Chordoma
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Purpose of review
To review developments in chordoma treatment.

Recent findings
Recent series with prolonged follow-up show that adequate margins are necessary for surgery to be curative. Safe margins are often difficult to obtain due to the anatomical sites of chordoma: sacrum, skull base and spine. Tumors in these sites are problematic for radiation therapy as well, and this adds to the need for high doses. Hadrons have therefore been used in addition to, or instead of, photons. New photon beam techniques, e.g. intensity modulated radiation therapy and stereotactic procedures, have recently been evaluated. Although less available than photons, hadrons possess certain advantages. While chemotherapy is poorly active, recent interest has focused on molecular-targeted agents. Imatinib was shown to be active, providing mainly nondimensional tissue responses in a significant proportion of patients, which may improve symptoms and progression-free interval. Epidermal growth factor receptor targeting, anti-angiogenics, and the combination of targeted agents with chemotherapy and radiation therapy are also under scrutiny.

Summary
Two major issues about local treatment remain unresolved: when to complement surgery with radiation therapy, and how best to deliver high doses of radiation therapy to the tumor tissue. Regarding systemic treatment, there is ongoing research into how to exploit molecular-targeted therapies.

Keywords
chordoma, hadron radiation therapy, imatinib mesylate, molecular-targeted therapy

Introduction
Chordomas [1] are very rare tumors of bone (their incidence rate is in the 0.1/100 000/year range). They arise from the sacrum, skull base and spine. Median age is around 60 years, but skull-base presentations affect a younger age, and may even occur in children and adolescents. Chordomas are thought to stem from embryonic rests of notochord, and show a dual epithelial-mesenchymal differentiation [2]. They are low-grade malignancies. In addition to the typical presentation, an aggressive, sarcomatous, or ‘dedifferentiated’, high-grade variety occurs in a minority of patients. The chondroid variety may have a more favorable prognosis than other chordomas. In general, the clinical course of the disease is slow and mainly local. Chordomas also have the potential for metastases, with extent to the lungs, bone and liver. Although this potential may have been underestimated so far, metastases tend to grow slowly. Therefore, local disease is generally the main problem. Long-term follow-up (in excess of 15 years) proves local recurrences to be frequent, eventually affecting most patients.

Classically, local treatment for chordoma has been surgery. The importance of radiation therapy, however, has increased over time. There are two main reasons, related to the most frequent sites of disease origin (sacrum, skull base and spine). First, long-term observation of case series has shown the inherent limitations of surgery, such as technical constraints and quality of life implications. Second, technological progress has made it possible to improve the way these sites can be irradiated.

Surgery
Recent papers have reinforced the notion that the main prognostic factor for local failure, and possibly survival, is quality of surgical margins [3,4,5**,6**]. Indeed, the expected local failure rate in case of a marginal resection is in excess of 70%. Technically, an adequate margin can be obtained in roughly half of sacrococcygeal presentations [3,4,7,8], and even less frequently for the mobile spine [6**] and skull-base lesions [5**,9–11]. Quality of life implications add to technical difficulties. For sacral presentations, surgical resections above the level of S2 are marked by a significant perioperative morbidity and long-term sequelae [12,13]. In fact, resections of both S2 roots result in urinary and bowel incontinence, while the loss of S3 roots may result in substantial problems in a significant proportion of patients.
In regard to prognosis after surgery, the expected disease specific survival at 10 years for sacral presentations is around 50% in published series, with a local control ranging from 20% to 50% [3,4,7,8,12–14]. In the few series with a prolonged follow-up, i.e. in excess of 10 years, these figures tend to worsen over time, and therefore only a minority of patients can be cured. In mobile spine presentations, long-term local control is even poorer, though limited data have been provided [6**]. In tumors arising from the base of the skull, local control beyond 10 years is around 30% [3,10]. These patients often receive repeated surgery during the course of their disease.

**Radiation therapy**

Unfortunately, the sites of origin of chordomas are equally challenging vis-à-vis radiation therapy. In fact, the tolerance dose of the spinal cord and brainstem, optic pathways, and the rectum is lower than the curative dose. This should at least be in the 70 Gy range [15], although the notion has been disputed [16]. Among other things, the use of metal implants for spinal lesions may produce artifacts that interfere with the target volume definition and reduce the accuracy of dose calculation. In the face of this, and so far in the lack of any effective medical therapy, there has been an obvious need to resort to radiation therapy in combination with surgery for positive or close margins, and even as the definitive treatment modality for unresectable lesions. At doses up to 40–60 Gy, however, local control at 5 years with conventional photon beam radiation therapy does seem to be in the 10–40% range [10,17,18].

Heterogeneous coverage of all the target volume through an effective dose is one cause [15,19]. As from the 1970s, therefore, hadrons (i.e. high-dose protons or charged particles, such as carbon ions, helium or neon), given either alone or in combination with conventional photon beam therapy have been used to improve the radiobiological effect [20,21]. This allows delivery of higher doses to the target volume, while sparing organs at risk. The physical and ballistic properties (Bragg peak) of hadrons allow a steeper dose gradient between the target volume and surrounding structures. Hadrons have been exploited for chordoma of skull base and proximal cervical spine, as well as for sacrocccygeal lesions. Local control at 5 years in published series on proton beam radiation therapy reaches the 50–60% range, thus being substantially higher than for photons [22–26]. Again, a longer follow-up is needed in chordoma patients, and local control at 10 years may be lower. Carbon ion radiation therapy may provide the same advantages as protons, possibly with improved biological effectiveness [27,28].

In recent years, the availability of more sophisticated photon beam techniques, including intensity modulated radiation therapy (IMRT) and stereotactic procedures, has suggested the use of conventional beams to solve the problem of dose maximization while sparing surrounding tissue [29–32]. Both options allow isodoses to be tailored to the gross tumor volume, delivering a potentially eradicating dose level in the 70 Gy range. Stereotactic techniques (i.e. radiosurgery) provide the accuracy of stereotactic guidance and deliver a high-dose hypofractionation. They are useful for small lesions. Dynamic arcs may help to avoid metal prostheses, if present. Interesting preliminary results in terms of local control rate have been reported for both IMRT and stereotactic techniques. An obvious advantage over hadrons would be availability (still limited for hadrons) and costs (one tenth that of hadrons). On the other hand, IMRT may also be used in combination with charged particles [33,34,35**]. The use of radiosensitizing agents has also been proposed [36].

In addition to which radiation beam modality to select, the other main uncertainty is when best to follow surgery with radiation therapy, whether following incomplete excisions only or as a complement to complete resections, aside from which degree of incompleteness matters. Obviously, formal demonstrations will seldom be achievable in such a rare disease, with such variations in local presentations and surgical completeness.

**Medical treatment**

Chemotherapy has long been known to be inactive in chordoma. Reports of tumor responses to regimens including anthracyclines, cisplatin and alkylating agents have been only anecdotal. Being high-grade sarcomas, the rare dedifferentiated chordomas may be more sensitive [37]. Chemotherapy has therefore never played a role in the disease, and best supportive care alone is an option once the disease extends and progresses. Recently, however, medical oncologists have shown interest in the disease with regard to its apparent sensitivity to the new molecular-targeted agents.

Imatinib has been shown to have antitumor activity in chordoma. Six cases were described in 2004 [38], and the wider institutional compassionate series of a total of 18 cases was then reported preliminarily [39]. Most patients responded to imatinib 800 mg daily, with nondimensional, tissue responses, marked by hypodensity and decreased contrast uptaking on computed tomography scan (and consistent changes on magnetic resonance imaging). A dimensional decrease was seen in a minority of patients receiving imatinib alone. Symptomatic improvement accompanies even nondimensional responses. Patterns of tumor response are reminiscent of those of solid tumors sensitive to the same agent, e.g. gastrointestinal stromal tumors (GIST). The length of tumor response was in the 1-year range, in a population of very advanced
patients. In a few patients, with exceedingly bulky lesions, a kind of liquefaction of the tumor led to major septic complications. All patients showed the presence of an activated platelet-derived growth factor (PDGF) receptor β and/or its ligand, PDGF β. A series of 31 chordoma samples were then analyzed [40**, showing that PDGF receptor β was overexpressed and activated in all cases, while PDGF receptor α and KIT were less expressed but activated. Activating point mutations were not found, as already suggested by others [41]. This favors the existence of an autocrine/paracrine loop. A formal phase II study on imatinib in advanced chordoma was then carried out, and results are awaited.

An antiangiogenic therapy was anecdotally reported to have been active in a patient [42], and the possibility that an antiangiogenic effect may be useful clinically is explored by some with new agents.

At the same time, a strong expression of EGFR and c-Met was described in a series of 12 chordomas [43], and a single case responding to the combination of cetuximab and gefitinib has been reported [44**]. The dual epithelial and mesenchymal differentiation of the disease may be worth recalling.

Conclusion

Surgery remains the treatment mainstay of chordoma. Its limitations, however, are well known, and its sequelae make it even more problematic, especially for sacral presentations. Radiation therapy may complement surgery, possibly helping overcome its inherent limitations, at least in a proportion of patients. Its addition to surgery may improve results, and this might reasonably become a more extensive treatment policy for resectable chordomas. Institutions differ on whether this should become regular practice, or postoperative radiation therapy should be restricted to subtotal resections (with the subsequent issue of when to label a resection as subtotal). Clearly, the high failure rate of surgery and the poor results of rescue treatments may suggest putting in place all available options to maximize chances of cure from the outset. In other patients, radiation therapy is resorted to as a substitute for surgery. Of course, this also depends on the degree of surgical sequelae one is willing to accept in the single case, but in which cases surgery should be done when margins are expected to be suboptimal is another matter of debate. Hadron-based therapy is advantageous over photon-based conventional radiation therapy, and a considerable amount of uncontested evidence has been provided to support this. There is a need to compare hadron-based radiation therapy with photon-based treatments delivered at the best of conformal technologies available, including IMRT and stereotactic procedures. Conformal technologies, however, may also add to hadrons, thus further improving the overall target coverage with doses adequate to the disease.

Despite its rarity, there has been some recent interest in the disease in regard to medical therapy. Chordomas seem to express receptors for currently available molecular-targeted therapies, namely PDGF receptor and EGFR. Evidence of antitumor activity has been provided for imatinib. Tumor response patterns recall observations in solid tumors paradigmatically responsive to the same agent, i.e., gastrointestinal stromal tumors. There are ongoing attempts to combine imatinib with chemotherapy, in an effort to increase the degree of tumor response [45]. In the framework of innovative multidisciplinary approaches, this might make medical therapy of interest even in the localized disease. Attempts to combine radiation therapy with imatinib are also ongoing. Indeed, room for medical therapy is apparently opening up, for the first time ever in a classically unresponsive disease. The hope is that the rarity of the disease will not pose insuperable problems to the study and development of new medical options and clinical approaches.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

+ of special interest
++ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 417).

Sarcomas


