Giant cell tumor (GCT; also known as osteoclastoma) is a locally aggressive, intermediate primary bone tumor characterized by osteoclast-like, multinucleated giant cells and the overexpression of receptor activator of nuclear factor kB ligand (RANKL) produced by stromal tumor cells. The tumor-igenesis seemed to be associated with mutations of a histone (H3F3A) gene. Prevalence of GCT can be different in different regions/ethnic groups; e.g., GCT is rare in the United States—approximately 4 to 5% of primary bone tumors—but more often occurs in China where it is 10 to 20%. Local recurrence is common in surgically treated cases. Globally, malignant transformation has been described in 10% of cases, and lung metastases have been described in 1 to 4% of cases. Metastasizing can occur in benign, primary lesions as well and more frequently in recurrent GCTs and in spinal lesions. According to the Enneking surgical staging system, GCT is rarely S1 (latent); in 90% of cases, it is S2 (active with extensive cortical thinning and bulging) or S3 (aggressive with soft-tissue component). Management of GCT is often challenging and requires a multidisciplinary approach. In the spine, the osteolytic lesion can result in pathological fracture and consequential instability. Furthermore, the locally aggressive expansion of the tumor can cause neurological symptoms even in its early stage. The Enneking appropriate, en bloc resection of an S3 spinal lesion is a technically challenging surgery with high risk for perioperative complications and functional loss.

The case report of Santiago-Dieppa et al demonstrates the complexity of such a surgery. Regarding the differential diagnosis, on one hand, the imaging studies present the typical diagnostic findings in the case of spinal GCT: lytic, aggressive tumor in L4–L5 with local extension across the L4–L5 disc and to the spinal canal. On the other hand, the patient was 58 years old. That age is not typical for the appearance of a GCT, which is usually diagnosed in the second to fourth decade. The patient had local and irradiating pain but no neurological symptom. Considering the unpredictable nature of the tumor and the high risk for local recurrence, the authors performed an en bloc L4–L5 spondylectomy followed by lumbopelvic reconstruction. The description of the technical details of the two-stage surgery clearly shows the difficulty of the management of such a patient; however, more data on the total time of the surgery, blood loss, and hospital stay would have been more informative. In the reported case, the sagittal alignment is properly reconstructed, but I would have been also interested about the bone-grafting procedure, which is the key element of the long-term stability of the lumbopelvic reconstruction. Despite the proper surgical technique and the careful perioperative care, complications occur in almost all of these patients. The reported deep wound infection and CSF leak are the most common complications after en bloc lumbar spondylectomies and lumbopelvic stabilization procedures. However, in some cases, the short- and long-term outcome of extended spinal surgery is not as good as in this patient.

The recently described pathological importance of the RANKL in the tumorigenesis of GCT led to human trials of the anti-RANKL monoclonal antibody (denosumab) in the management of the disease. Osteoclasts and their progenitors are dependent on RANKL, and the giant cells in the tumor produce unknown factors important for the survival of the stromal tumor cells. Denosumab was originally developed for the treatment of osteoporosis, but its inhibitory effect on osteoclasts blocks the bone resorption and the tumor progression in GCT. Moreover, in the absence of RANKL, the less cellular stroma starts to produce new osteoid matrix. After the successful phase 1 and 2 trials, denosumab was recently registered for the treatment of unresectable GCTs. Most of these studies comprised patients with GCT in the appendicular skeleton. The first report, with medium-term follow-up, about the use of denosumab in spinal GCT has been recently
published by Mattei et al who treated successfully a 22-year-old female with a C2 GCT, applying denosumab after a posterior stabilization procedure. The open-label, parallel-group, phase-2 study about the safety and efficacy of denosumab in GCT also included 75 spinal cases (26.5%). In the overall cohort, use of the drug was associated with the inhibition of tumor progression and the reduced need for morbid surgery with an acceptable safety profile. Unfortunately, sub-analysis of spinal cases was not reported in this study, despite the importance of the possible surgical morbidity-reducing effect. The first results promise to bring significant changes to the current therapeutic standards, but further multicentric studies on the effect of denosumab in spinal GCT are required to include the drug into the first-line treatment.

**References**