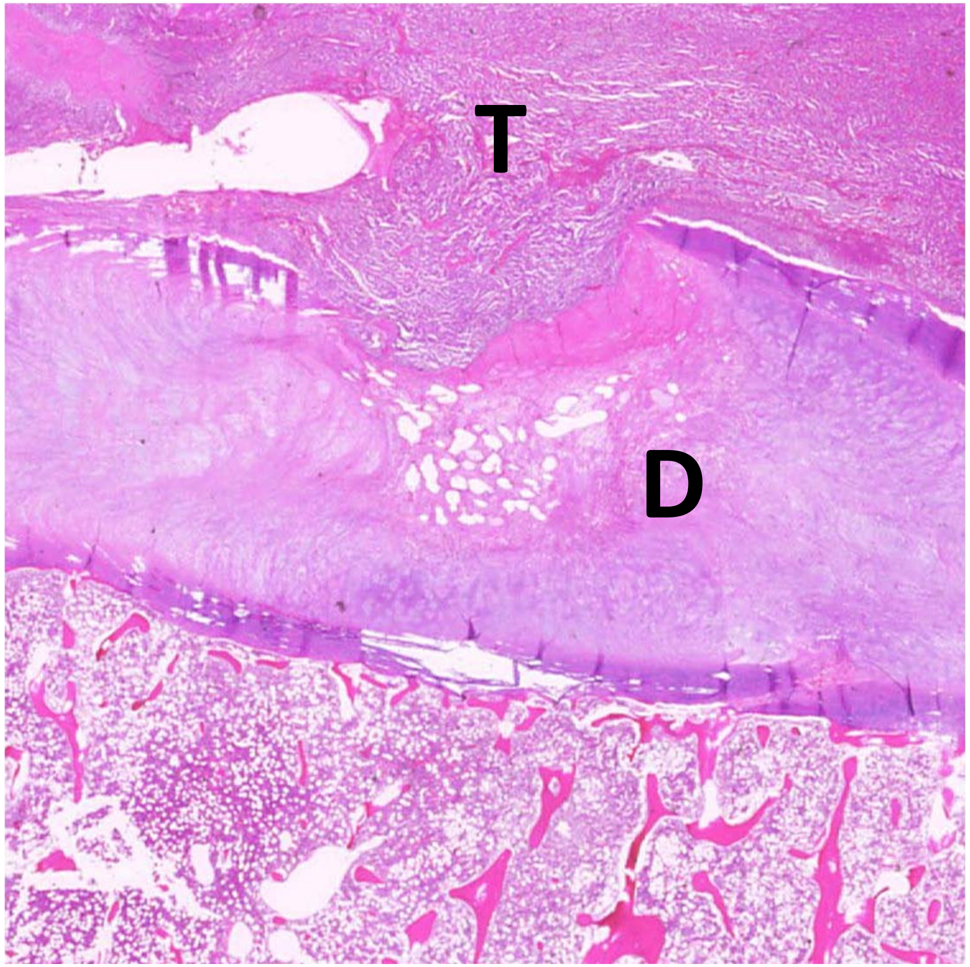

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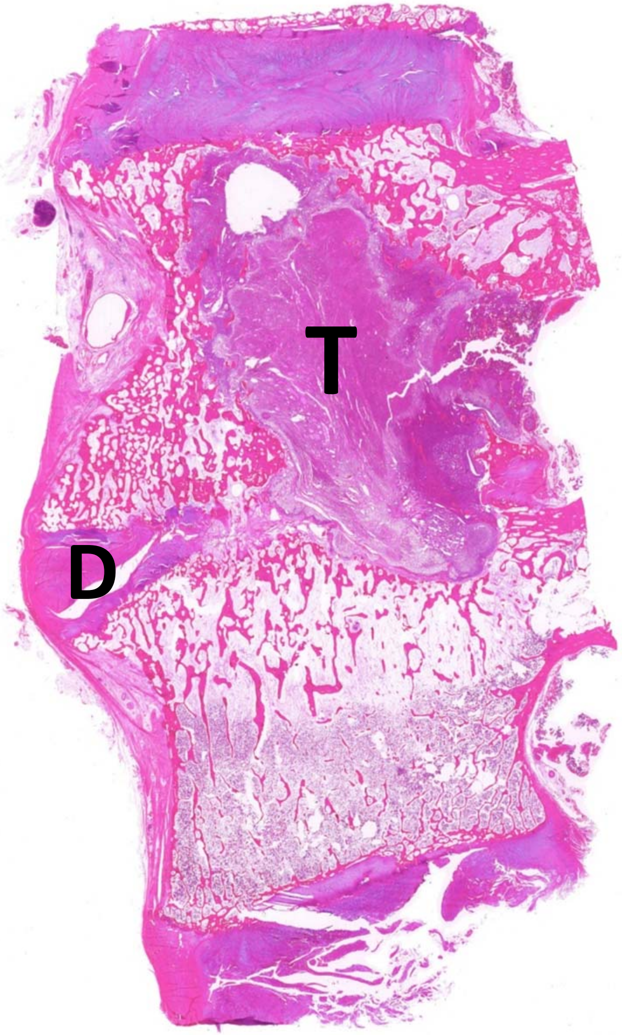
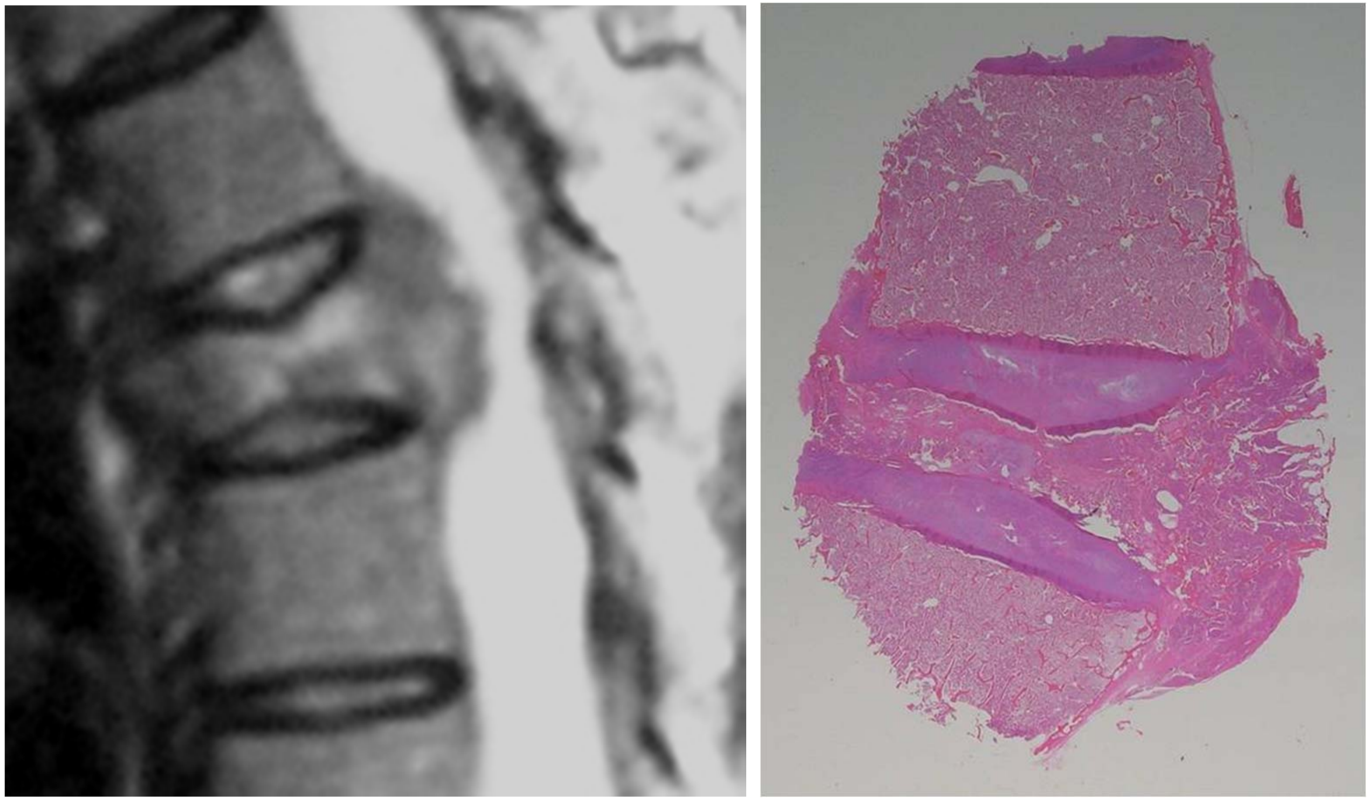
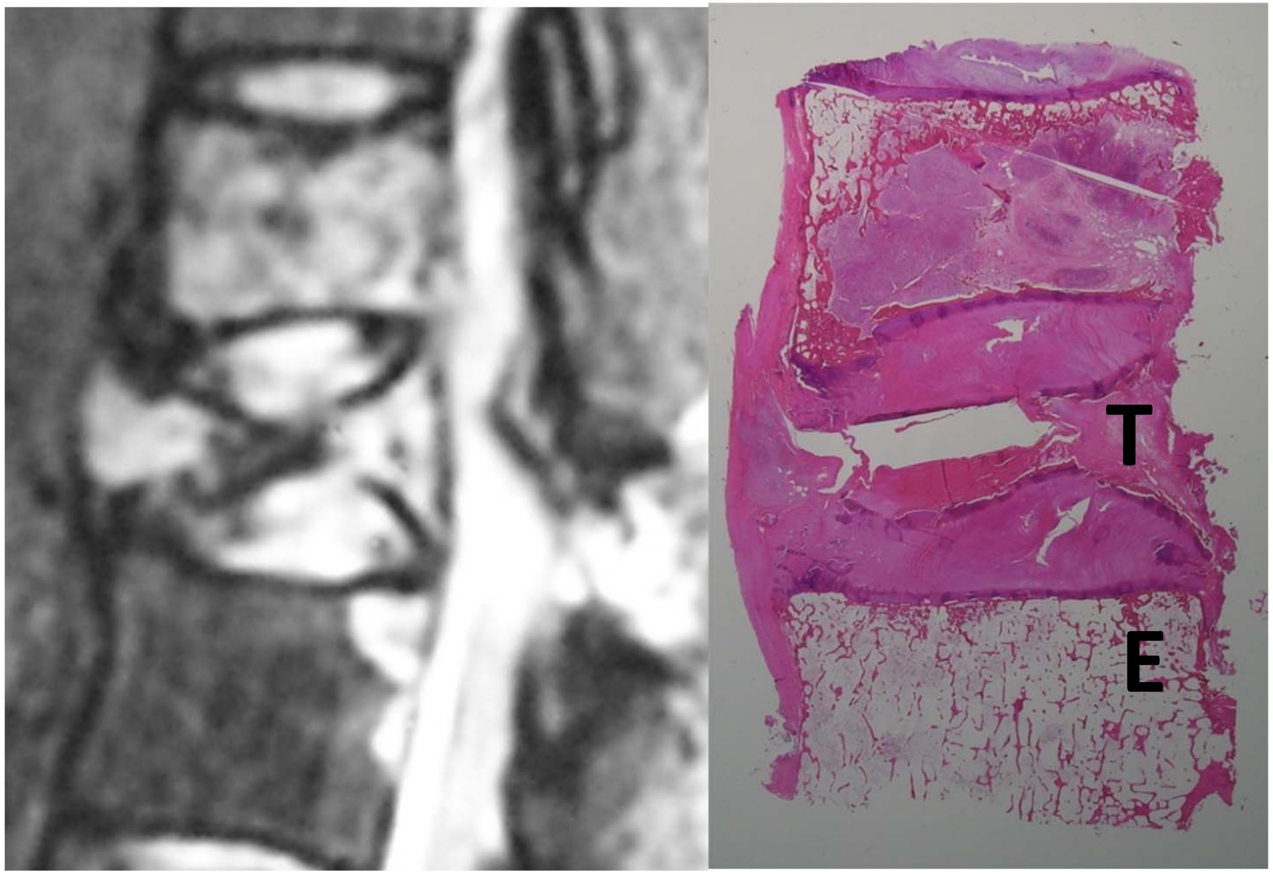


Figure 9.



A B

Figure 10.



A B

Figure 11.

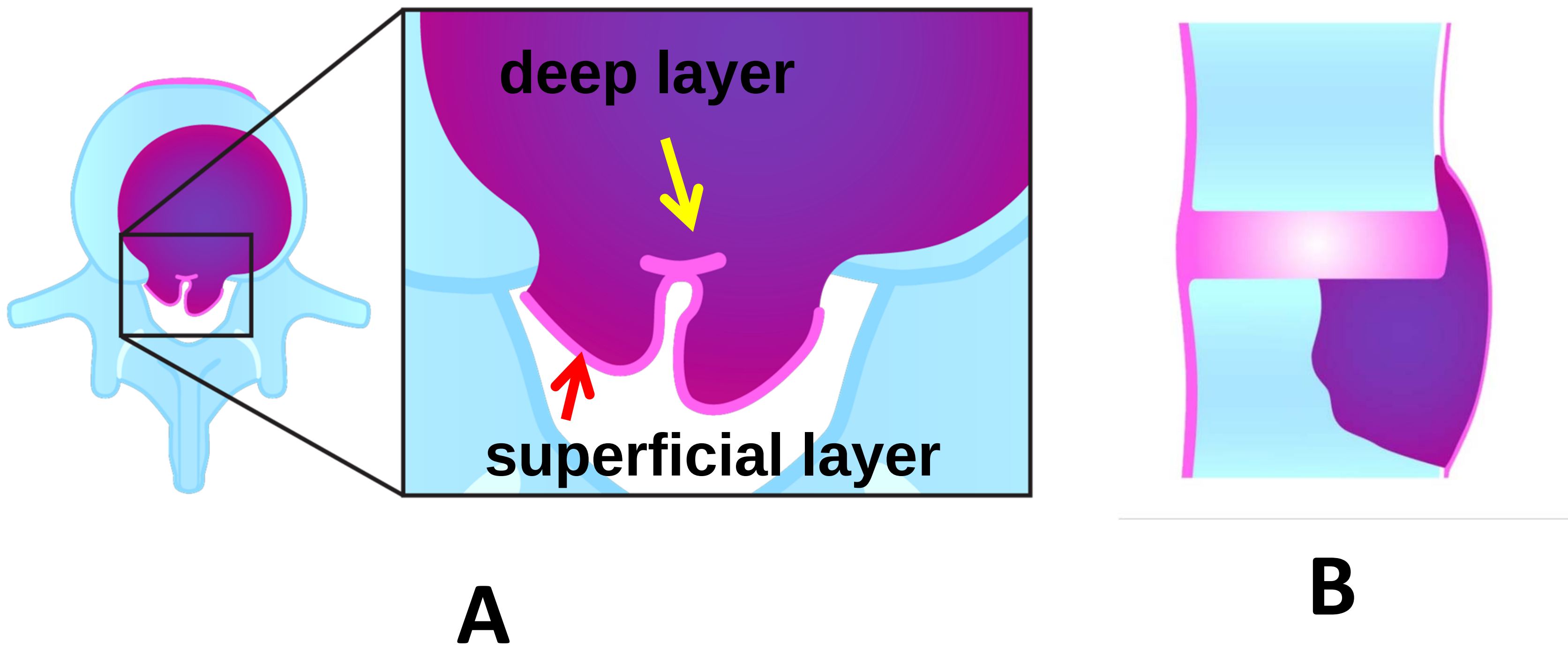
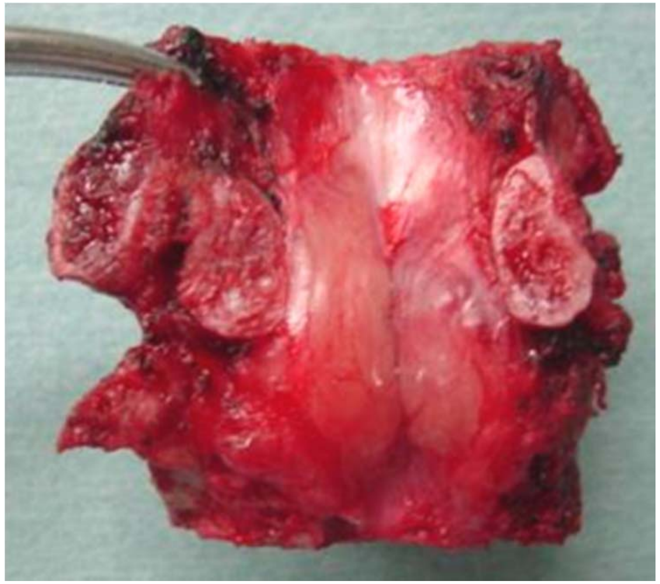


Figure 12.



C

Figure 12.