The sacral chordoma margin

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ABSTRACT

Objective: Aim of the manuscript is to discuss how to improve margins in sacral chordoma.
Background: Chordoma is a rare neoplasm, arising in half cases from the sacrum, with reported local failure in >50% after surgery.
Methods: A multidisciplinary meeting of the "Chordoma Global Consensus Group" was held in Milan in 2017, focusing on challenges in defining and achieving optimal margins in chordoma with respect to surgery, definitive particle radiation therapy (RT) and medical therapies. 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, are discussed.
Results: En-bloc tumor-sacrum resection is the cornerstone of treatment of primary sacral chordoma, aiming to achieve negative microscopic margins. Radical definitive particle therapy seems to offer a similar outcome compared to surgery, although confirmation in comparative trials is lacking; besides there is still a certain degree of technical variability across institutions, corresponding to different fields of treatment and different tumor coverage. To address some of these questions, a prospective, randomized international study comparing surgery versus definitive high-dose RT is ongoing. Available data do not support the routine use of any medical therapy as (neo)adjuvant/cytoreductive treatment.
Conclusion: Given the significant influence of margins status on local control in patients with primary localized sacral chordoma, the clear definition of adequate margins and a standard local approach across institutions for both surgery and particle RT is vital for improving the management of these patients.

Introduction

Chordoma is a rare mesenchymal neoplasm, accounting for 1.4% of primary bone tumors. 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 older age group [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 who usually die of local-regional disease.

This manuscript has been developed as part of a consensus meeting of the "Chordoma Global Consensus Group", held in Milan in September 2017. This group, consisting of multidisciplinary chordoma experts from both sides of the Atlantic and patients' advocates, has already attempted to define the best approach for managing primary and locally recurrent chordoma at all sites [4,5]. The 2017 meeting focused on the importance of margins in the treatment of this disease. A discussion of the current challenges in achieving optimal margins in sacral chordoma and of possible solutions was carried out.

This review reports on the outcome of the consensus meeting and provides a summary of the most recent evidence in this field.

Shaping surgical margins

Surgical margin status is the most important prognostic factor in sacral chordoma patients undergoing surgery (Table 1) [6–13]. En-bloc tumor-sacrum resection is the cornerstone of treatment of both primary and recurrent localized disease. Regardless of the

[1] contributed equally.

Table 1
Series of sacral chordoma patients reporting oncologic outcome according to the adequacy of surgical margins. *Data extrapolated from KM curves on available information.

Series	Year	No. Pts	Median FU (years)	Margin status %	R0				R1			
					5-year OS	5-year LR	10-year OS	10-year LR	5-year OS	5-year LR	10-year OS	10-year LR
Bergh P.	2000	30	8.1	R0 = 70 R1 = 14 R2 = 16	90%°*	10%*	95%°*	76%*	50%*	50%*	100%*	100%*
Fuchs B.	2005	52	7.8	R0 = 21 R1/R2 = 31	100%*	5%	100%*	–	25%*	71%	15%*	–
Kayani B.	2015	58	3.8	R0 = 48 R1 = 42 R2 = 10	85%*	36%	38%*	–	50%*	79%	13%*	–
Angelini A.	2015	71	9.5	R0 = 77% R1 = 23%	–	28%*	–	40%*	–	55%*	–	55%*
Ji T.	2017	115	4.9	R0 = 67 R1/R2 = 33	86%	32%	–	–	67%	74%	–	–
Radaelli S.	2016	99	8.7	R0 = 47 R1 = 43 R2 = 10	95%	18%	71%	31%	95%	38%	62%	58%
Yang Y.	2017	157	4.6	R0 = 21 R1 = 39 R2 = 40	–	17%	–	–	–	43%	–	–
Colangeli S.	2018	33	4.4	R0 = 52 R1 = 42 R2 = 6	–	10%*	–	10%*	–	100%*	–	100%*

approach used, the final goal is to achieve a wide local excision with negative microscopic margins [4,5,14].

Several retrospective analyses demonstrated the negative prognostic impact of positive microscopic margins on the outcome of sacral chordoma. However, even in patients where resection is microscopically complete, loco-regional relapses are seen in >50% of cases. Recurrences may occur late and only a minority of patients are disease-free at 15 years [4,5].

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 challenging, potentially requiring the sacrifice of important structures resulting in permanent, life-changing functional sequelae, while simultaneously increasing the chance of perioperative complications [15].

Furthermore, due to its gelatinous consistency, multi-lobulated morphology and possibly its underlying biology, chordoma exhibits a particular tendency for loco-regional 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 larger tumors, the best chance of obtaining adequate **lateral margins** strictly correlates with the extent of the muscular resection: both gluteus maximus and piriform muscles must be resected down to the posterior aspect of the iliac wings towards the greater sciatic notch. The superior gluteal vessels emerge at this point and must either be preserved or carefully ligated.

Additional important sites at risk of marginal margins are the sacrospinous and sacrotuberous ligaments. At this level, the neoplastic cells may invade these broad and thick fibers down to their bone insertion. In order 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 taking a fragment of ischial bone en-bloc with the ligaments.

A further major intraoperative concern is the protection of intrapelvic visceral and vascular structures. Particularly in large or proximally located tumors, 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. Neoplastic invasion of the posterior rectal wall is uncommon but if present, requires extended bowel resection and a colostomy (Fig. 1). When the rectum is only displaced anteriorly by the sacral chordoma, without infiltration, the surgical dissection may be carried out leaving the whole mesorectum on the specimen with the posterior rectal wall exposed. Thus, the tumor is kept entirely covered achieving an appropriate **anterior margin** (Fig. 2).

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, is carried out in order to reduce the blood supply to the tumor and the sacrum. This is considered the safest approach to minimize the risk of intra and post-operative blood loss.

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

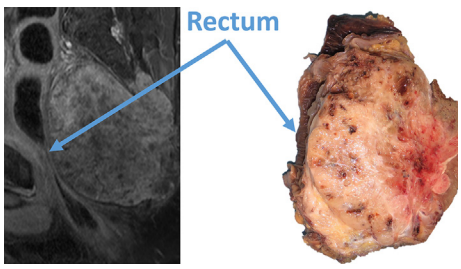

Fig. 1. Neoplastic invasion of the posterior rectal wall. The tumor is therefore resected en-bloc with the sacrum and the rectum.

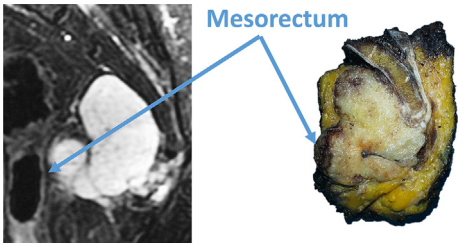

Fig. 2. The rectum is displaced anteriorly, without being infiltrated, by the sacral chordoma. The surgical dissection may be carried out leaving the whole mesorectum on the specimen with the posterior rectal wall exposed. Thus, the tumor is kept entirely covered achieving an appropriate anterior resection margin.

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

To some extent, neurological impairment is predictable as it is related to the level of the sacral nerve roots resection, which in turn depends on tumor size and 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 of 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 potentially recovering in up to 40% of patients. If only the S1 roots are spared, permanent fecal and urinary dysfunction are to be expected while the movement of the leg and foot is usually maintained. The loss of S1 nerve roots is accompanied by motor dysfunction in the lower limbs, predominantly regarding the feet [16].

The resection of the whole sacral vertebra above the tumor as well as a meticulous assessment of the spinal canal and the paraspinal muscles is strongly recommended in order to achieve a clear **superior margin.** In some cases, small satellite nodules may be present slightly above the primary tumor but their presence should normally be detected by the initial radiological work-up. In addition, a careful intra-operative evaluation of the level of bone resection should 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 radiological imaging, may also occur and are associated with a higher risk of local recurrence [17].

Once the sacrum is disconnected bilaterally and the anococcygeal ligament divided, careful manual palpation will identify the true extent of the tumor and space for the sacral transection can be created by blunt finger dissection.

A transverse side-to-side osteotomy is performed with an osteotome or 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 tumor level and to identify nerve roots and bone margins bilaterally. Orthopedic pins may be also superficially fixed on the bone, 2–3 cm away from the macroscopic tumor, in order to locate the line of the osteotomy and to ensure a tumor-free margin [18]. The whole specimen is therefore removed 'en-bloc' with the overlying skin including the biopsy track.

Reconstructive techniques

If the resection includes S1 (total sacrectomy), the pelvic skeleton loses its stability and spino-pelvic fixation is recommended, although some authors suggest no reconstruction also in this case, leaving the lumbar spine collapsing into the pelvis [19,20]. The most commonly employed option for reconstruction of the pelvic ring uses a sacral bar to fix the two iliac bones one to each other and spino-pelvic fixation by spine reconstruction devices. Autologous bone graft from the iliac bone and/or one or both autogenous or allogenic fibulas may be useful to promote the bony union and increase the strength of the reconstruction [21,22].

In order to prevent any posterior bowel herniation, an artificial mesh can 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. These cannot be used where the superior gluteal vessels have been ligated or the defect is very large and a rectus abdominis pedicled flap or a reverse rotational flap based on perforators from the posterior intercostal and lumbar vessels or a latissimus dorsi muscle free flap, may be considered [23–25].

Loco-regional relapse approach

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

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

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, where 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 [4,26],

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 (Table 2) [5,11,27–35]. The "sandwich" approach with preoperative radiation therapy (RT), surgery and postoperative-RT is of great interest, but it has been used so far in selected institutions [36]. Ten-year local control is usually not >50%, with only one series reporting a 8-year local control of 85% [37,38].

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 (Relative Biological Effect-RBE). Total dose to macroscopic disease should be at least 74 Gy RBE and even >77 Gy (RBE) have been employed [39,40].

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 [27]. Dose per fraction of 3 Gy (RBE) and total dose of 66 Gy (RBE) have been used in the German experience [33].

The radiobiological model used in Japan and Europe to calculate the RBE is different. In the attempt to reproduce the Japanese results, 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) [41–43].

Table 2
Comparison of oncologic outcomes for sacral chordoma treated with definitive haevy-particles RT. C = carbon ion; P = proton; N = neutron; IMRT = intensity modulated radiation therapy.

Series	Year	No. Pts	Median FU (years)	Therapy	5-year OS	10-year OS	5-year LR	10-year LR
Breteau N.	1998	13	4	N	61% (4yr)	–	44% (4yr)	–
Nishida Y.	2011	7	4.1	C	53%	–	0%	–
McDonald MW.	2013	16	1.9	P	80% (2 yr)	–	15% (2 yr)	–
Mima M.	2014	23	3.2	C or P	83% (3yr)	–	6% (3 yr)	–
Uhl M.	2015	56	2.1	C ± IMRT	52%	–	21%	–
Imai R.	2016	188	5	C	81%	67%	19%	50%
Kabolizadeh P.	2017	40	4.2	P ± IMRT	82%	–	15%	–
Youn SH.	2018	58	3.5	P	88%	–	12%	–
Aibe N.	2018	23	3.1	P	10% (3yr)	–	7% (3yr)	–

High doses are recommended in cases of gross residual disease. In cases of macroscopically clear resection with a microscopically involved (R1) margin, carbon ions will not be employed but instead low LET dose at reduced levels up to 70 Gy (RBE). In cases of R2 resection some authors recommend limiting the dose to the tumor bed to 70 Gy (RBE) and boosting the residual disease to 74–77 Gy (RBE) [37].

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 sandwich treatment with low LET radiation, 19.8–50.4 Gy (RBE) with conventional fractionation should be applied preoperatively.

The 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. Dose homogeneity, details about prescription point or dose volume histogram (DVH) point and acceptable target coverage are quite well established in proton beam therapy and should follow the recommendation of ICRU report 78. 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 topic is not dose homogeneity but target volume coverage, especially in case of radical treatment where over conservative constraints on the rectum may lead to significant under-dosage on 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 ml were considered beside the near minimum dose.

Volume

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%. In the chordoma series currently available, the CTV contouring strategy is described only briefly and there is still variability across institutions. In a large series of 188 patients treated at NIRS, the CTV is obtained expanding the gross tumor volume (GTV) with a geometric margin of 5 mm. This geometrical expansion is edited to avoid overlap with rectum or bowel [27]. This same approach has been followed in other Japanese and in German facilities [32,33]. The results from the 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 extraosseous 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. In the MGH study, the volumes were modified to avoid overlap with intraperitoneal 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 - SAcral Chordoma: a Randomized & Observational study on surgery versus definitive radiation therapy in primary localized disease (see below). Based on this initial consensus, general recommendations for extended target volume contouring are given below.

GTV

The macroscopic tumor can be easily detected with CT and MR scan and therefore GTV contouring is typically straightforward. T2 weighted images show better contrast between chordoma and surrounding bone and muscles. Satellite nodule(s) should be included in the GTV (Fig. 3).

Low-dose CTV

Cranial margin. One or two (one for preoperative radiation) vertebral bodies rostral to the GTV 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 both piriform muscles entirely. The degree of lateral extension into the gluteal muscles is debatable. 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. Nevertheless, at least 1.5 cm margin of radiologically normal muscle. If satellite nodules are detectable in the glutei, the low-dose CTV should include them all in a single volume. For preoperative radiation, these have been reported with high rates of local tumor control [17,38]. At 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.

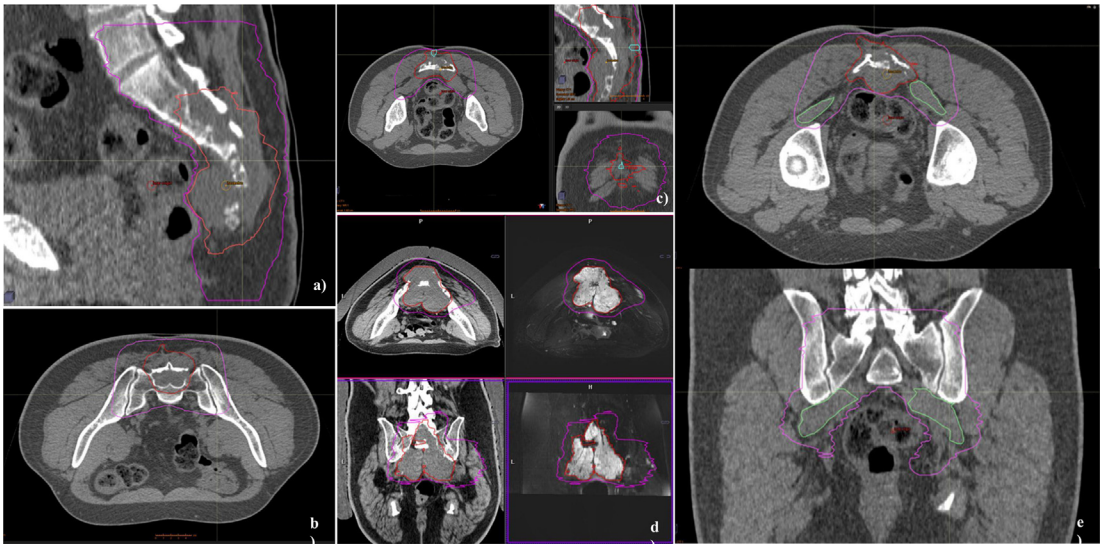

Fig. 3. GTV and CTV contouring of sacral chordoma by CT/MRI scan **a)** one or two vertebral bodies rostral to the GTV and the whole sacrum caudally should be included **b)** sacro-iliac joint contoured within the CTV **c)** biopsy tract or surgical scars should be included in the low-dose CTV **d)** the degree of lateral extension into the gluteal muscles is debatable albeit at least 1.5 cm margin of radiologically normal muscle should be included in the low dose CTV **e)** both piriform muscles should be entirely included in the CTV.

Anterior margin. The anterior margin can coincide with the GTV and with the anterior surface of the sacrum. 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 pelvic peritoneum or if preoperative radiation has been given.

Biopsy-tract and surgical scar. Biopsy tract or surgical scars should be included in the low-dose CTV. When passive beam is used and there is a concern regarding skin toxicity the biopsy-tract contour can be reduced to avoid overlap with the skin.

Surgical devices. In case of postoperative 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.

High-dose CTV

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

Toxicity

The most important toxicities related to 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 fractures were 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 only proton therapy [44,45]. The extent of surgical resection, the amount of irradiated bone and the maximum dose may be relevant in determining the risk of fracture [46].

Approaching margins medically

Medical therapies are considered in advanced patients with symptoms, where there is a clear evidence of progressive disease or both. Given the chemo-resistance of conventional chordoma and the low dimensional response rate observed with targeted agents (2–3%) [47], there is no clear indication for a (neo)-adjuvant treatment in this disease, even when tumor shrinkage would be beneficial. Similarly, outside clinical studies, the low expected dimensional response rate as well as the inability of medical therapies to impact upon the complexity of surgery or the extent of RT, argue against the use of any of these agents prior to surgery, RT or in association with radiation [1]. Nonetheless, 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 RT, or unwilling to undergo local treatments due to the associated morbidity [47,48].

Future perspectives

Currently, patients presenting with primary, localized sacral chordoma are often treated inconsistently.

The area affected by the highest variability is local treatment, as the approach spans from wide en-bloc resection (with or without adjuvant RT) to definitive RT (with or without pre-RT surgical debulking).

Since equipoise exists between these two approaches, a prospective international randomized clinical study (called “SACRO) 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 (NCT02986516).

This trial will be the first formal, prospective comparison between the two local treatments in chordoma. In order to accommodate the difficult clinical decision-making as well as encouraging patient participation, an observational arm was included into the study, paralleling the randomized component. Patients will either be 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 recurrence in primary localized sacral chordoma is still high and only very slow progress is being made. A large proportion of patients, in fact, still die of local disease and for those who do not relapse, quality of life is often poor as a result of surgical morbidity.

Much work still needs to be done in order to improve the state of the art in chordoma. Only a collaborative effort among major reference centers across the world may allow performing large clinical trials.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2020.04.028.

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