Article type: narrative review

Title: The sacral chordoma margin.

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Manuscript word count: XXX

Key points

Question. How can we best define margins in sacral chordoma?

Findings. The definition of margins is a crucial point not only for surgery but also for radiation therapy (RT), given the fact that currently available radical definitive particle therapy is an emerging alternative option for sacral chordoma patients with localized disease unwilling to undergo invalidating surgery.

Meaning. En-bloc tumour-sacrum resection still remainsthe cornerstone in the treatment of primary sacral chordoma with the goal to achieve a wide local excision with negative microscopic margins. Radical definitive particle therapy seems to offer a similar outcome compared to surgery, although a validation in prospective clinical trials is still lacking. Currently available data do not support the routine use of any of medical therapy prior to surgery, RT or in association with RT.

Abstract

Importance. Chordoma is a rare mesenchymal neoplasm, arising predominantly from the sacral spine. Although typically slow-growing, the natural history of chordoma is marked by a high tendency toward local recurrence, with reported local failure in approximately 40-50% of patients undergoing surgery.

Observations. In September 2017, a multidisciplinary meeting of the "Chordoma Global Consensus Group" was held in Milan, focusing on current challenges in defining and achieving optimal margins in chordoma, as far as surgery, definitive particle radiation therapy (RT) and medical therapies are concerned. This review aims to report on the outcome of the consensus meeting and to provide a summary of the most recent evidence in this field. Possible new ways forward, including on-going international clinical studies, will be discussed.

Conclusions and relevance. Given the significant influence of margins status on local control in patients with primary localized sacral chordoma, the clear definition of margins and a standard approach across institutions for both surgery and particle radiation therapy currently represent a crucial point in the management of these patients. As for surgery, regardless of the approach used, the final goal is to achieve a wide local excision with negative microscopic margins by performing an en-bloc sacral-tumor resection. Radical definitive particle therapy seems to offer a similar outcome compared to surgery. However, limited data are currently available on long-term side effects and there is still a certain degree of technical variability across institutions. To address some of these questions, a prospective, randomized clinical trial comparing the two approaches is currently on-going. The low expected objective response rate, as well as the limited impact do not support the routine use of any of medical therapy prior to surgery, RT or in association with RT.

Key words: sacral chordoma, margin, surgery, radiation therapy, outcome

1. Introduction

Chordoma is a rare mesenchymal neoplasm, accounting for 1.4% of all primary bone tumours. The reported yearly incidence is approximately 0.08/100,000 people[1,2]. It affects predominantly the axial skeleton, mostly the mobile spine and the sacrum in the elder age[3].

Although typically slow-growing, chordoma is characterised by local aggressiveness, with worldwide reported long-term local recurrence free survival rate less than 50% [4]. Local control is therefore undoubtedly a critical component in the cure of chordoma patients.

The present manuscript has been developed as part of a consensus meeting of the "Chordoma Global Consensus Group", held in Milan in September 2017. This group has already attempted to define the best approach to both primary and locally recurrent chordoma[4,5]. The 2017 meeting focused on the importance of margins in the treatment of this disease. Aim of this meeting, was to discuss the current challenges in achieving optimal margins in chordoma and possible solutions. The matter of defining adequate margins in sacral chordoma treatment does not apply only to surgery but also to radiology, being the preliminary assessment. The definition of the disease extent crucial in patient's management, and to radiation therapy (RT), where individualized RT plans are potentially variable across institutions corresponding to different fields of treatment and different tumor coverage.

This review will report on the outcome of the consensus meeting and provide a summary of the most recent evidence in this field.

2. Shaping surgical margins

Surgical margin status is considered the most important prognostic factor in sacral chordoma patients undergoing surgery. En-bloc tumour-sacrum resection is in principle considered the cornerstone in the treatment of both primary and recurrent localised disease[4,5]. Regardless of the approach used, the final goal is to achieve a wide local excision with negative microscopic margins. Several retrospective analyses have demonstrated the negative prognostic impact of positive microscopic margins on sacral chordoma outcome. However, patients resected with macroscopic complete resection may still develop loco-regional relapse in approximately 50% of cases. Recurrences can occur late, even after 5 to 10 years from initial surgery and only a minority of patients are disease free at 15 years.

2.1 Resection Margins

The anatomical conditions of the sacro-pelvic region represent a major constraint to achieve local control in sacral chordoma. Therefore, the goal of a radical resection may be difficult to achieve, potentially requiring the sacrifice of important anatomical structures which may lead patients to develop permanent functional sequelae, while simultaneously increasing the chance of perioperative complications.

Furthermore, due to its gelatinous consistency, multilobulated morphology and possibly its underlying biology, chordoma exhibits a particular tendency for locoregional spread with a typical infiltrative growth pattern which follows the path of least anatomical resistance; the neoplastic invasion of the surrounding posterior pelvic musculature represents a critical challenge for any sacral chordoma surgical approach.

Particularly in sizeable tumors, the best chance to obtain adequate **lateral margins** strictly correlates with the extent of the muscular resection: the full thickness of the right and left gluteus maximus and piriform muscles must be resected down to the posterior aspect of the iliac wings towards the greater sciatic notch where the superior gluteal vessels emerge and that must be preserved or carefully tied. Additional crucial sites at risk of marginal margins are the sacrospinous and sacrotuberous ligaments, which connect the sacrum with the ischial spine and tuberosity respectively, providing stability to the pelvic ring. At this level, the neoplastic cells may invade these broad and thick fibers down to their bone insertion. Aiming to minimize the chance of neoplastic contamination of the **postero-inferior margin**, both sacrospinous and sacrotuberous ligaments must be transected by means of an osteotome and ultimately disconnected en-bloc with a fragment of the ischial bone.

A further major intraoperative concern is the protection of the visceral and vascular intrapelvic structures. Especially in case of large or proximal tumours or proximal locations, the rectum may be displaced anteriorly, along with the common iliac vessels while the hypogastric arteries and veins may be encased within the neoplastic mass. This is potentially the most difficult part of the dissection: the mesorectum is a loose layer of adipo-lymphatic tissue, not always sufficient to provide a solid barrier against tumor spread. In addition, the surgical dissection aiming to separate the rectum from the tumor may increase the risk of tumor spillage at this level. The neoplastic invasion of the posterior rectal wall is uncommon but, if present, requires an extended bowel resection and a temporary colostomy; when the rectum is only displaced anteriorly by the sacral chordoma, without rectal infiltration, the surgical dissection may be carried out leaving the whole mesorectum on the specimen with the entire posterior rectal wall exposed. This allows to keep the tumour entirely covered achieving an appropriate **anterior margin.**

Similar to the bowel resection, management of vascular encasement requires an anterior abdominal approach. Careful preparation of the common iliac vessels, prophylactically ligating the iliolumbar vessels and the ischiatic/gluteal branches of the hypogastric arteries and veins, in order to reduce the blood supply to the tumour and the sacrum, is considered the safest approach to minimize the risk of intra and post-operative blood loss.

The need to perform vascular replacement is uncommon; uni/bilateral internal iliac vessels ligation, however, may be frequently required and carried out without complications.

The wide surgical approach required in sacral chordoma directly impacts the postoperative functional outcome, mostly secondary to temporary or permanent damage of the sacral and pudendal plexus.

To some extent, the neurological impairment might be predictable, as it is strictly related to the level of the sacral nerve roots resection, which in turn depends on tumour size and anatomical location. Preservation of the more proximal nerve roots is critical to limit the neurological sequelae. When bilateral S3 roots are preserved, normal bladder and bowel function are usually maintained; when only one of the S3 roots is preserved there is a chance to develop urinary and bowel sphincter disorders (acute urinary retention and/or fecal incontinence, sexual impotence), when only bilateral S2 roots are preserved, urinary and bowel sphincter disorders inevitably occur albeit being potentially recovered up to 40% of patients. If only S1 roots are spared, permanent fecal and urinary dysfunction are to be expected, while the motility of the leg and foot is normally maintained. The loss of S1 nerve roots implies motor dysfunction to the lower limbs (predominantly the feet).

The resection of the whole sacral vertebra above the tumour, such as a meticulous assessment of the spinal canal proximally, is strongly recommended in order to achieve a clear **superior margin.** In some cases, however, small satellite nodules may be present slightly above the primary tumor. Hence, their presence should be excluded by the initial radiological work-up. Besides an accurate intraoperative evaluation of the bone level resection should also rule out the presence of these skip lesions, which may eventually compromise the adequacy of the surgical result. Microsatellite nodules, generally below the resolution of radiologic imaging, may also occur and are associated with a higher risk of local recurrence[8].

Once the sacrum is disconnected bilaterally and ano-coccygeal ligament is divided, by a careful manual palpation, it is simpler to identify the real tumor extension and the space for the sacral transection can be prepared by a blunt finger dissection.

A transversal side-to-side osteotomy is performed with an osteotome or a saw at the sacral level usually chosen on the preoperative scan and then confirmed during the operation. Computer-assisted navigation may be of help to confirm the tumour level and to identify nerve roots direction and bone margins bilaterally. Orthopedic pins may be also superficially fixed on the bone, 2-3cm away from the macroscopic tumor, in order to locate the line of the osteotomy and to ensure a tumour-free margin[9].The whole specimen is therefore removed ‘en bloc’.

2.2 Reconstructive techniques

If S1 needs to beresected, the pelvic skeleton looses its stability and spino-pelvic fixation becomes mandatory. The most commonly employed option for reconstruction of the pelvic ring uses a sacral bar to fix the two iliac bones one to the other. Autologous bone graft from the iliac bone and one or both fibulas may be useful to accelerate the bony union and increase the strength of the reconstruction.

In order to prevent any posterior bowel herniation, an artificial mesh needs to be placed behind the rectum. According to the extent of the skin/soft tissue defect, different reconstructive options are available. The use of local flaps, such as unilateral or bilateral gluteus muscle sliding flaps, is the

preferred option. For larger defect or when viable tissue is required VRAM pedicled flap or latissimus dorsi muscle free flap, may be considered.

2.3 Loco-regional relapse approach

The clinical presentation of a locoregional recurrence can be variable. Skip lesions adjacent to the surgical field and spreading towards the gluteal muscles or the pelvic cavity are unfavourable presentations, usually associated with prior contaminated surgery.

Extensive local relapses may result in an exophytic mass ulcerating the skin, with a significant impairment for patients' QoL.

Post-relapse outcome is generally poor, even when a microscopically complete resection of the recurrence is carried out.

The goal of salvage re-resection with curative intent should be to achieve gross total resection, and, when feasible, en-bloc resection with negative surgical margins. The best candidates for a complete re-resection are patients with limited disease, long disease-free interval, good performance status and a reasonable likelihood of acceptable morbidity from surgery.

3. Planning radiation margins

Large series of primary sacral chordoma patients treated with either surgery or radical definitive particle therapy have been published, showing similar long-term outcome with both modalities[5,10,11]. The "sandwich" approach with preoperative-RT, surgery and post-operative RT is of great interest, but it has so far only been used in selected institutions[12]. 10-year local control is usually not higher than 50%, with only one series reporting a 8-year local control of 85% [13,14].

3.1 Dose

Proton therapy (and mixed photon/proton radiotherapy) has a low linear energy transfer (LET), therefore the classical radiobiological concepts apply. Dose per fraction used with low LET radiation is 1.8 – 2 Gy (RBE). Total dose to the macroscopic disease should be at least 74 Gy RBE and even higher than 77 Gy (RBE) have been employed[15,16].

Carbon ion is a high LET radiation and therefore less sensitive to fractionation. Moderately hypo-fractionated schedules have been employed with dose per fraction of 4 – 4.4 Gy (RBE) and total dose of 64 – 70.4 Gy (RBE) in NIRS[11]. Dose per fraction of 3 Gy (RBE) and total dose of 66 Gy (RBE) have been used in the German experience[17].

The Radiobiological model used in Japan and in Europe to calculate the RBE is different. In the attempt to reproduce Japanese results in Europe the nominal RBE weighted prescription doses should be increased by about 10%, and therefore the dose per fraction employed in Italy in CNAO was 4.4 – 4.8 Gy (RBE) to a total dose of 70.4 – 76.8 Gy (RBE)[18-20].

High doses are recommended in case of gross residual disease. In case of macroscopic gross resection with R1 margin, carbon ion will not be employed but rather low LET radiation at reduced dose levels up to 70 Gy (RBE). In case of R2 resection some authors recommend to limit the dose to the tumor bed to 70 Gy (RBE) and boost only the residual disease to 74 – 77 Gy (RBE)[13].

If postoperative RT is given after R0 resection the same dose of at least 70 Gy (RBE) should be applied to the tumor bed.

In case of sandwich treatment with low LET radiation, 19.8-50.4 Gy (RBE) with conventional fractionation should be applied preoperatively. The overall cumulative dose is the same as for postoperative only RT, although initial experience with reduction of the total dose to 64.8 Gy in patients who have had negative-margin, en bloc resections following core biopsy (i.e. no open biopsy, no tumor spillage) appears very encouraging (*DeLaney T., unpublished data*).

Many authors agree that a wider volume should be treated to a lower dose. With low LET and standard fractionation, this lower dose for the area at risk of microscopic infiltration is set at 50 – 54 Gy (RBE). With carbon ion at 4.4 – 4.8 Gy (RBE) per fraction the low dose is set at 39.6 – 43.2 Gy (RBE) in 9 fractions and with carbon ions at 3 Gy (RBE) per fractions it is set at.The current experience is based on a sequential boost approach with shrinking fields. Dose homogeneity, details about prescription point or DVH point and acceptable target coverage are quite well established in proton beam therapy and should follow the recommendation of ICRU report 78. In clinical practice, and according to ICRU recommendation, the prescription dose can be the near minimum dose (i.e. dose received by 98%) or dose to 95% of the target volume or he median dose (dose received by 50% of the target), in which case additional constraints are set on the near minimum dose. The uncertainty in carbon ion RBE is typically much larger (15%-20%) than the usual ICRU requirement of dose homogeneity (+-5%). In the authors opinion the most relevant issue is not dose homogeneity but rather target volume coverage. The empirical rule widely applied in clinical practice of covering 98% of the target volume with 95% of the prescribed dose may result in unacceptable under-dosage of the tumor, simply because of the large size of the target. In fact the volumes of PTV in sacral chordoma can easily exceed one litre, therefore the 2% under-dosed volume may mean that 20 -25 ml of tumor do not receive an adequate dose and local control can be affected. This issue is especially relevant in case of radical treatment where over conservative constraints on the rectum may lead to significant under-dosage of the macroscopic tumor. It would be advisable that constraints were given in terms of absolute rather than relative volume and the dose to 1-2 cc were considered beside the near minimum dose.

3.2 Volumes

Defining the clinical target volume (CTV) is intrinsically a probabilistic procedure. There is a *de facto* consensus in radiation oncology to include in the CTV areas with a risk of microscopic tumor involvement higher than 10%.

Regarding published series of particle therapy in sacral chordoma, , the CTV contouring strategy is only briefly described. However there is still a clear difference across institutions. In the large series of 188 patients treated at NIRS, the CTV is obtained expanding the GTV with a geometric margin of 5 mm (moreover, an additional 5 mm margin is added for the planning target volume PTV). These geometrical expansion are edited to avoid overlap with rectum or bowel[11]. This same approach has been followed in other Japanese and in German facilities[17,21]. The results of NIRS show a 5- and 10-year local control rate of 77.2% and 52.0% respectively. At MGH, a margin of 1.5 cm around extra osseous tumor was employed and specific care was given to the risk of infiltration along the glutei and piriform muscles. One whole vertebral body cranial and caudal to the gross disease was included and all scar and all stabilization devices were also contoured as areas at risk for the low dose volume. Also in MGH experience the volumes were modified to avoid overlap with intra-peritoneal organs. An initial attempt to standardize and harmonize the contouring strategy for sacral chordoma has been carried out in the framework of the SACRO trial. Based on this initial consensus, general recommendations for extended target volume contouring are given below.

3.2.1 GTV

The Macroscopic tumor can be easily detected with CT and MR scans and therefore the gross tumor volume (GTV) contouring is typically straightforward. T2 weighted images usually show better contrast between chordoma and surrounding bone and muscles. Satellite nodule(s) should of course be included in the GTV.

3.2.2 Low-dose CTV

Cranial margin

One or two (one for preoperative radiation) vertebral bodies rostral to the GTV should be included. If the GTV extends to S1, L5 should be included. For sacral tumors, it is almost never necessary to include L4. If the GTV is involving S2 but not S1, the CTV should not extend to L5. For tumors lower than S2, two sacral levels above should be included. In case of sacral canal invasion, the whole thickness of the sacrum must be included in the CTV. However, if the tumor grows anteriorly and has a cranial tail along the pre-sacral fascia, the cranial expansion can be limited to the anterior part of the sacrum.

Caudal margin

For postoperative radiation, the whole sacrum and coccyx should be included. For selected case of S1 or S2 tumors with minimal bone erosion it may be acceptable to limit the caudal border to 1-2

levels below. For preoperative radiation, a single vertebral level distal to the caudal extent of tumor seems enough.

Lateral margin

Both piriform muscles should be entirely included in the CTV. The CTV should extend to the bony lamina. In selected cases (e.g. small unilateral tumors in S1-S2 confined to the bone) it may be possible not to include entirely both piriform muscles. Lateral extension in the gluteal muscles is indeed an extremely delicate point. If the GTV does not extend to the glutei, the amount of muscles to be included is left to clinical judgment. If the GTV extends laterally and or caudally outside the sacrum and the muscles are clearly infiltrated all areas where edema or enlarged blood vessels are present (as detectable with CT and T2 MR sequences) should be included in low dose CTV. However, at least 1.5 cm of radiologically normal muscle should be contoured. If satellite nodules are detectable in the glutei, the low dose CTV should include them all in a unique volume. For preoperative radiation, 1.5-2 cm beyond gross tumor and inclusion of areas of tumor associated T2 edema has been associated with high rates of local tumor control[8,14]. In all sacral levels where there is macroscopic tumor the lateral margin should extend to the sacroiliac joints.

Posterior margin

If the tumor infiltrates the subcutaneous soft tissues, CTV should extend to the skin. If posterior bony wall of the sacrum is intact it is not necessary to include the subcutaneous tissue in the CTV.

Anterior margin

The anterior margin can coincide with the GTV and with the sacrum anterior wall. Nerve roots exiting from the foramina should also be included. The CTV should not include the rectal wall, the peritoneum or the ileo-psoas muscles (unless clearly infiltrated). If a surgical procedure has been performed to displace the rectum/bowel from the high dose volume it is possible, depending on the operation performed, that microscopic tumor is displaced together with the rectal wall. It is therefore recommended that low dose CTV includes the spacer if the presacral and/or mesorectal space has been violated. It is not necessary to include the spacer in the CTV if it has been inserted with an anterior approach without opening the presacral peritoneum or if preoperative radiation has been given.

Biopsy tract and surgical scar

Biopsy tract or surgical scars from any previous operation should be included in the low dose CTV. When passive fields are used and there is a concern on skin toxicity biopsy, tract contour can be reduced to avoid overlap with the skin.

Surgical devices

In case of post operative irradiation, all implanted stabilization devices are to be considered at risk of tumor seeding and should be included in the CTV if this can be done with acceptable morbidity.

3.2.3 High -dose CTV

High dose CTV should be a geometric expansion of GTV enlarged by 5-10 mm and not extending outside low dose CTV.

3.3 Toxicity

The most relevant toxicities of high dose particle therapy are sacral neuropathy and sacral fractures. For sacral neuropathy, a dose threshold around 74 Gy for conventional fractionation and 70 Gy (RBE) for hypo fractionation seems to exist.

Sacral insufficiency fracture was reported in 47% of patients treated at MGH with combined surgery and proton therapy, in 52% of patients treated with carbon ion radiotherapy without surgery and in 33% of patients treated with exclusive proton therapy[22,23]. The extent of surgical resection, the amount of irradiated bone and the maximum dose may be relevant in determining the risk of fracture[24].

4. Approaching margins by medical interventions

Medical therapies are considered only for symptomatic patients and/or when there is clear evidence of progressive disease. Given the chemo-resistance of conventional chordoma and the low dimensional response rate observed with targeted agents (2-3%) [25], there is no clear indication for neo(adjuvant) chemotherapy in this disease, even when a tumor shrinkage would be beneficial. Poorly differentiated chordoma and dedifferentiated chordoma have a more aggressive behavior that is associated to a greater risk of local and distant relapse compared to conventional chordoma[26]. Unfortunately, in these subtypes, data available on the activity of cytotoxic agents are limited and the level of evidence is insufficient to routinely offer chemotherapy in the setting of localized disease.

The low expected dimensional response rate as well as the lack of impact of a possible non-dimensional response on surgery or RT complexity do not support the use of any of the medical therapies currently available prior to surgery, RT or in association with RT [1]. Still, the results of available studies (all in the setting of advanced disease), leave medical therapy as an option to be discussed with patients deemed unfit for surgery or high-dose radiation therapy, or unwilling to undergo local approaches because of expected sequelae[25,27].

5. Future perspectives

Still patients presenting with primary and localized sacral chordoma are currently treated in an inconsistent way.

One of the areas affected by the highest management variability is local treatment of sacral chordoma, as the approach spans from a wide en bloc resection ± RT to definitive RT ± pre-RT surgical debulking.

Since a equipoise does exist between these two approaches, a prospective international randomized clinical trial comparing surgery (plus/minus postoperative RT) with definitive high-dose RT has recently started recruiting patients to assess both relapse-free survival and quality of life (QoL) (NCT 02986516).

This trial will be the first formal comparison between two local treatments in chordoma. Of note, in order to accommodate the difficult clinical decision-making as well as patient acceptance across clinical presentations, an observational study is inbuilt in this effort, paralleling its randomized component. Patients will be either randomized or allocated to their preferred treatment and prospectively observed. A Bayesian approach has been selected, thus valuing prior probabilities and continuously updating probability distributions of outcomes as long as new patients are evaluated.

In conclusion, the rate of local recurrences in primary localized sacral chordoma is still high and only a few steps forward have been made. A large proportion of patients, in fact, still succumb due to local disease progression. For those who do not relapse, QoL is often poor as a result of surgical sequelae.

A lot remains in order to improve state of the art in chordoma. Only a joint effort among major reference centers across the world might allow doing large studies.

Acknowledgements

None

Funding

None declared

Disclosure

The authors have declared no conflicts of interest.

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