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Analysis of distribution, incidence and survival of chordoma patients in the United States from 2000 to 2010

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Zusammenfassung:

Einleitung: Chordome sind langsam wachsende, lokal rezidivierende, maligne Tumore, welche aus Überresten der Chorda dorsalis entstehen. Sie machen 1-4% aller bösartigen Knochentumore aus. Aufgrund des seltenen Auftretens gibt es nur wenige Studien bezüglich Inzidenz und Überleben.

Methoden: Mit dem neuesten Datensatz des „Surveillance Epidemiology and End Results“ (SEER) Programms des „National Cancer Institutes“ haben wir eine retrospektive Studie durchgeführt. Es wurden Inzidenzen und Überlebensraten für 795 mikroskopisch bestätigte Chordomfälle in einem Zeitraum von 2000 bis 2010 berechnet. Des Weiteren wurden diverse Variablen analysiert um relevante prognostische Faktoren zu bestimmen. Morphologische Kodierungen der „International Classification of Diseases for Oncology“ (ICD-O3) wurden herangezogen um Fälle zu identifizieren. Mit Hilfe der statistischen Software SEER*Stat wurden Inzidenzraten und relatives Überleben berechnet und gemäß Geschlecht, Alter, Rasse, lateinamerikanischer Herkunft, Lokalisation, Größe und Therapie analysiert. Für Mortalitätsberechnungen und weitere statistische Tests wurde das Programm SAS 9.2 verwendet.

Ergebnisse: Die altersangepasste Inzidenzrate für Chordome war 0,9 Fälle pro eine Million Einwohner pro Jahr. Es zeigten sich höhere Raten bei Männern im Vergleich zu Frauen. Die häufigste Lokalisation war kranial. Zusätzlich wurden jüngeres Alter, lateinamerikanische Herkunft und kleine Tumorgröße (<5cm) mit höherer Wahrscheinlichkeit assoziiert kranial aufzutreten. Große Tumore waren häufiger in sakralen Regionen zu finden. Die relative 5- und 10-Jahres-Überlebensrate lag bei jeweils 78% und 57%. Prognostische Faktoren für besseres Überleben waren jüngeres Alter, kraniale Lokalisation und chirurgische Intervention. Kleine Tumorgröße zeigte auch einen Trend in Richtung bessere Prognose, dies war jedoch statistisch nicht signifikant. Faktoren welche das Überleben nicht beeinflusst haben waren Geschlecht, Rasse, lateinamerikanische Herkunft und Radiotherapie.

Konklusion: Mit den neuesten Daten von 18 amerikanischen Krebsregistern, enthalten im SEER Programm, liefert diese Studie wertvolle, aktuelle Informationen bezüglich Verteilung von Inzidenz und Überleben sowie zu prognostischen Faktoren von Chordomen.

Abstract:

Introduction: Chordoma is a slow growing highly recurrent malignant tumor that arises from remnants of the notochord. It constitutes 1-4% of all primary malignant bone tumors. Due to the rare occurrence the number of studies concerning incidence and survival on this form of cancer is limited.

Methods: With the use of the most recent dataset from the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute we conducted a retrospective analysis calculating distribution and incidence patterns for 795 cases of microscopically confirmed chordoma from 2000 to 2010. Furthermore we analysed outcome to determine relevant prognostic factors for survival. The World Health Organization's ICD-O3 morphological codes for chordoma (9370/3 chordoma NOS, 9371/3 chondroid chordoma, 9372/3 dedifferentiated chordoma) were used to identify the cases. We calculated frequencies, age-adjusted incidence rates and relative survival (RS) rates using the statistical software SEER*Stat. Cases were analysed by gender, age, race, Hispanic origin, primary site of presentation, tumor size and treatment. For mortality calculations and further statistical tests, SAS 9.2 was used.

Results: The overall age-adjusted incidence rate for chordoma was 0.9 per million population. We observed higher rates in males than in females and lower rates in blacks than in whites. The most common site of presentation was the cranial region. In addition, younger age, Hispanic origin and small tumor size (<5cm) were associated with greater likelihood of cranial presentation. Large tumor size (≥ 5cm) was most common in sacral sites. 5- and 10-year relative survival was found to be 78% and 57%, respectively. Concerning prognostic factors, younger age, cranial presentation and surgery were significantly associated with a better outcome. Small tumor size also showed a trend towards better prognosis. Survival, however, was not influenced by sex, race, Hispanic origin and radiation therapy.

Conclusion: With 18 registries included in the most recent dataset of the SEER program this study provides the latest series of chordoma cases with substantial information concerning incidence and survival patterns of chordoma in the United States including relevant prognostic factors.

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Glossary:

SEER	Surveillance Epidemiology and End Results
NCI	National Cancer Institute
CSPG4	Chondroitin sulphate proteoglycan 4
CDKN2A	Cyclin-dependent kinase 4 inhibitor A
CDKN2B	Cyclin-dependent kinase 4 inhibitor B
FNA	Fine-Needle aspiration
CNB	Core-needle biopsy
CT	Computed tomography
MRI	Magnetic resonance imaging
CD24	Signal transductor; protein
SOX-9	Transcription factor; protein
FDG	Fluorodeoxyglucose
PET	Positron emission tomography
Gy	Gray; unit of absorbed radiation
IMRT	Intensity-modulated radiotherapy
PDGFR	Platelet-derived growth factor receptor
KIT	Cytokine receptor
EGFR	Epithelial growth factor receptor
mg	Milligrams
ICD-0-3	International Classification of Diseases for Oncology, 3rd edition
NOS	Not otherwise specified
cm	Centimeters
IR	Incidence rate
RR	Rate ratio
CI	Confidence interval
RS	Relative survival
KM-curve	Kaplan-Meier-curve
HR	Hazard ratio
AJCC	The American Joint Committee on Cancer
CS	Collaborative stage system

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1 Introduction

Chordomas are rare bone tumors, which constitute 1-4% of all primary malignant bone cancers (1). It is assumed that they originate from remnant cells of the human notochord, which can be found in areas of the axial skeleton including base of the skull, mobile spine, sacrum and coccyx (2). Apart from the correspondance of notochordal cell groups with chordoma locations, similarities in morphology and immunophenotype support the notochordal hypothesis (2,3). Further evidence is in the transcription factor brachyury, which is expressed in the embryonic notochord as well as overly expressed in chordoma cells (3). Most of all chordomas are sporadic, however, there are reports of familial clustering (4,5).

An accurate diagnosis of the tumor is of valuable prognostic relevance. This is why a fine-needle or, in cases of bony lesions, core-needle biopsy is conducted to establish a distinct diagnosis before resection (3). Chordoma is categorized into three different histological variants: Classical (conventional), chondroid or dedifferentiated (6). The connection between histopathological features and clinical, biological behaviour is often discussed and remains an active and controversial area of research (3). Although metastasis is rare in chordomas, every procedure must be done with special care to avoid tumor seeding (7).

The main course of treatment is radical en-bloc surgery if possible (8). In the mobile spine and sacrum aggressive resection with achievement of wide surgical margins improves the rate of local disease recurrence significantly (9,10). For intracranial lesions (especially for lesions of the clivus) gross total resection is often not possible with regard to preservation of neurological functions. In those cases near total intralesional resection is recommended, followed by postoperative radiation (3,11).

Due to its rare occurrence, chordoma has mostly been described in small institutional series with a limited number of cases. There are only a few bigger population-based surveys analysing distribution, incidence and survival patterns (12-14). Some of the surveys use the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute, which is the largest source of cancer information in the United States. However, previous attempts to categorize

epidemiological and survival patterns include case series only looking at certain anatomical regions and analyses that group chordoma with other bone tumors (15-17). A recent study by Smoll et al asses the effects of age and sex on survival using all chordoma cases in the SEER database, but provides no information concerning other potential prognostic factors like race, site of presentation, tumor size and surgical or radiation treatment (13).

1.1 Aim of the study

Incidence and survival patterns have been reported before using data from the Surveillance Epidemiology and End Results (SEER) program. The aim of this study is to provide an update on epidemiological and clinicopathological distribution of chordoma using the latest SEER data. Furthermore we analysed outcome with the goal of determining relevant prognostic factors for survival. This information may help guide physicians about the presentation and management of these rare tumors and evaluate the effectiveness of current treatment options.

2 Chordoma background

2.1 Embryology

The human notochord is rod-shaped and functions as a primitive axis of the body (2). It acts as an embryotic organiser and is formed from cells originating from the ectoderm during the third week of development, which is also the time of the trilaminar germ disc formation and the primitive streak formation (2). From that time onwards, the notochord is encased in thick homogenous membranous coat, within which cells continue to proliferate to form a solid but flexible rod (2). It extends as far as the limit of the hypophysis cerebri, is present for a short distance on the posterior surface of the basilar cartilage, and is also found in the region of the sella turgica (2). The cranial extension will later on become the basilar part of the occipital bone and the caudal part of the body of the sphenoid (2). During the fourth to sixth week of development, the vertebral bodies are formed by mesenchymal cells from adjacent sclerotomes (1). Chondrification and segmentation of the mesenchymal elements of the vertebrae is induced by the primitive notochord, which degenerates during this process (1). It remains, however, between the vertebral bodies in the intervertebral disc to expand and form the nucleus pulposis in the prenatal period (1,2). Later on, the chordal tissue will undergo a progressive replacement by fibrocartilage from the surrounding tissues (2).

It is believed that the degeneration of the notochord is incomplete in the center of the vertebral bodies at the junction of the adjacent sclerotome regions, where residual notochordal cells remain (1). This tissue is thought to undergo neoplastic change and is the basis of the development of chordoma (1).

2.2 Pathogenesis

Virchow first characterized chordomas in 1857 and described unique, intracellular bubble-like vacuoles, calling them “physaliphorous” because of a foamy appearance (18). He hypothesised them to be derived of cartilage, which was disproven by the theory that they originate from undifferentiated notochordal remnants that persist in vertebral bodies and throughout the axial skeleton (3,19). Due to the notochordal theory H. Ribbert was the first one to introduce the name chordoma in 1894 (2). Cell-fate-tracking experiments in mice also revealed a topographical association between notochordal cell nests and sites of chordoma occurrence (20). Apart from morphological and localisation similarity between chordoma cells and notochordal physaliphorous cells, they also show a shared immunophenotype (2). They both contain vimentin, S100 protein, human polymorphic mucin, and low molecular weight cytokeratins, but are negative for high molecular weight cytokeratins (2,21). Some of these immunophenotypes, however, are also shared with chondroid tumors (e.g. chondrosarcomas) which make a distinction in diagnosis quite problematic, especially in cases of clival chordoma where only small biopsies can be obtained (21). Another marker is chondroitin sulfate proteoglycan 4 (CSPG4) which is unfortunately expressed by just a fraction of the tumors and can produce false negatives (21). Hallor et al. found an important step in chordoma development in the genomic abnormality, including common polysomy of chromosome 7 and loss of loci 9p21 (22). CDKN2A and CDKN2B, which are situated on 9p21 were homozygously or heterozygously lost in 70% of the tumors (22). They are associated with the regulation of the G1 phase arrest and often appear to be missing in other cancers as well (8).

2.3 Tumor marker: brachyury

The most compelling evidence of the notochordal hypothesis as well as the highly specific chordoma tumor marker that has been searched for was found in the brachyury gene, a T-box transcription factor (23). Samples from familial chordoma patients show duplications of the 6q27 region, which contains brachyury, when looked at with high-resolution comparative genomic hybridization (CGH) (4). Brachyury is known as regulator of mesodermal differentiation, takes a major part in the formation of the human notochord, and is thus expressed in normal, undifferentiated embryonic notochord (21). Vujovic et al. looked at expression profiles of chordomas (n=53) and other chondroid tumors (n=323) and found that brachyury was restrictively present in all chordoma cells and none of the others (23). Recent discoveries revealed brachyury to be a promoting mediator in the epithelial-mesenchymal transition (EMT), which down regulates epithelial markers, up regulates mesenchymal markers, hence increasing cell migration and invasion (24). The exact role of brachyury in the pathogenesis of chordoma is still unclear; evidence suggests however, that it has a major part in it.

2.4 Pathology

For the most part chordoma is a slow growing, low grade malignancy (6). Primary lesions are relatively uncommon to infiltrate surrounding structures, whereas recurrent tumors after surgery or radiation are likely to infiltrate structures, in the case of sacral lesions, such as rectal muscularis, gluteus maximus and nerve tissue (1). Histologically, chordoma can be divided into three subgroups: **classic (conventional) chordoma**, which is most common, **chondroid chordoma**, and **dedifferentiated chordoma** (21). The latter two types make up less than 10% of all chordomas.

Morphologically chordomas show physaliphorous characteristics, meaning they contain bubble-like vacuoles mostly intracellular but also localized extracellularly (21). Cells show variable degrees of atypia and pleomorphism, have round, small, dark nuclei and a few mitotic figures (6,25). Areas of calcification, haemorrhage

and haemosiderin deposition can be found regularly, whereas necrosis is infrequent (25)

In classical chordomas the physaliphorous cells form groups of large grey-white cells that are lobulated by fibrous septa (21). They are surrounded by a basophilic myxoid stroma, rich in mucin and glycogen, in which other cell types, like giant cells or inflammatory cells, may also be found (1,6,21). Due to an overlapping appearance of cartilage tumors and chordomas, problems of differentiation might be encountered (1).

This is especially true for chondroid chordomas which show histological features that resemble both chordoma as well as chondrosarcoma (21). The appearance is similar to hyaline cartilage suggesting an alternative classification as “hyalinized chordoma” (26). They, however, retain an epithelial phenotype and express chordoma specific markers such as low molecular weight molecules and S-100 protein, which are not to be found in cartilaginous tissue (26). Prognostically chondroid chordomas show a low grade behaviour and a favourable long-term outcome, whereas dedifferentiated chordomas demonstrate the most aggressive clinical course, resembling features of malignant fibrous histiocytoma, fibrosarcoma, or osteosarcoma (6,8).

Macroscopically chordomas appear as lobulated and pseudoencapsulated grey tissue, which may vary consistency from jelly-like with large areas of cystic degeneration to firm regions of cartilaginous-like tissue (1).

2.5 Clinical presentation

Manifestation varies and is highly dependent on tumor location. General symptoms include local pain from invasion and compression of adjacent structures including neural tissue (8). The unspecific nature of many early symptoms often causes the diagnosis to be delayed until late in the course of the disease (27). Because of this, approximately 5% of chordomas initially present with metastasis to the lungs, bone, skin, or brain and 65% are metastatic in very advanced cases of disease (28).

Patients with skull base chordomas usually present with headache and cranial-nerve deficits (3). At first physical evaluation findings include visual field defects, double vision due to extra-ocular motility defects (typically caused by abducens nerve involvement), loss of visual acuity, and lower cranial nerve palsy (29). Further rare presentations show epistaxis, intracranial haemorrhage, and, depending on size and involvement of the sella turgica, endocrinopathy (3,30).

The presenting symptoms in the vast majority of patients with chordomas of the mobile spine and sacrum is local deep pain or radiculopathies related to the spinal level at which they occur (3,27). At times pain can also radiate to the buttocks (31). Sacral chordomas most commonly arise in the midline and involve the level S4 and S5 (27). Unfortunately lytic sacral lesions are easily missed in traditional plain radiographs, and CT and MRI often stop at S2 (27). When diagnosed in an advanced stage, symptoms may include neurologically impaired bladder or bowel function, sexual dysfunction. If the lesion extends presacrally, obstipation, constipation, tenesmus, or haemorrhoids can be caused (8,27). In this case, tumor mass may be palpable when examined rectally or gynecologically (27).

Cervical chordomas can cause dysphagia, obstruction of the airway, dysphonia, Horner syndrome and may present as an oropharyngeal mass (8).

2.6 Diagnosis

An accurate diagnosis of the tumor is of valuable prognostic relevance. It is therapeutically important, however, diagnostically challenging to separate chordoma from mimics such as chondrosarcoma and metastatic mucinous adenocarcinoma (32). The preferred means of diagnosis before surgical intervention is the use of minimally invasive imaging-guided biopsy methods being fine-needle aspiration (FNA) and core-needle biopsy (CNB) (32). Since chordomas seem to be able to grow on any tissue, tumor seeding may occur along the route of the biopsy or at a site where tissue is harvested. Thus the needle tract should be labelled and excised with the tumor (7,8). The variable proportion of cell and stroma within a lesion and between tumors adds to the diagnostic challenges, especially in small biopsies (32). Previously the histopathological features and immunoreactivity for S-100 protein and epithelial markers such as cytokeratins were used to diagnose chordoma (8). Due to their common reactivity for S-100 the discrimination between chordoma and chondrosarcoma remains challenging, which is why brachyury seems to emerge as the distinguishing biomarker (33). Oakley GJ et al. analysed paraffin blocks (tissue microarray constructed from whole-tissue sections) from 103 chondroid tumors of the skull base and neck to show that the classic marker cytokeratin has the best distinguishing capabilities and, combined with brachyury, improves sensitivity and specificity for detection of chordoma to about 100% (33). CD24 (another possible discriminatory factor shown to be expressed by the nototchord-derived nucleus pulposus), SOX-9 (a chondrogenesis-selective marker) and podoplanin (positive marker of chondrosarcoma) did not outperform other markers, and are less useful in the chordoma-chondrosarcoma differential diagnosis (33).

Jo et al. confirmed the diagnostic utility of brachyury for chordoma in fine-needle aspiration and core-needle biopsy and also showed an increased sensitivity to 100% when added to a conventional panel of keratin and S-100 (32). They conclude that an all-inclusive immunohistochemical panel (brachyury, epithelial markers, S-100) can be seen as the gold standard for diagnosis (32).

2.7 Radiological evaluation

Chordomas appear as midline lesions (clivus, vertebral body, or sacrum) and present radiographically as a destructive bone tumor (3). Their epicentre is usually in the vertebral body, surrounded by a soft tissue mass and, contrary to osteosarcomas and chodosarmocas, is locally invading intervertebral disc space (1,3,27). Chordomas usually present extradural, well-circumscribed, often compressing and occasionally encasing adjacent neurovascular structures (8). Sacral lesions commonly involve multiple vertebral levels and can display rather large presacral masses. Clival chordomas also demonstrate parts of soft tissue mass and varying degrees of enhancement of the adjacent brain.

CT scans show osteolytic as well as osteosclerotic bone destruction with intratumoral calicification in 30-70% of the cases (3,27), which may be nodular or flake-like (3,25,27). On T1 weighted MR imaging, tumor lesions appear isointense to slightly hypointense, sometimes showing some small foci of hyperintensity representing intratumoral haemorrhage (25,34). On T2 weighted images they appear hyperintense, which most likely reflects a high fluid content of the cellular vacuols and makes for excellent differentiation from adjacent neural structures (35). Lesional heterogeneity represents a variable mix of calcification, haemorrhage, entrapped bony trabeculae and density of cellular arrangement within the tumor (25,35). Furthermore linear bands of hypointense signal correspond to the multilobulated gross morphology of the tumor. Finally, the larger part of chordomas show enhancement with the contrast material gadolinium (3,34).

On scintigraphic bone scans there is a normal or reduced uptake of radioisotope at the site of the tumor, possibly explained by either a reduced bone blood supply caused by the lesion, or a lack of reactive bone tissue due to gross bone destruction (36). To date there have only been a few reports analysing 18F-fluorodeoxyglucose (18F-FDG) uptake in chordomas on metabolic imaging with positron emission tomography (PET)/CT (37). They describe low or intermediate uptake of FDG and suggest that chordomas should be taken in consideration when an osteolytic mass with hyper-metabolism is found on FDG-PET (38).

2.8 Treatment

The gold standard treatment for chordoma is the en-bloc resection of the tumor mass followed by radiation therapy (39). Local relapse, however, is the marker for, and the predominant type of treatment failure for chordoma, often occurring in spite of aggressive surgical procedures and high dose radiation (40). Long-term survival rates are reduced by local recurrence, which is why a combined treatment approach with experienced surgeons and radiation oncologists is essential (40). Primary treatment is critical, because for the most part, only permanent local tumor control offers a chance of cure (40). Whether this goal can be achieved or not, depends on factors such as tumor size, resection margins, location, dedifferentiation, and infiltration of important surrounding tissue (41).

2.8.1 Surgery of sacral chordomas

En-bloc resection for sacral chordomas was first introduced in the 1970s by Stener and Gutenberg and has since then been the norm in surgical management (3,42). Kaiser et al. then demonstrated that the recurrence rate in patients with tumor contamination of the surgical wound was significantly higher than in patients who had complete excision of the tumor without destroying the integrity of the tumor capsule (43). Fuchs and colleagues have further corroborated these findings by showing decreased local recurrence in patients in for whom wide margins could be achieved during initial surgery (44). In fact, it is generally agreed on, that the adequacy of the resection margins is the most important factor of long-term survival following sacrectomy (9,10,41,44,45). Unfortunately en-bloc resection is only possible in approximately half of all sacrectomy procedures (41). Hanna et al. suggest that the reason for local recurrence after procedures with inadequate surgical margins is due to intraoperative seeding or contamination of tumor cells into healthy tissue (46). Another possibility is the presence of occult satellite lesions within a pseudocapsule surrounding the tumor, which, if not removed completely, is cause of recurrence (46,47). Procedures with wide excision margins feature the best long-term survival outcomes but may result in the sacrifice of

adjacent nerve roots, muscle tissue, sacroiliac joints and pelvic bone, thus causing neurological deficits as well as mechanical instability (48,49).

The surgical approach mainly depends on the localisation, especially on the involved sacral vertebral level, and the extent of the lesion (41). Chordomas at S3 and caudal to S3 are primarily treated with a posterior approach (50). It has the advantage of a single stage procedure with shorter operating time and less blood loss, but has a greater risk of violation of the pelvic viscera or ureters during osteotomy and removal of the specimen (44,51). For sacrectomies above the level of S3 a combined anterior-posterior approach is favoured (44). Because of the involvement of the sacroiliac joint, however, it presents a considerably bigger technical challenge (27). Some centers prefer simultaneous dorsal and ventral exposures for better visualisation of anterior structures during osteotomy, but the required lateral positioning may make neither exposure optimal for operating (27). More commonly used is a sequential approach enabling the visceral organs (rectum, ureter, major vessels) to be mobilized away from the tumor at first, before resecting the specimen from the posterior exposure (41,44). Ligation of the internal iliac arteries may also prove beneficial concerning intraoperative bleeding (44). The combined anterior-posterior approach includes the destruction of proximal sacral nerve roots, generally demanding colostomy and ileal conduit formation (41). When faced with large sacral defects where local flap closure is contraindicated, transpelvic rectus abdominis myocutaneus flap is used for reconstruction and shows good results in closure of wound defects (52). Due to all those technically demanding challenges, multidisciplinary cooperation is needed, involving experienced surgical oncologists and plastic surgeons (27). Fuchs et al. reported that wide resection margins could more commonly be achieved using combined anterior-posterior approach compared to the posterior approach (44). This, however, is not reflected in long-term survival, which shows no difference between the two surgical approaches (44).Furthermore tumor size was not found to significantly influence survival (44). When it comes to the level of involvement Yang et al. saw a difference in the continuous disease-free survival time between tumors located below and above S3 (53). Higher tumor location showed both increased disease recurrence as well as reduced survival (53,54). Other factors increasing the tendency of recurrence include infiltration of the sacroiliac joints and the surrounding muscle tissue, even after wide excision of the

tumor (46,54). The involvement of these structures may indicate a more advanced stage with a greater possibility of satellite lesions (41). Moreover, resection of the sacroiliac joints is accompanied by significant mechanical instability and needs to be accounted for when planning a surgical procedure (41).

Concerning neurological deficits, the level of the sacrectomy and extent of the nerve root excision determines the degree of urological, gastrointestinal, sexual, sensory and motor dysfunction (41). Excision of nerve roots distal to S-3 generally show limited deficits with a majority of patients retaining normal bowel as well as bladder function and some reduced perineal sensation (27,55). When both S-2 and S3 levels are involved the extent of the neurological deficits seem to be very inconsistent (27,56). Loss of voluntary control of bowel and bladder is the result following the resection of any of the S-2 nerve roots (57). If both S-2 roots are preserved and at least one S-3 root remains intact, bowel and bladder function is not impaired in the majority of patients (55). Excision of the S1 nerve roots most definitely leads to total loss of sphincter control and sexual ability and may cause significant motor deficits (27). All of the above are not rigid rules but trends and probabilities to help patients to anticipate the results of sacrectomies (55).

2.8.2 Surgery of chordomas of the lumbar, thoracic and cervical spine

Chordomas are generally less common in regions of the mobile spine and therefore literature is very limited. In a study by Bjornsson et al. 40 patients showed a distribution of 35% lumbar chordomas, 17% thoracic chordomas and 48% cervical chordomas (28). En-bloc surgical procedures are possible for vertebral chordomas through methods of successfully replacing elements of the spine, thus helping patients remain functional throughout the recovery period and after (28).

Lumbar locations are usually accessed through an anterior retroperitoneal approach for mid to lower level lesions (1). Some tumors may be in need of the removal of the bulk of the midlumbar vertebra in which case a posterolateral approach can be performed (1). Sivabalan et al. presented a case of a very large chordoma treated with extensive vertebrectomy in a two-staged posterior and anterior approach (58). Reconstruction was very complex involving pedicle screw

fixation, vascularised bone grafting, anterior expandable cage support and bilateral vascularised latissimus dorsi flaps to cover the massive loss of tissue (psoas muscle and paraspinal muscle) (58).

The surgical treatment for thoracic lesions is using a thoracotomy, which sometimes requires laminectomy in a staged approach (1,59). Oppenlander et al. describe a safe and effective way of en-bloc resection of a multilevel chordoma of the thoracic spine through a simultaneous throracoscopic and posterior approach (60). This technique allows for the establishment of a clear plane between the mediastinum and the lesion for a safe osteotomy from posterior (60). In addition, thoracoscopy instead of thoracotomy features smaller size of incision and dissection of the chest wall, reduced pain, as well as less blood loss (60).

There are many different surgical treatment options when it comes to chordomas of the upper cervical spine and craniocervical junction (61). Achieving en bloc resection is especially challenging because of the tumor's close proximity to important structures like the spinal cord, cervical roots and vertebral artery (62). The standard transoral approach and the "open-door" maxillotomy are the most commonly performed operations. Other possibilities are a transoral approach with palate split, transmandibular approach and anterolateral approach (61). Which option is selected, depends on level and extension of the tumor. Complications include chest infection, meningitis, cranial nerve palsy and cerebrospinal fluid leakage (61). Even though it is technically demanding, en-bloc excision of chordomas of the cervical spine, whether wide or marginal, can be accomplished with reasonably acceptable morbidity rates (62).

2.8.3 Surgery of cranial chordoma

Extensive tumor removal with the goal of en-bloc resection is also associated with longer survival rates when it comes to skull base chordoma, and therefore remains the most important objective in surgical therapy (63). Advanced techniques allow total radical resection, sparing vital structures in an increasing number of cases (64). There are two philosophies regarding the aggressive treatment of cranial chordoma: Resection followed by radiotherapy for patients with tumor remnants and resection followed by radiotherapy regardless of the presence of remnants (29). State-of-the-art imaging technology as part of the presurgical evaluation provides detailed information of the lesion, suggesting the best surgical approach (64). Which approach is used in the end depends mainly on the location as well as the surgeon's preference (65). Chordomas arising from the clivus, the ventral part of the occipital bone, are among the most challenging tumors to treat in head and neck surgery (11). In order to help with the selection of the best surgical approach, the clivus is divided into three parts (11). Lesions centered in the upper clivus (or extending laterally) are best reached through an orbitozygomatic approach (11,64). The midclivus is accessed by anterior, posterior, or total petrosectomy (11,64). A transmaxillary, transoral, or high cervical route is used for lesions of the lower clivus extending into the nasopharynx or the craniocervical junction (11,64). Aggressive surgical strategy, however, is associated with a high complication rate (29). It is reported, that 80% of the patients experience cranial nerve deficits including abducens nerve palsy, hearing loss, permanent facial palsy and visual decline (66). The most frequent complication is postoperative leakage of cerebrospinal fluid, which is proven to increase the risk of permanent disability (66). Nasoseptal flap repair techniques are used to prevent cerebrospinal fluid leakage after violation of the skull base dura (67).

In recent years a new approach was created applying endonasal endoscopy to cranial base surgery (29). The endoscopic endonasal approach takes advantage of the natural sinus corridor and may provide a less invasive approach for clival chordomas (67). With adequate experience it is a safe procedure with similar resections compared with traditional cranial base approaches, while potentially limiting morbidity (67). The frequency of gross-total tumor removal ranges from 50%-88% for newly diagnosed chordomas and from 12,3%-30% for recurrent

chordomas (67-69). In some cases multiple staged surgeries are needed to achieve radical removal (68).

If en-bloc surgery or gross-total tumor resection is not achievable, subtotal resection followed by postoperative radiation therapy presents acceptable results with respect to surgical and functional outcome and overall survival (70). Potluri et al. show that a small residual lesion can be managed using high-dose photon radiotherapy (71). The need for total removal should not be at any price, but must rather be weighed against the probability of neurological impairment (70). Overall it can be stated that the treatment goal is not in tumor resection alone, but must take the patient's neurological functions and quality of life into account (3).

2.8.4 Radiotherapy

Despite the efforts of surgical intervention through advanced operative techniques, radical en-bloc resection is only achievable for approximately half of the sacral chordomas and even fewer for cranial chordomas; This leads to a high rate of local recurrence due to residual tumor lesions (27,29,44,70,72). Radiation therapy is generally advocated for residual tumors after surgery as well as for unresectable lesions or recurrent cases (73). Although different radio therapeutic treatment regimens are broadly debated, chordomas are generally known to be relatively radioresistant lesions (74). There is a clearly established dose-response relationship with effective doses requiring 70 Gy and higher (74). The problem, however, is that the tolerance dose of adjacent structures like the spinal cord, brainstem, optic pathways, and the rectum is lower than the curative dose (75). Conventional ionized radiation with doses 40 Gy - 60 Gy show limited effect concerning progression-free and overall survival, yet provide useful palliation of pain for most patients (76).

In the 1970s radiation therapies using high-dose protons or charged particles such as carbon ions, helium or neon called hadrons were introduced (75). This advancement allows the administration of high doses of total radiation to a lesion while achieving a rapid reduction in dose outside the defined target (77). Recent evidence suggests hadron-based therapy is more effective in the treatment of chordomas than compared to conventional photon-based therapy (3). Reports of

local control with proton-based therapy range from 59% to 82% at 5 years (78-80). Nowadays proton-beam radiation following en-bloc resection is the standard management in most cancer centers regarding chordoma treatment (3). Delaney and colleagues achieved 5 and 8-year local control rates of 94% and 85% for primary tumors of the spine after total resection (81). Park et al. show similar promising results for chordomas of the sacrum and emphasize that local control rate is significantly higher for surgical and radiation treatment of primary compared to recurrent tumors (82). These findings highlight the importance of optimizing local therapy using radiation at initial presentation to avoid recurrence and the associated morbidity (8). In cases where chordomas are judged unresectable due to medical reasons or surgery is refused, carbon ion radiotherapy offers a promising alternative to surgery with 5-year overall survival rates between 52% and 86% and 5-year local control rate of around 90% (83,84). A study by Nishida et al directly compared the outcome in patients with carbon ion radiotherapy with surgery and concluded that a greater local control rate was achieved after carbon ion radiotherapy than after surgery with less post-treatment urinary and anorectal dysfunction (85). Because of the low number of cases (n=17) and short follow-up time, however, further evaluation is needed (85).

In recent years more sophisticated photon beam techniques including radiosurgery, intensity-modulated radiotherapy (IMRT), and fractionated stereotactic radiotherapy became available with improved dose maximization (75). IMRT has produced promising results especially in skull base chordomas, either alone or in combination with hadron-based therapy (73). It is also reported that local control after IMRT is significantly higher in patients treated for primary tumors compared to recurrent tumors, which underlines yet again the importance of radiotherapy as part of the initial treatment of chordomas (86). Stereotactic radiosurgery (gamma knife) may be a potent treatment option for small to medium sized recurrent tumors after aggressive initial resection (87,88). Because of the high cost (10 times higher than photon therapy) and still limited availability of hadron-based therapy, advanced photon-based treatment modalities can be considered a valid alternative in some cases (75).

2.8.5 Chemotherapy and future molecular targets

Chordomas have generally been considered to be insensitive when it comes to medical therapy, especially conventional chemotherapy (75). There are only anecdotal reports of tumor responses to treatment regimens including anthracyclines, cisplatin, alkalyting agents and camptothecin analoges (75). Fleming and colleagues suggest chemosensitivity of dedifferentiated chordoma, a more aggressive histological variant with characteristics similar to high-grade sarcomas (89). Systematic reviews in literature, however, found no meaningful results regarding the effect of chemotherapy on control of local recurrence or survival rate (31).

Recently molecular characterization has shown an overexpression of platelet-derived growth factor receptors (PDGFR) A and B as well as KIT receptors in chordoma cells, suggesting possible responsiveness to new molecular-targeted agents (75,90). Casali and colleagues reported tumor sensitivity to imatinib, a tyrosine-kinase inhibitor specific for PDGFR and KIT receptors (91). In this series six patients were treated with imatinib mesylate at a dose of 800 mg daily and showed decreased contrast enhancement on MRI and decreased glucose uptake on positron emission tomography (91). A phase II study including 56 patients is further corroborating the antitumor activity in advanced chordoma (92). Another tyrosine-kinase inhibitor, sunitinib, has shown clinical improvements as well (3). One trial reported that 44% of patients displayed stable disease for at least 16 weeks after starting treatment with sunitinib (3). Clinical benefits and objective tumor regressions were further observed in cases of advanced chordoma treated with EGFR inhibitors such as gefitinib, cetuximab and erlotinib (93).

Finally, brachyury, apart from being an identifying marker, also plays an important role in chordoma pathogenesis (73). The silencing of brachyury in vitro results in the interruption of cell growth due to cancelation of transcriptional activation of many downstream genes (73). Furthermore, brachyury is only expressed in tumor cells, which makes it an ideal candidate for molecular targeted therapy (73). The American national cancer institute is currently evaluating the safety of a brachyury-based immune therapy for patients with cancer including chordoma (8).

3 Materials and methods

Using Surveillance Epidemiology and End Results (SEER) data we conducted a retrospective analysis including chordoma cases diagnosed from 2000 to 2010.

3.1 SEER database

The SEER program of the National Cancer Institute is the largest source of cancer information in the United States. Over almost 4 decades, SEER has been compiling incidence and survival data from population based cancer registries throughout the country. Many variables are collected for each case including patient demographics, histology, date of diagnosis, primary site, initial modality of treatment (surgery and radiation), stage at diagnosis, size, date of death and others. After the merge of two NCI programs, namely the End Results Program and the Third National Cancer Survey, SEER 9 was formed by the first nine member registries in 1973: Connecticut, Utah, Hawaii, New Mexico, Iowa, Detroit, San Francisco/Oakland, Seattle (Puget Sound) and Atlanta (94). Together they represented roughly 9.5% of the US Population (14). Since then many new registries including San Jose-Monterey, Los Angeles, Greater California, Alaska, Kentucky, Louisiana, New Jersey, Rural Georgia and Greater Georgia followed to join the program and were grouped as SEER 18 (95,96). Available since 2000, it covers approximately 28% of the population with a wide geographical variation (95). Cancer cases missed to be reported range around 2.3% (97). Although SEER data are generally representative of the United States population, areas have a more urban than rural tendency and therefore include a higher percentage of foreign born individuals (94). Moreover, some races and minorities are proportionally larger covered than whites or blacks (98). Nonetheless, size as well as long follow-up periods make the database incredibly useful when studying rare malignancies like chordomas.

3.2 Study population

Microscopically confirmed cases of chordoma diagnosed in a 11 year period between 2000-2010 were included in our study and identified using the following three histological codes from the Word Health Organization's International Classification of Diseases for Oncology, 3rd edition (ICD-O-3): 9730/1 Chordoma not otherwise specified (NOS), 9731/1 chondroid chordoma, 9732/1 dedifferentiated chordoma (99). Because of Hurricane Katrina's large impact on the Louisiana population during the July-December 2005 time period, cases diagnosed in these six months are by default not analysed when using a SEER dataset (1 case excluded). After exclusion of another 36 cases (6 unknown confirmation; 30 only radiographic confirmation) that lacked microscopic validation 795 cases remained in our study.

3.3 Distribution of characteristics

Cases were analysed by age, sex, race, Hispanic origin, year of diagnosis, site of presentation, geographic area, extent of disease (tumor size) and first course of therapy.

3.3.1 Primary site of presentation

The primary sites were grouped in a similar way to a paper by McMaster et al (14) into cranial, spinal and sacral sites (*Table 1*). "Other" includes extra-axial, non categorizable and unknown sites.

3.3.2 Therapy

The variables for surgery and radiation in the SEER database include various categories. The detailed coding for the purpose of our study is outlined in *Table 2.* We used these data to assess the initial treatment of chordoma. Due to the unknown application of surgery or radiation in some cases, 38 cases were missing in the treatment variable (radiation only, surgery only, both, neither).

3.3.3 Tumor size

The “CS tumor size” variable is part of the Collaborative Stage System (CS) maintained and managed by The American Joint Committee on Cancer (AJCC) (100). It is available in the SEER program since 2004 and records the largest diameter of the primary tumor more accurately than other staging methods concerning chordoma. We followed the approach by Lee et al. (12) and categorized tumors larger and smaller than 5cm. The detailed coding scheme is displayed in *Table 3*. Lesions smaller than 5cm include numbers 000-049 and 991-995, lesions equal and larger than 5cm include numbers 050-989, and lesions with unknown size include number 999.

Table 1. Detailed coding for primary site of presentation

Cranial:	**Spinal:**
C10.3-Posterior wall of oropharynx	C38.2-Posterior mediastinum
C11.1-Posterior wall of nasopharynx	C41.2-Vertebral column
C11.9-Nasopharynx, NOS	C47.3-Periph nerves & autonomic nervous system: thorax
C13.9-Hypopharynx, NOS	C47.6-Periph nerves & autonomic nervous system: trunk, NOS
C14.0-Pharynx, NOS	C48.0-Retroperitoneum
C30.0-Nasal cavity	C49.6-Connective, subcutaneous, other soft tissue: trunk, NOS
C31.2-Frontal sinus	C72.0-Spinal cord
C31.3-Sphenoid sinus	**Sacral:**
C31.9-Accessory sinus, NOS	C41.4-Pelvic bones, sacrum, coccyx and associated joints
C41.0-Bones of skull and face and associated joints	C47.5-Periph nerves & autonomic nervous system: pelvis
C41.1-Mandible	C49.5-Connective, subcutaneous, other soft tissue: pelvis
C49.0-Connective, subcutaneous, other soft tissue: head, face, neck	C76.3-Pelvis, NOS
C69.9-Eye, NOS	**Other:**
C71.0-Cerebrum	C34.1-Upper lobe, lung
C71.2-Temporal lobe	C38.0-Heart
C71.4-Occipital lobe	C40.2-Long bones of lower limb and associated joints
C71.6-Cerebellum, NOS	C41.9-Bone, NOS
C71.7-Brain stem	C47.9-Autonomic nervous system, NOS
C71.8-Overlapping lesion of brain	C49.2-Connective, subcutaneous, other soft tissue: lower limb, hip
C71.9-Brain, NOS	C49.4-Connective, subcutaneous, other soft tissue: abdomen
C72.5-Cranial nerve, NOS	C49.9-Connective, subcutaneous, other soft tissue: NOS
C75.1-Pituitary gland	C72.9-Nervous system, NOS
C76.0-Head, face or neck, NOS	C80.9-Unknown primary site

Table 2. Detailed coding for therapy

Surgery	
Yes	• Tumor destruction; no pathologic specimen or unknown whether there is a pathologic specimen • Resection; pathologic specimen • Surgery NOS. A surgical procedure to the primary site was done, but no information of surgical procedure is provided
No	• None; no surgical procedure of primary site; diagnosed at autopsy only
Unknown	• special codes for hematopoietic, reticuloendothelial, immonoproliferative, myeloproliferative diseases; ill-defined sites; and unknown primaries, except death certificate only • Unknown if surgery performed; death certificate only
Radiation	
Yes	• Beam radiation • Radioactive implants • Radioisotopes • Combination of beam with implants or isotopes • Radiation, NOS method or source not specified • Other radiation (1973-1987 cases only)
No	• None • Refused
Unknown	• Recommended, unknown if administered • Unknown
Treatment	
Radiation only	Radiation without surgery
Surgery only	Surgery without radiation
Both	Surgery and Radiation
Neither	No surgery and no radiation

Table 3. Detailed coding for tumor size

Code	Description
0	No mass/tumor found
001-988	Exact size in millimeters
989	989 millimeters or larger
990	Microscopic focus or foci only and no size of focus is given
991	Described as “less than 1 cm”
992	Described as “less than 2 cm,” or “greater than 1 cm,” or “between 1 cm and 2 cm”
993	Described as “less than 3 cm,” or “greater than 2 cm,” or “between 2 cm and 3 cm”
994	Described as “less than 4 cm,” or “greater than 3 cm,” or “between 3 cm and 4 cm”
995	Described as “less than 5 cm,” or “greater than 4 cm,” or “between 4 cm and 5 cm”
996-998	Site-specific codes where needed (no cases with this coding is present in our data)
999	Unknown; size not stated Not documented in patient record

3.4 Chordoma incidence

We calculated age standardized incidence rates (IRs) expressed as new cases per million population. For standardization the 2000 US standard population (19 age groups – Census P25-1130) was used. Additionally, rate ratios (RRs) and 95% confidence intervals (CIs) are presented.

3.5 Survival analysis

Survival is defined as the time from diagnosis to either date of death, loss to follow-up, or study cut-off date, i.e. the 31. December 2010. Of 795 microscopically confirmed chordoma cases, 107 were excluded because of second or later primaries and 6 were excluded because survival information was not available, leaving 682 cases for survival analyses. To avoid influence by death from other causes relative survival (RS) was calculated, which is defined as the ratio of the observed survival rate in a group of cancer patients to the expected survival rate in a population (101). In our study the following expected survival table was used: U.S. 1979-2007 by individual year (White, Black, Other (AI/API) All races for Other unspec 1991+ and Unknown*).* Because of significant inconsistencies across SEER registries when coding causes of death, we rather used RS estimation over traditional cause-specific survival methods (13).

3.6 Statistical analysis

Incidence and distribution was calculated using SEER*Stat (version 8.1.5), a public use software provided by the SEER program. 5- and 10-year survival was also calculated with SEER*Stat using the relative survival method. Additional analysis was performed with help from the Institute for Medical Informatics, Statistics and Documentation using SAS (version 9.2). For comparison of distributions, X^2-tests and non-parametric tests (Kruskal-Wallis-Test, Mann-Whitney-U-test) were used. To compare overall survival between sex, race in three categories (white, black, other), Hispanic origin, age in five categories (0-19, 20-39, 40-59, 60-79, 80+), primary site of presentation, tumor size (as defined in section 3.3.3), radiation (yes/no), surgery (yes/no) and treatment in four categories (see *Table 2*) Kaplan-Meier plots and log rank tests were used. Furthermore, univariate Cox proportional hazard regression was used to obtain hazard ratios (HRs) and 95% CIs. A p-value of <0,05 indicates statistical significance.

4 Results

4.1 Demographic and clinicopathologic data

In the time period from 2000 to 2010 795 cases with chordoma were included in our study. The detailed patient demographics and clinicopathological characteristics are displayed in *Table 4*. The median age at chordoma diagnosis was 57 years (range: 0-91) and varied between the histological types: chondroid chordoma (48 years; range: 13-82) and dedifferentiated chordoma (26 years; range 3-80).

Table 4. Patient demographics and clinicopathological characteristics

	N	%
All patients	795	100,0
Histological type		
Chordoma, NOS	735	92,5
Chondroid chordoma	53	6,7
Dedifferentiated chordoma	7	0,9
Sex		
Male	461	58,0
Female	334	42,0
Age		
0-19	55	6,9
20-39	130	16,3
40-59	255	32,1
60-79	276	34,8
80+	79	10,0

Race		
White	687	86,4
Black	26	3,3
Other	70	8,8
Unknown	12	1,5
Hispanic		
Non-Spanish-Hispanic-Latino	690	86,8
Spanish-Hispanic-Latino	105	13,2
Tumor size (2004+)* N=534		
<5cm	196	36,7
≥5cm	164	30,7
Unknown	174	32,6
Primary site		
Cranial	334	42,0
Spinal	203	25,5
Sacral	245	30,8
Other	13	1,6
Radiation		
Yes	329	41,4
No	433	54,5
Unknown	33	4,2
Surgery		
Yes	651	81,9
No	135	17,0
Unknown	9	1,1
Treatment N=757**		
Radiation only	56	7,4
Surgery only	354	46,8
Both	272	35,9
Neither	75	9,9

* data not available for all patients

** cases with radiation or surgery unknown were excluded

The distribution of characteristics by primary site of presentation is displayed in *Table 5*.

The most common site of presentation for conventional chordoma (NOS) was cranial with 39,7%. Chondroid chordoma showed an even higher proportion of cranial presentation with 77,4%. On the contrary 6 out of 7 dedifferentiated chordoma cases had the sacrum as primary site.

No statistically significant association was found between sex and site of presentation ($p = 0,64$). Across the age groups, however, primary site of presentation was differently distributed. Patients with cranial presentation were significantly younger (median age: 48,5 years) compared to patients with spinal (59,0 years; $p < 0,01$) as well as sacral presentation (64,0 years; $p < 0,01$).

In African Americans, chordomas present more common in cranial locations (61,5%), compared to whites (40,8%) and other races (52,9%). In the Spanish-Hispanic-Latino community there is a specifically low frequency of sacral chordomas (15,2%) compared to non-Spanish-Hispanic-Latinos (33,2%; $p < 0,01$).

When it comes to tumor size 261 cases were missing since the variable is not available before 2004. Of the remaining 534 cases, 174 were unknown, 196 were smaller and 164 larger than 5cm. The majority of smaller tumors were located in cranial regions (66,3%) followed by spinal (19,9%) and sacral (12,8%). In contrast, larger tumors were mostly located in sacral regions (66,5%) then spinal (15,2%) and cranial (17,1%). We found no significant variation between the histological subtypes and size ($p = 0,19$). However, Patients with small lesions at diagnosis were significantly younger (median age: 54 years) compared to patients with large lesions (63 years; $p < 0,01$).

Table 5. Distribution by primary site of presentation

	Cranial		Spinal		Sacral		Other		p-value
N=795	N	%	N	%	N	%	N	%	
Histological type									
Chordoma, NOS	292	39,7	196	26,7	235	32,0	12	1,6	<0,01
Chondroid chordoma	41	77,4	7	13,2	4	7,6	1	1,9	
Dedifferentiated chordoma	1	14,3	0	0,0	6	81,7	0	0,0	
Sex									
Male	187	40,6	117	25,4	150	32,5	7	1,5	0,64
Female	147	44,0	86	25,8	95	28,4	6	1,8	
Age									
0-19	34	61,8	13	23,6	6	10,9	2	3,6	<0,01
20-39	87	66,9	26	20,0	15	11,5	2	1,5	
40-59	118	46,3	63	24,7	73	28,6	1	0,4	
60-79	88	31,9	77	27,9	103	37,3	8	2,9	
80+	7	8,9	24	30,4	48	60,8	0	0,0	
Race*									
White	280	40,8	189	27,5	207	30,1	11	1,6	0,02
Black	16	61,5	3	11,5	7	26,9	0	0,0	
Other	37	52,9	8	11,4	23	32,9	2	2,9	
Hispanic									
Non-Spanish-Hispanic-Latino	270	39,1	180	26,1	229	33,2	11	1,6	<0,01
Spanish-Hispanic-Latino	64	61,0	23	21,9	16	15,2	2	1,9	
Tumor size (2004+)*									
<5cm	130	66,3	39	19,9	25	12,8	2	1,0	<0,01
≥5cm	28	17,1	25	15,2	109	66,5	2	1,2	

* unknown cases were excluded

The distributions of characteristics by surgery (yes/no), radiation (yes/no) and treatment, a combination of both, are given in *Tables 6-8*. Concerning treatment, surgery alone or a combination of surgery and radiation were the most common options. Patients with chordoma located in the cranial region (92,8%) received surgery more often compared to patients with sacral presentation (72,1%; $p < 0,01$) (*Table 6*). This also applies to radiation being more commonly delivered to the cranium (47,5%) than to the sacrum (35,6%; $p = 0,03$) (*Table 7*). A combination of both surgery and radiation was most commonly applied to the cranium as well (43,3%). Sacral sites were more likely to receive radiation alone (12,6%) or no treatment at all (16,0%) when compared to the spinal (8,1% for radiation alone; 13,2% neither) and cranial sites (3,5% for radiation alone; 3,5% neither) (*Table 8*).

Furthermore, patients treated with either surgery alone (median age: 52,7 years) or surgery combined with radiation (50,7 years) were significantly younger than patients who received only radiation (68,7 years) or no treatment at all (65,7 years; $p < 0,01$).

Small lesions were more likely to be treated surgically (93,9%) compared to large lesions (76,8%, $p < 0,01$). In regards to the application of radiation there is a trend towards smaller size as well (50,8% <5cm, 40,4% >5cm; $p = 0,05$). Moreover, Large lesions were less likely to receive a combination of surgery and radiation (31,1%) compared to small lesions (47,0%; $p < 0.01$).

Table 6. Distribution by surgery

	No		Yes		p-value
N=786	N	%	N	%	
Sex					
Male	77	17,0	377	83,0	0,85
Female	58	17,5	274	82,5	
Age					
0-19	2	3,6	53	96,4	<0,01
20-39	15	11,5	115	88,5	
40-59	26	10,2	228	89,8	
60-79	46	17,1	223	82,9	
80+	46	59,0	32	41,0	
Race*					
White	112	16,5	568	83,5	0,15
Black	3	11,5	23	88,5	
Other	17	25,0	51	75,0	
Primary site					
Cranial	24	7,2	308	92,8	<0,01
Spinal	43	21,2	160	78,8	
Sacral	67	27,9	173	72,1	
Other	1	9,1	10	90,9	
Tumor size (2004+)*					
<5cm	12	6,1	184	93,9	<0,01
≥5cm	38	23,2	126	76,8	

* unknown cases were excluded

Table 7. Distribution by radiation

	No		Yes		p-value
N=762	N	%	N	%	
Sex					
Male	256	57,5	189	42,5	0,64
Female	177	55,8	140	44,2	
Age					
0-19	29	53,7	25	46,3	0,06
20-39	75	61,0	48	39,0	
40-59	121	50,0	121	50,0	
60-79	157	59,0	109	41,0	
80+	51	66,2	26	33,8	
Race*					
White	373	56,7	285	43,3	0,51
Black	17	68,0	8	32,0	
Other	37	55,2	30	44,8	
Primary site					
Cranial	168	52,5	152	47,5	0,03
Spinal	107	54,3	90	45,7	
Sacral	150	64,4	83	35,6	
Other	8	66,7	4	33,3	
Tumor size (2004+)*					
<5cm	91	49,2	94	50,8	0,052
≥5cm	96	59,6	65	40,4	

* unknown cases were excluded

Table 8. Distribution by treatment

	Radiation only		Surgery only		both		neither		p-value
N=757	N	%	N	%	N	%	N	%	
Sex									
Male	33	7,5	210	47,7	155	35,2	42	9,6	0,92
Female	23	7,3	144	45,4	117	36,9	33	10,4	
Age									
0-19	2	3,7	29	53,7	23	42,6	0	0,0	<0,01
20-39	4	3,3	66	53,7	44	35,8	9	7,3	
40-59	10	4,2	104	43,2	111	46,1	16	6,6	
60-79	20	7,6	129	49,2	88	33,6	25	9,5	
80+	20	26,0	26	33,8	6	7,8	25	32,5	
Race*									
White	47	7,2	308	47,2	237	36,3	61	9,3	0,41
Black	1	4,0	15	60,0	7	28,0	2	8,0	
Other	6	9,0	26	38,8	24	35,8	11	16,4	
Primary site									
Cranial	11	3,5	155	48,7	141	44,3	11	3,5	<0,01
Spinal	16	8,1	81	41,1	74	37,6	26	13,2	
Sacral	29	12,6	111	48,1	54	23,4	37	16,0	
Other	0	0,0	7	63,6	3	27,3	1	9,1	
Tumor size (2004+)*									
<5cm	7	3,8	87	47,0	87	47,0	4	2,2	<0,01
≥5cm	15	9,3	73	45,3	50	31,1	23	14,3	

* unknown cases were excluded

4.2 Incidence

Among the 18 SEER registries the overall incidence rate for chordoma was 0,89 per one million population. When it comes to gender, chordoma incidence was lower in females (IR = 0,70) than in males (IR = 1,11; RR = 0,63; p < 0,01). Although found in all age groups chordoma was more common at higher age with a cumulative incidence rate of 2,50 per million population for people over 60 years then compared to the rate of 0,57 per million population for people under 60 (RR = 4,41; p < 0,01). As seen in *Table 9* incidence rates show a gradually progressive increase towards older age groups peaking at ages 80+.

Across the races chordoma seemed to have an especially low incidence in African Americans (IR = 0,25) compared to whites (IR = 0,96; RR = 0,26; p < 0,01). The "other" group including American Indians, Alaska Natives and Asian, or Pacific Islanders had approximately the same rate compared to the white population (IR = 0,81; RR = 0,84; p = 0,20). Spanish-Hispanic-Latinos showed a slightly lower incidence rate (IR = 0,78) compared to non-Spanish-Hispanic-Latinos (IR = 0,90). However, this was not significant (RR = 0,87; p = 0,22). There has been some variation between the different SEER registries with Louisiana having the lowest rate (0,54 per million population) and Iowa showing the highest rate (1,18 per million population) (*Table 10*).

Table 9. Incidence

	Rates per million population	95% Confidence interval (CI)	Rate ratio (RR)	p-value
Overall	0,89	0,83 - 0,95		
Histological type				
Chordoma, NOS	0,82	0,76 - 0,88	-	-
Chondroid chordoma	0,06	0,04 - 0,08	-	-
Dedifferentiated chordoma	0,01	0,003 - 0,016	-	-
Sex				
Male	1,11	1,01 - 1,21	Reference	
Female	0,70	0,63 - 0,78	0,63	<0,01
Age				
0-19	0,25	0,18 - 0,33	Reference	
20-39	0,51	0,43 - 0,61	2,05	<0,01
40-59	1,01	0,89 - 1,14	4,03	<0,01
60-79	2,45	2,17 - 2,76	9,80	<0,01
80+	2,72	2,15 - 3,39	10,89	<0,01
Race*				
White	0,96	0,89 - 1,04	Reference	
Black	0,25	0,16 - 0,38	0,26	<0,01
Other	0,81	0,63 - 1,03	0,84	0,20
Hispanic				
Non-Spanish-Hispanic-Latino	0,90	0,83 - 0,97	Reference	
Spanish-Hispanic-Latino	0,78	0,63 - 0,96	0,87	0,22

* unknown cases were excluded

Table 10. Incidence by geographical location

	Rates per million population	95% Confidence interval (CI)
San Francisco-Oakland SMSA	0,95	0,69 - 1,27
Connecticut	0,98	0,70 - 1,33
Detroit (Metropolitan)	0,74	0,50 - 1,04
Hawaii	0,68	0,32 - 1,25
Iowa	**1,18**	**0,85 - 1,61**
New Mexico	0,85	0,51 - 1,34
Seattle (Puget Sound)	0,93	0,67 - 1,24
Utah	0,85	0,50 - 1,33
Atlanta (Metropolitan)	0,60	0,35 - 0,97
San Jose-Monterey	0,98	0,62 - 1,46
Los Angeles	0,91	0,73 - 1,12
California excluding SF/SJM/LA	0,99	0,86 - 1,13
Kentucky	0,71	0,49 - 0,99
Louisiana	**0,54**	**0,35 - 0,79**
New Jersey	1,09	0,90 - 1,32
Greater Georgia	0,60	0,42 - 0,83

4.3 Survival

For the survival analysis 682 cases were included with a median follow-up time of 42 months (minimum 1 month; maximum 120 months). The overall median survival was 9.3 years. Patients had 78,0% 5-year relative survival (95% CI: 73,4-81,9) and 56,7% 10-year relative survival (95% CI: 48,5-64,0), respectively. Detailed results of the relative survival analysis are summarized in *Table 11.* Log-rank tests did not reveal a significant difference concerning sex (p = 0,64), race (p = 0,45), and Spanish-Hispanic-Latino origin (p = 0,67) (*Fig. 1-3*).

When it comes to age, however, differences can be seen in the KM-curves (log-rank test: p < 0,01) (Fig. 4). We chose the age group 40-59 as the reference for analysis of hazard ratios. Patients aged 80 and older had the worst prognosis with a 8,62 times greater rate of mortality compared to the reference group (p < 0,01). Surprisingly, the youngest group, aged 0-19 years, also showed a 2,20 times higher risk of death compared to the reference group (p < 0,01). *Table 12* illustrates predictors of mortality in detail.

Regarding site of presentation, patients with cranial and spinal chordoma showed a better survival compared to patients with sacral chordoma (log-rank test: p < 0,01) (*Fig. 5*). When risk of death is compared, sacral presentation was associated with a significantly higher rate of mortality compared to cranial presentation (HR: 1,69; 95% CI: 1,21-2,36; p < 0,01).

Concerning surgery there was a significant difference in survival seen in the KM-curves (log-rank test: p < 0,01)(*Fig. 6*), which is also reflected in a decreased risk of death for patients who received surgery compared to those who did not (HR: 0,45; 95% CI 0,32-0,62; p < 0,01). In contrast, there was no significant difference between patients who received radiation and those who did not (HR: 0,89; 95% CI: 0,67-1,2; p = 0,45)*(Fig.7)*.

The treatment groups (neither, radiation only, surgery only, both) displayed the poorest survival for patients who received neither surgery nor radiation (log rank test: p < 0,01)(*Fig. 8*). Compared to the “neither” group patients had a decreased risk of death when treated with surgery alone (HR: 0,49; 95% CI: 0,32-7,75; p < 0,01) or surgery combined with radiation (HR: 0,41; 95% CI: 0,26-0,65;

p < 0,01). No significant difference in mortality was found between “neither” treatment and radiation alone (HR: 1,12; 95% CI: 0,64-1,98; p = 0,69).

In regard to tumor size, a trend is seen in the KM-curves toward lower survival in lesions over 5cm (log-rank test: p = 0,054) (*Fig. 9*). This trend is also seen in a higher mortality rate in large tumors compared to small tumors (HR: 1,63; 95% CI: 0,99-2,7; p = 0,057).

Table 11. Relative survival

	5 year RS (%)	95% Confidence interval (CI)
All patients	78,0	73,4 - 81,9
Sex		
Male	78,5	72,3 - 83,4
Female	77,2	69,7 - 83,0
Age		
0-19	61,6	45,2 - 74,4
20-39	84,1	75,1 - 90,1
40-59	89,0	82,3 - 93,2
60-79	71,0	60,5 - 79,2
80+	46,6	21,7 - 68,3
Race*		
White	78,1	73,1 - 82,3
Black	85,9	49,3 - 96,8
Other	71,3	54,6 - 82,8
Hispanic		
Non-Spanish-Hispanic-Latino	78,5	73,5 - 82,6
Spanish-Hispanic-Latino	74,7	60,7 - 84,3
Size (2004+)*		
<5cm	80,8	69,5 - 88,2
≥5cm	69,1	53,3 - 80,5
Primary site*		
Cranial	80,8	74,6 - 85,7
Spinal	79,3	69,6 - 86,2
Sacral	69,8	58,5 - 78,6
Radiation*		
Yes	78,8	71,3 - 84,6
No	75,8	69,3 - 81,0
Surgery*		
Yes	80,2	75,3 - 84,2
No	67,0	52,2 - 78,1
Treatment*		
Neither	58,8	39,8 - 73,6
Radiation only	70,4	45,7 - 85,5
Surgery only	80,4	72,2 - 84,3
Both	79,0	72,4 - 86,3

*unknown cases were excluded

Table 12. Results of univariate Cox regression models

	Hazard ratio	95% Confidence interval (CI)	p-value
Sex			
Male	Reference	-	-
Female	0,93	0,7 - 1,25	0,64
Age			
0-19	2,20	1,27 - 3,82	<0,01
20-39	1,02	0,62 - 1,68	0,95
40-59	Reference	-	-
60-79	2,55	1,75 - 3,73	<0,01
80+	8,62	5,38 - 13,81	<0,01
Race*			
White	Reference	-	-
Black	0,78	0,34 - 1,76	0,54
Other	1,28	0,81 - 2,01	0,29
Hispanic			
Non-Spanish-Hispanic-Latino	Reference	-	-
Spanish-Hispanic-Latino	0,91	0,59 - 1,41	0,67
Tumor size (2004+)*			
<5cm	Reference	-	-
≥5cm	1,63	0,99 – 2,70	0,057
Primary site*			
Cranial	Reference	-	-
Spinal	1,17	0,82 - 1,68	0,38
Sacral	1,69	1,21 - 2,36	<0,01
Radiation*			
No	Reference	-	-
Yes	0,89	0,67 - 1,20	0,45
Surgery*			
No	Reference	-	-
Yes	0,45	0,32 - 0,62	<0,01
Treatment*			
Neither	Reference	-	-
Radiation only	1,12	0,64 - 1,98	0,69
Surgery only	0,49	0,32 - 0,75	<0,01
Both	0,41	0,26 - 0,65	<0,01

* unknown cases were excluded

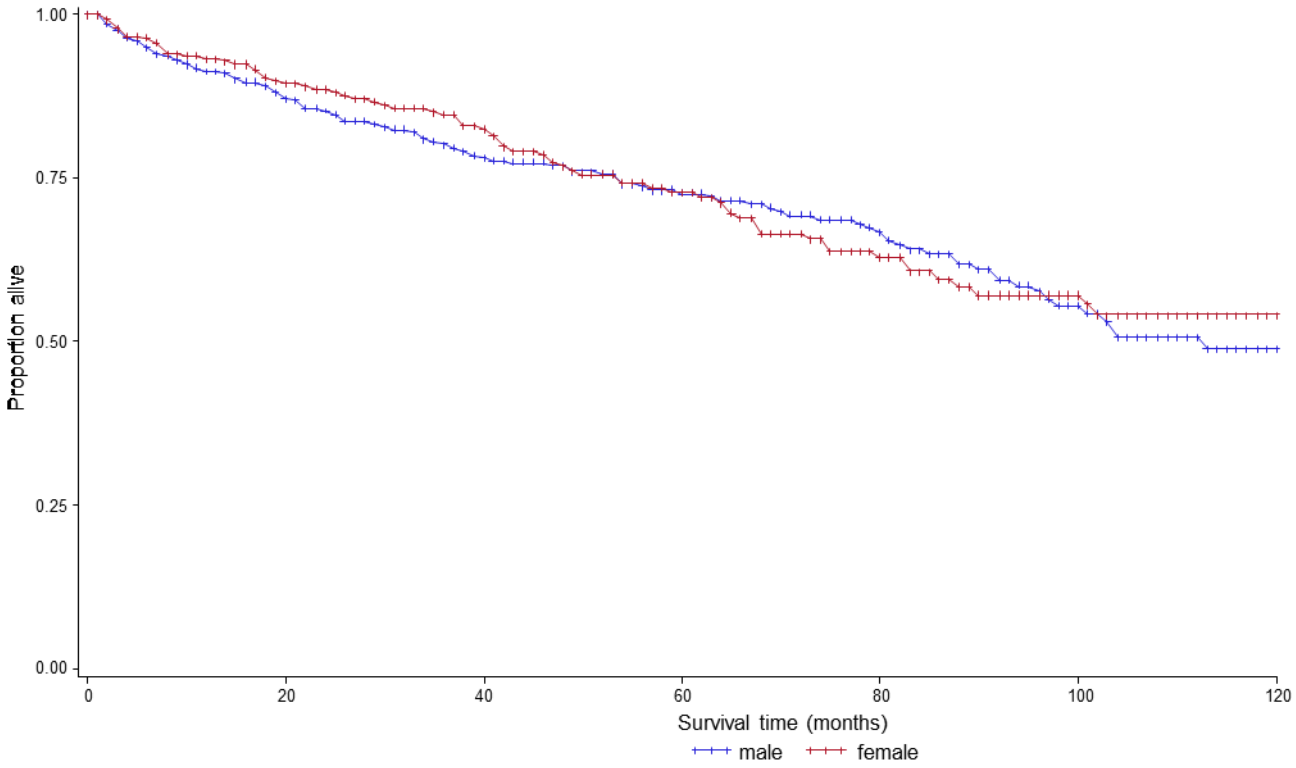

Fig. 1. Survival by sex

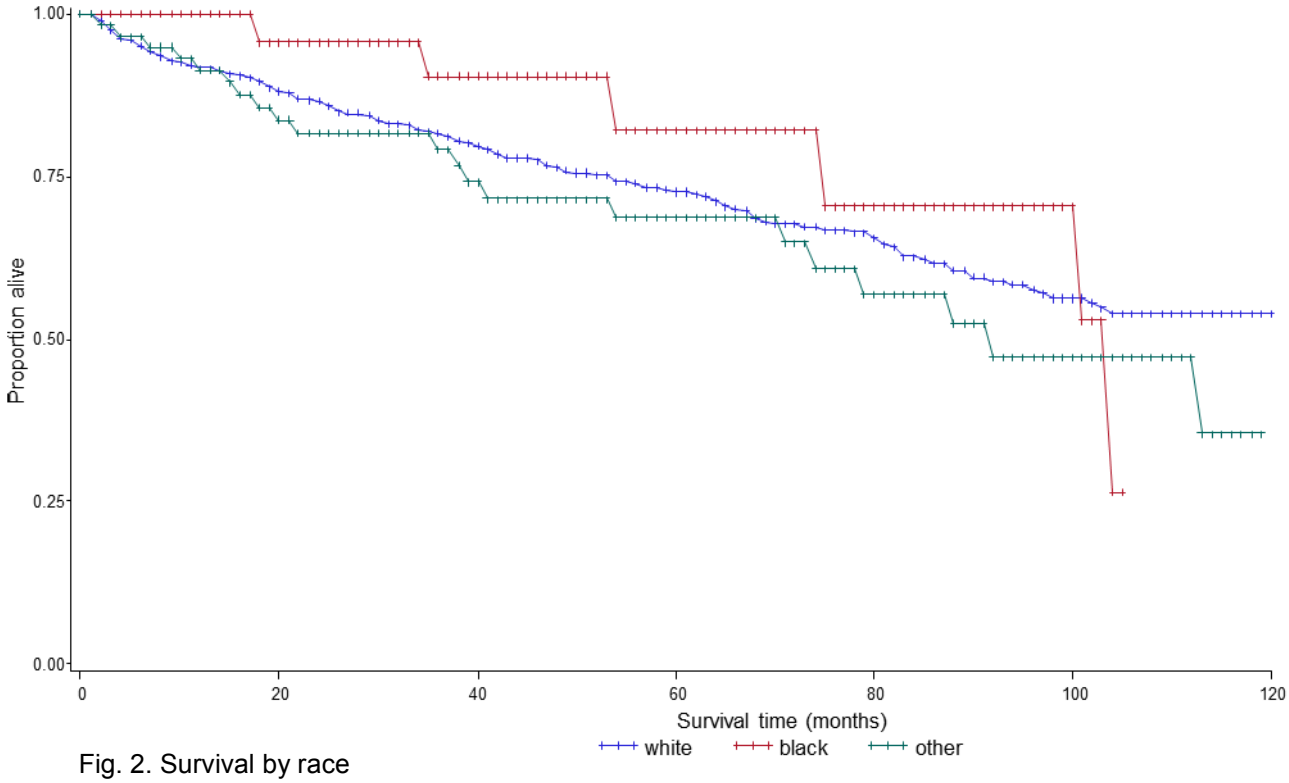

Fig. 2. Survival by race

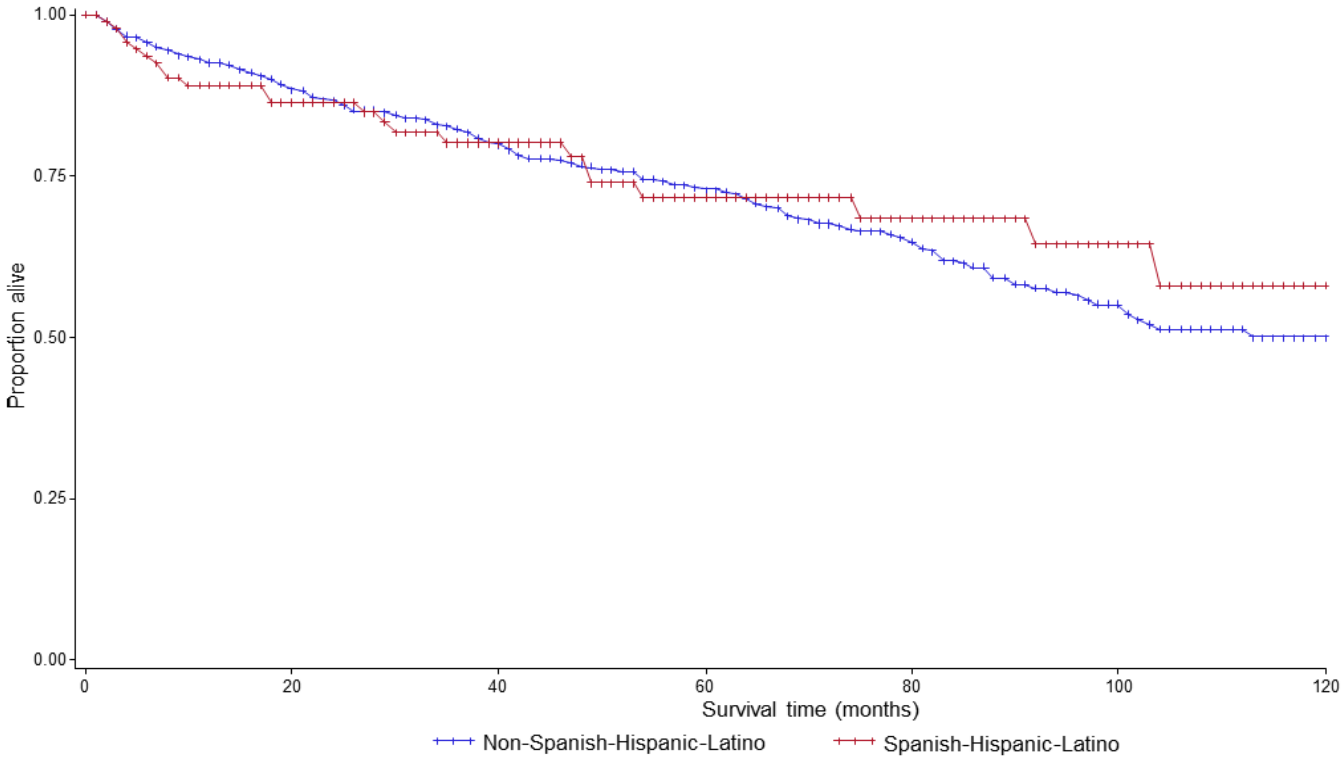

Fig. 3. Survival by Hispanic origin

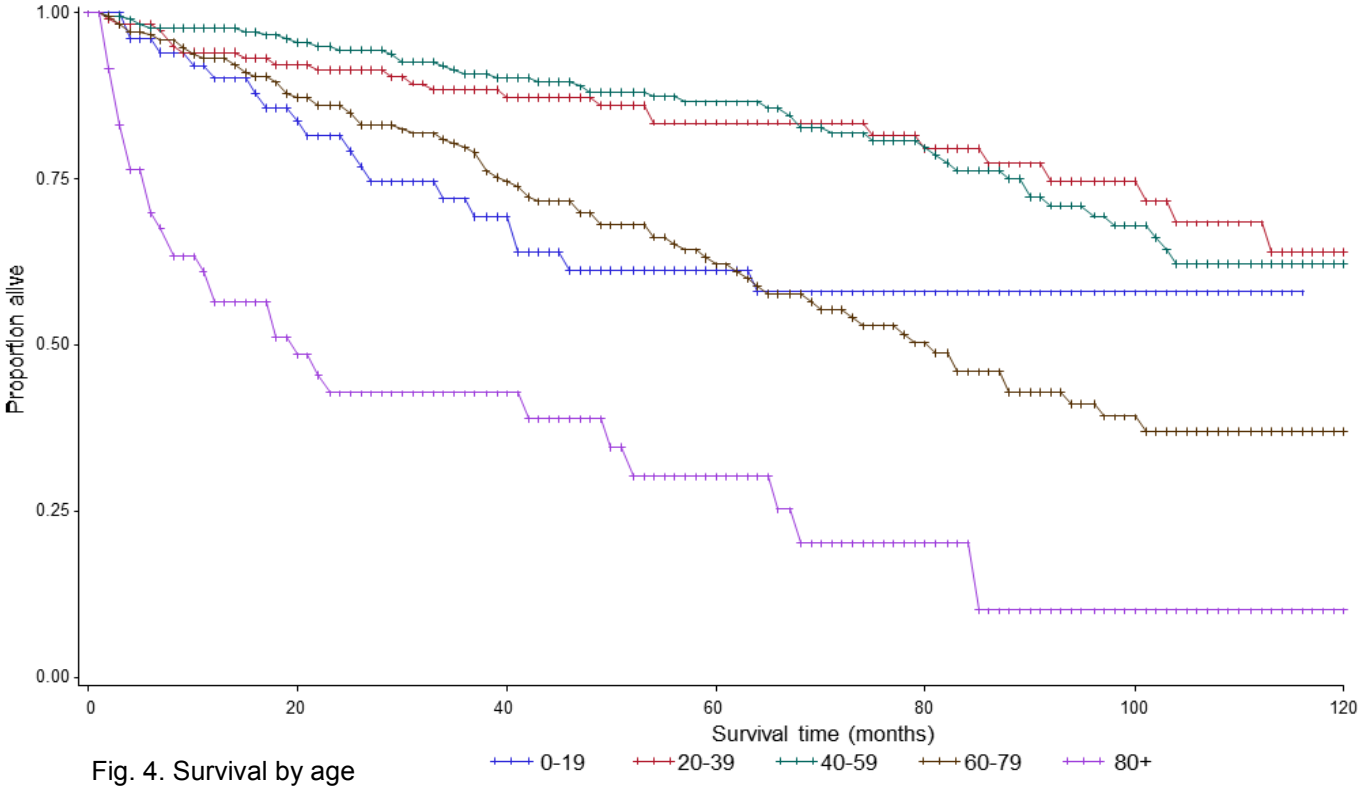

Fig. 4. Survival by age

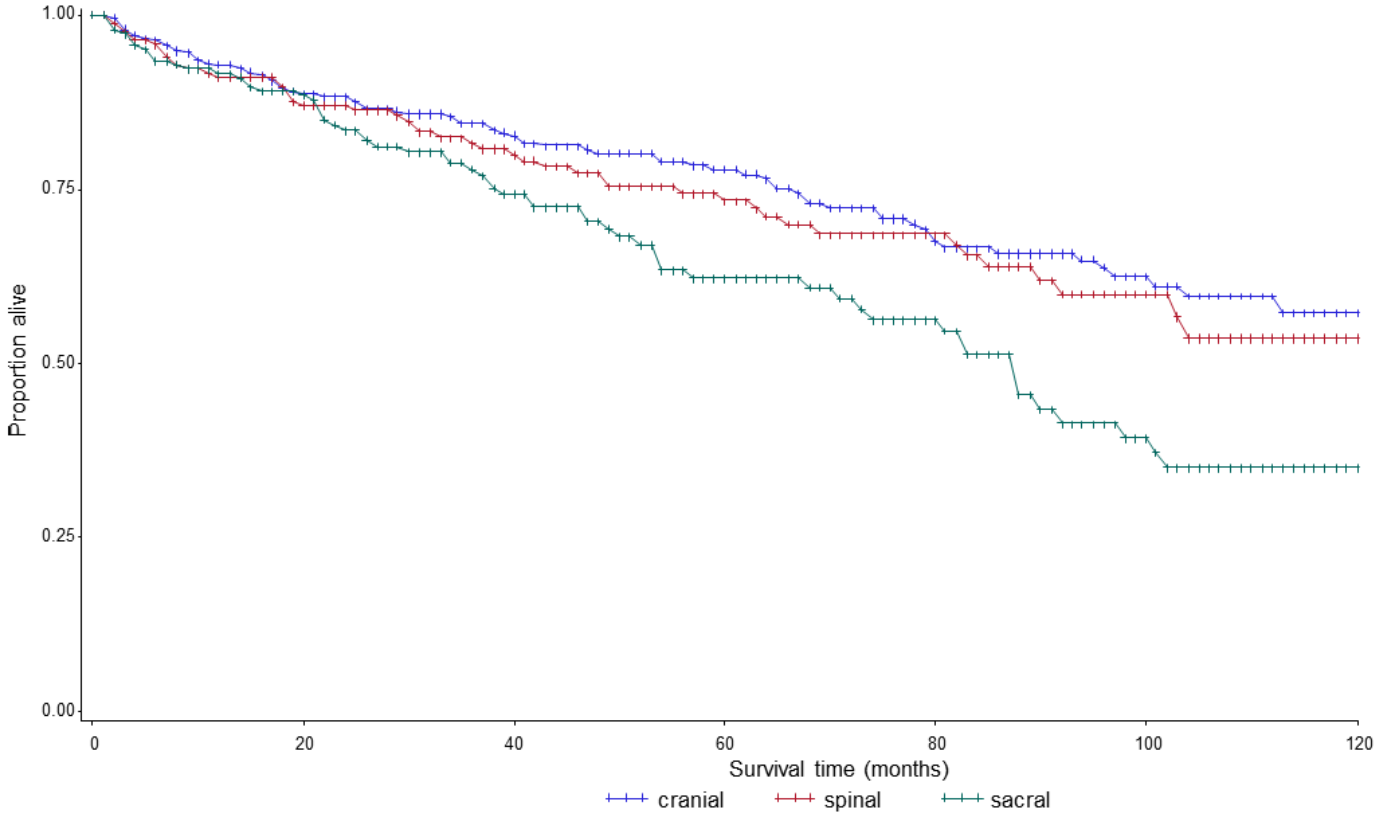

Fig. 5. Survival by site of presentation

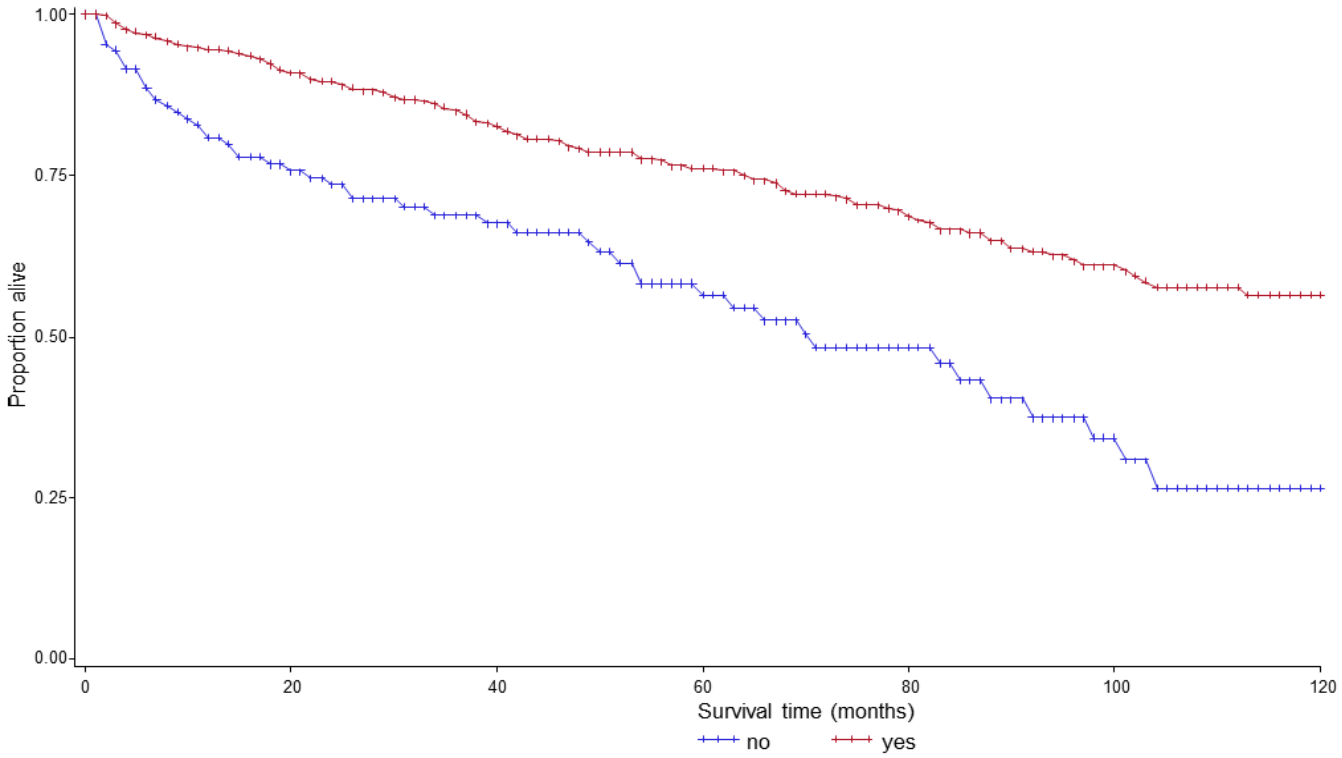

Fig. 6. Survival by surgery

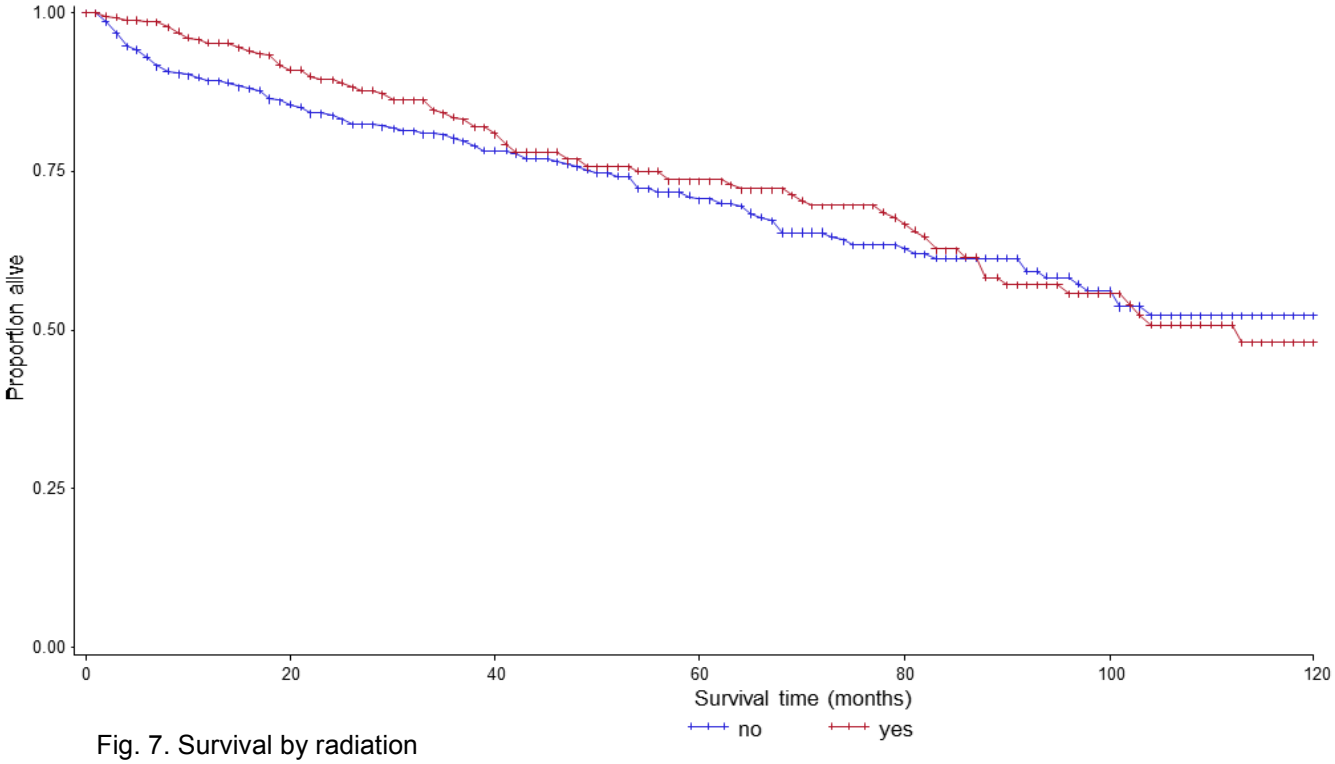

Fig. 7. Survival by radiation

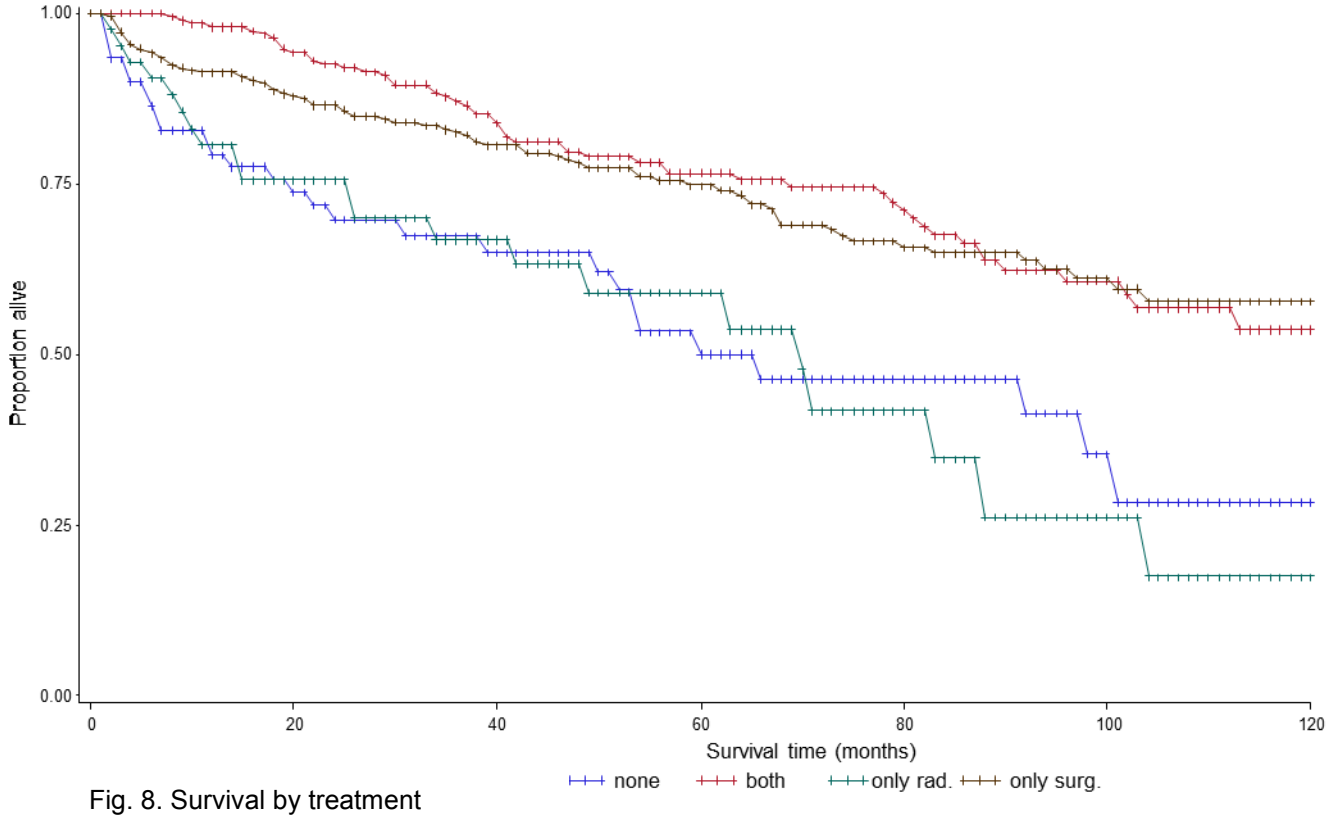

Fig. 8. Survival by treatment

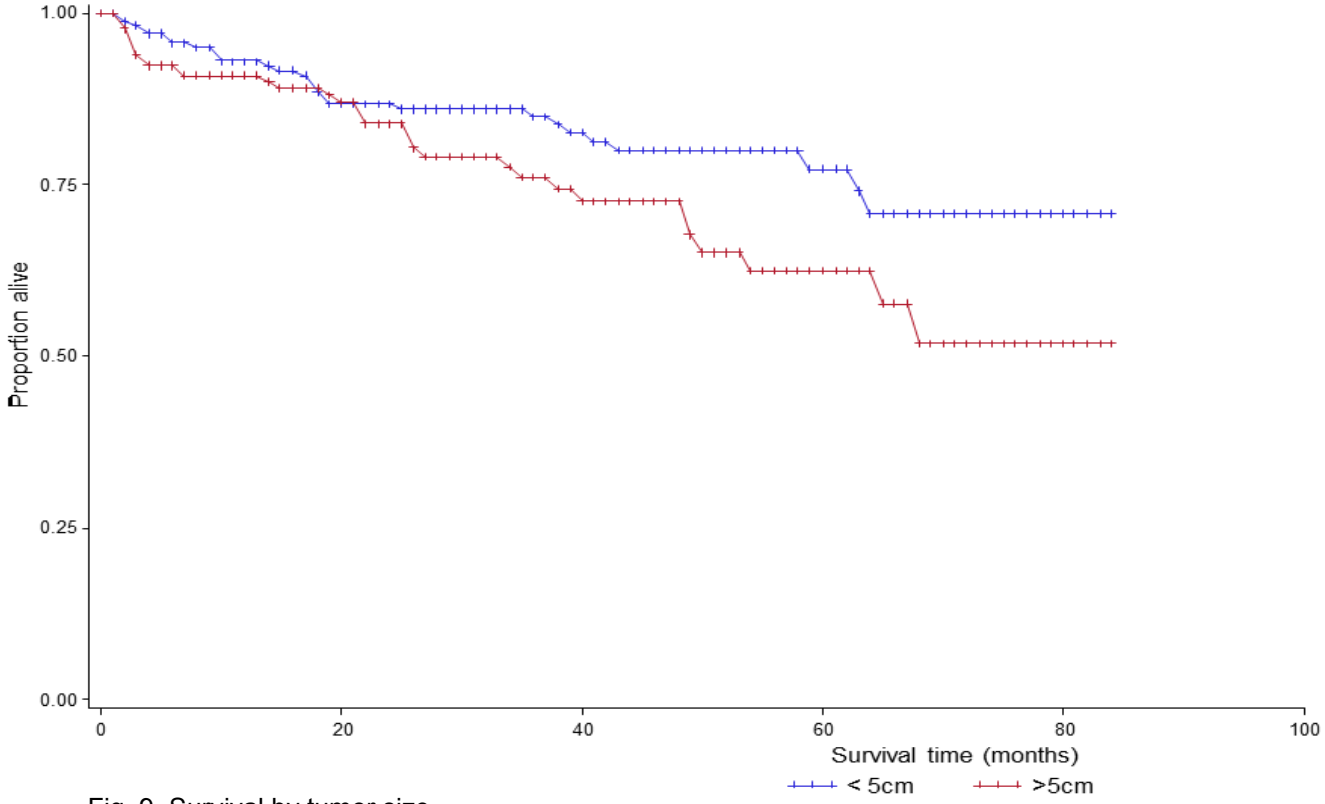

Fig. 9. Survival by tumor size

5 Discussion

The overall age-adjusted incidence rate of chordoma is still low at 0,9 per million population, but has slightly risen compared to a previous study by McMaster et al that reported 0,8 per million population in a time period from 1973-1995 (14).
Similar to earlier studies, our analysis revealed chordomas being more commonly diagnosed in females rather than males with a rate ratio of 0,6 and incidence rates increasing progressively with age (13,14). Incidence seemed to be especially low in African Americans with chordomas only being one-fourth as common in blacks compared to whites, confirming earlier observations (14,102). The geographical area of Louisiana showed the lowest incidence rate, which might be due to a high proportion of African Americans among the population. About one eighth of the patients was of Spanish-Hispanic origin and had around the same incidence rate as non-Hispanics.
In our study, cranial chordoma accounts for 42%, spinal for 26% and sacral for 31% of all chordomas, which is around the same as previously reported using SEER data (14,15). Lee et al in corporation with the California cancer registry showed a slightly higher occurrence in cranial locations (49%) and lower occurrence in sacral locations (25%) (12). Interestingly, we found that the histological subtype of chondroid chordoma is with 77% even more common in cranial locations than conventional chordoma. In contrast, all but one of the 7 cases of dedifferentiated chordoma presented sacrally, which might explain why studies almost exclusively describe dedifferentiated chordomas of the sacral and coccygeal regions (103-105). Previous reports of females having a higher likelihood of cranial presentation could not be confirmed in our analysis, where both genders showed equal variation of distribution, when it comes to the three sites of presentation (12,14). However, there was a significantly greater likelihood of cranial involvement in Spanish-Hispanic-Latinos compared to non-Hispanics, which goes along with an earlier observation (12). In regards to race, cranial presentation was most common in blacks, although there were too few cases to asses this association properly.
Our data revealed an association between site and age, with cranial chordoma patients being significantly younger than patients with sacral chordoma.

Furthermore, small tumors (<5cm) were most common in cranial locations, whereas large tumors (≥5cm) were mostly found in sacral locations. Patients with small tumors were also significantly younger compared to those with large tumors. This leads to the assumption that a big tumor volume is more likely to cause symptoms in an intracranial region relative to a sacral location, and would hence be diagnosed earlier.

The most common treatment option for chordoma remains surgery, which in many cases is followed by an additional application of radiotherapy. Surgical intervention was found to be more frequent in young patients, cranial locations and small tumor sizes. No treatment or radiation as a single modality was most common in older patients and sacral sites. These findings are similar to earlier observations and might be due to the fact that elderly patients are less likely fit for surgery because of comorbidities and sacral lesions may present with more extensive or metastatic disease, resulting in less aggressive palliative therapy (12,14).

In this study 5- and 10-year relative survival was found to be 78% and 57%, respectively. Previous SEER based series analysing data of the 70s 80s and 90s showed worse 5- and 10-year survival at around 65% and 35% (14,106). This trend towards improved survival in the latest decade was also described in a study by Chambers and colleagues, which analysed cranial chordoma, and may be the result of improved surgical techniques as well as better radiation targeting with safe delivery of higher doses to the designated destination (15).

A recent report by Smoll et al using SEER data from 1973- 2009 found 5- and 10-year relative survival to be 72% and 48%, respectively (13). Similar to our results, they found an association between age and survival with adults (ages 40-64 years) and elderly (aged 65+ years) showing steeper survival curves compared to younger age groups. Sex did not influence outcome of chordoma, which goes along with our findings. Although Smoll et al investigated a longer time period compared to our analysis, their assessment of prognostic factors is limited to age and sex. To provide information concerning other potentially important prognostic factors like race, Hispanic origin, site of presentation, size and surgical or radiation treatment, we used additional variables included in the SEER database in our study.

It has been suggested in literature that children and young adolescents may have worse survival rates than adults due to unusual morphology and more aggressive behaviour (107). This can be confirmed with our results showing a 2,2 times higher mortality rate in ages 19 years and below compared to the reference group (ages 40-59 years).

Regarding race, there was no significant difference in survival between whites, blacks and other races. Contrary to earlier reports we did not see an improved survival in Spanish-Hispanic-Latinos compared to non-Hispanics (12,108).

Our study supports past series, showing that tumors in cranial locations displayed the best prognosis with 5-year survival rates of 81% closely followed by spinal locations with 79% (12,15,108). Sacral chordomas showed the worst prognosis with a rate of 70%. Larger anatomical spaces in sacral sites compared to cranial sites might lead to symptoms occurring not until later stages of disease and could thus be the reason for a worse survival.

Both, institutional series as well as larger population-based surveys, show surgical resection to be related to significantly better survival (9,12,15,16,54,108-110), which could be confirmed in our analysis. In contrast radiation as a single prognostic factor was not associated with better survival. When treatment with surgery alone and surgery combined with radiation is compared, there was also no difference in survival. However, as Lee et al point out, radiation therapy has been usually reserved for patients with complex or inoperable tumors and in palliative care, which might create a selection bias undermining positive effects of radiation therapy (13).

When it comes to tumor size there are studies confirming it to be an independent risk factor (9,12,16,108), whereas others do not (111). In our study a trend was seen toward worse survival in patients with lesions over 5cm compared to patients with lesions below 5cm with 5-year relative survival rates of 69% and 81%, respectively. Furthermore, patients with large tumors had a 1,6 times greater risk of death compared to those with small tumors. Although this trend is slightly above the significance level with a p-value of 0,057 we strongly believe that there is a relationship between size and survival.

However, size as a prognostic factor may be influenced by age, since older patients show a worse survival and patients with large tumors tend to be older compared to those with small tumors.

Furthermore, size varies between different sites of presentation with studies reporting sacral lesions ranging around 8-10 cm (47,110) and cranial lesions ranging around 2-5 cm (34,112). A stratified size analysis according to the different sites is thus needed to determine the tumor diameter above which prognosis significantly decreases.

6 Limitations

Due to small numbers of cases in certain variable subsets used in this study, the statistical power of some analyses is reduced. Furthermore, limitations of the SEER database include the lack of information regarding local recurrence, metastasis, extend of surgery (resection margins), chemotherapy and patient comorbidities. Unfortunately the possibility of differentiation from overall and chordoma-specific survival is also not provided and cause of death is often not known (15).

7 Conclusion

Chordoma remains a very rare disease with an incidence rate of 0,9 per million population. 5- and 10-year relative survival was found to be 78% and 57%, respectively. Younger age, cranial presentation and surgery were significantly associated with a better prognosis in univariate analysis. Small tumor size also showed a trend towards better outcome. Survival, however, was not influenced by sex, race, Hispanic origin and radiation treatment.

With 18 registries included in the most recent dataset of the Surveillance Epidemiology and End Results program this study provides the latest series of chordoma cases with updated information concerning incidence and distribution patterns in the United States. Furthermore, after examining outcomes, relevant prognostic factors were identified for this rare disease.

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