Quality of life in patients post sacral resection using patient reported outcomes measurements.

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Quality of Life in Patients Post Sacral Resection using Patient Reported Outcomes Measurements

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A thesis submitted to the Royal College of Surgeons in Ireland for award of MCh

Supervisor(s): Mr Denis Collins

Dr Patrick Boland

September 2015

I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree MCh is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

Signed 

Student Number 05678587

Date – 04/09/2015

Table of Contents

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List of figures

List of tables

List of abbreviations

Table of Abbreviations

ANOVA	Analysis of variance
BNCT	Benign notochord cell tumors
ESFT	Ewing sarcoma family tumors
IRT	Item Response Theory
NIH	National Institutes of Health
PROMIS	Patient Reported Outcomes Measurement Information System
PSC	PROMIS Statistical Center
RANKL	Receptor activator of nuclear factor kappa-B ligand
SCC	Statistical Coordinating Center
SD	Standard deviation
WHO	World Health Organization
CPT	Current Procedural Terminology
DM –	Diabetes Mellitus
FDA	Food and Drug Association
GCT –	Giant Cell Tumor
IMRT	Intensity Modulated Radiation Therapy
IRB	Institutional Review Board

MC The Mayo Clinic

MGH Massachusetts General Hospital

QoL Quality of Life

RANK Receptor activator of nuclear factor kappa-B ligand

S.E.E.R. Surveillance, Epidemiology, and End Results

STIR - Short TI Inversion Recovery

Abstract

BACKGROUND CONTEXT: There is little consensus about what tools to use to assess quality of life in these patients who undergo enbloc removal of the sacrum for malignant disease. Symptoms can vary from wound complications to loss of bowel, bladder and sexual function. It is clear that no one questionnaire can cover the full spectrum of symptoms.

PURPOSE: To assess physical and mental function, pain intensity and pain interference in patients after resection of a primary sacral tumor.

STUDY DESIGN: This was a multi-institutional pilot cross-sectional study.

PATIENT SAMPLE: Consecutive patients who visited the out-patient clinic for follow-up post sacrectomy at MSKCC, MGH and MC between January 2012 and October 2013 were included. The study population comprised of 79 patients.

OUTCOME MEASURES: Patients were classified as having had a total, hemi, high or low sacrectomy based on the level of sacral resection.

METHODS: Patient data was collected using a tablet PC in the out-patient clinic and stored in an online database. Further data was collected from clinic notes and hospital records that included operative notes and radiology reports.

RESULTS: Total and hemi sacrectomies were associated with worse pain intensity compared to high and low sacrectomies ($p<.001$). No statistical significance was found between sacrectomy groups with respect to physical and mental function. 97.5% (N=77) of patients reported they would undergo their surgery again despite the significant morbidity associated with it. Internal consistency of the PROMIS Global health questionnaires was low, as indicated by the Cronbach alpha of 0.67 and 0.48 respectively. PROMS Pain Interference SF and PROMIS Pain Intensity had substantial floor effects; 19% (24 of 79) and 16% (20 of 79) respectively. For these questionnaires, this indicates poor coverage when the patient is in good health.

CONCLUSIONS: The pool of literature regarding sacrectomy QoL outcomes is virtually nonexistent. This study demonstrates the need for a universal QoL tool which measures overall QoL, physical function, mental function, pain, bowel, bladder and sexual function. To our knowledge this is the first study to attempt to measure the QoL in patients post sacrectomy.

Chapter 1 Introduction

1.1 Introduction

Primary tumors of the sacrum are rare, accounting for 1-7% of all primary spinal tumors (2). Chordoma and Chondrosarcoma account for the majority and are known to be resistant to radiotherapy and chemotherapy (3). Unfortunately these tumors usually have late presentations with pain being the most common symptom due to compression of the sacral plexus. The preferred treatment is en bloc resection of the affected area of the sacrum. This resection is made difficult by the anatomical location within the pelvis and it can be difficult to obtain negative margins, especially given the proximity of the rectum. These extensive operations can also leave large soft tissue defects, requiring flap reconstruction.

Given the importance of obtaining negative pathological margins for long term control this usually requires the sacrifice of sacral nerves given their location within the sacral canal. The sacral nerves control the patients' bowel, bladder, sexual function and gait. The loss of these capabilities can have a huge impact on quality of life, and as such, it is very important that the physician is able to give patient accurate and realistic expectations about what they can expect after surgery. If some or all of these nerves are sacrificed this can significantly impact a patient's QoL. However if the tumor is not removed then these nerves will inevitably become compressed and the same loss of function will occur with perhaps involvement of more sacral nerve roots. The objective in surgical resection of a sacral tumor is to preserve as much functionality as possible while still maintaining a grossly negative surgical margin.

Classification of the sacrectomy by level of resection has been shown to be useful method for predicting post operative function (3). It has been demonstrated that bilateral sparing of L5 is required to retain a functional gait and that bilateral sparing of S2 is required to walk normally. Bilateral sparing of S3 is required for normal bowel, bladder and sexual function, whereas bilateral sparing of S2 is required to retain some bowel, bladder and sexual function (4-6).

There is little consensus about what tools to use to assess quality of life in this patient population. Symptoms can vary from wound complications to loss of bowel, bladder and sexual function. It is clear that no one questionnaire can cover the full spectrum of symptoms.

The purpose of this thesis was;

- To further clarify and expand on the relationship between the level of sacrectomy and outcomes of this particular cohort of patients as they recover from this life changing surgery, with particular focus on physical function, mental function and pain.
- To analyze the coverage, precision and reliability of the aforementioned questionnaires and their suitability for use in a future longitudinal prospective study.
- To recommend the use of QoL instruments based on the results and current literature.

We hypothesized that QoL would be worse in the more invasive sacrectomy subgroups, i.e. Total sacrectomy worse than, high, worse than low, worse than hemi-sacrectomy

1.2 Current QoL Literature

Studies describing the QoL in patient's post sacrectomy are extremely sparse in the current published literature. The one published study measured qualitative assessment of patient experiences following sacrectomy(7). The study by Davidge et al used qualitative research methods. This is a method of inquiry which aims to gather an in depth understanding of human behavior and the reasons behind such behavior. It investigates the why and how of decision

making. The authors' interviewed 12 patients post sacrectomy and used interview techniques to examine their experiences and quality of life. They had a mean interview time of 34 minutes. They identified similar themes which recurred during the interview process with each patient.

The basis of their study was using a "Grounded theory" guided generation of interview guide and analysis. This is an iterative process of generating hypotheses while reviewing and interpreting raw data

The first step is data collection. Key findings from their data was coded and organized into similar concepts and grouped into themes. These themes were utilized to generate hypotheses about the data. There was minimal inter-reader variation in theme recognition

Theme 1 – Patients described tangible impact on both the individual's life but entire family network. Despite a gradual improvement over time they noted their lives never returned to normal

Theme 2: Patients found nursing staff invaluable during recovery and identified a sense of isolation given long hospital stay

Theme 3: Neurogenic pain, exacerbated by long periods of sitting. Intolerance to sitting had an important impact on patients' long term quality of life

Theme 4: Patients felt overwhelmed by the amount of information provided to them at the time of surgery. Few patients recognized or understood the impact of sacrectomy on postoperative morbidity and were focused on other aspects of the surgery such as the creation of a colostomy or urostomy. Patients expressed the need for additional information relating to sacrectomy and in particular long term follow-up. Interestingly patients did not feel that speaking to other patients who had underwent the same procedure beneficial as each patient considered their operation unique.

Theme 5: Patient's gratitude to be alive

Patients were unanimous in expressing their gratitude to be alive. Particularly to have time to spend with their families and children.

They noted that the small sample size limited the impact of their study and no quantitative analysis was performed.

1.2.1 Functional outcome studies

Functional outcome in sacrectomy patients has been evaluated in several studies over the past 50 years. Gunterberg investigated detrusor function in five patients with bilateral division of the sacral nerves below S2 level and found no active detrusor contractions were registered, while in four patients with unilateral division of the sacral nerves 1 to 5 or 2 to 5 a normal micturation reflex was registered (6).

He also investigated the anorectal function in 3 patients with bilateral and 4 patients with unilateral welldefined loss of sacral nerves after radical tumor excision.

The patients with bilateral loss of sacral nerves had serious impairment of function. Constipation was their only safeguard against incontinence. The preservation of the first and second sacral nerves bilaterally was not sufficient for discrimination between different qualities of rectal contents passing the anal canal. The sensation of rectal distension was also impaired.

In patients with total unilateral loss of the sacral nerves no significant impairment of anorectal function was noted (5).

Another study looked at the sexual function of nine patients with severance of sacral nerves bilaterally (five patients) or unilaterally (four patients). In four of the five male patients an attempt was made to collect electromyography recordings from the external urethral and anal sphincters during ejaculation. Bilateral loss of S3 to S5 nerves in two women seemed not to affect their sexual function. Unilateral loss of all sacral nerves did not impair previously normal sexual function, although the penises and vulvae of these patients were anesthetic on one side (8).

1.3 Functional Anatomy

Knowledge of the bony anatomy and surrounding structures is essential for the surgeon prior to beginning any sacral resection. The functional anatomy is also essential to understanding how a sacrectomy affects a patient's quality of life. The sacral plexus controls bowel, bladder and sexual function as well as providing motor branches to form the sciatic nerve. Interruption of the sacro-iliac joint can lead to spinal instability, increased pain and decreased lower extremity function.

1.3.1 Embryology

The axial skeleton includes the vertebrae, ribs, sternum and skull. The notochord is the first structure of the future axial skeleton to form in utero. It usually appears at the midline of the embryonic disc at 15 days of development as a cord of cells which bud from a mass of ectoderm known as Hensen's node. The notochordal cells become temporarily intercalated in the endoderm, which forms the roof of the yolk sac. After separating from the endoderm, the notochord becomes a slender rod of cells running the length of the embryo between the neural tube and the developing gut (Figure 1). Chordomas are thought to arise from remnants of the embryonic notochord (9-11). Notochord cells normally persist after birth lodged inside the spine and skull, and rarely these cells can undergo a malignant transformation that leads to the formation of a Chordoma (11).

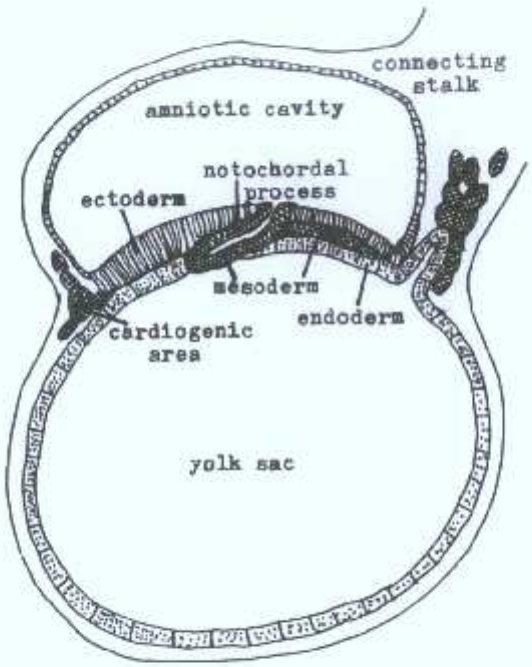


Figure 1 – Human embryo at 16 days

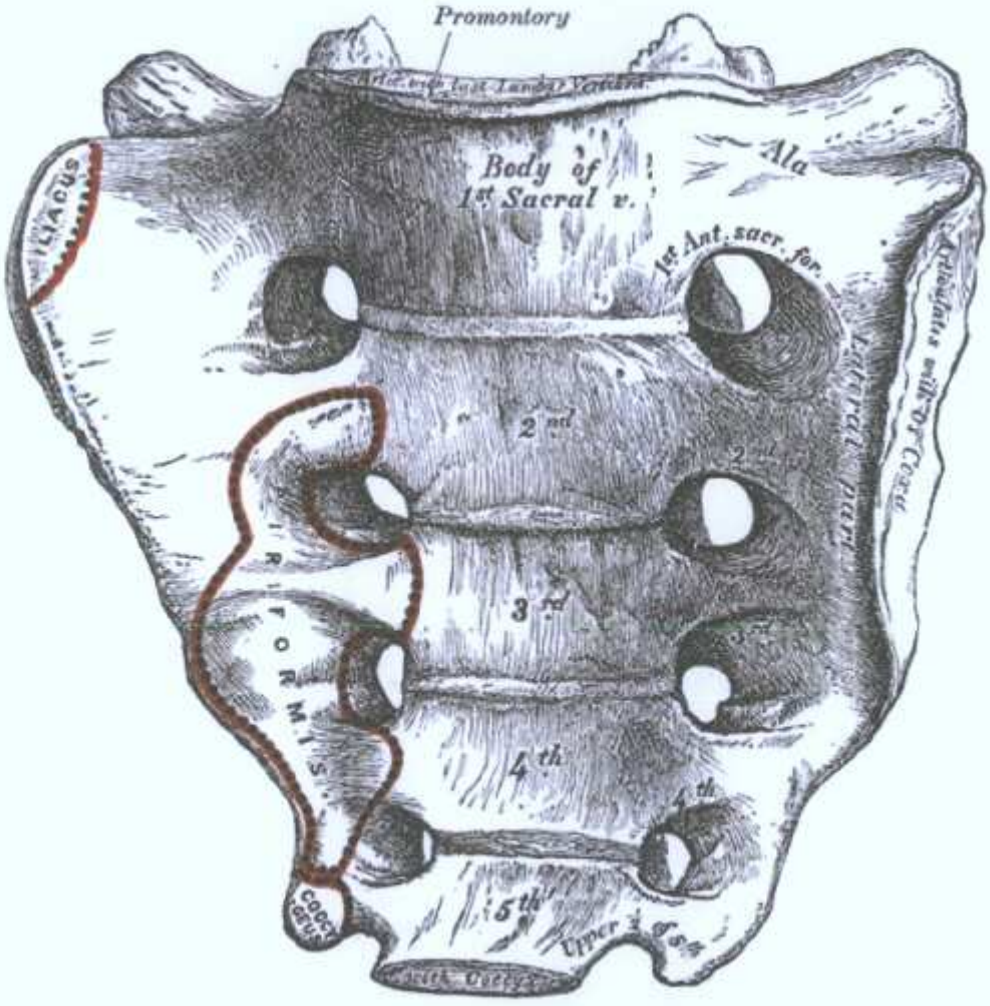
The vertebral column is formed from the 44 mesodermal somatomeres through primary neurulation. The 30th somite corresponds with the S1-S2 junction. S2 to the coccyx are formed from the 31st to 44th somites and are formed through secondary neurulation (12). Ossification of the sacral ala begins late in the first year of life and continues for approximately 30 years. There are five ossification centers in each sacral vertebra (13).

1.3.2 Sacral Bone

The sacrum (figure 2) or "hieron osteon" meaning the high protuberant bone as designated by Hippocrates, is a triangular shaped bone at the base of the spine formed by the fusion of the five sacral vertebrae (14). It slopes backwards and downwards and is concave anteriorly (figure 3). The sacral canal is a continuation of the vertebral canal enclosed by fused pedicles and laminae. The canal contains the lower part of the cauda equina which is comprised of the roots of the sacral and coccygeal nerves. It terminates as the sacral hiatus. The anterior rami of the upper four sacral nerves pass into the pelvis via the four anterior sacral foramina and contribute to the sacral plexus.

Figure 2: Sacral Bone Pelvic Surface

Henry Gray (1825–1861). Anatomy of the Human Body. 1918.

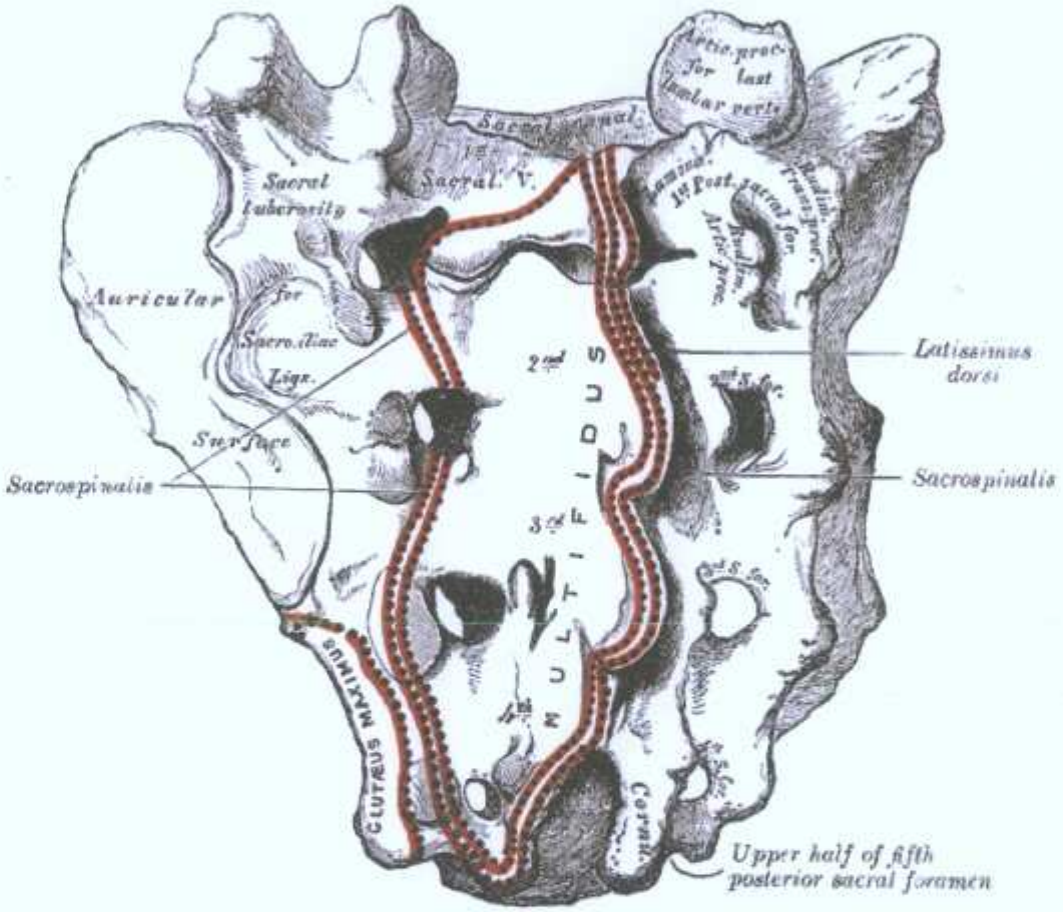


The upper surface of the sacrum carries the lumbosacral disc. The two superior articular processes of the sacrum face backwards and articulate with the inferior processes of the fifth lumbar vertebra. The dorsal surface of the sacrum gives attachment to the lowest fibers of erector spinae and to the posterior ligaments of the sacro-iliac joint and the sacrotuberous ligament. The anterior and posterior longitudinal ligaments of the vertebral column terminate inferiorly by attaching to the sacrum. S1, S2 and half of S3 are covered by peritoneum.

In the event of a sacral resection being performed, the ability to retain the S1 body or a portion of the S1 body improves ability of the pelvic girdle to resist vertical load without breaking. Retaining the S1 body weakens the posterior arch of the pelvis by 33% whereas leaving only half of the S1 body weakens the pelvis by 50%. However this residual strength is sufficient for normal weight bearing load in the standing position (15).

Figure 3 – Sacral Bone Dorsal Surface

Henry Gray (1825–1861). Anatomy of the Human Body. 1918.



1.3.3 Joints and Ligaments

The pelvic circle is a stable structure designed to transmit weight from the lower limb and the trunk. It is reinforced by the lumbosacral joint, the sacro-iliac joints, the pubic symphysis and the sacro-coccygeal joint. These joints are supported by strong ligaments.

The sacro-iliac joint is a diarthrodial synovial joint and there is minimal movement at the SI joints due to the fact the articulating surfaces of their synovial cavities are irregular and the posterior interosseus ligament is behind each cavity. Only the anterior third of the interface between the sacrum and ilium is a true synovial joint. The rest of the joint is supported by the anterior and posterior sacro-iliac ligaments and the iliolumbar, sacrospinous and sacrotuberous ligaments (figure 4).

The iliolumbar ligament attaches medially to the fifth lumbar vertebra and laterally to the iliac crest and front of the sacro-iliac joint. The sacrospinous ligament passes from the lateral margins of the sacrum and coccyx to the ischial spine. The larger sacrotuberous ligament passes from the side and dorsum of the sacrum and the posterior surface of the ilium to the ischial tuberosity. These two ligaments convert the greater and lesser sciatic notches into the greater and lesser sciatic foramina.

The pubic symphysis is a secondary cartilaginous joint formed by the union of the pubic bones in the median plane; it contains a fibrocartilaginous interpubic disc and is reinforced by the superior pubic ligament and inferior arcuate ligament.

A study by Vrahas et al on the ligamentous contributions to pelvic stability in thirteen cadaveric specimens found that the posterior sacro-iliac ligament and the pubic symphyseal ligaments contributed most to pelvic stability, They also noted that the sacrotuberous and sacrospinous ligaments contributed little to overall pelvic stability(16). Loss of these ligamentous attachments can lead to decreased physical function and increased pain following sacrectomy, substantially affecting a patient's quality of life.

Figure 4 – Sacral Ligaments

Henry Gray (1825–1861). Anatomy of the Human Body. 1918.

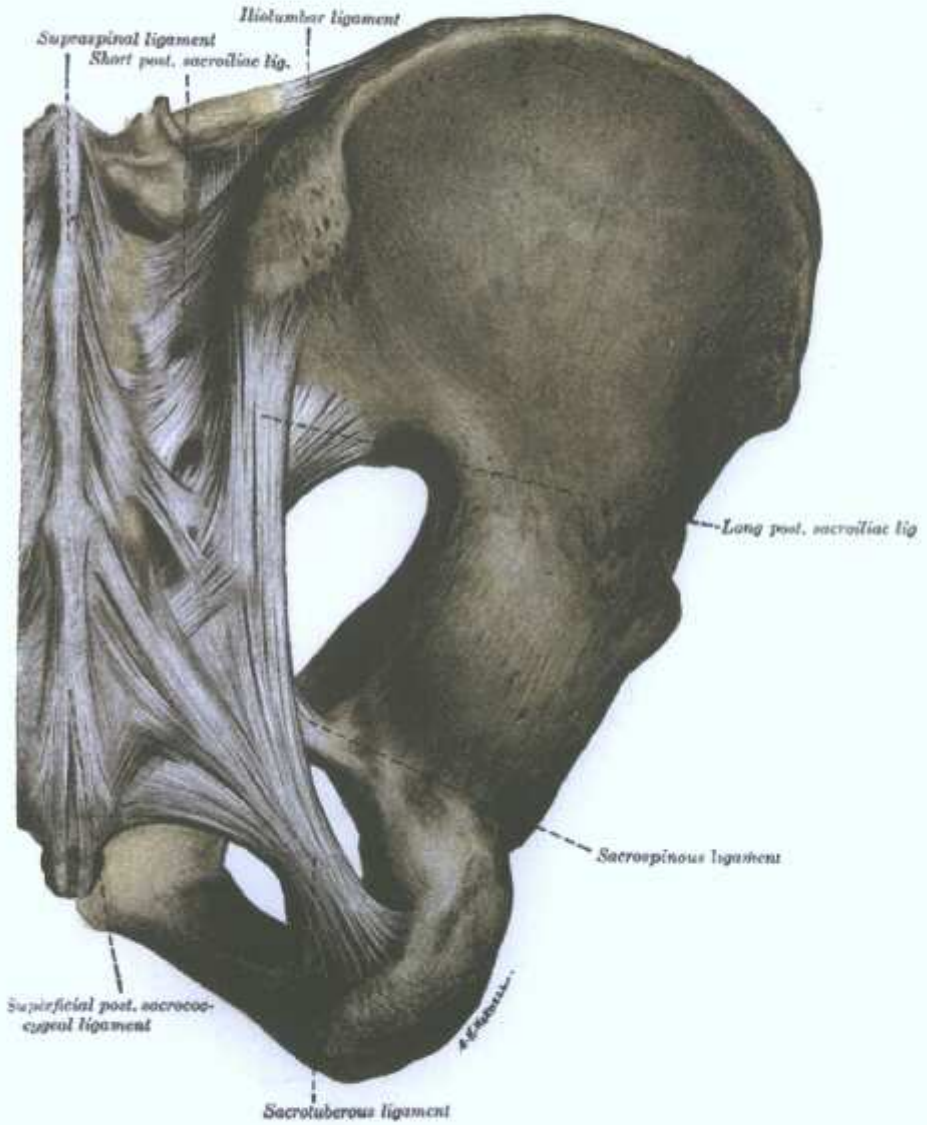
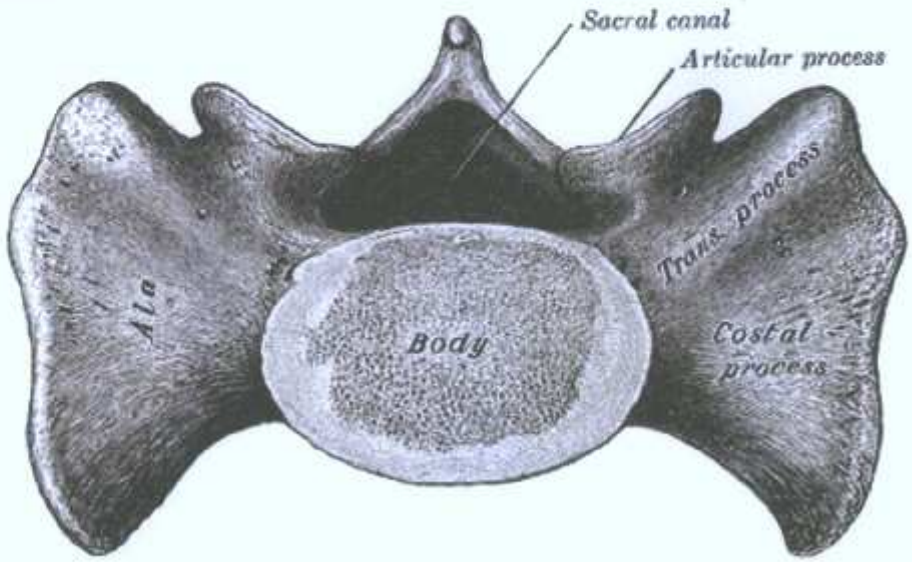


Figure 5 - Axial View of Sacrum



1.3.4 Vascular anatomy

Principal blood supply to pelvis comes from internal iliac artery. It arises from the common iliac artery,

It supplies the walls and viscera of the pelvis, the buttock, the generative organs, and the medial side of the thigh. It is a short, thick vessel, smaller than the external iliac, and about 4 cm. in length. It arises at the bifurcation of the common iliac, opposite the lumbosacral articulation, and, passing downward to the upper margin of the greater sciatic foramen, divides into two large trunks, an anterior and a posterior. It is in close association with the sacro-iliac joint.

Anterior Division of Internal Iliac Artery

Although variations are common, the internal iliac artery usually ends at the superior edge of the greater sciatic foramen by dividing into anterior and posterior divisions. The branches of the anterior division of the internal iliac artery are mainly visceral, but they also include parietal branches that pass to the thigh and buttocks. The arrangement of the visceral branches is variable.

Inferior Gluteal Artery

The inferior gluteal artery is the larger terminal branch of the anterior division of the internal iliac artery, but may arise from the posterior division. It passes posteriorly between the sacral nerves (usually S2 and S3), and leaves the pelvis through the inferior part of the greater sciatic foramen, inferior to the piriformis muscle. It supplies the muscles and skin of the buttock, and the posterior surface of the thigh.

Posterior Division of Internal Iliac Artery

When the internal iliac artery divides into anterior and posterior divisions, the posterior division typically gives rise to the following three parietal arteries:

Iliolumbar artery

This artery runs supero laterally to the iliac fossa. Within the fossa, the artery divides into an iliac *branch*, which supplies the iliacus muscle and ilium, and a lumbar branch, which supplies the psoas major and quadratus lumborum muscles.

Lateral sacral arteries

Superior and inferior lateral sacral arteries may arise as independent branches or via a common trunk. The lateral sacral arteries pass medially and descend anterior to the sacral anterior rami, giving off *spinal branches*, which pass through the anterior sacral foramina, and supply the spinal meninges enclosing the roots of the sacral nerves. Some branches of these arteries pass from the sacral canal through the posterior sacral foramina and supply the erector spinae muscles of the back and the skin overlying the sacrum (17).

Superior gluteal artery

The largest branch of the posterior division, the superior gluteal artery supplies the gluteal muscles in the buttocks. Passes through sciatic foramen above piriformis muscle. Inferior gluteal artery may arise from the anterior or posterior divisions of the internal iliac artery and they pass with the sciatic nerve through the sacral foramen below the piriformis muscle. Supplies gluteus medius and minimus and tensor fascia lata.

Median Sacral artery

This artery originates from the posterior surface of the aorta just superior to the aortic bifurcation at the level of L4. It descends in the midline, crosses the pelvic inlet and then courses along the anterior surface of the sacrum and coccyx. It gives rise to the last pair of lumbar arteries and to branches that anastomose with the ilio-lumbar and lateral sacral arteries (18).

Venous anatomy

Venous anatomy displays a great deal of variability. In contrast to arterial anatomy the middle sacral vein drains into the left common iliac vein rather than the inferior vena cava and the iliolumbar veins drain to the common iliac veins (19).

Pelvic venous plexuses are formed by the interjoining veins surrounding the pelvic viscera. These intercommunicating networks of veins are clinically important. The various plexuses within the lesser pelvis unite and are drained mainly by tributaries of the internal iliac veins, but some of them drain through the superior rectal vein into the inferior mesenteric vein of the hepatic portal system, or through lateral sacral veins into the internal vertebral venous plexus (20).

The internal iliac veins form superior to the greater sciatic foramen and lie postero-inferior to the internal iliac arteries. Tributaries of the internal iliac veins are more variable than the branches of the internal iliac artery with which they share names, but roughly accompany them, draining the same territories that the arteries supply. However, there are no veins accompanying the umbilical arteries between the pelvis and the umbilicus, and the iliolumbar veins from the iliac fossa of the greater pelvis usually drain into the common iliac veins instead. The internal iliac veins merge with the external iliac veins to form the common iliac veins, which unite at the level of vertebra L4 or L5 to form the inferior vena cava (17).

Lateral sacral veins

The lateral sacral veins anastomose with the internal vertebral venous plexus providing an alternate collateral pathway to reach either the inferior or superior vena cava. It may also provide a pathway for metastasis of prostatic or ovarian cancer cells to vertebral or cranial sites.

1.3.5 Sacral Nerves

Autonomic nerves

The sacral sympathetic trunks continue are a continuation of the lumbar sympathetic trunks. The trunks are located on the pelvic surface of the sacrum, medial to the sacral foramina. They often unite to form the ganglion impar anterior to the coccyx. The sympathetic trunks then descend posterior to the rectum in connective tissue. They send branches to the median sacral artery and inferior hypogastric plexus. These sympathetic trunks primary function is to provide sympathetic innervation to the lower limb.

Parasympathetic nerves

Parasympathetic nerves control, defecation, sexual function and micturition. These nerve fibers arise from the splanchnic nerves which exit the spinal cord in the second, third and fourth sacral nerve roots (S2, S3 & S4). This plexus also provides innervation to the sigmoid colon through the hypogastric plexus which is distributed with branches of the inferior mesenteric artery. They hypogastric plexus also give rise to the middle rectal plexus, the vesical plexus, and the uterovaginal plexus.

Sympathetic nerves

Sympathetic fibers supply smooth muscle of the reproductive organs. The sympathetic fibers which make up the pelvic plexus arise for the upper lumbar and lower thoracic portion of the spinal cord. They descend in the hypogastric plexus to arrive in the pelvis. The trunks pass behind the common iliac vessels and pass in front of both the sacrum and piriformis. They then meet in the midline on the anterior coccyx.

Sacral plexus

The sacral plexus (Fig 6) is located on the posterior wall of the pelvis; it is closely related to the anterior surface of the piriformis muscle and must be protected prior to. The descending part of the L4 nerve unites with the anterior rami of the L5 nerve to form the lumbosacral trunk. This trunk then passes inferiorly, anterior to the ala of the sacrum to unite with the anterior rami of the upper four sacral nerves to form the sacral plexus. The branches of the sacral plexus are supply the lower limb, pelvic walls, floor and perineum. The branches which leave the pelvis travel with the piriformis muscle through the greater sciatic foramen to enter the buttock. The nerve to obturator internus and the pudendal nerve then pass forward through the lesser sciatic foramen to gain access to the perineum.

Figure 6: Diagram of sacral plexus

Henry Gray (1825–1861). Anatomy of the Human Body. 1918.

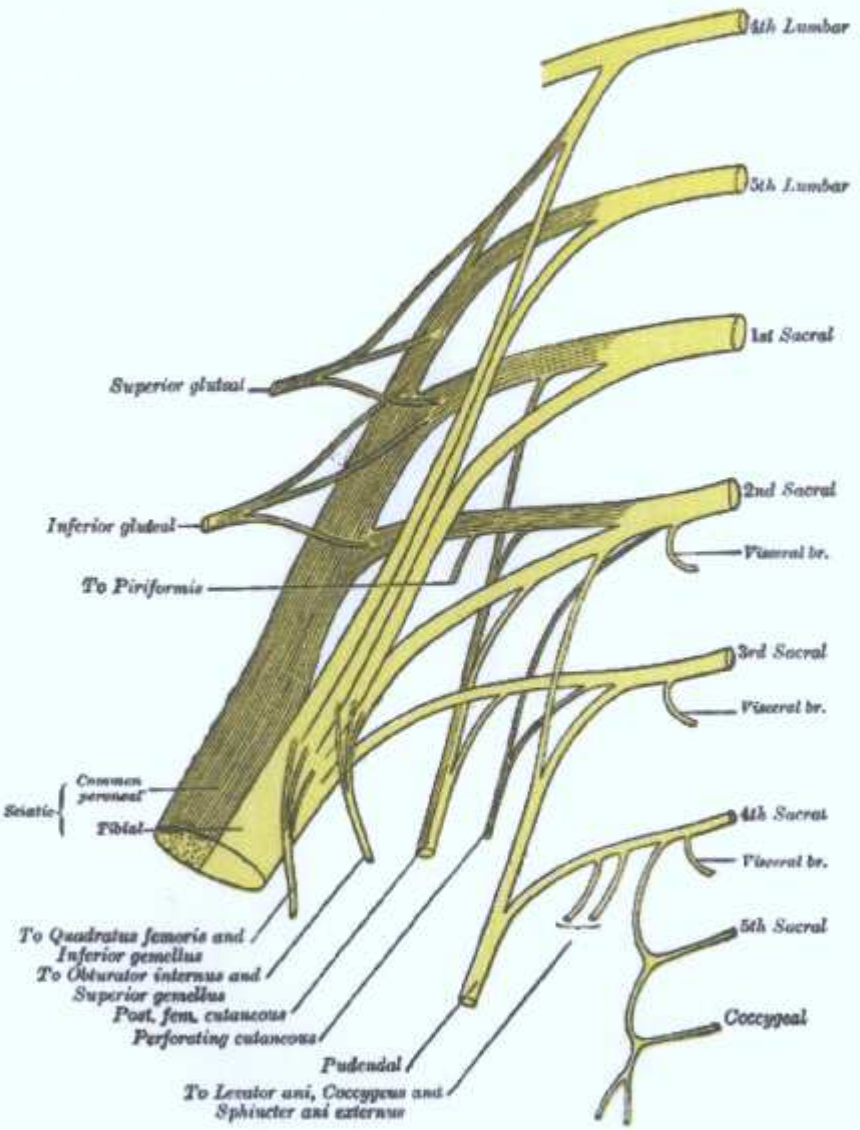
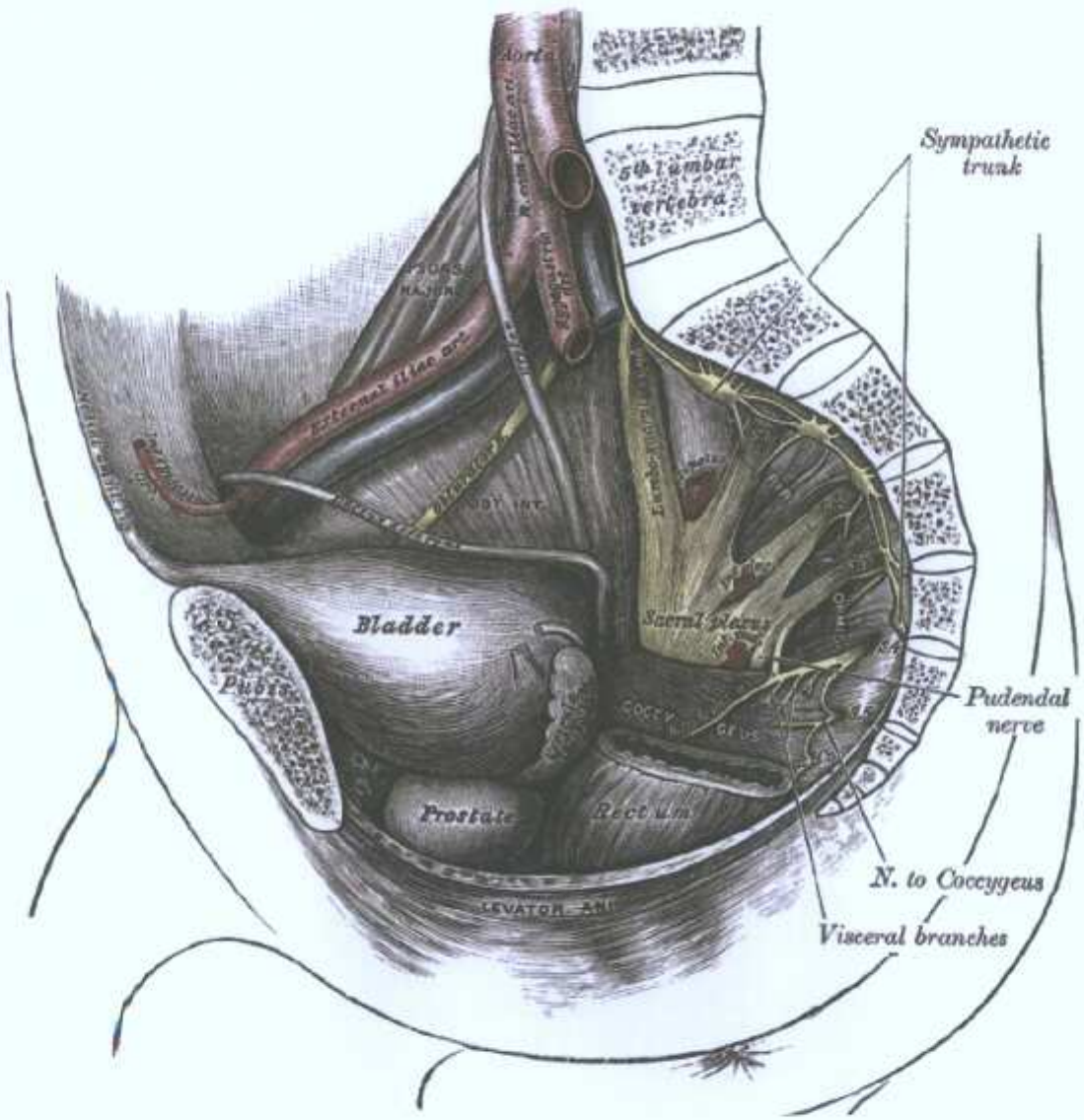


Figure 7 – Sagittal view of the sacral plexus

Henry Gray (1825–1861). Anatomy of the Human Body. 1918.



Pudendal nerve

The pudendal nerve (figure 7) is a sensory and somatic nerve which originates from the ventral rami of the second, third, and fourth (and occasionally the fifth) sacral nerves roots. After branching from the sacral plexus, the PN leaves the pelvis through the less sciatic foramen and travels three main regions: the gluteal region, the pudendal canal, and the perineum. It accompanies the internal pudendal vessels upward and forward along the lateral wall of the ischiorectal fossa, being contained in a sheath of the obturator fascia termed the pudendal canal. The pudendal nerve gives off three distal branches, the inferior rectal nerve, the perineal nerve and the dorsal nerve of the penis in males, corresponding to the dorsal nerve of the clitoris in females.

The PN innervates the external genitalia of both sexes, as well as sphincters for the bladder and the rectum. As the bladder fills, the pudendal nerve becomes excited. Stimulation of the pudendal nerve results in contraction of the external urethral sphincter. Contraction of the external sphincter, coupled with that of the internal sphincter, maintains urethral pressure (resistance) higher than normal bladder pressure. The storage phase of the urinary bladder can be switched to the voiding phase either involuntarily (reflexively) or voluntarily. The pudendal nerve then causes relaxation of the levator ani so that the pelvic floor muscle relaxes.

The pudendal nerve also signals the external sphincter to open. The sympathetic nerves send a message to the internal sphincter to relax and open, resulting in a lower urethral resistance. The PN is also known to have a potential modulative effect on bladder function. Somatic afferent fibers of the pudendal nerve are supposed to project on sympathetic thoracolumbar neurons to the bladder neck and modulate their function. This neuromodulative effect works exclusively at the spinal level and appears to be at least partly responsible for bladder neck competence and at least continence(21). If the pudendal nerve is sacrificed during surgery, bowel and urinary continence will be compromised even if the S2, S3, and S4 nerve roots are saved.

Sciatic nerve

The sciatic nerve (figure 7) is the thickest nerve in the body and innervates the posterior compartment of the thigh and most compartments of the lower leg and foot. It is formed in the pelvis from the ventral rami of the L4–S3 spinal nerve roots, and enters the lower limb via the greater sciatic foramen below the piriformis together with the posterior cutaneous, pudendal, inferior gluteal nerves, inferior gluteal artery with veins, internal pudendal artery and veins. It descends between the greater trochanter and ischial tuberosity (22).

Piriformis muscle

The fascia of the piriformis is very thin and is attached to the front of the sacrum and the sides of the greater sciatic foramen; it is prolonged on the muscle into the gluteal region. At its sacral attachment around the margins of the anterior sacral foramina it comes into intimate association with and ensheathes the nerves emerging from these foramina. Hence the sacral nerves are frequently described as lying behind the fascia. The internal iliac vessels and their branches, on the other hand, lie in the sub peritoneal tissue in front of the fascia, and the branches to the gluteal region emerge in special sheaths of this tissue, above and below the piriformis muscle (13, 22). The piriformis represents are vital anatomical landmark for the surgeon during a sacrectomy. It aids in identification of the sciatic nerve, pudendal nerve and internal iliac vessels.

Table 1 Nerve of the Sacral and Coccygeal Plexus

Adapted from Essential Clinical Anatomy 2nd Edition(1)

Nerve	Origin	Distribution	Function
Sciatic	**L4, L5, S1, S2, S3**	Hip joint, knee flexors all muscles in leg & foot	Motor and sensory supply to lower limb
Superior gluteal	**L4, L5, S1**	Gluteus medius & minimus	Hip abductors
Inferior gluteal	**L5, S1, S2**	Gluteus maximus	Hip extension
Nerve to piriformis	**S1, S2**	Piriformis	Lateral rotation of hip
Nerve to quadratus femoris	**L4, L5, S1**	Quadratus femoris & inferior gemellus	Lateral rotation & adduction of thigh
Nerve to obturator internus	**L5, S1, S2**	Obturator internus & superior gemellus	Lateral rotation & abduction of thigh
Pudendal	**S2, S3, S4**	Perineal muscles, urethral sphincter	Motor supply to anal sphincter, clitoris, bulbospongiosus&ischiocavernosus muscles, sensory to perineum & anus
Nerves to levator ani and	**S3, S4**	Levator ani & coccygeus	Supports viscera of the pelvis

coccygeus			
Posterior femoral cutaneous	**S2, S3**	Cutaneous branch to buttock	Provides innervation to the skin of the posterior surface of the thigh&leg, as well as to the skin of the perineum
Pelvic splanchnic	**S2, S3, S4**	Pelvic viscera through inferior hypogastric and pelvic plexus	Sensory innervation of the pelvic&genital organs.Motor control of emptying of the urinary bladder&the rectum as well as sexual function.

1.4 Tumors of the Sacrum

The purpose of this chapter is to explore the important primary tumors of the sacrum which are treated with a sacrectomy. I will briefly discuss the pathological and radiologic findings of the most common sacral tumors.

1.4.1 Chordoma

Chordoma is a slow growing locally destructive malignant bone tumor believed to arise from vestigial or ectopic notochordal tissue.

1.4.1.1Epidemiology

Analysis of the S.E.E.R. data indicates that Chordoma accounts for 8.3% of all primary bone tumors making it the 4th most common (23). It is the most common primary malignant sacral neoplasm (24). While it occurs almost exclusively in the axial skeleton, rare cases have been reported in the appendicular skeleton and soft tissues. Anatomically the sacro-coccygeal, spheno-occipital and mobile spine are involved in that order of frequency. It is already known that this tumor expresses transcription factor T (Brachyury) which is required for notochordal development(9). Duplication of the Brachyury locus has been shown to increase susceptibility to develop familial Chordomas and amplification is noted in 5% of sporadic disease (25, 26)

Chordoma is rare in children and adolescents. The overall incidence increases with age and the median age at diagnosis is 58 years (27). Spheno-occipital tumors are more common in younger patients, while sacral involvement predominates in older age groups. The male to female ratio is 1.8:1 (28).

1.4.1.2 Presentation

Long standing low back pain is common in sacro-coccygeal tumors; however sciatica and bowel or bladder dysfunction usually indicate advanced disease. Late symptoms include dysuria, limping sphincteric paresis. Rarely there is palpable swelling and as such a rectal examination should always be performed. Metastases to the lungs, bone and subcutaneous tissues are late manifestations of Chordoma and occur in 5 - 43% of cases (29, 30) .

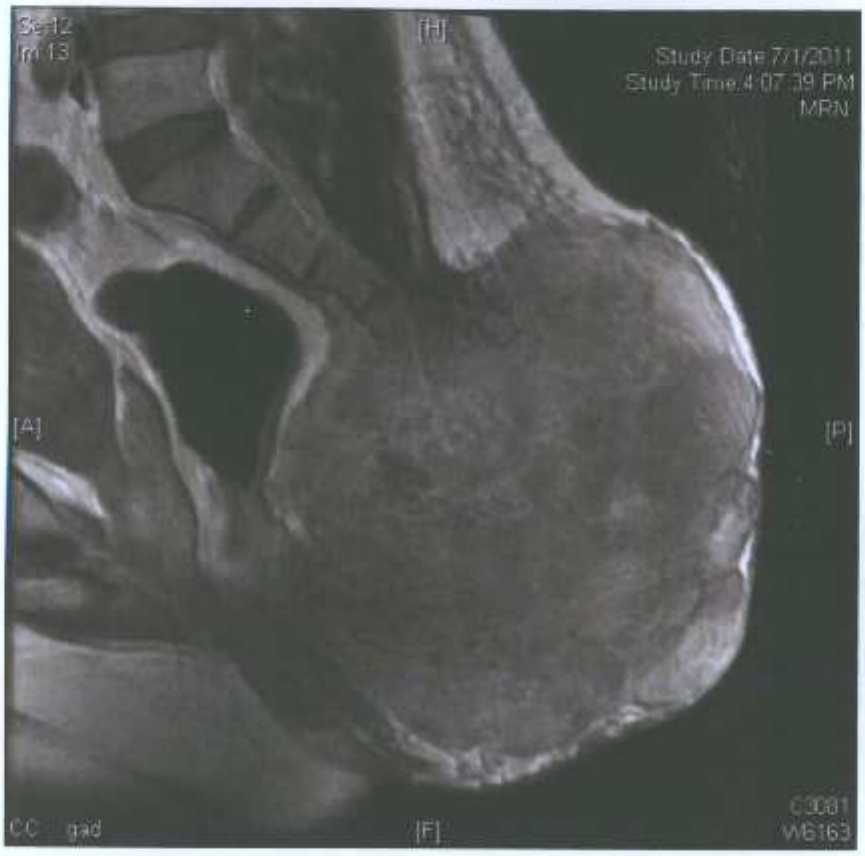
1.4.1.3 Imaging

Radiographically, Chordomas are lytic, with an epicenter in the mid vertebral body (24). Sacro-coccygeal tumors are difficult to see on plain radiographs and thus are frequently overlooked (31). Bone scintigraphy may show reduced or normal radio-isotope uptake.

MRI scan is the most useful imaging modality (figure 8). In addition to central vertebral body lysis, anterior and posterior cortical destruction is a common feature in Chordoma (32). In sacral lesions extension into the piriformis muscles and sacro-iliac ligaments is common and important to note when planning for surgery. CT scans show bone lysis and bone destruction in Chordoma (33).

Fig 8: Typical Chordoma

Sagittal view of the sacrum showing Chordoma with bony destruction and soft issue extension both anteriorly and posteriorly



1.4.1.4 Pathology

Diagnosis can usually be made with a carefully planned core biopsy. Histologically three types of Chordoma are described; classic, chondroid and dedifferentiated.

In classic Chordoma lobules containing cells arranged in cords or nests in myxoid stroma are identified. The cells typically have vacuolated cytoplasm (physaliphorous cells). Mitotic figures and pleomorphism are present (34).

The chondroid variant accounts for 15% of Chordoma. They occur in the spheno-occipital area and have a better prognosis than others. They contain features overlapping with Chondrosarcoma. Dedifferentiated Chordoma contain areas of high-grade malignant spindle cells and have a poor prognosis (35).

Immunohistochemical staining for S-100 and epithelial markers are positive (28). Recently, staining for T - Brachyury, a transcription factor expressed by notochordal cells has become routine in the diagnosis of all notochordal tumors (9). This immuno profile is helpful in distinguishing Chordoma from Chondrosarcoma and most other tumors.

1.4.1.5 Treatment

Chordoma on the other hand require radical treatment. Surgery is the main-stay of treatment and resection of sacro-coccygeal tumors is usually possible. Several series report significant improvement in local control and survival with wide resection when compared to intra lesional or marginal excision.

Wide resection of Chordoma of the mobile spine is recommended but is not always possible in which case incomplete resection and radiotherapy is recommended.

Advances in radiation oncology using image guided photons, protons and hadron therapy using Carbon ions have provided means of administering large effective doses of radiation therapy to Chordomas while sparing sensitive neural or visceral structures (36). Early results using these modalities in addition to surgery are encouraging (37). Chordomas are resistant to conventional chemotherapy and targeting of known molecular pathways are being investigated (38, 39).

1.4.2 Osteogenic Sarcoma

Osteogenic sarcoma is a high-grade malignant tumor composed of mesenchymal cells producing osteoid and immature bone. It is the most common primary malignant tumor of bone (23). Osteogenic sarcomas originating in the sacrum are very rare accounting for 4% of primary malignant tumors of the sacrum(40) . Only one patient in our series suffered from this disease.

1.4.2.1 Presentation

Pain is usually the first symptom. Over time a soft tissue swelling may occur over the area of the sacrum affected. High temperature and limited joint motion are late signs. Patients may also present with a pathological fracture. Alkaline phosphatase is often markedly elevated; Lactate dehydrodgenase may also be elevated but less frequently.

1.4.2.2 Imaging

Plain X-Rays and CT imaging may demonstrate a lytic, blastic or mixed lesion. CT further demonstrates extension of the tumor into the paravertebral and extradural soft tissues (figure 9)(24). Plain radiographs are not sensitive in identifying the extent of the softtissue involvement of the tumor. The radiographic appearance of osteosarcoma is usually a radio dense metaphyseal lesion with ill-defined margins. The normal trabecular pattern of the bone is distorted. Characteristic radiographic features such as the Codman triangle and sunburst appearance are common.

MRI helps to demonstrate the extent of softtissue involvement and presence of skip lesions (figure 10). Dynamic MRI allows vascularity to be quantified following contrast administration.

Chest CT is sensitive for detecting lung lesions less than one cm.

Figure 9 Axial CT of the Sacrum demonstrating Osteogenic Sarcoma

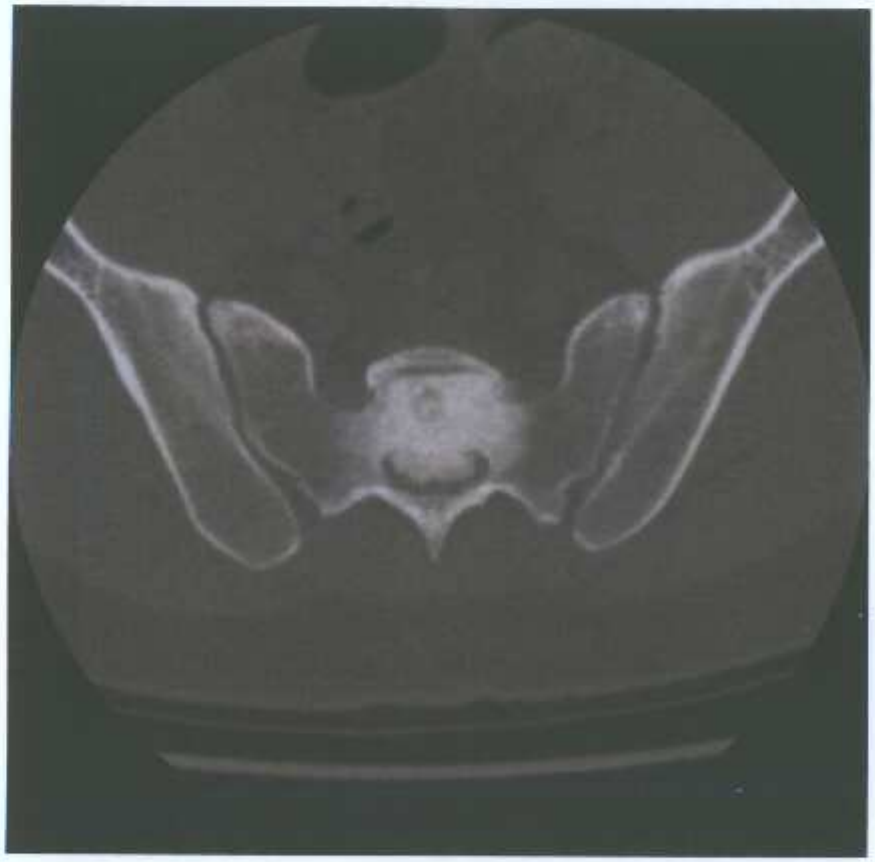
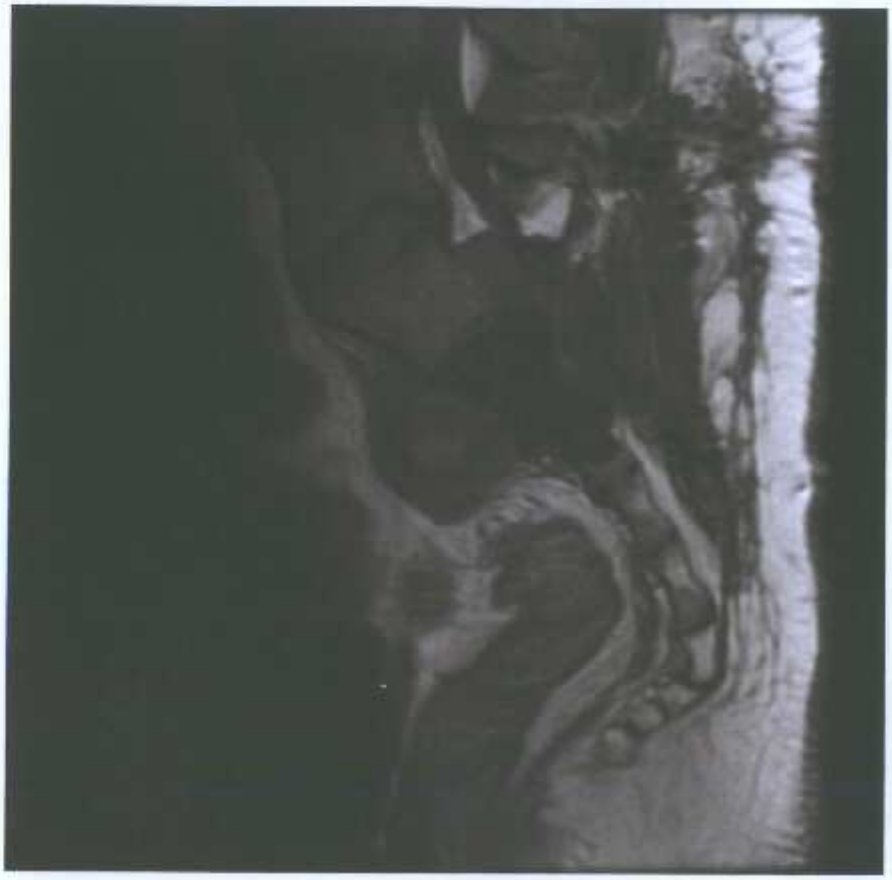


Figure 10 Sagittal T1 MRI of the Sacrum demonstrating Osteogenic Sarcoma



1.4.2.3 Pathology

Osteogenic sarcoma is characterized by high-grade sarcomatous cells producing oteoid and woven bone. The less Osteogenic areas of tumor are highly cellular and show evident features of high-grade malignancy. Cells are usually large, pleomorphic, hypochromic with prominent nucleoli and frequent atypical mitoses (28).

1.4.2.4 Treatment

Osteogenic sarcoma of the sacrum typically has a very poor prognosis with a median survival of 11 months (41). Treatment consists of neoadjuvant chemotherapy followed by radical resection of the tumor followed by adjuvant chemotherapy.

Complete en bloc resection of the tumor for local control of osteosarcoma is the standard of care. There is no agreement as to how wide the margin of resection should be, but tumor free margins are essential for local control.

Cytotoxic agents with the highest single agent activity in osteosarcoma include methotrexate, cisplatin, doxorubicin and ifosamide. Current studies suggest that 70% of patients with localized osteosarcoma outside of the sacrum treated with combination three drug chemotherapy and wide surgical resection can expect long term relapse-free survival. Patients with metastatic disease at presentation undergoing the same aggressive therapy however demonstrate less than 20% longterm relapse-free survival (42-44).

The one Osteogenic sarcoma patient in our series underwent a total Sacrectomy. He succumbed to his disease after 14 months secondary to widely metastatic disease; he did not however have a local recurrence to the pelvis.

1.4.3 Chondrosarcoma

Chondrosarcomas are malignant tumors with cartilaginous differentiation. Sacral involvement with Chondrosarcoma is a rare entity. While Osteogenic sarcoma is the most common primary malignant bone tumor, Chondrosarcoma is more common in the spine (45). The anatomic distribution of Chondrosarcoma strongly favors the axial and proximal appendicular skeleton.

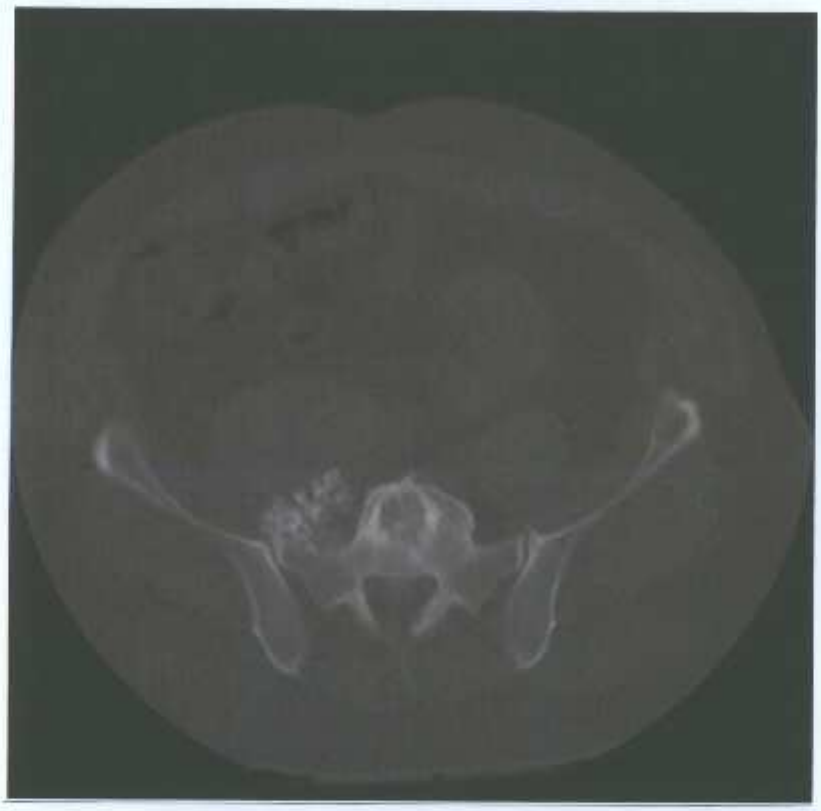
1.4.3.1 Presentation

Chondrosarcoma of the sacrum typically presents with deep, discontinuous mild pain. In the advanced stage a soft tissue mass may be present (46). Pathological fractures are an uncommon presentation.

1.4.3.2 Imaging

On plain films, an intraossesus, osteolytic lesion with diffuse irregular granules and radiopaque rings of calcifications is seen. The cortex is scalloped, thinned or destroyed. On CT scan there is a calcified radiolucency, endosteal scalloping, buttressing and the lesion is often well contained (figure 11). Calcifications are also visible in any soft tissue components (24).

Figure 11 Axial Pelvic CT demonstrating Chondrosarcoma of sacrum



1.4.3.3 Pathology

Conventional Chondrosarcomas are graded from 1- 3. Histologically they appear as lobules of hyaline cartilage separated by fibrovascular septations. They usually have very slow growth and typically progress from low to high-grade or to another malignant tumor (28).

1.4.3.4 Treatment

The treatment of Chondrosarcoma of the sacrum is surgery only. These tumors are radio and chemo resistant. Wide or radical resections can be curative. There is a high risk of recurrence with microscopic margins or due to inadequate incisional biopsies which may cause tumor cells to be implanted into soft tissue (47).

1.4.4 Ewing's Sarcoma

Ewing's sarcoma is a highly malignant poorly differentiated tumor composed of small round cells. It is the second most common primary malignancy of bone (48). Male to female ratio is 3:1. It is the fourth most common primary malignant tumor of the spine and the most common site is the sacrum (40, 49). 75% of cases occur within the first two decades of life (50).

1.4.4.1Presentation

Pain is the earliest symptom, in the sacral area nerve impingement is common and pain can present as intense and localized. Swelling is also a common early sign. Patients may report a low grade fever which has been present for some time. Initially laboratory testing often reveals an increased serum HDL and erythrocyte sedimentation rate. Spine based presentations can be associated with bowel or bladder dysfunction, radiculopathy or myelopathy. The median time from symptom onset to diagnosis varies, but the latency period is typically between 5- 9 months. Metastases almost always occur by hematogenous spread. The lungs are the primary site of involvement followed by bone.

1.4.4.2 Imaging

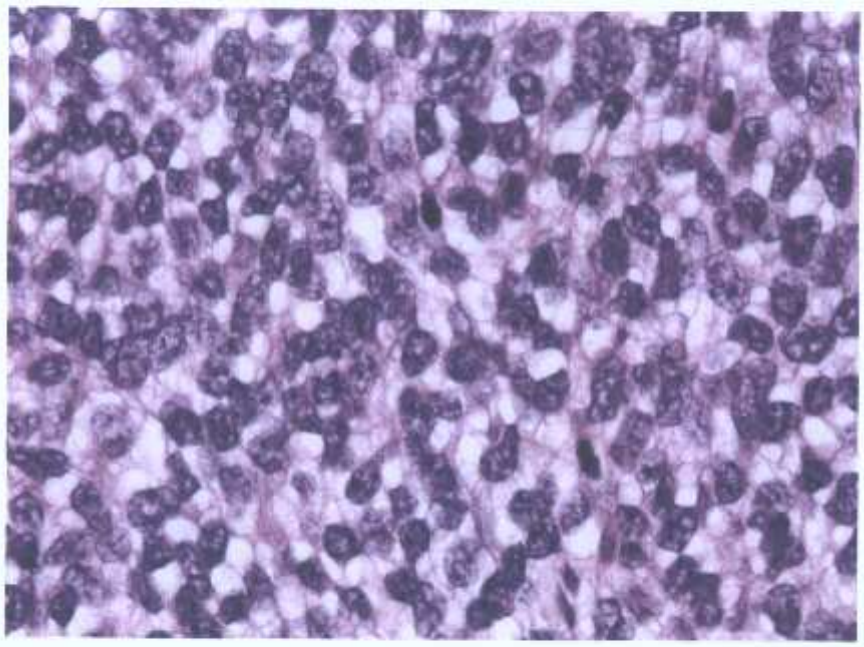
Commonly a poorly defined permeative osteolysis with expansion and sclerosis is noted (51). The cortex is almost regularly breached by the tumor or destroyed. A radiolucent extraosseus tumor is usually present (51). CT is useful in defining alterations of bone and of the extraosseus mass which has a density similar to muscle tissue. MRI using the STIR technique is the best method of studying tumor extension into marrow spaces. Sacral Ewing's may present predominantly as a soft tissue mass which may extend to pelvic structures or directly into the spinal canal (31).

1.4.4.3Pathology

The tumor is uniformly made of sheets of small round cells closely packed and without matrix (figure 12). The cytoplasm is scarce, pale, and granular, with poorly defined limits. Nuclei are round-oval with a distinct nuclear membrane, powder-like chromatin. Mitotic figures are usually rare (52)

Immunohistochemisty is positive for S-100. A characteristic chromosomal abnormality is present in Ewing sarcoma with a reciprocal translocation present in chromosomes 11 and 22 (28). Ewing sarcoma tumors strongly express CD99 antigen, or MIC2.

Figure 12 Histological specimen demonstrating Ewing's Sarcoma – small round blue cells



1.4.4.4 Treatment

Ewing's sarcoma is sensitive to chemotherapy and radiotherapy but surgery plays a key role in the treatment of this tumor. Therefore treatment always consists of chemotherapy both pre and post operatively, surgery whenever possible and radiotherapy as an alternative to surgery. Sadly Ewing's sarcoma of the sacrum has the worst prognosis of all Ewing's with local control in only 62.5% and long term survival of only 25% (53). Durable local control of Ewing sarcoma has been reported using radiation therapy, surgical resection, or both. Many attempts have been made to compare these treatment modalities in terms of local recurrence and survival rates. There is a bias toward using radiation therapy where resection is not possible or excessively morbid. Studies have shown there is increased risk of local control failure with radiation therapy alone in localized EWING SARCOMA, as well as increased risk of secondary malignancy

(54). Patients with non metastatic pelvic Ewing sarcoma fared better with surgical resection in terms of local control (surgery 82.6% versus radiation therapy 66.7%) and 5-year EFS (surgery 73.9% versus radiation therapy 30.3%) (55)

Chemotherapy regimens usually consistent of vincristine, doxorubicin and cyclophosphamide alternating with ifosfamide and eptoposide (VDC/IE) with myeloid growth factor support (56). In a randomized control trial patients with localized Ewing sarcoma were randomized to receive VDC/IE chemotherapy either every 3 weeks or every 2 weeks. EFS was improved in the more frequent dosing arm (76% versus 65%) (57) .

1.4.5 Giant Cell Tumor

Giant cell tumor is an intramedullary tumor composed of mononuclear cells and osteoclast-like multinucleated giant cells, with a variable and unpredictable potential for growth. They make up 5 % of all bone tumors and there is a slight preference for females. Giant cell tumor makes up 13% of sacral tumors (58). Sacral giant cell tumors commonly extend to involve both sides of the midline (59).

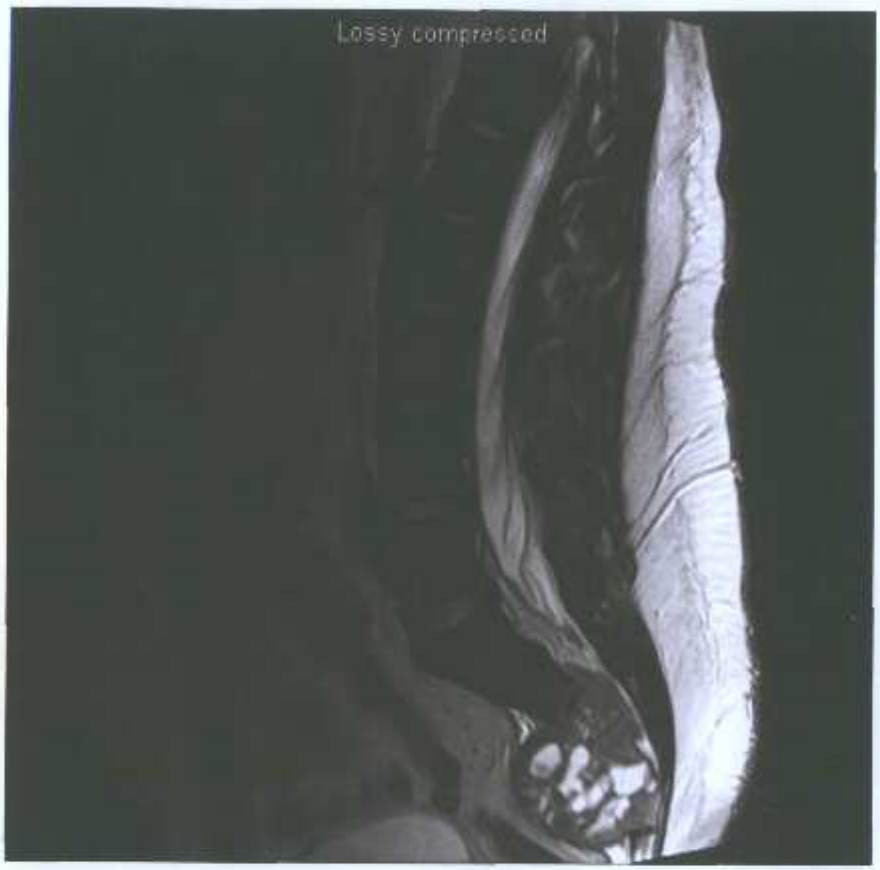
1.4.5.1 Presentation

Pain and stiffness is the most common presenting symptom. It is often insidious in nature with reports of a dull ache that gradually increases over time. The patient may notice eventual swelling of the affected joint with associated soft tissue swelling. Approximately 10% of patients will present with a pathologic fracture (60).

1.4.5.2 Imaging

Plain film x-ray demonstrates a purely lytic lesion with well defined margins. There is usually thinning of the cortex which may be expanded or violated. Soft tissue recurrence usually has an ossified rim.

Figure 13 Sagittal CT of spine demonstrating giant cell tumor of Sacrum



1.4.5.3 Pathology

Microscopically mononuclear cells and giant cells are uniformly distributed. The nuclei of mononuclear cells and giant cells are identical. There is mitotic activity but no atypical mitoses or cytological atypia.

1.4.5.4 Treatment

Stage 1, 2 and stage 3 lesions without massive bone destruction may be treated with curettage. When there is massive bony destruction of the sacrum a total or partial sacrectomy may be

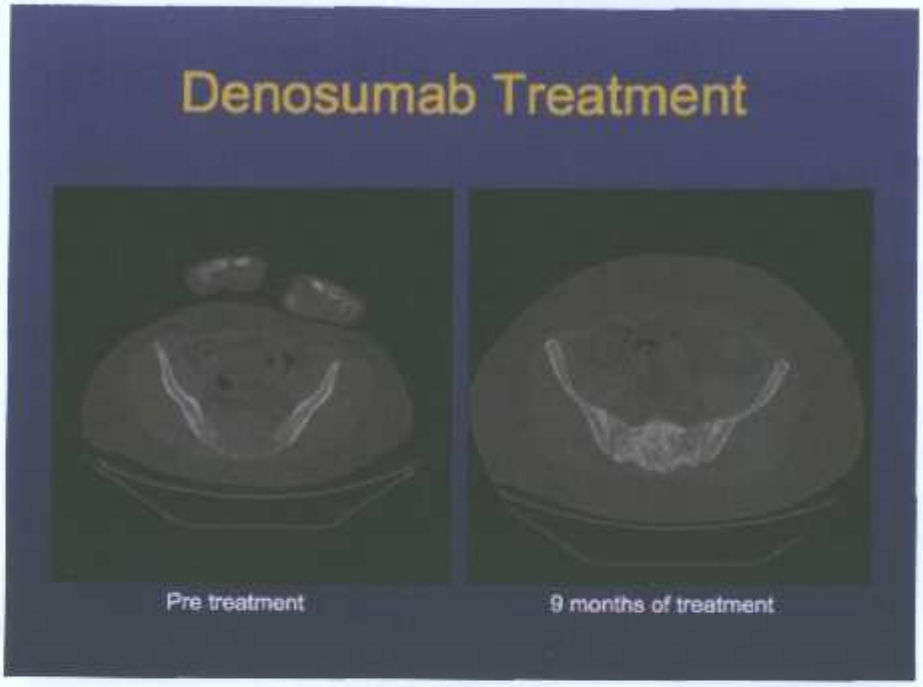
necessary depending on the extent of involvement (61). Recent reports have suggested that embolization alone may be an effective treatment forsacral GCT (62-64).Radiation therapy and RANK-L antibodies such as Denusomab may be used as adjuncts to surgery (65, 66).

RANKL(receptoractivatorofnuclearfactorkappa-Bligand)hasbeenimplicatedin GCT (67, 68)'Thehumanmonoclonalantibody Denosumabbindsto RANKLtopreventRANK activation,therebylimitingthedestructivepropertiesofGCTandreducingthegiantcell population (69).Denosumabhasbeenapproved byFDAtotreatunresectablegiantcelltumorof boneinadultoradolescentwhoareskeletallymature (70).

Denosumab'sapprovalwasbasedonthe17 durableobjectiveresponsesachievedintwomulticenteropenlabeltrials (71, 72).Onewasa multicenterphaseIItrialof37patientswithunresectableorrecurrentGCTwhoweretreated monthlywithsubcutaneousDenosumab.Of35assessablepatients,30(84%)reportedimproved functionalstatusordecreasedpain (65).

The second trial wasamultinationalphaseIIstudyof Denosumabin282surgicallysalvageableandunsalvageableGCTpatients,thedrugwaswell toleratedandwasassociatedwithinhibiteddiseaseprogression (99%)andareducedrequirement forsurgery (71).Thesepositiveresults (figure 14) mayheraldtheintroductionofapre-operativeregimenof DenosumabforsacralGCTtohelpdiminishthehighmorbidityassociatedwithsacraltumor resection.

Figure 14 – Effects of Denosumab treatment on GCT



1.4.6 – Locally Invasive or Recurrent Adenocarcinoma of the Rectum

Local recurrence of rectal cancer may occur despite achieving an apparently curative resection. Between 5 and 35 percent of patients will experience local recurrence. Radiotherapy, either alone or in combination with chemotherapy, has been shown to improve symptoms in the majority of patients (73-75) . Despite these interventions five-year survival is usually less than 5 percent. Radical resection of the locally recurrent tumor has been shown to be the only option that offers a significant improvement in prognosis (75). In patients with pelvic recurrence of rectal cancer where the tumor is confined to the pelvis with no evidence of distant spread the tumor may be removed if it is technically amenable to surgical excision (76, 77).

1.4.6.1 – Presentation

Patients with recurrent invasive rectal adenocarcinoma are usually found during routine surveillance post treatment. One study quoted a median time to recurrence of 30.8 months (78).

1.4.6.2 – Imaging

CT of the chest, abdomen and pelvis should be performed to exclude distant metastases and to assess involvement of the bony pelvic ring. The presence of extensive abdominal or thoracic metastases is considered to be a contraindication to resection of the pelvic recurrence. MRI of the pelvis should also be performed to assess the location of the tumor, its direction of invasion, and involvement of local viscera and the pelvic sidewall structures.

1.4.6.3 – Pathology

More than 90% of colorectal carcinomas are adenocarcinomas originating from epithelial cells of the colorectal mucosa (79). Other rare types of colorectal carcinomas include neuroendocrine, squamous cell, adenosquamous, spindle cell and undifferentiated carcinomas. Conventional adenocarcinoma is characterized by glandular formation, which is the basis for histologic tumor grading. In well differentiated adenocarcinoma >95% of the tumor is gland forming. Moderately differentiated adenocarcinoma shows 50-95% gland formation. Poorly differentiated adenocarcinoma is mostly solid with <50% gland formation. In practice, most colorectal adenocarcinomas (~70%) are diagnosed as moderately differentiated. Well and poorly differentiated carcinomas account for 10% and 20%, respectively.

1.4.6.4 – Treatment

Along with surgical resection, neoadjuvant chemotherapy and radiotherapy has been shown to improve survival in patients with resectable rectal adenocarcinoma

The efficacy of preoperative combined modality therapy for locally recurrent rectal cancer in previously non irradiated patients has been supported by data from a retrospective series (80-82) and a randomized trial of chemo radiotherapy versus preoperative RT alone that included patients with locally recurrent disease (83).

Additional data on long-term prognosis come from a retrospective Mayo clinic series of 123 patients with previously non irradiated locally recurrent rectal cancer who were treated with a combination of external beam RT and concomitant 5-FU, maximal surgical resection, and IORT (80). The five-year local control rate was 63 percent and overall survival at five years 20 percent. It is important to note that the presence of neoadjuvant or adjuvant radiation therapy will affect wound healing, due to fibrosis and diminished blood flow.

1.5 The Sacrectomy

The purpose of this section is to describe the technical aspects of the sacrectomy procedure. Primary tumors of the sacrum are rare. Approximately 6% of malignant bone tumors involve the sacrum(84). The amount of sacral resection depends on the amount of bony involvement of tumor and the ability to obtain a negative margin as quite often these tumors extend into the soft tissue and vasculature. For the purposes of our study we divided our patients into those who had undergone;

- Total Sacrectomy where the entire sacral bone was removed
- Hemi-sacrectomy where a portion or all of the sacrum on one side of the midline was removed
- High Sacrectomy where a portion of the S1 or S2 vertebrae and below was taken
- Low sacrectomy where any portion of the S3 vertebra and below was taken

This allowed us to stratify our patients easily into subgroups. For the purpose of explanation the Total Sacrectomy procedure will be described in this chapter.

1.5.1 History

A sacrectomy is typically reserved for the purposes of resecting aggressive local and life-threatening disease. Details of this procedure were first reported in the literature in 1948 by Ralph. F Bowers, a surgeon at a VA hospital in Kentucky. He described the surgical approach of a

giant cell tumor of the sacrum (85). Post operatively he reported that "the rectal and urinary sphincters were not functioning", and noted that "these handicaps are not as distressing as the leg weakness, according to the patient". Dr. Bowers recognized the importance of measuring the patient's QoL even at this early stage of the procedure. He sent the patient questionnaires at 3 and 6 months.

1.5.2 Indications

The aim of surgery is to achieve a wide margin while preserving life and reasonable function. Radiotherapy and chemotherapy are available as an adjuvant to surgery.

- The most common indication for sacrectomy is primary sacral malignancy requiring resection for cure.
- Patients with primary or recurrent pelvic visceral tumors (usually colorectal or gynecological by direct extension) with no evidence of metastatic disease.

A strong relative contraindication for sacrectomy is the presence of disseminated malignant disease. Given the significant neurological sequelae of this procedure, loss of bowel, bladder, sexual function it is inappropriate to pursue a sacrectomy unless there is a potential for cure. The inability obtain a negative tumor margin is also a relative contraindication.

1.5.3 Pre-operative Planning

Systemic staging should first be performed by obtaining a CT of the chest abdomen and pelvis. All sacral tumors should be biopsied prior to surgery through a posterior approach as close to the midline as possible, in order to facilitate removal of the biopsy tract at the time of surgery. The biopsy can either be an open surgical procedure (incisional biopsy), or can done under CT imaged guidance by an interventional radiologist (core biopsy using a tru-cut needle).

Lesions at the level below S2 can generally be accessed via a posterior approach only unless there is involvement of pelvic viscera or surrounding vasculature. Lesions cephalad to S2 are best treated with anterior approach and mobilization of the pelvic structures as well as ligation of the internal iliac vessels and an anterior sacral osteotomy. During the anterior approach a pedicled myocutaneous rectus abdominus flap can also be harvested and left in the pelvis for closure as part of the posterior approach. The use of the pedicle flap has aided greatly in the difficult posterior wound closure, particularly if the patient has received radiation therapy prior to their surgery (86).All patients undergoing an anterior approach should complete a bowel preparation pre-operatively. If there is a high likelihood of losing bowel continence(5, 87). The decision to remove the rectum should be made preoperatively and in consultation with the patient. The only absolute indication for removal of the rectum is direct invasion of the rectal wall with tumor. In cases of recurrent rectal cancer where the rectum is still present this is always the situation. Invasion of the rectum by aggressive sacral tumors is always an indication for rectal resection. Resections which involve deinnervation of the rectum are not considered absolute indications for proctectomy since satisfactory bowel rehabilitation is usually satisfactory. However some patients may elect to have an end colostomy rather than suffer incontinence. Other patients will request retention of the rectum and always have the option of a diverting colostomy post operatively if they do not have adequate symptom management which may be possible to perform laparoscopically.

The staged abdomino-sacral approach has markedly reduced patient morbidity in terms of reduction of operating time, blood loss, anesthesia complications, and wound complications (88). The aim of the anterior approach is to expose the anterior portion of the tumor and to identify and ligate and vessels which are feeding the tumor (89)

1.5.4 Anterior Technique

Positioning

The patient is placed in the supine position on the operating table. Essential landmarks for the anterior exposure include the sacral promontory, anterior sacral foramina and the sacro-iliac joints.

Bilateral ureteral stents can be placed to aid with identification of the ureters as well as providing protection against accidental injury. A midline laparotomy incision is made from the xiphoid to the pubic symphysis. It is important to identify and protect the inferior epigastric arteries as they will provide vascular supply to the VRAM flap. The abdomen is approached via a transperitoneal approach; the rectum is mobilized or transected depending on disease involvement. The middle sacral vein and the internal iliac artery and vein are identified and ligated (89). The level of sacral osteotomies are localized using anatomic landmarks and radiographic guidance if needed (90). A burr or osteotome can be used to perform the osteotomies. Some surgeons choose to place a small fragment screw or tack in the bone just cephalad to the osteotomy in order to verify level of resection during the posterior procedure. Once the osteotomies and pelvic dissection is completed a silastic sheet can be placed between the tumor mass and mobilized structures to protect them during the posterior approach. The pedicled flap is then placed on top of the silastic sheet and the laparotomy incision is closed. If indicated a colostomy is matured on the opposite side the rectus flap was harvested.

1.5.5 Posterior approach

In the case of a low sacrectomy a posterior only approach is required, however for a total or high sacrectomy the posterior approach is a continuation of the anterior approach which is typically staged over 24-48 hours (91).

Positioning

The patient is placed in the prone position on a Wilson frame on a Jackson table in maximum reverse Trendelenburg position. The head is firmly immobilized using a device such as Mayfield 3 pin skull clamp. The patient is prepped wide to allow for possible gluteal flap mobilization. The anus is sutured to decrease the risk of fecal contamination in the surgical field.

Technique

A midline incision from L5 to the coccyx is made, remembering to ellipse the biopsy tract (92). Dissection continues down to the fascia to expose the sacrum posteriorly. It is important to avoid entering the tumor mass and as such the surgeon aims to stay cephalad. The posterior iliac crest and sciatic nerve should be exposed bilaterally (Fig 3.2). Fluoroscopy is then used to identify the lumbosacral junction. If this is a continuation of the anterior procedure, the screw left from the anterior osteotomy is visualized to guide resection. A dorsal sacral laminectomy is now performed to expose the most cephalad sacral nerve roots which will be preserved if not involved by tumor. Having reviewed the patients' pre-operative MRI the level at which the thecal sac ends will have been previously identified. The thecal sac should end at the level of the S2 segment and if ligation of the sac is required it is ligated with 0 silk sutures. Once lateral exposure is completed an osteotomy is performed at the appropriate sacral level. Once the osteotomy is completed the specimen should be delivered en bloc from proximal to distal, this allows protection of the nerve roots which are being saved, if any (92). It is essential that the pudendal nerve is dissected out and saved if possible. The pudendal nerve can then be identified in the ischiorectal fossa by exposing the sacrotuberous ligament. If the S3 –S4 sacral

nerve roots are spared and the pudendal nerve is sacrificed then bowel continence will also be sacrificed. If the rectum is excised with the tumor then dissection should be performed ventral to the rectum.

The gluteal musculature is transected laterally which uncovers the piriformis muscles that are, in turn, divided at their musculotendinous junction as tumor extension, particularly Chordoma, may occur along this muscle (93). Tumor involvement of the piriformis, gluteus maximus, and sacroiliac joints, as seen on Preoperative MR images in patients with sacral chordomas should be scrutinized to look for tumor involvement of the piriformis, gluteus and SI joint. This has been shown to be an important predictor of local recurrence, even after wide en bloc resection.(94).

The anus and anal sphincter are then removed with the tumor. Meticulous hemostasis is then ensured. In the case of a total sacrectomy where resection occurs proximal to the S1 neural foramina instrumented spinopelvic reconstruction should occur.

Figure 15 - Diagram of the sacrum indicating the sacral vertebrae

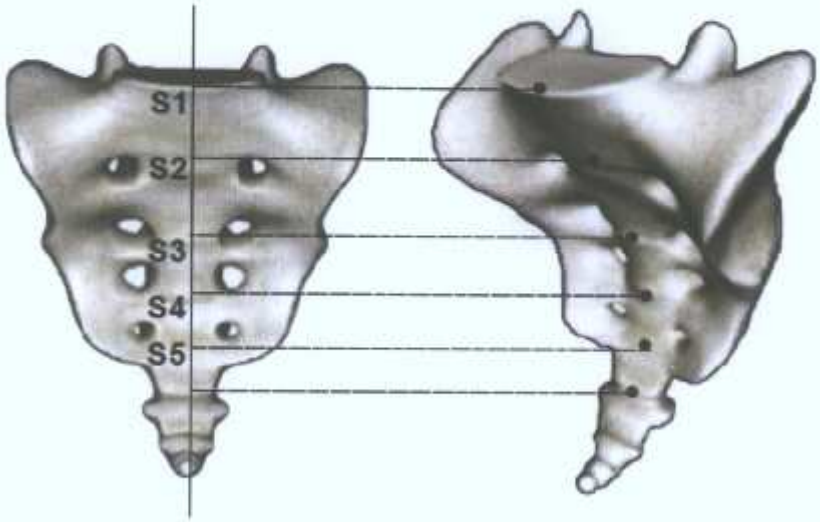
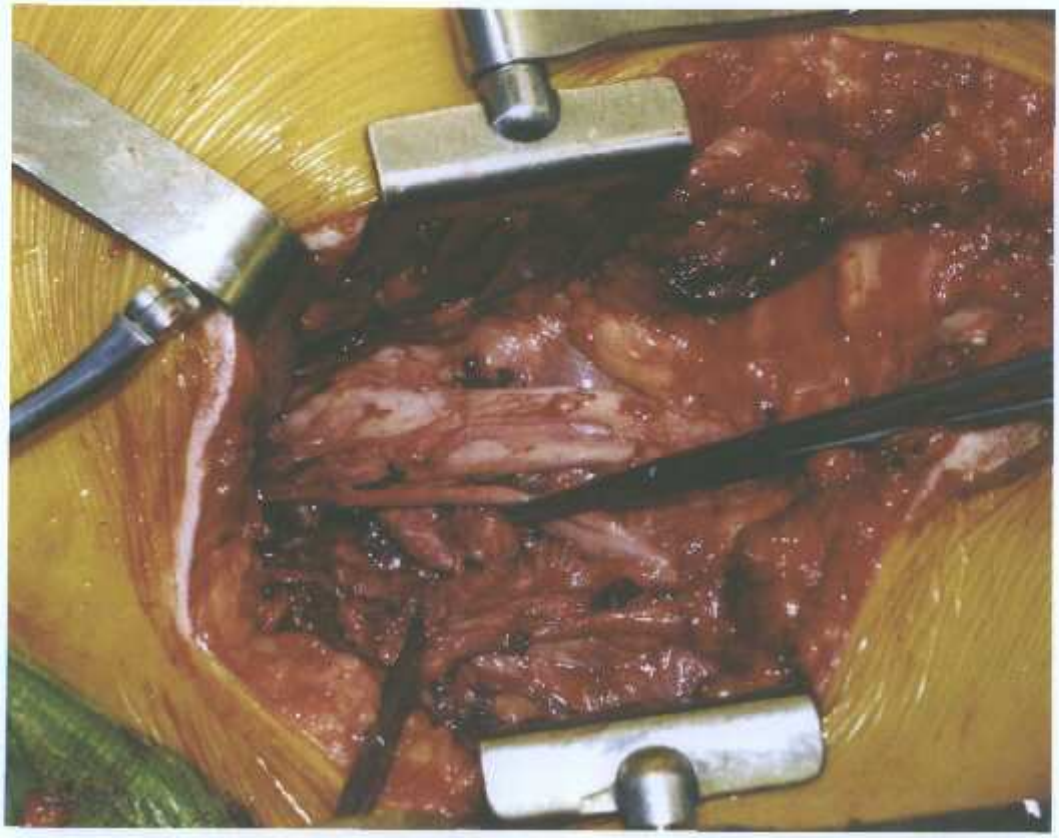


Figure 16 - Posterior dissection of sciatic nerve



Laminectomies of L5 and S1 then allows for exposure of the thecal sac and cauda equine. The sacral nerve roots are divided and the thecal sac is closed. The area is now ready for osteotomies posteriorly and the sacrum is freed from its remaining soft tissue and muscular attachments and removed dorsally en bloc with tumor. The wound is then irrigated and closure using the previously harvested rectus abdominis flap is completed (Fig 3.3).

Figure 17 - Rectus Flap for sacral wound closure

1.5.6 Reconstruction

The advantage of a total sacrectomy is en bloc removal of tumor, which can potentially prove to be a curative resection in the absence of distant disease. Decision regarding total or subtotal sacrectomy is dependent on radiological evaluation and aggressiveness of the disease process. The major disadvantage of the total sacrectomy is instability of the pelvis due to discontinuity of the SI joint.

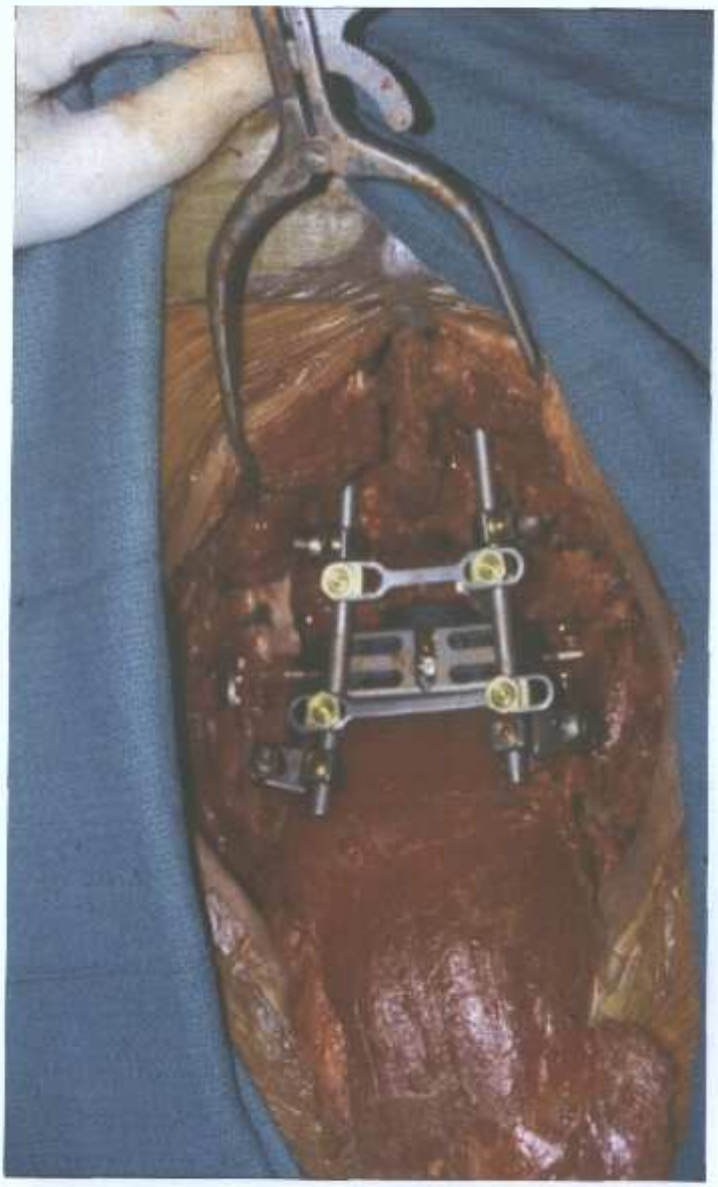
The integrity of the lumbosacral junction following sacrectomy is dependant on the extent of the sacral bone which is removed. Studies by Gunterberg demonstrated that when the sacrum

was resected between the levels of the s1 and s2 vertebrae the strength of the pelvic ring was decreased by approximately 30%. When the sacrum was resected through the s1 vertebra the pelvic ring strength was diminished by up to 50% (15). Another study by Stener and Gunterberg demonstrated that if 50% of the S1 vertebra is preserved then instability is not observed and surgical stabilization may not be required (95).

Following Total Sacrectomy the spine can be left to float freely in the pelvis. Some spine groups have decided not to perform reconstruction following total Sacrectomy, however this is associated with prolonged hospital stay and bed rest (96-98). These patients were maintained in hip spicas for prolonged periods with ambulation dependent on scar tissue formation in the pelvis. Patients in some reconstruction groups were mobilizing out of bed within 2 weeks, whereas those who had not undergone a reconstructive procedure were bed ridden for 10 – 12 weeks (99) (Fig 3.4).

In centers where a reconstruction is preferred there are several techniques including sacro-iliac joint screw fixation, iliac-sacral screw fixation, posterior iliosacral plating and screw fixation, custom made prosthesis and transiliac rods. In cases of total sacrectomy, which requires bypass stabilization of the ilium to the lumbar spine; the Galveston Rod Technique and Modification has been shown in the literature to achieve effective overall stabilization, provide significant pain relief and preserve ambulatory capacity.

Figure 18 – Sacral reconstruction with rectus flap visible



Chapter 2 - PROMIS

2.1 PROMIS

Patient–Reported Outcomes (PROs) is the term used to denote health data that is provided by the patient through a reporting system. A patient–reported outcome is a patient's description of their feelings or what they are able to do as they are dealing with chronic diseases or conditions. PROs can also be prospectively measured when patients are undergoing treatment.

As stated on the National Institutes of Health (NIH) PROMIS website, "PROMIS® stands for Patient Reported Outcomes Measurement Information System, which is a system of highly reliable, precise measures of patient–reported health status for physical, mental, and social well–being. PROMIS® tools measure what patients are able to do and how they feel by asking questions. PROMIS' measures can be used as primary or secondary endpoints in clinical studies of the effectiveness of treatment, and PROMIS® tools can be used across a wide variety of chronic diseases and conditions and in the general population."

The rationale for using PROMISPROs for sacrectomy patients is that it thoroughly assesses physical, mental, social and sexual health in a cohort of patients who have undergone extensive radical surgery. Examples include physical abilities, fatigue, pain, depression, sexual function, and satisfaction with social participation (or interactions). PROMIS is flexible and questionnaires can be designed to measure PROs in any disease or medical condition or they can be designed to measure certain PROs that are of specific importance to one disease, such as the importance of fatigue to cancer.

PRO data are especially important to evaluating the effectiveness of health care for conditions which have no cure, or have chronic morbidity. The goal of treatment therapy is to improve patients' abilities to function and to reduce symptoms associated with the condition. PROMIS has been developed specifically for use in research on chronic health conditions.

I decided to use PROMIStools to measure what Sacrectomy patients are able to do and how they feel. These tools are in the form of questionnaires that are asked in interviews, given to patients in written form and by computer. PROMIS allows the answers patients give to be

accumulated into reliable reports that can be used by patients and physicians to improve communication and manage diseases by finding the most appropriate treatment plan. PROMIS tools can help us as surgeons to better understand how various treatments might impact what patients are able to do and the symptoms they experience.

There were several advantages for using PROMISas opposed to other PRO systems. PROMISdata is comparable because there are common measurements across domains. The measures are reliable and valid. They have gone through rounds of rigorous review and testing to ensure that the measurements are precise, consistent, and accurate. Furthermore PROMISis flexible. Our questionnaire was delivered at multi-institutions via an online environment ensuring maximum uptake of respondents.

2.1.1 Overview

In late 2004, a group of outcomes scientists from seven institutions and the NIH formed a cooperative group funded under the NIH Roadmap for Medical Research Initiative to re-engineer the clinical research enterprise (http://www.nihroadmap.nih.gov). This initiative - the PatientReported Outcomes Measurement Information System (PROMIS) - aims to revolutionize the way patientreported outcome tools are selected and employed in clinical research and practice evaluation. It aims to establish a national resource for accurate and efficient measurement of patientreported symptoms and other health outcomes in clinical practice.

2.1.2 Development of PROMIS Domains

Domain framework

The first task of the PROMIS network was to create a protocol for developing a domain map (framework) that portrayed the structure of each target domain and its conceptual framework. Existing outcome assessment questionnaires use an explicit or implicit framework that typically includes the concepts of physical function or limitation, mental health or distress, and social function, with many also including symptoms (e.g., fatigue, pain). PROMIS framework was developed through independent literature reviews and the Statistical Coordinating Center (SCC), followed by statistical analysis of available data regarding dimensionality of health status assessment. Early in the first year, the SC endorsed the World Health Organization (WHO) physical, mental, and social health framework. PROMIS network investigators used a modified Delphi approach combined with quantitative analysis of existing relevant data, to inform multiple rounds of framework review and revision until consensus was reached on a detailed articulation of subordinate domains beneath the broad physical, mental, and social headings. The PROMIS SC then resolved to begin item development and testing in pain, fatigue and at least one sub domain in each of physical, mental and social health.

Domain definitions

Physical functionis defined as one's ability to carry out various activities that require physical capability, ranging from self-care (activities of daily living) to more vigorous activities that require increasing degrees of mobility, strength, or endurance (Haley et al, 1994a; 1994b; Stewart &Kamberg, 1992; Wilson & Cleary, 1995). Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Chang, 1999; Mersky & Bogduk, 1994; Meuser et al, 2001; Sherbourne, 1992).

Finally, Global healthrefers to evaluations of health in general rather than specific elements of health. The global health items include global ratings of the five primary PROMIS domains

(physical function, fatigue, pain, emotional distress, and social health) and general health perceptions that cut across domains. Global items allow respondents to weight together different aspects of health to arrive at a 'bottom-line" indicator of their health status.

2.1.3 Item Bank Development

For its first set of item banks, PROMIS chose to focus on pain, fatigue, emotional distress, physical function, and social function. Six phases of item development are documented: identification of existing items, item classification and selection, item review and revision, focus group input on domain coverage, cognitive interviews with individual items, and final revision before field testing. Item banks were therefore developed using mixed qualitative and quantitative methods as described below

Literature review for items

Drawing from decades of experience reflected in published literature and previous work of the investigators, PROMIS began the item bank development by cataloguing items from well-established instruments that had been extensively tested and had excellent track records. PROMIS investigators across the network conducted inclusive searches and evaluations of existing instruments to enrich the pool of domain-relevant items that were considered potential candidates for the PROMIS item banks.

Currently there are 12 NIH-funded studies taking place across the country. All are implementing PROMIS® tools in efforts to expand the body of knowledge about and further validate PROMIS. This is not the first time the PROMIS tool has been used in an Orthopaedic population (100) and the use of PROMIS in clinical research is now becoming more prevalent in the literature (101, 102). An exciting aspect of PROMIS is its use of Item Response Theory (IRT) which we have included in our study. A recent paper evaluated Physical Function scales using

item improved or IRT-based items can result in greater responsiveness and precision across a broader range of physical function. This can reduce sample size requirements and thus study costs(103). This cost saving is particularly important in the current climate where the availability of research grants are at a premium and cost management is a priority.

With the advent of tablet PCs, the delivery of this survey in the out-patient setting has been simplified. The PROMIS website has been specifically formatted to make it Apple iPad compatible and as mentioned in previous reports I purchased two iPads using funds from our research grant. A pilot study using iPad's for PROMIS data collection is currently underway in Multiple Sclerosis patients. They found that patients were able to complete the assessment in the clinic's waiting room and indicated they would be interested in using a similar system on a regular basis. Many relevant symptoms were assessed in a short period of time with scores directly comparable to the general US population mean(104).

2.1.4 Validating PROMIS

From July 2006 to March 2007, data were collected from the U.S. general population and multiple disease populations. The sampling plan was developed for collecting responses to the candidate items from the targeted PROMIS domains and was designed to accommodate multiple objectives:

1. create item calibrations for each domain;
2. estimate profile scores for various disease populations;
3. create linking metrics to legacy questionnaires (e.g., SF–36);
4. confirm the factor structure of the domains; and
5. Conduct item and bank analyses. Because of the large total number of items (> 1000), it was not possible for participants to respond to the entire pool. Based on an estimate of 4 questions per minute, the number of items administered to any respondent was limited to about 150 (37 minutes).

Two data collection designs ("full bank" and "block administration") were used. Some individuals were administered full banks of 56 items for a subset of the PROMIS Calibration Studies domains while others were administered 14 blocks of 7 items selected from the 14 item banks (3 physical functioning banks, anxiety, depression, anger, substance abuse, fatigue impact, fatigue experience, social–role performance, social–role satisfaction, pain interference, pain quality, pain behavior). In addition to the PROMIS items and appropriate "legacy" items (items from widely used fixed length measures such as the SF–36) completed by those administered full banks of items, participants were administered approximately 21 auxiliary items consisting of global health rating items and socio-demographic variables including age, income, number of hospitalizations, disability days, whether they take prescribed medicines, body mass index, gender, race/ethnicity, whether the person was married or living with someone, educational attainment, and whether the person was working full–time, a full time student, or not working full time or going to school full–time. There were also a series of questions about the presence and degree of limitations related to 25 chronic medical conditions: hypertension, angina, CAD, heart failure, heart attack, stroke or TIA, liver disease, kidney disease, arthritis or rheumatism, osteoarthritis, migraines, asthma, COPD, diabetes, cancer, depression, anxiety, alcohol or drug problems, sleep disorder, HIV/AIDS, spinal cord injury, Multiple Sclerosis, Parkinson's disease, epilepsy, and amyotrophic lateral sclerosis.

The full–bank administration allows for evaluation of dimensionality and calibration within item banks (domains). The block administration permits an evaluation of associations between domains. The ability to calibrate items on a common metric (item linking) is possible because of the administration of blocks of items from the full bank to general population and clinical samples. Each item was administered to at least 900 respondents from the general population and 500 respondents with a chronic medical condition.

The PROMIS Calibration Studies sample included 21,133 respondents, with 1,532 recruited from primary research sites associated with PROMIS network sites and the vast majority (19,601) from YouGovPolimetrix's panel sample. YouGovPolimetrix sample data was collected using their website on a secure server. The PROMIS network site data was collected using the PROMIS Assessment System.

The PROMIS Statistical Center (PSC) received de–identified datasets from YouGovPolimetrix. Each of the 7,005 individuals (6,676 from YouGovPolimetrix, 236 from UNC, and 93 from Stanford) assigned to administration of full item banks was administered a pair of the 14 item banks. The 7–item blocks for each of the 14 banks were administered to 14,128 individuals (6,245 general population, 7,883 clinical samples). The clinical samples included persons with heart disease (n = 1,156), cancer (n = 1,754), rheumatoid arthritis (n = 557), osteoarthritis (n = 918), psychiatric illness (n = 1,193), chronic obstructive pulmonary disease (n = 1,214), spinal cord injury (n = 531), and other conditions (n = 560).

Chapter 3 - Methods

Methodology

Overview

In this chapter I will outline the methodology used in this thesis.

3.1 Study Design

This study was a pilot cross-sectional study of individuals who underwent a sacrectomy for a primary or locally invasive tumor of the sacrum. The objectives of the study were to

1. Provide potential sacrectomy patients with information that will allow them to become aware of the health-related risks and benefits associated with surgery and ultimately make more-informed decisions.
2. Compare the physical function outcomes of patients in each sacral resection subgroup
3. Compare the mental outcomes of patients in each sacral resection subgroup
4. Compare the pain intensity and pain interference outcomes of patients in each sacral resection subgroup
5. Analyze the coverage, precision and reliability of the PROMIS questionnaires for patients who have undergone a sacrectomy

Patients at MSKCC, MC, and MGH would be administered a survey consisting of items covering the domains of global health, physical function, mental health, pain intensity and pain interference as well as satisfaction with surgery. These items were extracted from existing patientreported outcomes instruments and would be administered via an electronic reporting platform at www.assessmentcenter.net

This research study was undertaken as the foundation to creating a universal questionnaire that would form part of a larger prospective study which aims to follow patients diagnosed with a

sacral tumor from the time of diagnosis and subsequently at 1, 3, 6 and 12 months post operatively.

3.2 Rationale

Sacral tumors, and sacral surgery, are relatively rare. When sacral tumors occur, they are managed at large tertiary referral centers. However, because of the small number of cases, outcome reports from any single center lack statistical power to generalize results (105) .Furthermore, the relatively small number of cases managed at any single center restricts surgeons' ability to treat the full spectrum of disease and their experience with different treatment modalities. We hypothesized that the collective experience of the three major institutions will provide more meaningful and reliable data. To obtain an adequate sample size for this study, the involvement of multiple institutions is essential.

3.3 Sample size calculations

As this is a pilot study no formal calculation of sample size was performed. It was decided to consider all patients who have underwent a sacral resection at the three institutions in the past 20 years.

3.4 Ethical Approval

Ethical approval was sought and granted in each institution. Approval was granted at from the hospital's Institutional Review Board. (Appendix 3)

3.5 Recruitment procedure

Patients who have previously undergone a sacral resection were identified at each institution using an analysis of CPT and ICD-9 codes which linked to a sacral resection. This database was then further analyzed to only include patients who are living. Patients who were scheduled for follow up clinic appointments were then recruited in the office setting. Patients with no scheduled follow-up were recruited via e-mail or by telephone. The inclusion and exclusion criteria were set out as follows:

3.5.1 Inclusion Criteria

Individuals who fulfilled the following inclusion criteria were admitted into the study.

- Males and females aged 12 years and over
- Diagnosis of a primary sacral tumor or local invasion of the sacrum from another primary tumor
- Patients who have underwent a sacrectomy at any level, at MSKCC, MGH or MC

3.5.2 Exclusion criteria

- Patients who had a sacral nerve root removed only
- Patients who underwent a sacral laminectomies without removal of a vertebra

Patients who were eligible for inclusion in the study were first approached while waiting for their clinic appointment in the waiting room. The questionnaire was explained to them and they were given an information sheet – see Appendix 2.

Patients who would not be following up in clinic were contacted via e-mail. The patients were provided with a link where they could take the questionnaire online.

3.5.3 Controls

Given the rare patient population and the pilot nature of this study the different subgroup of sacral resections were considered to be control groups against each other

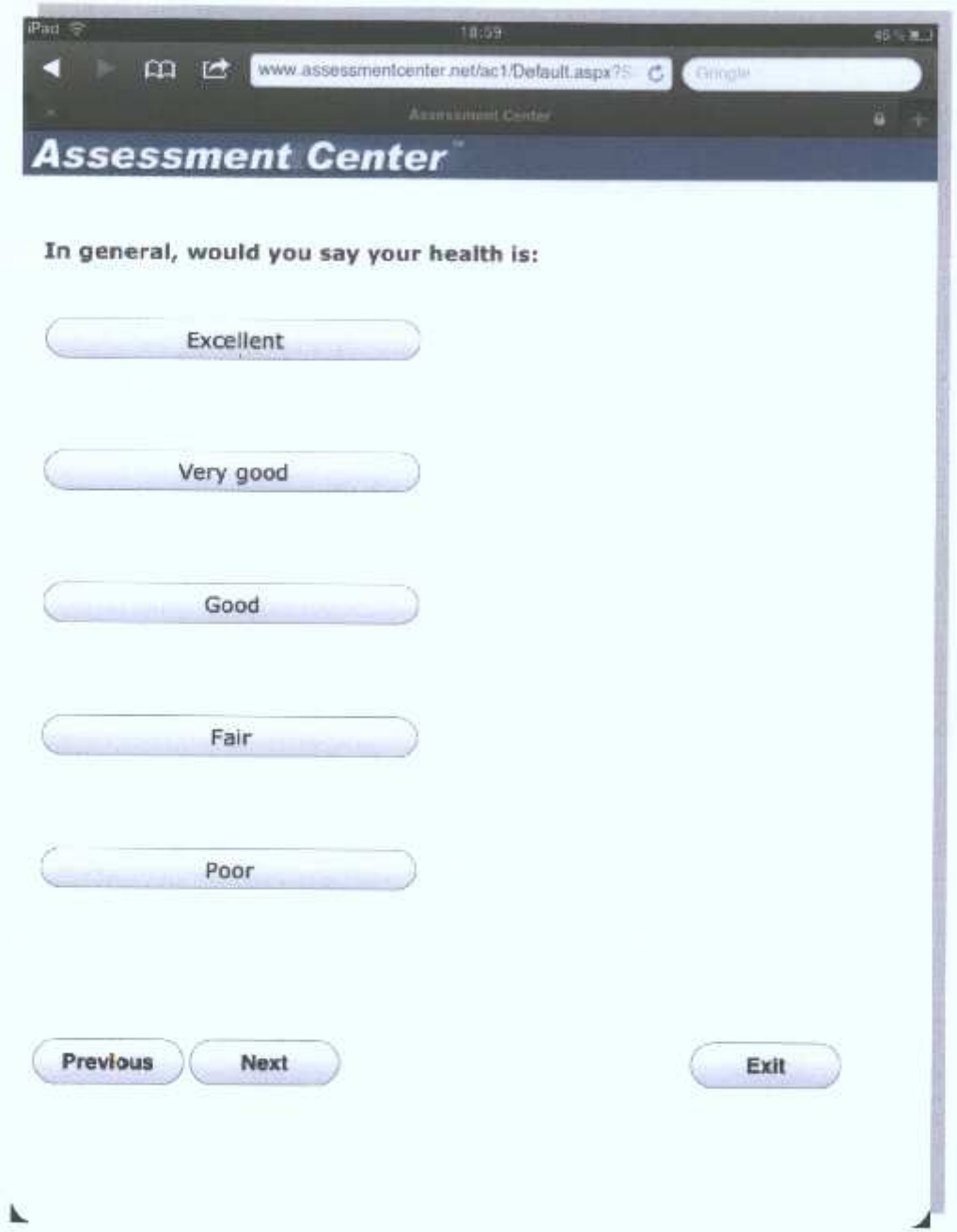
3.6 Consent

All individuals were consented by the attending physician and by the author. As per the IRB protocols at the institutions regarding questionnaires this consent was documented electronically as part of the questionnaire. A separate paper consent form was not necessary though an information sheet was provided. This was the protocol at all three institutions.

3.7 Data collection

Patients completed the survey using a tablet computer and data was collected through NIH Assessment Center (https://www.assessmentcenter.net) Assessment Center is and online data collection tool that enables researchers to create study-specific surveys to capture participant data securely online.

Figure 19 - Sample PROMIS QoL question on tablet computer



The short form questionnaires which measured various domains of are described in detail below. The paper format of these questionnaires is included however the survey was completed electronically. The paper format is included for completion. (Appendix 1)

1. Global QoL
    a. Physical Health
    b. Mental Health
2. Pain Interference
3. Pain Intensity

3.7.1 PROMIS Global Health

The **PROMIS Global Health item pool/scale** assesses health in general (i.e. overall health). The global health items include global ratings of the five primary PROMIS domains (physical function, fatigue, pain, emotional distress, and social health) as well as perceptions of general health that cut across domains. Global items allow respondents to weigh together different aspects of health to arrive at a "bottom-line" indicator of their health. Similar global health items have been found predictive of future health care utilization and mortality. The PROMIS Global Health items include the most widely used single self-rated health item ("In general, would you say your health is . . ."). Previous research has shown that this item taps physical and mental health about equally but reflects physical health more than mental health among respondents at lower income levels. PROMIS Global Health items include specific ratings of physical health and mental health, as well as a rating of overall QoL. The remaining items provide global ratings of physical function, fatigue, pain, emotional distress, and social health. The PROMIS Global Health items can be administered as individual items or combined to produce separate physical and mental health summary scores(106).

3.7.2 PROMIS Pain Intensity

The PROMIS Pain Intensity instrument is a 3 question short form instrument which assesses how much a person hurts. Patients are usually able to provide quantitative pain intensity estimates relatively quickly, and most measures of pain intensity tend to be closely related to one another. This suggests that pain intensity is a fairly homogeneous dimension, and one that is relatively easy for adults to identify and gauge. This instrument is generic rather than disease-specific. The first two items assess pain intensity over the past seven days while the last item asks patient to rate their pain intensity "right now".

3.7.3 PROMIS Pain Interference

The PROMIS Pain Interference instruments measure the self-reported consequences of pain on relevant aspects of one's life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. Pain interference also incorporates items probing sleep and enjoyment in life, though the item bank only contains one sleep item. The pain interference short form is generic rather than disease-specific. It assesses pain interference over the past seven days (107).

The scoring manuals for the individual PROMIS instruments have been included in this thesis. (Appendix 3)

3.8 Statistical analysis

The data was analyzed using the statistical package SPSS, Release Version 20. For Categorical and parametric variables I chose to use descriptive statistics, the

One-way ANOVA was performed to determine whether there are was any statistically significant differences between the high, low, total and hemi-sacrectomy groups with respect to physical function, mental health, pain interference and pain intensity. The level of significance was set at 5%. Results are expressed as mean value +- standard deviation (SD).

Levene's test was used to assess Variance homogeneity, which is a precondition for parametric tests such as the t-test and ANOVA. The test can be used with two or more samples. With two samples, it provides the test of variance homogeneity for the t-test. With more samples, it provides the test for ANOVA.

If the significance from this test is less than 0.05, then variances are significantly different and parametric tests cannot be used and a non-parametric test should be used instead.

Levene's test works by testing the null hypothesis that the variances of the group are the same. The output probability is the probability that at least one of the samples in the test has a significantly different variance. If this is greater than a selected percentage (usually 5%) then it is considered too great to be able to usefully apply parametric tests.

With respect to assessing coverage, precision and reliability of each questionnaire we determined median scores with range, floor and ceiling effects. Floor and ceiling effects describe the situation when patients score the lowest (floor) or the highest possible score (ceiling) on a questionnaire, leaving it impossible for the researcher to discriminate between these patients. This causes skewing of the data and as an effect it will influence the analysis

(108). It shows there is too little variation for the patient group it is being used in. Calculation of a Cronbach alpha assessed reliability. It uses a scale from 0 to 1 measuring internal consistency, with a higher score dictating higher internal consistency. A score of 0.9 or higher might indicate question redundancy and low validity, therefore a Cronbach alpha between 0.7 to 0.9 is recommended (109, 110).

Spearman rank correlation coefficient was used to measure the extent the PROMIS Pain Interference SF 6b and PROMIS Pain Intensity 3a questionnaires converge. Spearman measures the strength of association of two variables. All correlation analyses express the strength of linkage or co-occurrence between to variables in a single value between -1 and +1. This value is called the correlation coefficient. A positive correlation coefficient indicates a positive relationship between the two variables i.e. the larger A, the larger B, while negative correlation coefficients express a negative relationship i.e. the larger A, the smaller B. A correlation coefficient of 0 indicates that no relationship between the variables exists at all. However correlations are limited to linear relationships between variables. Even if the correlation coefficient is zero a non-linear relationship might exist.

Compared to Pearson's bivariate correlation coefficient the Spearman Correlation does not require continuous-level data (interval or ratio), because it uses ranks instead of assumptions about the distributions of the two variables. This allows us to analyze the association between variables of ordinal measurement levels. Moreover the Spearman Correlation is a non-paracontinuous-level test, which does not assume that the variables approximate multivariate normal distribution.

There is no rule for determining what size of correlation is considered strong moderate or weak. The interpretation of the co-efficient usually depends on the content of the study. In our case when we were studying domains which are difficult to measure we expect correlation co-efficients to be lower. Correlations below 0.2 are considered weak and between 0.2-0.4 are considered moderate. High correlation coefficients show a strong relationship between scores within the same construct (domain). When questionnaires are validated, a correlation coefficient between questions in the same domain that is higher than 0.4 is considered

satisfactory (111, 112). Using data from previous questionnaire validity studies I considered a correlation coefficient higher than 0.4 to be indicative of redundancy of the questionnaires within the same domain, meaning that there was significant overlap between questionnaires within the same domain (113, 114).

I used box plots to graphically present my findings. The box plot (a.k.a. box and whisker diagram) is a standardized way of displaying the distribution of data based on the five number summary: minimum, first quartile, median, third quartile, and maximum.

3.8.1 Definition of Level of sacral resection

Patients who have undergone a sacral resection were divided into one of four separate groups depending on their level of resection. The total Sacrectomy group included all patients who underwent a removal of the entire sacrum. The hemi-sacrectomy group included patients who had a portion of, or the entire hemi sacrum removed on one side only. The high sacrectomy group included patients that had a bilateral sacral resection that began at the S1 to S3 vertebra. The low sacrectomy group included patients who had a sacral resection from the S4 vertebra or below.

The individuals in each group were used as controls against each other. In terms of pain intensity, pain interference, physical function and global QoL a one-way ANOVA test was computed to determine if there was a statistically significant difference in the mean T-scores of each group. A box plot was also prepared to display the descriptive results in a graphical form.

Chapter 4 - Results

Overview

The aim of this chapter is to present the findings of my research conducted at Memorial Sloan Kettering Cancer Center, The Mayo Clinic and Massachusetts General Hospital from January 2012 to October 2013.

4.1 Population Characteristics

Fifty-four of the patients were diagnosed with a Chordoma, ten with adenocarcinoma, five with a Chondrosarcoma, two with an Osteogenic sarcoma, two with a Ewing's sarcoma, two with a radiation sarcoma and four patients with a giant cell tumor, myxoid liposarcoma, fibroblastic sarcoma and leiomyosarcoma. (Table 4) Forty-one patients underwent a high sacrectomy, 18 a low sacrectomy and 8 a total sacrectomy. Additionally, twelve hemisacrectomies were performed. (Table 3)

The study population included 53 men and 26 women. The mean age was 55.8 years (standard deviation [SD] = 18.1; range 13 – 85 years) (Table 2)

Table 2: Demographics of study participants

		Frequency (n)	Percent
	Male	53	67.1
	Female	26	32.9
	Total	79	100.0

Table 3: Age of patients in each sacral resection subgroup

		N	Mean	Std. Deviation	Minimum	Maximum
Age	**High**	41	60.44	14.67	21	84
	Low	18	51.94	18.40	15	72
	Hemi	12	54.25	20.54	23	85
	Total	8	43.00	24.23	13	75
	Overall	79	55.80	18.12	13	85

Table 4 - Table identifying pathologies of participants involved in study

		Frequency	Percent
	Chordoma	54	68.4
	Adenocarcinoma	10	12.7
	Chondrosarcoma	5	6.3
	Osteogenic Sarcoma	2	2.5
	Ewing's Sarcoma	2	2.5
	Radiation Sarcoma	2	2.5
	Fibroblastic Sarcoma	1	1.3
	Myxoid Liposarcoma	1	1.3
	Leiomyosarcoma	1	1.3
	Giant Cell Tumor	1	1.3
	Total	79	100.0

4.2 Global Health

The PROMIS Global health instrument is a 10 Question short form which measures physical and mental global health. A total of 79 patients completed this section. The patients were divided into subgroups of S1-S3 bone resection, S4-S5 bone resection, hemi-sacrectomy and total Sacrectomy as described in the previous chapter. The results are presented as mean T-scores.

An ANOVA was performed between the 4 groups to determine if there was a statistical difference between the mean T-scores (Table 5).

T-Score distributions are standardized such that a 50 represents the average (mean) for the US general population, and the SD around that mean is 10 points. A high score always represents more of the concept being measured. For example a person who has T-scores of 60 for the Global Physical Health or Global Mental Health scales is one SD better (more healthy) than the general population.

4.2.1 Physical Health

Table 5 PROMIS Global Health Physical Function Scores

	N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
				Lower Bound	Upper Bound		
High	41	44.99	8.15	42.41	47.56	34.90	67.70
Low	18	45.23	6.63	41.94	48.53	34.90	61.90
Hemi	12	40.96	5.74	37.31	44.61	29.60	47.70
Total	8	42.63	6.83	36.92	48.35	32.40	54.10

Table 6 Test of Homogeneity of Variances of Physical Function

Levene Statistic	df1	df2	Sig.
1.074	3	75	.365

There was homogeneity of variances, as assessed by Levene's Test of Homogeneity of Variance ($p = .365$).

Figure 20: Box plot of Mean T-Score of Physical Health

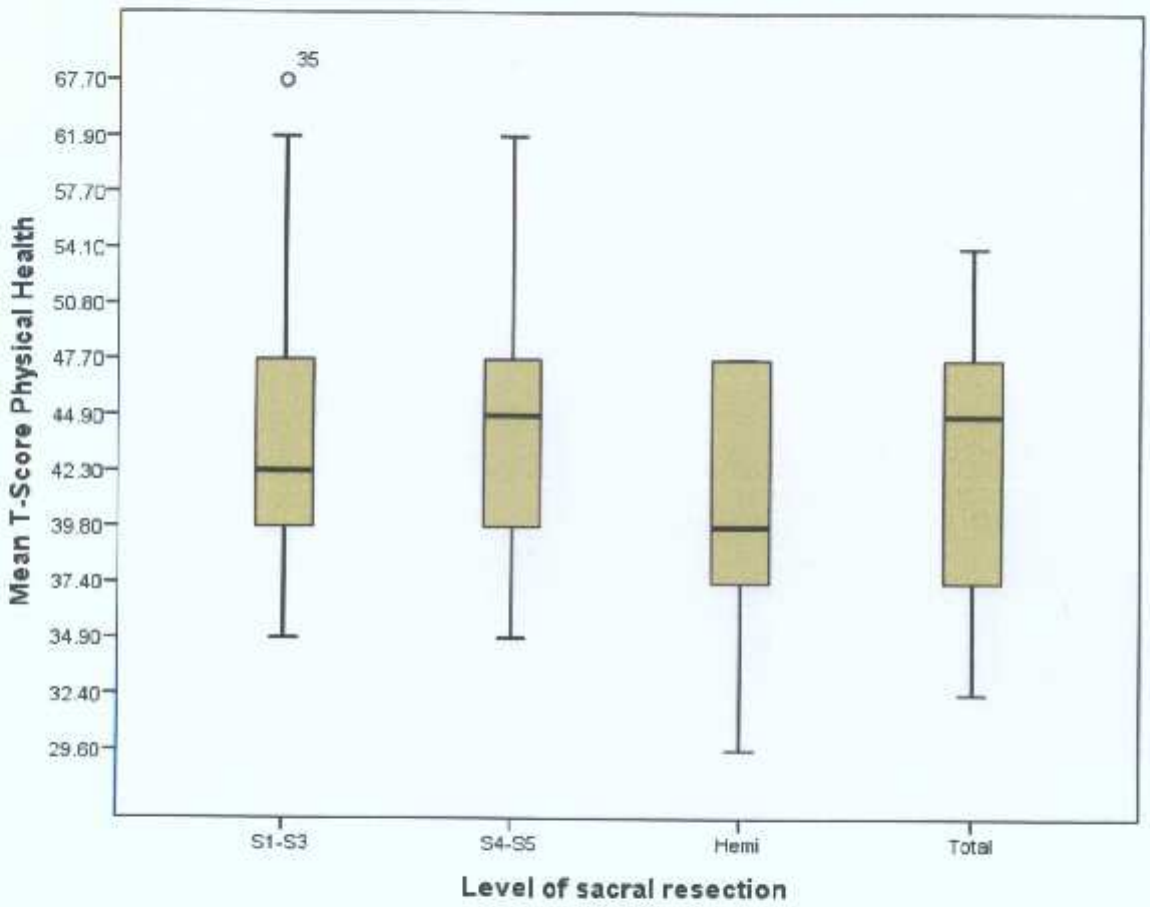


Table 7: ANOVA of Physical Health

	Sum of Squares	df	Mean Square	F	P value
Between Groups	190.015	3	63.33	1.15	.331
Within Groups	4099.464	75	54.66		
Total	4289.479	78			

There was no statistically significant differences in mean T-scores between the sacral resection groups, p = .331.

4.2.2 Conclusion

A one-way ANOVA was conducted to determine if the mean T-scores for the physical function subset of the Global health instrument was different for the different groups of sacral resection. Participants were classified into four groups: Total sacrectomy (n = 8), hemi-sacrectomy (n = 12), high sacrectomy (n = 41) and low sacrectomy (n = 18). There was one outlier in the high sacrectomy group, as assessed by box plot. There was homogeneity of variances, as assessed by Levene's test of homogeneity of variances (p = .365). Data is presented as mean
± SD. Physical function mean T-score increased from the hemi-sacrectomy group (41 ± 5.7), to total sacrectomy group (42.6 ± 6.8), to high sacrectomy group (45 ± 8.1), to low sacrectomy group (45.2 ± 6.2) in that order, but the difference between these sacral resection groups was not statistically significant, p = .331.

4.2.3 Mental subset of Global Health

Table 8: PROMIS Global Health Mental Health Scores

	N	Mean	Std. Deviation	95% Confidence Interval for Mean		Min	Max
				Lower Bound	Upper Bound		
High	40	47.18	8.87	44.34	50.02	28.40	67.60
Low	18	47.28	11.51	41.56	53.01	25.20	62.50
Hemi	12	46.51	6.91	42.12	50.91	36.30	58.00
Total	8	46.85	6.80	41.15	52.54	38.80	58.00

Figure 21: Box plot of Mean T-Score of Mental Health

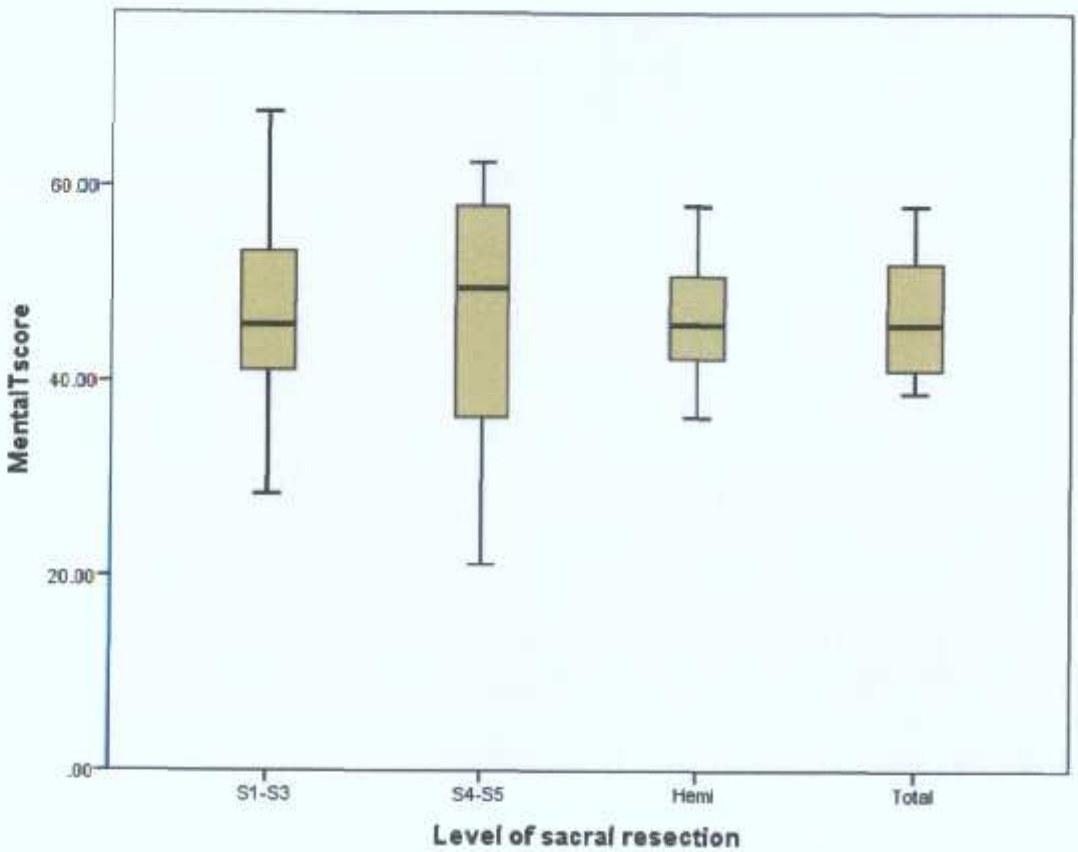


Table 9 Test of Homogeneity of Variances of mental health T-Score

Levene Statistic	df1	df2	Sig.
1.980	3	74	.124

There was homogeneity of variances, as assessed by Levene's Test of Homogeneity of Variance (p = .124).

Table 10: ANOVA of Mental Health

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	5.430	3	1.810	.022	.996
Within Groups	6174.052	74	83.433		
Total	6179.482	77			

4.2.4 Conclusion

A one-way ANOVA was conducted to determine if the mean T-scores for the mental health subset of the Global health instrument were different for the different groups of sacral resection. Participants were classified into four groups: Total sacrectomy (n = 8), hemi-sacrectomy (n = 12), high sacrectomy (n = 41) and low sacrectomy (n = 18). There were no outliers, as assessed by box plot. There was homogeneity of variances, as assessed by Levene's test of homogeneity of variances (p = .124). Data is presented as mean ± SD. The mental health mean T-score increased from the hemi-sacrectomy group (46.5 ± 6.9), to total sacrectomy group (46.9 ± 6.8), to high sacrectomy group (47.2 ± 8.9), to low sacrectomy group (47.3 ± 11.5) that order, but the difference between these sacral resection groups was not statistically significant, p = .996.

4.3 Pain Intensity

The pain intensity instrument is a 3 question short form. It is designed to assess how much a person "hurts". Through using this instrument patients are able to provide quantitative pain intensity estimates accurately and quickly. The questionnaire has been designed to be generic rather than disease-specific. The first two items assess pain intensity over the past 7 days, while the last question requires the patient to quantify their pain intensity "right now".

A higher PROMIS T-score represents more of the concept being measured. For negatively-worded concepts like pain intensity, a T-score of 60 is one SD worse than average. By comparison, a pain intensity T-score of 40 is one SD better than average.

Table 11: PROMIS Pain Intensity Scores

	N	Mean	Std. Deviation	95% Confidence Interval for Mean		Min	Max
				Lower Bound	Upper Bound		
S1-S3	41	43.00	8.94	40.18	45.82	30.70	57.50
S4-S5	18	42.34	9.16	37.78	46.90	30.70	60.50
Hemi	12	52.65	6.93	48.24	57.05	46.30	64.10
Total	8	51.70	8.44	44.64	58.75	40.20	64.10

Figure 22: Box plot of Mean T-Score of Pain Intensity

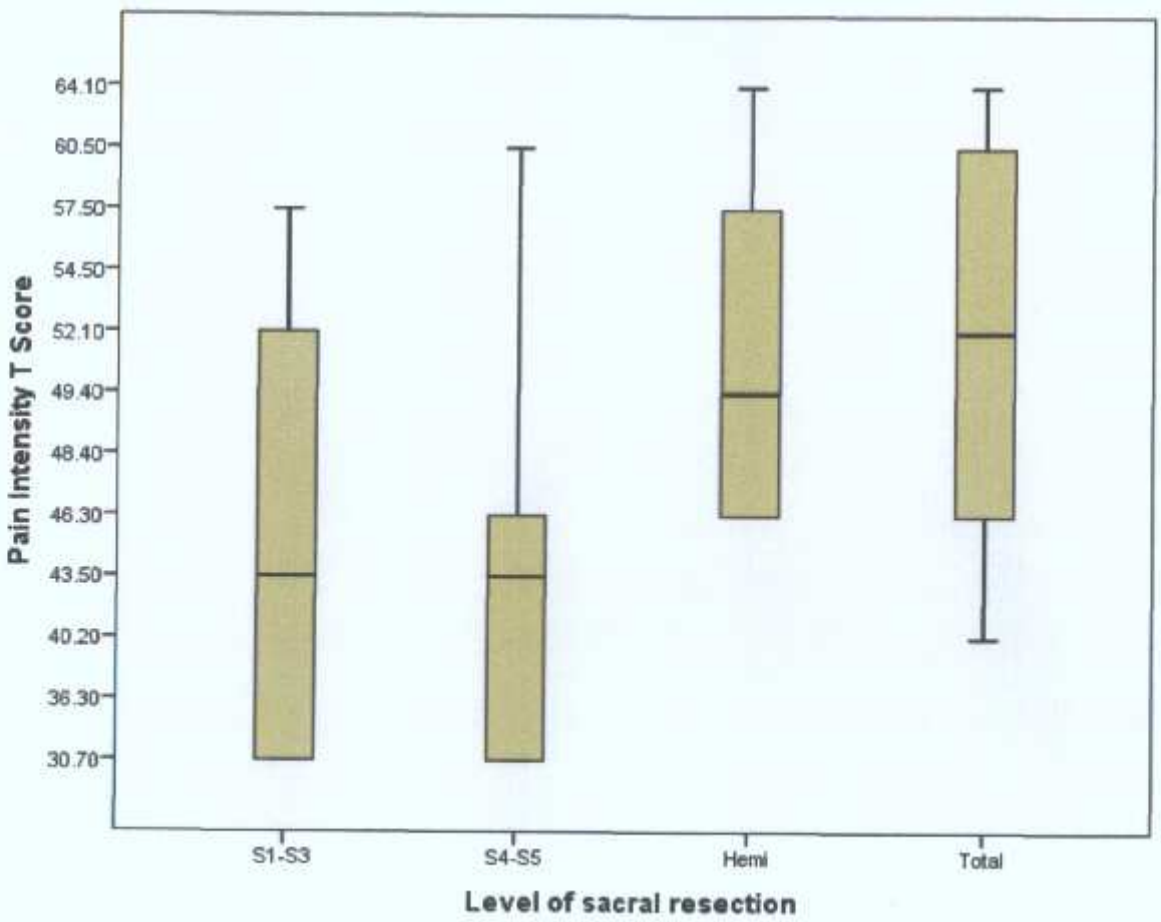


Table 12 Test of Homogeneity of Variances of Pain Intensity

T-Score Table

Levene Statistic	df1	df2	Sig.
.471	3	75	.703

There was homogeneity of variances, as assessed by Levene's Test of Homogeneity of Variance (p = .703). (Table 12)

Table 13: ANOVA of Pain Intensity

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	1348.8	3	449.60	5.964	.001
Within Groups	5653.7	75	75.38		
Total	7002.5	78			

4.3.1 Conclusion

A one-way ANOVA was conducted to determine if the mean T-scores for the Pain intensity instrument was different for the different groups of sacral resection. Participants were classified into four groups (table 11): Total sacrectomy (n = 8), hemi-sacrectomy (n = 12), high sacrectomy (n = 41) and low sacrectomy (n = 18). There were no outliers, as assessed by box plot. There was homogeneity of variances, as assessed by Levene's test of homogeneity of variances (p = .703). Data is presented as mean ± SD. The mean pain intensity T-score decreased from the hemi-sacrectomy group (52.7 ± 6.9), to total sacrectomy group (51.7 ± 8.4), to high sacrectomy group (43 ± 8.9), to low sacrectomy group (42.3 ± 9.1) in that order.and the difference between these sacral resection groups was statistically significant, p = .001 (table 13)

4.4 Pain Interference

The PROMIS Pain Interference instruments measure the self-reported consequences of pain on relevant aspects of one's life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. Pain interference also incorporates items probing sleep and enjoyment in life, though this particular short form only contains one sleep item. This short form measures pain interference over the past seven days

Again as mentioned regarding the previous PROMIS results, a higher PROMIS T-score represents more of the concept being measured. For negatively-worded concepts like pain interference, a T-score of 60 is one SD worse than average. By comparison, a pain interference T-score of 40 is one SD better than average

Table 14: PROMIS Pain Interference Scores

	N	Mean	Std. Deviation	95% Confidence Interval for Mean		Min	Max
				Lower Bound	Upper Bound		
S1-S3	41	53.47	8.64	50.74	56.19	41.00	72.60
S4-S5	18	53.98	9.79	49.11	58.85	41.10	69.80
Hemi	12	58.04	6.83	53.70	62.38	41.10	66.70
Total	8	58.96	9.94	50.64	67.27	41.10	72.60

Figure 23: Box plot of Mean T-Score of Pain Interference

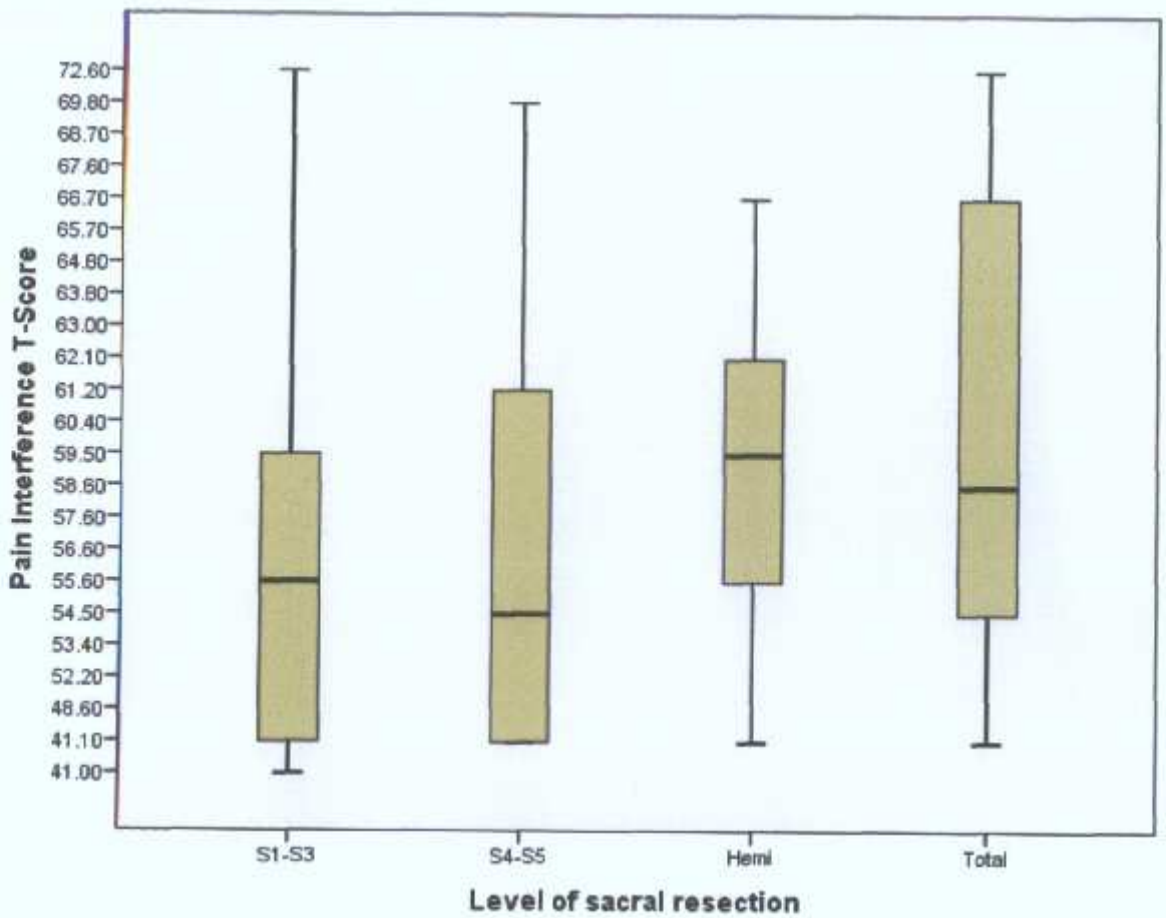


Table 15 Test of Homogeneity of Variances of Pain Interference

T-Score Table

Levene Statistic	df1	df2	Sig.
1.078	3	75	.364

There was homogeneity of variances, as assessed by Levene's Test of Homogeneity of Variance (p = .364).

Table 16: ANOVA of Pain Interference

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	348.878	3	116.293	1.498	.222
Within Groups	5824.211	75	77.656		
Total	6173.088	78			

4.4.1 Conclusion

A one-way ANOVA was conducted to determine if the mean T-scores for the Pain interference instrument were different for the different groups of sacral resection. Participants were classified into four groups (table 14): Total sacrectomy (n = 8), hemi-sacrectomy (n = 12), high sacrectomy (n = 41) and low sacrectomy (n = 18). There were no outliers, as assessed by box plot. There was homogeneity of variances, as assessed by Levene's test of homogeneity of variances (p = .364). Data is presented as mean ± SD. The mean pain intensity T-score decreased from the total sacrectomy group (59 ± 10), to hemi-sacrectomy group (58 ± 8.6), to low sacrectomy group (54 ± 9.8), to high sacrectomy group (53.5 ± 9.1) in that order, and the difference between these sacral resection groups was not statistically significant, p = .222 (table 16)

4.5 Questionnaire validity

Table 17: Internal consistency, floor and ceiling effect and score distribution per PROMIS questionnaire

Scales	Items per scale	Number	Range	Possible range	Cronbach's Alpha	Floor effect (%)	Ceiling effect (%)	High score indicates
Global Item Mental SF	4	79	25.2 67.6	21.2 – 67.6	.67	0 (0)	1 (0.8)	Better health
Global Item Physical SF	4	79	29.6 – 67.7	16.2 – 67.7	.48	0 (0)	1 (0.8)	Better health
Pain Interference	6	79	41 – 72.6	41.0 – 78.3	.94	19 (24)	0 (0)	Worse pain interference
Pain Intensity	3	79	30.7 – 64.1	30.7 – 71.8	.87	16 (20)	0 (0)	Worse pain intensity

PROMIS Global Item SF had minimal floor and ceiling effect in both domains; *Mental Health* 0% (0 of 79) and 0.8% (1 of 79) respectively, and *Physical Health* 0% and 0.8% (1 of 79) respectively. This indicates adequate coverage for this patient population at both ends of the scale. The internal consistency of these questionnaires was low, as indicated by the Cronbach alpha of 0.67 and 0.48 respectively (Table 17)

PROMS Pain Interference SF and PROMIS Pain Intensity had substantial floor effects; 19% (24 of 79) and 16% (20 of 79) respectively. For these questionnaires, this indicates poor coverage when the patient is in good health. Internal consistency of these questionnaires was high, as indicated by the Cronbach alpha of 0.94 and 0.87 respectively.

4.6 Analysis of hypothesized domains (Table18)

Factor trait analysis demonstrated similar trait being measured by the PROMIS Pain Intensity SF and Pain Interference SF. Spearman correlation coefficient was higher than 0.4 indicating fairly

high correlation between the two questionnaires and therefore rendering them possibly redundant.

Table 18. Spearman Correlation of Pain Intensity and Pain Interference

Correlations

			Pain Intensity	Pain Interference
Spearman's rho	Q1	Correlation Coefficient	1.000	.862**
		Sig. (2-tailed)	.	.000
		N	87	87
	Q2	Correlation Coefficient	.862**	1.000
		Sig. (2-tailed)	.000	.
		N	87	87

**. Correlation is significant at the 0.01 level (2-tailed).

4.7 Patient choice

We asked our patients at the end of each survey "If given the choice to reconsider would they have this surgery again" They were provided with a Yes or No response. An overwhelming 97.5% indicated they would undergo this procedure again.

Table 19 – Patient Choice of repeat surgery

If you were given the option, would you choose to have this surgery again?	
Yes	77 (97.5 %)
No	2 (2.5%)

Chapter 5 – Discussion

5.1 Summary of findings

This study aimed to quantitatively evaluate the QoL in patients following a sacral resection using patient reported outcome measurements. The original hypothesis was that quality of life would be worse in the more invasive sacrectomy subgroups, i.e. Total sacrectomy worse than, high, worse than low, worse than hemi-sacrectomy. My findings were that there were no statistically significant differences between these groups in terms of physical function, mental function or pain interference. I did find a statistically significant difference between the sacrectomy groups with respect to pain intensity. Pain intensity was significantly worse in the total and hemi-sacrectomy groups compared to the high and low sacrectomy groups which were in keeping with our original hypothesis.

5.2 Global quality of life

The PROMIS global health instrument was chosen as it had the benefit of being comparable covering both physical and mental well being which served to give a general overview of our participants QoL. It also had the added benefit of correlating with another widely used QoL instrument the EQ-5D (115). My hypothesis prior to collecting data was that a clear trend would emerge in this data. I predicted that patients who underwent a Total Sacrectomy would report the worst overall global QoL followed by the hemi-sacrectomy patients, then the high sacrectomy and finally the low sacrectomy group.

With respect to physical function the trend matched my initial assumptions however the results were not statistically significant. My impression is that given the small sample size of our study and the rarity of the disease, this makes it difficult for the power of the study to provide statistically significant results. The differences between the mean T-scores are small but the trend still remains. I postulate that a longitudinal prospective study will yield similar trends but

with greater statistical power. I was surprised however that there were not greater differences between the groups as I expected a markedly decreased mean T-score in the total sacrectomy group compared to the low sacral resection group.

Another interesting point is that the mean T – Scores are in the 40 – 50 range, as mentioned earlier PROMIS instrument results are represented as T-score distributions that are standardized such that a 50 represents the average (mean) for the US general population, and the SD around that mean is 10 points. Therefore our patients are within one SD of the general population for physical health. My rationale for this is that as patients adapt to their condition post operatively they no longer compare their QoL to their pre-operative conditioning. I feel that they choose responses based on their maximal expectations for their QoL in the present and answer accordingly. Another possibility is that the questions which are administered are not specific enough to our patient population. Sacrectomy patients often refer to the inability to sit for prolonged periods of time; however no question in our instrument addresses this.

5.3Pain Intensity

The pain intensity instrument yielded some interesting results. I again would have anticipated the same trend of results as in the previous instrument however it turned out that the hemi-sacrectomy group reported the worst pain intensity scoring a 52.6 compared to 51.7 for the Total Sacrectomy group. These results were statistically significant. It is possible that stability of the hemi-sacrectomy group post operatively plays a large role in this result. While the total sacrectomy patients will have undergone reconstruction and stabilization, the patients in the hemi-sacrectomy group were not stabilized. Another possibility is that in the hemi-sacrectomy cohort of individuals loss of sciatic nerve function unilaterally may be more impactful than in

those patients who have lost function bilaterally as they learn to cope with complete loss of function as opposed to partial loss.

The most interesting aspect of this subsection of results is that patients with low and high sacral resection reported a mean T-score in the 40-50 range, which is actually better than the average US population. These results are confusing and warrant further investigation. Again it is possible that over time patients adapt to their situation and may be desensitized to a high level of pain. Another possibility is that patient's may be on long term pain medication and I would propose that in a prospective study that opiate dosages and frequency should be recorded to improve the validity of our results.

5.4 Pain Interference

The PROMIS Pain Interference instruments measure the self-reported consequences of pain on relevant aspects of one's life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. The trend of pain interference was similar to my original hypothesis of Total Sacrectomy to Low sacrectomy in order of high to low. Unfortunately on analysis these results were not statistically significant.

Overall the results are consistent with what one would expect between each subsection

5.5 Validity of questionnaire

Given that this is the first time a study of this kind has been carried out on this particular patient population I felt it was important to assess the coverage, precision and reliability of the PROMIS instruments. We assessed floor and ceiling effects for each domain as well as a calculation of a Cronbach alpha to assess reliability. The PROMIS Pain Intensity and PROMIS

Pain Interference instruments demonstrated high reliability but large floor effects, while the PROMIS Global Health SF demonstrated borderline reliability but no ceiling or floor effects showing good coverage and precision. My impression is that these instruments should be used in our longitudinal prospective study as they will be assessing patients at similar points in time, whereas this study was given to patients at varying times post operatively.

5.6 Patient choice

I included a question on patient choice at the end of the questionnaire which asked patients "If given the choice to reconsider would they have this surgery again" They were provided with a Yes or No response.

I was surprised that 97.5% of patients indicated that they would choose to undergo this life changing, morbid procedure again if given the choice. Anecdotally I found that patients felt that the time they gained by choosing the procedure to spend with friends and loved ones was worth the complications that this procedure brings with it. I found that the majority of patients felt "lucky to be alive" and would continuously proclaim a huge amount of gratitude on their particular surgeon. It would seem that patients may be subconsciously downplaying the effect of this procedure on their QoL as a trade off for not succumbing to the inevitable mortality they would have faced had they not underwent this procedure.

5.7 Limitations of this study

5.7.1 Multi-institutional

There were some reportable difficulties which arose due to the fact this was a multi-institutional study. Notably, IRB approval took varying amounts of time depending on the

institution. There was a variation in availability of staff able to assist patients in taking the questionnaire at each institution.

5.7.2 Data analysis

Given that this is a rare disease entity analysis of the data is extremely difficult. The major limitation of this study is its retrospective nature. The questionnaire was given to patients post operatively and we are asking them to assess their QoL here and now without having a fair judge of their QoL pre-operatively. Another issue is the timing of the questionnaires; patients were given the questionnaire once at random time points, some participants were several months out from their procedure while others were several years. Patients in the first year of the procedure would be expected to report a more severe decline in overall QoL, whereas patients many years out will have adjusted and compensated more with their condition and may report an improvement in QoL when compared with their first year post op. The low floor effect shown in the pain intensity and pain interference analysis demonstrates that it has poor coverage for patients on the healthier end of the scale within a sacrectomy population. Furthermore questionnaires measuring similar constructs seem too redundant when combined in domains.

The variety of pathologies involved is another significant factor. Chordoma made up the majority of disease burden in this study, but we must take into account the severity of each disease process. For example, one would expect a patient with Osteogenic sarcoma of the sacrum to have a more systemic disease process than a patient with a benign giant cell tumor of the sacrum. Patients undergoing systemic therapy for their disease such as chemotherapy or radiation therapy would also be expected to report a worse QoL.

I recognize that these factors are important but difficult to measure given the low numbers of patients we can expect to recruit. The proposed solution is to create a prospective study using

patient reported outcome measurements which are cover the more specific areas of our patient population, specifically bowel, bladder and sexual function.

Another significant difficulty of this study was the lack of previous investigations to compare our findings too. This is the first study of its kind and our hope is that it will serve as a solid comparison for future studies in this rare patient population.

Chapter 6

Future Research

6.1 Implications for clinical practice

Patient satisfaction is an integral part of surgical outcomes. For a surgery as morbid as a sacrectomy patients should be fully informed of the potential consequences of their procedure and the data we record is essential in providing the patient with information which will allow to them to provide informed consent and psychologically come to terms with the post operative QoL they will come to expect.

If surgeons had hard data of what patient's QoL was in those patients who will suffer from bowel dysfunction without a stoma versus those who choose stoma formation, patients may choose to undergo a procedure at the time of their sacrectomy rather than electively in the future.

My goal was to develop a QoL tool based on previously validated instruments which we felt would be most applicable to our rare patient population. Our aspiration was for the results of this instrument to be disseminated out to the spinal oncology community and for it to be accepted as a standardized measure of QoL in sacrectomy patients from both a prospective and retrospective stand point. Unfortunately given our small patient population and the retrospective nature of the study this data is not reliable to provide patients with accurate QoL expectations. However we feel that using our results from this study we can look forward to creating a validated patient-generated assessment tool for QoL. Since the beginning of this study, new validated PROMIS instruments have become available. This will be discussed in the future research section. With the experience I have gained our hope is that by the completion of our longitudinal prospective QoL study we will obtain statistically significant data which will allow patients to make informed decisions about their treatment and will reduce the gap between their expectations and actual outcome. Accurate patient expectations are associated with better postoperative results.

6.2Development of prospective questionnaire

I recommend, as we partly showed in our results, to create a total of 6 domains which I believe will adequately cover the areas that affect patients who undergo a sacrectomy in the future; *Mental Health, Physical Health, Pain, GastrointestinalSymptoms, Urinary Incontinence* and *Sexual Function*. This will be used to form part of a prospective study following patients with newly diagnosed sacral tumors who will undergo sacrectomy. The questionnaire should be administered at time of diagnosis, then at 1, 3, 6 and 12 months post operatively.

Mental health and Physical health

I recommend continuing to use the PROMIS Global SF as part of future studies. It has the benefit of measure mental and physical domains and eliminates the need for individual questionnaires. PROMIS has individual short form questionnaires including the PROMIS Depression, PROMIS Anxiety and PROMIS QoL Lower Extremity Function questionnaires. However this would increase the complexity and time burden of the questionnaire.

Pain

I suggest using the PROMIS Pain Intensity questionnaire. It shows high correlation with PROMIS Pain Interference, but contains fewer items.

Gastrointestinal symptoms

In 2015 PROMIS added its new PROMIS Gastrointestinal Symptoms Scale, containing the domains *Constipation* (9 items) and *Bowel Incontinence/Soilage* (4 items). This questionnaire

can be used to capture the effects of bowel incontinence and constipation in patients following loss or damage to the sacral nerve roots following sacrectomy.

Urinary Incontinence

Unfortunately PROMIS does not currently have a question bank or domain that covers Urinary Incontinence. It would be possible to add the Incontinence Impact Questionnaire and Urogential Distress Inventory which is frequently used in urinary incontinence patients and validated for use in males and females. However I believe the use of external questionnaires should be avoided if possible. An alternative would be to work with PROMIS to develop a urinary incontinence questionnaire.

Sexual Function

We recommend adding the PROMIS Sexual Function questionnaire to cover the *Sexual Function* domain.

6.3 Final Thoughts

Despite the invasive and life altering complications that arise from a sacrectomy, this author believes that it is a surgery with merit. The patients in this study clearly placed their determination for survival over the prospect of loss of quality of life. This was reflected by the fact that 97.5% of patients in our survey noted that if given the choice they would have the same surgery again. I believe that patients place the ability to spend time with loved ones, attend weddings, graduations and birthdays as a worthy trade off to the diminished physical function, often times crippling pain and altered bowel habits. As such it is imperative we are able to record patients' emotional and physical well being accurately and longitudinally. By

following patients from the time of diagnosis, through the early post operative period all the way to one year post resection, we will be able to track the improvement or decline in their overall quality of life. These indices will set a marker or goal for future patients who will no longer go into this procedure with the uncertainty or pessimism which undoubtedly stigmatizes this invasive procedure.

Sacrectomy will continue to be the mainstay of treatment for primary tumors of the sacrum for the foreseeable future. New targeted molecular pathway drugs, proton beam therapy radiation and chemotherapy agents are being developed but are nowhere near ready enough to take the place of surgical resection.

With respect to improving patient outcomes, it is imperative that we have a multi-disciplinary approach. Early involvement of the pain service, physical and occupational therapists and psychiatry will link the patient into a necessary support system. Post operatively early mobility and aggressive weaning of narcotic medication will pay dividends.

6.4 Conclusion

A sacrectomy is one of the most morbid procedures in the oncologic surgeon's arsenal. The effects of this operation are not purely physical but psychological as well. This pilot study aims to be a stepping stone to show that there is a need for long term prospective study on this rare cohort of patients. Despite the small sample size I did show statistical significance in pain intensity across our sacral resection subgroups. The decisions we make as surgeons should be evidence based in order to provide the best care for our patients. Given the involvement of various subspecialties prior to surgical resection including, oncology, orthopaedics, general surgery, urology, gynecology, radiation oncology to name a few, patients are often overwhelmed by the volume of information coming at them.

The pool of literature regarding sacrectomy QoL outcomes is virtually nonexistent. This study demonstrates the need for a universal QoL tool which measures overall QoL, physical function,

mental function, pain, bowel, bladder and sexual function. To our knowledge this is the first study to attempt to measure the QoL in patients post sacrectomy.

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Appendix 1

PROMIS SHORT FORMS

Global Health Scale

Please respond to each item by marking one box per row.

	Excellent	Very good	Good	Fair	Poor
In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In general, would you say your quality of life is:.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In general, how would you rate your physical health?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In general, how would you rate your mental health, including your mood and your ability to think?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

	Completely	Mostly	Moderately	A little	Not at all
To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In the past 7 days...

		Never	Rarely	Sometimes	Often	Always
Global10	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

		None	Mild	Moderate	Severe	Very severe
Global08	How would you rate your fatigue on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Global07	How would you rate your pain on average?	☐ 0 No pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 Worst imaginable pain

Pain Intensity – Short Form 3a

Please respond to each item by marking one box per row.

	In the past 7 days…	Had no pain	Mild	Moderate	Severe	Very severe
PAINQL4	How intense was your pain at its worst?....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAINQL5	How intense was your average pain?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
		No pain	Mild	Moderate	Severe	Very severe
PAINQL6	What is your level of pain right now?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Pain Interference – Short Form 6b

Please respond to each item by marking one box per row.

In the past 7 days…

	Not at all	A little bit	Somewhat	Quite a bit	Very much
How much did pain interfere with your enjoyment of life?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with your ability to concentrate?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with your day to day activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with your enjoyment of recreational activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with doing your tasks away from home (e.g., getting groceries, running errands)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

In the past 7 days…

	Never	Rarely	Sometimes	Often	Always
How often did pain keep you from socializing with others?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix 2

Information Leaflet

Memorial Sloan-Kettering Cancer Center

Welcome to the Sacral Resection Quality of Life Questionnaire.

This questionnaire has been designed for patients who underwent a sacral resection at Memorial Sloan Kettering Cancer Center. We are extremely interested in your progress. We have created this questionnaire in order to better understand how this disease and surgery has affected your life.

The following questions will examine a variety of aspects of your life, including:

- **General Quality of Life**
- **Pain**
- **Physical Function**

Please complete all questions. Your time and effort is greatly appreciated. Your input will aid in our future care of patients who will undergo a similar procedure to you. If you have any questions, please contact Dr. Boland's office at 212-639-8293.

If you already have a Login and Password, please enter them in the boxes.

Login

Password

If you are a first time user, click Start below.

Start

If you have any questions or problems, please contact mckeownd@mskcc.org.

If you would like to bookmark this page, click this **Add to Favorites** link.

Appendix 3

IRB Approval

Prospective Collection and Study of Data-
Application for Exemption from IRB/PB Review
(including a waiver of authorization & informed consent)

Purpose: If your research is either (1) exempt from IRB/PB review or (2) does not meet the definition of human subject research please complete this form and submit to the IRB/PB Office. Please note: If your research is retrospective, please do not complete this form. A *Collection or Study of Existing Data Exemption Form* should be completed and submitted to the IRB/PB review and approval.

Part A – General Information			
Project Title	Quality of Life in Patients following Sacral Resections		
MSK Staff*	**Name**	**Department/Service**	
Principal Investigator	Patrick Boland, MD	Surgery/Orthopaedic	
Co-investigator(s)	John Healey, MD	Surgery/Orthopaedic	
	David McKeown, MBBCH	Surgery Orthopaedic	
	Chanhanarat Chandhanayingyong, MD	Surgery/Orthopaedic	
	Emily Zabor, MS	Epidemiology/Biostatistics	
	Martin Weiser, MD	Surgery/Colorectal	
	Garrett Nash, MD	Surgery Colorectal	
Other Personnel	Jesse Galle (RPC)	Surgery/Orthopaedic	
	Fumiko Egawa (RSA)	Surgery/Colorectal	
Outside Site**	**Name**	**Location**	**Phone #**
Massachusetts General Hospital	Joseph Schwab, MD	Boston, MA	617-724-8636
The Mayo Clinic	Peter Rose, MD	Rochester, MI	507-284-2995

* Please Note: All MSK participating staff must have completed the mandatory Human Subjects Education and Certification Program. Please see the IRB/PB website @ http://mskweb5.mskcc.org/intranet/html/70792.cfm for instructions on completing the required training.
**Outside Site(s) must provide a letter that they are going to partake in this research.

Part B – Funding Information	
Type: Peer-Reviewed Grant/Project (NIH, RO1, etc.)	**Awardee:** Patrick Boland, MD
Funding Source with Grant # (if applicable): Orthopaedic Research & Education Foundation	**Amount:** $ 20,000
Award Period: From 1/1/2012 To 1/1/2013	**Status:** Active

Verify if there is a Conflict of Interest:

Investigator	☐ Yes	☒ No
Institutional	☐ Yes	☒ No

If yes, please explain:

Part C – Regulatory Criteria for Exemption

Exemption cannot be granted for the following categories:

- **FDA Regulated Projects:** FDA-regulated agents or devices cannot be declared exempt under above categories.
- **Children:** Surveys and interviews involving children cannot be declared exempt.
- **Prisoners:** Research involving prisoners cannot be declared exempt.
- **Miscellaneous:** If the research involves significant infringement upon the privacy of subjects, the research cannot be declared exempt.

Regulatory Criteria for Exemptions: To claim exemption from the human subject protection regulations and IRB/PB review, the reviewer must have sufficient information to verify that all components of the research fit the categories described below (45 CFR 46.101).
Please check off the following categories that describes your research:

☐ Research conducted in established or commonly accepted educational settings, involving normal educational practices as:

- Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods. (45 CFR 46.101(b)(1))

☒ Research involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, where:

- Information obtained is unidentifiable, or
- Identifiable information obtained – if disclosed outside the research- could not reasonably place subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation. (45 CFR 46.101(b)(2))

Please provide Justification/Rationale for your category selection:

The research to be collected will be de-identified questionnaire results regarding the quality of life of patients who underwent total or partial sacrectomy. Retrospective capture of information is needed to initially identify the patients and determine their eligibility. The type of operation is required, which can only be performed by examination of medical

records. The majority of these patients don't follow-up on a regular basis. Therefore, the survey needs to be emailed to certain patients. For those patients that follow up on a regular basis, surveys will be filled out during a regularly scheduled clinic visit. Patients will be initially identified using the Orthopaedic Surgical Database. PHI will be deleted from the data set, and a unique identifier (not an MSKCC MRN) will then be used to identify the data. The unique identifier will be entered on the corresponding electronic or paper questionnaire given to the patients, so the questionnaire can be linked back to the de-identified data.

Part D – Project Information

Please explain your project in the following sections:

1. **Synopsis of proposed project**

   a. *Background/Rationale*

   Tumors of the sacrum are rare, limiting the experience of any single center, and putting a premium on sharing experience between centers. Furthermore, the anatomic complexity of the sacro-pelvic area demands multispecialty expertise in all aspects of the evaluation, diagnosis, surgery, adjuvant therapy, rehabilitation and follow up of these patients. The Massachusetts General Hospital and The Mayo Clinic have agreed to participate in this study, which will help increase the number of patients eligible for this study.

   b. *Objectives*

   The objectives of this study are to evaluate the quality of life in patients who underwent sacral resection, to evaluate the functional outcome of these patients, to improve patient education prior to undergoing a sacral resection, and to further advance knowledge of sacral tumors in the surgical community as a whole.

   c. *Design/Method of obtaining data & estimated duration of study*

   Outline and include any questionnaires, surveys, or other intervention tools to be used. Estimated duration of the study (recruitment, data collection, and data analysis) must be included.

   At the 2012 Annual Sacral Conference at the Mayo Clinic, appropriate quality of life (QoL) instruments, including the NIH's new Patient Reported Outcomes Measurement Information System (PROMIS), were selected for a multi-institutional cross-sectional study of sacrectomy patients. The participating institutions at the conference were Memorial Sloan-Kettering Cancer Center, Massachusetts General Hospital, and The Mayo Clinic.

emailed to patients who don't follow-up on a regular basis, and given electronically to patients who do follow-up regularly in clinic on the web-based platform. The Assessment Center is web-based, allowing the data from all participating institutions to be stored in one central location. Dr. Boland, David McKeown, and the MSKCC Statistician will complete the data analysis. Any data shared between sites will be de-identified. Furthermore, Dr. Schwab and Dr. Rose are previous MSKCC Orthopaedic Oncology Fellows, and regularly in contact with Dr. Boland and David McKeown. This will ensure any issues that potentially arise will be resolved in a timely manner.

2. Recruitment Plan

How you will access subjects, what kind of permission you will seek from subjects and how that permission will be documented.

A voluntary survey will be emailed to patients that were identified as meeting the study criteria, or patients will fill the survey out during a regularly scheduled clinic visit on an electronic tablet (iPad). The electronic questionnaires completed on the iPads will not allow the patient to leave any identifying information. An Orthopaedic Research Fellow or Research Study Assistant will be present in the clinic or available on the phone to aid the patient with any questions or difficulties they may have in relation to the questionnaire.

Study Population Descriptors

Age:	**Gender of Participants:**	**Estimated # of Participants 100**
Minimum Age: 18_yrs	☒Male ☒Female	
Maximum Age: _85__yrs		

3. Data Collection

Please answer the following questions:

1. Does the project involve obtaining information about deceased individuals?
   ☐ Yes ☒ No

2. Does the project involve prospective collection of human data?
   ☒ Yes ☐ No
   - If yes, please describe where the data will be stored, who will have access to the data, and outline how the data will be coded and labeled: Patients will be initially identified using the Orthopaedic Surgical Database. Outside sites (The Mayo Clinic and MGH) will identify eligible patients using their own institutional databases. PHI will be deleted from the data sets, and a unique identifier (not an MSKCC MRN) will then be used to identify the data. Any exported data will be stored on a protected MSKCC network drive. This file will be password protected, effectively limiting access to the investigators listed above. The unique identifier will be placed on the corresponding paper and electronic questionnaires given to the patients, so the

2) List the individuals or groups outside MSKCC that PHI will be disclosed to. (*e.g., research collaborators from other institutions or a research sponsor*). If PHI will NOT be released outside MSKCC in this study, please make a statement to that effect: PHI will not be released outside of MSKCC. Peter Rose, MD (The Mayo Clinic) and Joseph Schwab, MD (MGH) will send and receive de-identified data.

e. Does the use or disclosure of PHI involve a privacy risk to the individuals?
☐ Yes ☒ No
If yes, describe:

f. Describe the plan to protect identifiers from unauthorized use or disclosure. Indicate where the PHI will be stored and specify the measures that will be implemented for both paper and electronic forms of PHI: All surveys will not contain any PHI. Patients will be initially identified using the Orthopaedic Surgical Database. Outside sites (The Mayo Clinic and MGH) will identify eligible patients using their own institutional databases. PHI will be deleted from the data sets, and a unique identifier (not an MSKCC MRN) will then be used to identify the data. The data det will be stored on a protected MSKCC network drive. This file will be password protected, effectively limiting access to the investigators listed above. The unique identifier will be placed on the corresponding electronic questionnaire given to the patients, so the questionnaire can be linked back to the de-identified data. At the conclusion of the study, all information will be deleted from the protected MSKCC drive. The de-identified electronic survey results will be stored on the NIH Assessment Centers' online secured database, and can only be accessed by the investigators listed in this study. PROMIS and the Assessment Center have been and continue to be used widely across the country at various institutions. The following statement is from the NIH PROMIS Assessment Center website in regards to security measures in place for online data capture. "Assessment Center takes security very seriously. The last long section of the Assessment Center User Manual (www.nihpromis.org) includes information about security including details about the system architecture, SSL encryption, and server security. Additionally, within a study Assessment Center utilizes role-based permissions. Only team members are able to get access to a given study. Their access is limited based on their assigned role. Only individuals with the appropriate role are able to access participants' data." (The National Institutes of Health. PROMIS®: Dynamic Tools to Measure Health Outcomes from the Patient Perspective [website]. Available at: http://nihpromis.org. Accessed March 1, 2012.)

Note: The Privacy Rule requires researchers to keep a detailed accounting of releases of PHI outside MSKCC. If you share health information that is de-identified, or that is a limited data set

Appendix 4

Scoring manuals for PROMIS

Patient-Reported Outcomes Measurement Information System
Dynamic Tools to Measure Health Outcomes From the Patient Perspective

PAIN INTENSITY

A brief guide to the PROMIS Pain Intensity instrument:

ADULT
PROMIS Scale v1.0 - Pain Intensity 3a

ABOUT PAIN INTENSITY

The PROMIS Pain Intensity instrument assesses how much a person hurts. Patients are usually able to provide quantitative pain intensity estimates relatively quickly, and most measures of pain intensity tend to be closely related to one another. This suggests that pain intensity is a fairly homogeneous dimension, and one that is relatively easy for adults to identify and gauge. The Pain Intensity short form is universal rather than disease-specific. The first two items within the short form assess pain intensity over the past seven days while the last item asks patient to rate their pain intensity "right now".

Pain Intensity instrument is available for adults (ages 18+).

(For complete definition see http://nihpromis.org/measures/domainframework2)

INTRODUCTION TO ASSESSMENT OPTIONS

There is one administration options for assessing Pain Intensity: short form. When administering the short form, instruct participants to answer all of the items (i.e., questions or statements) presented. Short forms are preferable when administrators wish to ask the same question of all respondents or of the same respondent over time, to enable a more direct comparability across people or time, or when paper administration is preferred. When one uses this short form, the score metric is Item Response Theory (IRT), a family of statistical models that link individual questions to a presumed underlying trait or concept of pain intensity represented by all items in the item bank.

SHORT FORM DETAILS

The Pain Intensity short form (3a) was constructed by the domain team with a focus on representing the range of the trait and also representing the content of the item bank. Domain experts reviewed short forms to give input on the relevance of each item. Psychometric properties and clinical input were both used and likely varied in importance across domains.

SCORING THE INSTRUMENT

Short Forms: PROMIS instruments are scored using item-level calibrations. This means that the most accurate way to score a PROMIS instrument is to utilize scoring tools within Assessment Center that look at responses to each item for each participant. We refer to this as "response pattern scoring." Response pattern scoring tools within Assessment Center can be used even if data was collected on paper or in another software package. Because response pattern scoring is more accurate than the use of raw score/scale score look up tables, it is preferred. However, if you aren't able to use response pattern scoring, you can use the instructions below which rely on raw score/scale score look-up tables.

Each question has five response options ranging in value from one to five. To find the total raw score for the short form, sum the values of the response to each question. For example, the lowest possible raw score is 3; the highest possible raw score is 15 (see all short form scoring tables in Appendix). All questions must be answered in order to produce a valid score

For the PROMIS Pain Intensity 3a short form, a raw score of 10 converts to a T-score of 54.5 with a standard error (SE) of 2.9 (see scoring table for the 8b short form in appendix). Thus, the 95% confidence interval around the observed score ranges from 48.8 to 54.5 (T-score $\pm$ (1.96*SE) or 54.5 $\pm$ (1.96*2.9).

For most PROMIS instruments, a score of 50 is the average for the United States general population with a standard deviation of 10 because calibration testing was performed on a large sample of the general population. The T-score is provided with an error term (Standard Error or SE). The Standard Error is a statistical measure of variance and represents the "margin of error" for the T-score.

Important: *A higher PROMIS T-score represents more of the concept being measured.* For negatively-worded concepts like Pain Intensity, a T-score of 60 is one SD worse than average. By comparison, a Pain Intensity T-score of 40 is one SD better than average.

STATISTICAL CHARACTERISTICS

There are four key features of the score for Pain Intensity:

- **Reliability**: The degree to which a measure is free of error. It can be estimated by the internal consistency of the responses to the measure, or by correlating total scores on the measure from two time points when there has been no true change in what is being measured (for z-scores, reliability = $1 - SE^2$).
- **Precision**: The consistency of the estimated score (reciprocal of error variance).
- **Information:** The precision of an item or multiple items at different levels of the underlying continuum (for z-scores, information = $1/SE^2$).
- **Standard Error (SE):** The possible range of the actual final score based upon the scaled T-score. For example, with a T-score of 52 and a SE of 2, the 95% confidence interval around the actual final score ranges from 48.1 to 55.9 (T-score $\pm$ (1.96*SE) = 52 $\pm$ 3.9 = 48.1 to 55.9).

The final score is represented by the T-score, a standardized score with a mean of 50 and a standard deviation (SD) of 10.

PREVIEW OF SAMPLE ITEM

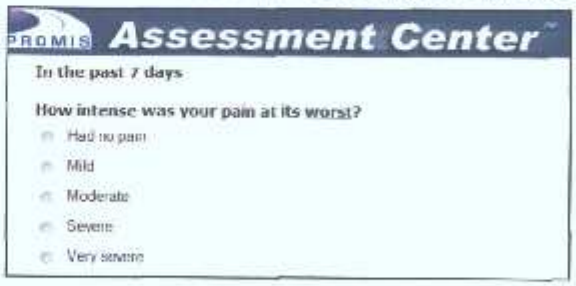


Figure 1

Figure 1 shows a Pain Intensity item from the short form as it would appear to a study participant during data collection in Assessment Center. Several formats for presenting the items are available for computer-based administration through Assessment Center (see FAQ section).

Figure 2 is an excerpt from the paper version of the three-item short form.

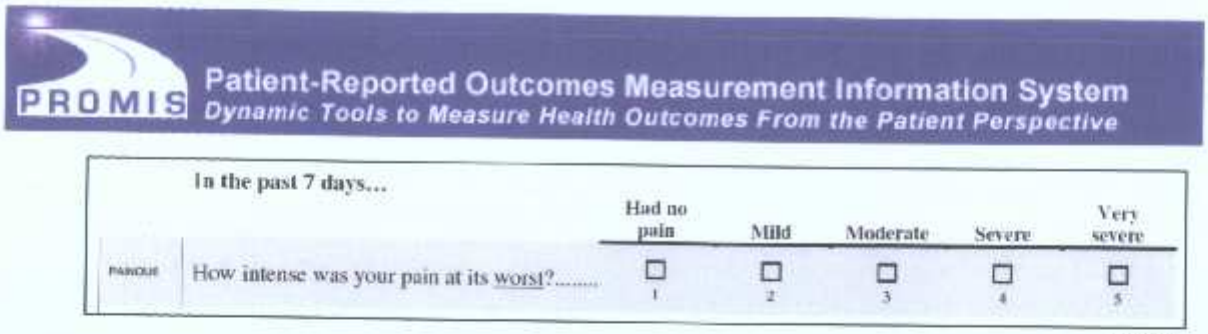


Figure 2

FREQUENTLY ASKED QUESTIONS (FAQ)

Q: *I am interested in learning more. Where can I do that?*

All instruments are available on the PROMIS website through Assessment Center, which houses all PROMIS instruments for each domain.

Assessment Center is a free online research management tool. It enables researchers to create study-specific websites for capturing participant data securely. Studies can include measures within the Assessment Center library, as well as custom instruments created or entered by the researcher. PROMIS instruments (short forms, CATs, profiles) are a central feature of the instrument library within Assessment Center. Any PROMIS measure can be included in an online study or downloaded for administration on paper.

Detailed statistical information and development history about PROMIS items and instruments are available for review at nihpromis.org or assessmentcenter.net. To learn more, contact help@assessmentcenter.net.

Q: *Do I need to register with PROMIS to use this instrument?*

Yes, to get a copy of these instruments, we ask that you register with Assessment Center and endorse the PROMIS Terms and Conditions of Use, so that we are better able to track who has accessed instruments for research. Assessment Center is available at assessmentcenter.net.

Q: *Is this instrument available in other languages?*

This instrument is currently available in Spanish in Assessment Center. The PROMIS group is also working to translate this form into other languages. Information on available translations is updated periodically at http://nihpromis.org/measures/translations.

Q: *Can I make my own short form?*

Yes, custom Pain Intensity short forms can be made by selecting any items from the item bank. Instructions for creating a custom short form in Assessment Center can be found in the Assessment Center User Manual https://www.assessmentcenter.net/UserManuals.aspx.

Q: *How do I handle multiple responses when administering a short form on paper?*

Guidelines on how to deal with multiple responses have been established. Resolution depends on the responses noted by the research participant.

- If two or more responses are marked by the respondent, and they are next to one another, then a data entry specialist will be responsible for randomly selecting one of them to be entered and will write down on the form which answer was selected. *Note: To randomly select one of two responses, the data entry specialist will flip a coin (heads - higher number will be entered; tails – lower number will be*

entered).To randomly select one of three (or more) responses, a table of random numbers should be used with a statistician's assistance.

- If two or more responses are marked, and they are NOT all next to one another, the response will be considered missing.

Q: *What is the minimum change on a PROMIS instrument that represents a clinically meaningful difference?*

This question is related to an area of active research in the PROMIS network, namely the determination of the "minimally important difference" or "MID" for a PROMIS instrument. A manuscript in the *Journal of Clinical Epidemiology* outlines the process for MIDs for adult PROMIS measures and estimates the MIDs for six PROMIS-Cancer scales: Yost, K. J., Eton, D. T., Garcia, S. F., & Cella, D. (2011). Minimally important differences were estimated for six PROMIS-Cancer scales in advanced-stage cancer patients. *Journal of Clinical Epidemiology, 64(5)*, 507-16.

As described in that manuscript, the MID is a tool to enhance the interpretability of patient-reported outcomes and is often defined as the "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management" (Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Controlled Clinical Trials* 1989; 10(4):407-415).

APPENDIX- SCORING TABLE

Pain Intensity 3a *Short Form Conversion Table*		
Raw Score	T Score	SE*
3	30.7	4.5
4	36.3	3.1
5	40.2	3
6	43.5	3
7	46.3	3
8	49.4	2.9
9	52.1	2.8
10	54.5	2.9
11	57.5	3.1
12	60.5	3.1
13	64.1	3.8
14	67.4	4.2
15	71.8	5

*SE=Standard Error on Tscore metric

Adult version

PROMIS Patient-Reported Outcomes Measurement Information System
Dynamic Tools to Measure Health Outcomes From the Patient Perspective

PAIN INTERFERENCE

A brief guide to the PROMIS Pain Interference instruments:

ADULT	ADULT CANCER	PEDIATRIC	PARENT PROXY
PROMIS Item Bank v1.0 – Pain Interference PROMIS Item Bank v1.1 – Pain Interference PROMIS Short Form v1.0 – Pain Interference 4a PROMIS Short Form v1.0 – Pain Interference 6a PROMIS Short Form v1.0 – Pain Interference 6b PROMIS Short Form v1.0 – Pain Interference 8a	PROMIS-Ca Bank v1.0 – Pain Interference PROMIS-Ca Bank v1.1 – Pain Interference	PROMIS Pediatric Bank v1.0 – Pain Interference PROMIS Pediatric Short Form v1.0 – Pain Interference 8a	PROMIS Parent Proxy Bank v1.0 – Pain Interference PROMIS Parent Proxy Short Form v1.0 – Pain Interference 8a

ABOUT PAIN INTERFERENCE

The PROMIS Pain Interference instruments measure the self-reported consequences of pain on relevant aspects of one's life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. Pain Interference also incorporates items probing sleep and enjoyment in life, though the item bank only contains one sleep item. The Pain Interference short form is universal rather than disease-specific. It assesses pain interference over the past seven days.

Pain Interference instruments are available for adults (ages 18+), pediatric self-report (ages 8-17) and for parents serving as proxy reporters for their child (youth ages 5-17).

(For complete definition see http://nihpromis.org/measures/domainframework1)

INTRODUCTION TO ASSESSMENT OPTIONS

There are two administration options for assessing Pain Interference: short forms and computerized adaptive test (CAT). When administering a short form, instruct participants to answer all of the items (i.e., questions or statements) presented. With CAT, participant responses guide the system's choice of subsequent items from the full item bank (40 items in total). Although items differ across respondents taking CAT, scores are comparable across participants. Some administrators may prefer to ask the same question of all respondents or of the same respondent over time, to enable a more direct comparability across people or time. In these cases, or when paper administration is preferred, a short form would be more desirable than CAT. This guide provides information on all Pain Interference short form and CAT instruments.

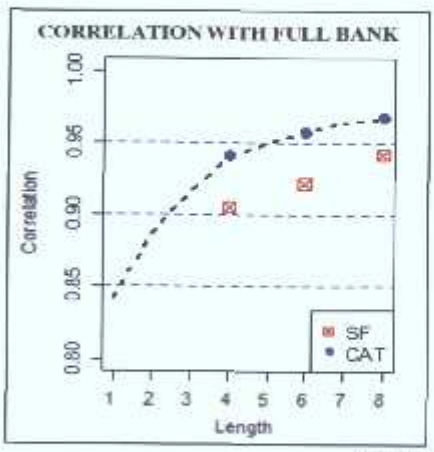


Figure 1

Whether one uses a short form or CAT, the score metric is Item Response Theory (IRT), a family of statistical models that link individual questions to a presumed underlying trait or concept of pain interference represented by all items in the item bank. When choosing between CAT and a short form, it is useful to consider the demands of computer-based assessment, and the psychological, physical, and cognitive burden placed on respondents as a result of the number of questions asked.

Figure 1 illustrates the correlations (strength of relationship) of the full bank with CAT and with short

forms of varying length. The correlation of CAT scores with the full bank score is greater than a short form of any length. A longer CAT or longer short form offers greater correlation, as well as greater precision. When evaluating precision, not all questions are equally informative. The flexibility of CAT to choose more informative questions offers more precision.

Some PROMIS domains have multiple versions of instruments (i.e. Item Banks/Computerized Adaptive Tests (CATs) and Short Forms). Generally, it is recommended that you use the most recent version available which can be identified as the instruments with the highest version number.

Instruments are changed for various reasons. For example, the original PROMIS Bank version 1.0 – Physical Function included 124 items after being tested in a diverse sample. Later, during an effort to translate instrument items into multiple languages, translation challenges were identified. Therefore, minor modifications to the English source items were required (e.g. metric equivalents to measurements such as "Over 10 pounds/ 5 kg" were added). These modifications (19 in total) resulted in the creation of a version 1.1 item bank. Later, version 1.2 was created by eliminating two items due to restrictions in their use.

In most cases, an instrument that has a decimal increase (v1.0 to v1.1 or v1.2) retains the same item-level parameters as well as instrument reliability and validity. In cases where a version number increases by a whole number (e.g., v1.0 to v2.0), the changes to the instrument are more substantial. For example, the PROMIS Bank v1.0 – Satisfaction with Participation in Social Roles is a small item bank comprised of 14 role function items. While the PROMIS Bank v2.0 – Satisfaction with Social Roles and Activities instrument includes a broader range of item content. Version 2.0 was re-calibrated independent of version 1.0, and is a larger (44 items), superior item bank. Details on the specific differences between instrument versions can be found in scoring manuals available on the Assessment Center homepage.

SHORT FORM DIFFERENCES

You will notice that there are 4 Pain Interference short forms for adults. Items in the 4a, 6a, and 8a short forms were selected based on rankings using two psychometric criteria: (1) maximum interval information; and 2) CAT simulations. Item rankings were similar for both criteria. For the maximum interval criterion, each item information function was integrated (without weighting) for the interval from the mean to 2 SDs worse than the mean. For the CAT simulations, responses to all items in each bank were generated using a random sample of 1,000 simulees drawn separately for each bank (centered on 0.5 SD worse than the general population mean). Items were rank ordered based on their average administration rank over the simulees. Content experts reviewed the items and rankings and made cuts of 4, 6, and 8 items. For each domain, 4-item, 6-item and 8-items have been selected so that the items are nested/overlap (e.g., the 8-item form is the 6-item form plus two additional items). The 4a, 6a, and 8a short forms can be administered with short forms of similar length from other domains (Depression, Physical Function, Anxiety, Fatigue, Sleep Disturbance, and Satisfaction with Participation in Social Roles v1.0) as part of a PROMIS Profile (see PROMIS-29, 43 or 57 Profile v2.0), though they can also be administered individually.

The original short form (6b) was constructed by the domain team with a focus on representing the range of the trait and also representing the content of the item bank. Domain experts reviewed short forms to give input on the relevance of each item. Each domain group worked independently and the original short forms are 6-10

items long depending on the domain. Psychometric properties and clinical input were both used and likely varied in importance across domains.

In selecting between short forms, the difference is instrument length. The reliability and precision of the short forms within a domain is highly similar. If you are working with an adult sample in which you wanted the most precise measure, select the 8a short form. If you are working in an adult sample in which you expected huge variability in a domain area and wanted different subdomains covered, you should select the 6b short form. If you had little room for additional measures but really wanted to capture something as a secondary outcome, you should use one of the shorter instruments (4a, 6a). For pediatric self-report and parent proxy report, there is only one short form available.

SELECTING THE ADULT CANCER INSTRUMENT

In selecting whether to use the adult cancer instrument (PROMIS-Ca) for this domain, it is important to consider the patient population being studied. All PROMIS-Ca instruments were developed for use with any cancer patient. This was done by having content experts review the adult PROMIS item bank to determine if there was a need to develop additional items or remove items because they conveyed a different meaning in cancer. Next, calibration testing with cancer patients with different diagnoses and treatments was conducted and data was analyzed to determine the final set of items and calibrations. The PROMIS-Ca Pain Interference CAT contains a total of 35 items, 32 of which are also in the PROMIS Pain Interference CAT. Some PROMIS-Ca items use calibrations that are different from the PROMIS adult calibrations. The Cancer calibration sample is selected by default when you add the PROMIS-Ca CATs to a study in Assessment Center. There are no short form instruments created specifically for an adult cancer population in Assessment Center.

SELECTING A PEDIATRIC OR PARENT PROXY INSTRUMENT

In selecting whether to use the pediatric or parent proxy instrument for this domain, it is important to consider both the population and the domain which you are studying. Pediatric self-report should be considered the standard for measuring patient-reported outcomes among children. However, circumstances exist when the child is too young, cognitively impaired, or too ill to complete a patient-reported outcome instrument. While information derived from self-report and proxy-report is not equivalent, it is optimal to assess both the child and the parent since their perspectives may be independently related to healthcare utilization, risk factors, and quality of care.

SCORING THE INSTRUMENT

Short Forms: PROMIS instruments are scored using item-level calibrations. This means that the most accurate way to score a PROMIS instrument is to utilize scoring tools within Assessment Center that look at responses to each item for each participant. We refer to this as "response pattern scoring." Response pattern scoring tools within Assessment Center can be used even if data was collected on paper or in another software package. Because response pattern scoring is more accurate than the use of raw score/scale score look up tables, it is preferred. However, if you aren't able to use response pattern scoring, you can use the instructions below which rely on raw score/scale score look-up tables.

For adults, each question has five response options ranging in value from one to five (for pediatrics and parent proxy it is 0 to 4). To find the total raw score for a short form with all questions answered, sum the values of the response to each question. For example, for the adult 6-item form, the lowest possible raw score is 6; the highest possible raw score is 30 (see all short form scoring tables in Appendix 1).

A score can be approximated if a participant skips a question. If items are missing, first check how many items were answered. For short forms with at least 5 items, confirm that 4 or 50% of items, whichever is greater, were answered. For example, a 4-item short form can only be scored with complete data. A 5-item short form can be scored as long as 4 items were answered. A 10-item short form can be scored as long as the participant answered at least 5 items. For branched instruments (e.g., Alcohol Use), the screening question is not used in calculating the score and therefore shouldn't be counted when assessing if the minimum number of items were answered. After confirming that enough responses were provided, sum the response scores from the items that were answered (not including any screening question). Multiply this sum by the total number of items in the short form. Finally, divide by the number of items that were answered. For example, if a respondent answered 5 of 8 questions and answered all items with the second lowest response option (2), you would sum all responses (10), multiply by the number of items in the short form (8) and divide by the number of items that were answered (5). Here (10x8)/5=16. If the result is a fraction, round up to the nearest whole number. This is a pro-rated raw score.

Again, the formula is:

$$\frac{\text{(Raw sum x number of items on the short form)}}{\text{Number of items that were actually answered}}$$

Locate the applicable score conversion table in Appendix 1 and use this table to translate the total raw score or pro-rated score into a T-score for each participant. The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10. Therefore a person with a T-score of 40 is one SD below the mean. It is important to note that Assessment Center will convert a participant's pattern of responses to a standardized T-score after they have finished a CAT. The standardized T-score is reported as the final score for each participant.

For the adult PROMIS Pain Interference 6b short form, a raw score of 10 converts to a T-score of 53.8 with a standard error (SE) of 1.8 (see scoring table for the 6b short form in Appendix 1). Thus, the 95% confidence interval around the observed score ranges from 50.3 to 57.3 (T-score $\pm$ (1.96*SE) or 53.8 $\pm$ (1.96*1.8).

For pro-rated scores, this calculation assumes that responses are missing at random. This isn't always true. Therefore, use caution when interpreting the final pro-rated T-score.

CAT: A minimum number of items (4 for adult and adult cancer CATs and 5 for Peds and Parent Proxy CATs) must be answered in order to receive a score for Pain Interference CAT. The first item is selected because it provides the most information about the U.S. general population (or a general cancer population in the case of the adult cancer instruments). The response to this item will guide the system's choice of the next item for the participant. The participant's response to this item will dictate the selection of the following question, and so on. As additional items are administered, the potential for error is reduced and confidence in the respondent's score increases. CAT will continue until either the standard error drops below a specified level, or the participant has answered the maximum number of questions (12), whichever occurs first.

For most PROMIS instruments, a score of 50 is the average for the United States general population with a standard deviation of 10 because calibration testing was performed on a large sample of the general population. However, adult cancer, pediatric and parent proxy instruments were not calibrated on a national sample and so a score of 50 represents the average of the calibration sample which was generally more enriched for chronic illness (i.e. cancer). In these instruments, a score of 50 likely represents somewhat sicker people than the general population. The T-score is provided with an error term (Standard Error or SE). The Standard Error is a statistical measure of variance and represents the "margin of error" for the T-score.

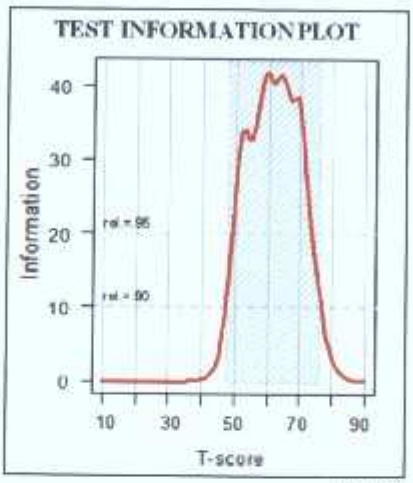


Figure 2

Important: *A higher PROMIS T-score represents more of the concept being measured.* For negatively-worded concepts like Pain Interference, a T-score of 60 is one SD worse than average. By comparison, a Pain Interference T-score of 40 is one SD better than average.

STATISTICAL CHARACTERISTICS

There are four key features of the score for Pain Interference:

- **Reliability**: The degree to which a measure is free of error. It can be estimated by the internal consistency of the responses to the measure, or by correlating total scores on the measure from two time points when there has been no true change in what is being measured (for z-scores, reliability = $1 - SE^2$).
- **Precision**: The consistency of the estimated score (reciprocal of error variance).
- **Information**: The precision of an item or multiple items at different levels of the underlying continuum (for z-scores, information = $1/SE^2$).
- **Standard Error (SE)**: The possible range of the actual final score based upon the scaled T-score. For example, with a T-score of 52 and a SE of 2, the 95% confidence interval around the actual final score ranges from 48.1 to 55.9 (T-score $\pm$ (1.96*SE) = 52 $\pm$ 3.9 = 48.1 to 55.9).

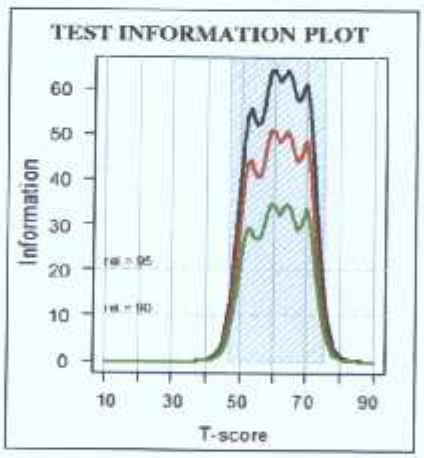


Figure 3

The final score is represented by the T-score, a standardized score with a mean of 50 and a standard deviation (SD) of 10.

In Figure 2 (adult 6b short form), the two dotted horizontal lines each represent a degree of internal consistency reliability (i.e., .90 or .95) typically regarded as sufficient for an accurate individual score. The shaded blue region marks the range of the scale where measurement precision is comparable to the reliability of .90 for the six-item form. Figure 2 also tells us where on the scale the form is most informative based upon the T-score. This form would typically be more informative than a Pain Interference form with fewer items.

Scaling Model Used For Calibration	Promis
Total Number of Items	41

Sample	N	Alpha Reliability
Promis	15903	0.99

Score Distributions									
	Mean	SD	P5	P10	P25	P50	P75	P90	P95
Raw	87.14	51.51	33.00	36.00	42.00	66.00	131.00	170.00	183.00
Scale	55.92	10.82	39.98	39.98	47.48	55.22	65.34	70.30	72.84

	Conditional Reliability									Min	Max
Scale Score	10.0	20.0	30.0	40.0	50.0	60.0	70.0	80.0	90.0	40.0	84.2
SE	51.60	12.60	2.80	.50	.10	.10	.10	.20	.70		
Reliability	.00	.00	.00	.71	.99	1.00	.99	.96	.48		

Figure 4

Figure 3 (Adult 4a, 6a & 8a short forms) also tells us where on the scale the form is most informative based upon the T-score: the 8-item form is more informative than the 6-item form, which is more informative than the 4-item form. See additional test information figures for Pediatric and Parent Proxy instruments in Appendix 2.

Figure 4 is a sample of the statistical information available in Assessment Center for the adult Pain Interference CAT.

More information is available online via Assessment Center (assessmentcenter.net).

PREVIEW OF SAMPLE ITEM

Figure 5 shows a Pain Interference item from the adult full item bank as it would appear to a study participant during data collection in Assessment Center. Several formats for presenting the items are available for computer-based administration through Assessment Center (see FAQ section).

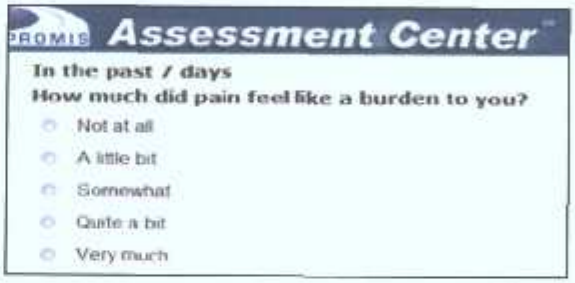
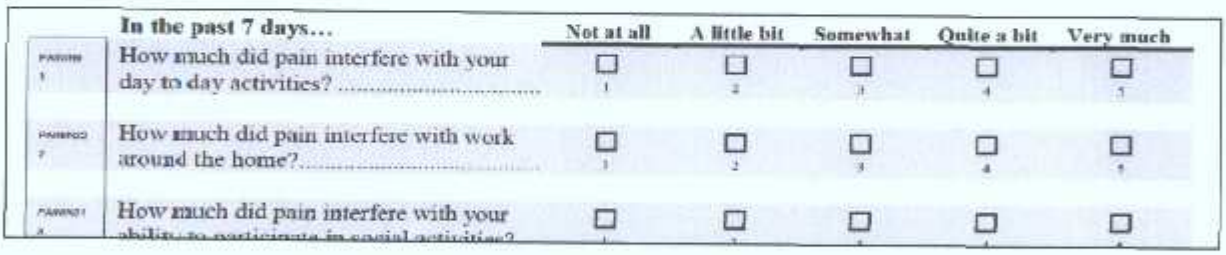


Figure 5

Figure 6 is an excerpt from the paper version of the adult six-item short form. This is the paper version format used for all Pain Interference instruments. It is important to note, CAT is not available for paper administration.

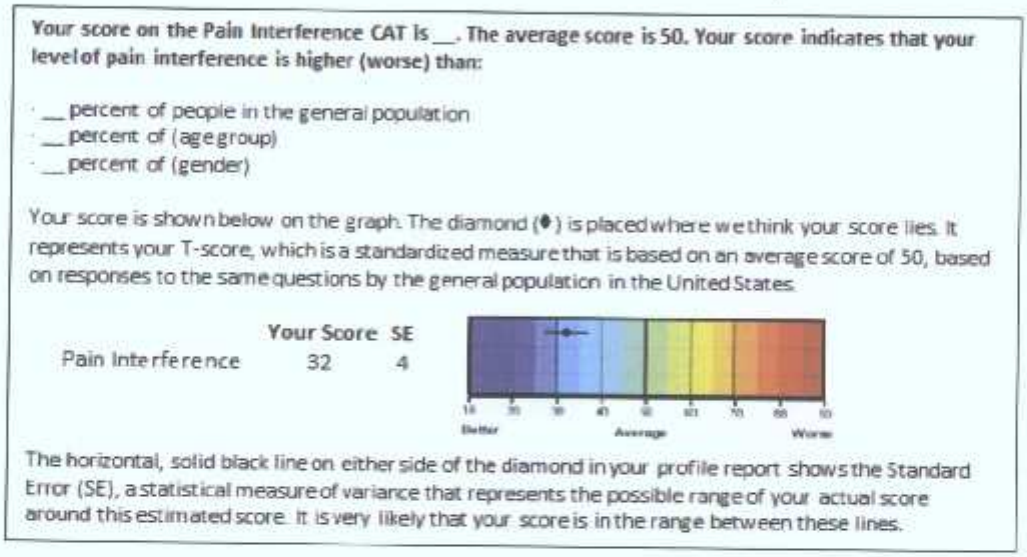


	In the past 7 days...	Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAINREC	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAINSOC	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Figure 6

DATA REPORTS

Upon completion of an adult CAT for Physical Function, Depression, Anxiety, Pain Interference, Fatigue, Sleep Disturbance, and Satisfaction with Participation in Social Roles v1.0, a data report is available in Assessment Center. Figure 7 demonstrates some of the information available on the data reports.



Your score on the Pain Interference CAT is __. The average score is 50. Your score indicates that your level of pain interference is higher (worse) than:

- __ percent of people in the general population
- __ percent of (age group)
- __ percent of (gender)

Your score is shown below on the graph. The diamond (♦) is placed where we think your score lies. It represents your T-score, which is a standardized measure that is based on an average score of 50, based on responses to the same questions by the general population in the United States.

	Your Score	SE
Pain Interference	32	4

The horizontal, solid black line on either side of the diamond in your profile report shows the Standard Error (SE), a statistical measure of variance that represents the possible range of your actual score around this estimated score. It is very likely that your score is in the range between these lines.

Figure 7

To access a sample report for Pain Interference, complete the CAT demo at nihpromis.org. More than one CAT domain can be completed at a time; results for all domains selected will be generated and displayed within the one report.

Data reports are also available if you choose to administer an adult PROMIS Profile instrument, which includes a short form from seven PROMIS domains (Physical Function, Depression, Anxiety, Fatigue, Pain Interference, Satisfaction with Participation in Social Roles, and Sleep Disturbance).

FREQUENTLY ASKED QUESTIONS (FAQ)

Q: *I am interested in learning more. Where can I do that?*

All instruments are available on the PROMIS website through Assessment Center, which houses all PROMIS instruments for each domain.

Assessment Center is a free online research management tool. It enables researchers to create study-specific websites for capturing participant data securely. Studies can include measures within the Assessment Center library, as well as custom instruments created or entered by the researcher. PROMIS instruments (short forms, CATs, profiles) are a central feature of the instrument library within Assessment Center. Any PROMIS measure can be included in an online study or downloaded for administration on paper.

Detailed statistical information and development history about PROMIS items and instruments are available for review at nihpromis.org or assessmentcenter.net. To learn more, contact help@assessmentcenter.net.

Q: *Do I need to register with PROMIS to use these instruments?*

Yes, to get a copy of these instruments, we ask that you register with Assessment Center and endorse the PROMIS terms and conditions of use, so that we are better able to track who has accessed instruments for research. Assessment Center is available at assessmentcenter.net.

Q: *Are these instruments available in other languages?*

Yes, these instruments are currently available in Spanish and German in Assessment Center. The PROMIS group is also working to translate this form into other languages. Information on available translations is updated periodically at http://nihpromis.org/measures/translations.

Q: Can I make my own short form?

Yes, custom Pain Interference short forms can be made by selecting any items from the item bank. Instructions for creating a custom short form in Assessment Center can be found in the Assessment Center User Manual https://www.assessmentcenter.net/UserManuals.aspx.

Q: How do I handle multiple responses when administering a short form on paper?

Guidelines on how to deal with multiple responses have been established. Resolution depends on the responses noted by the research participant.

- If two or more responses are marked by the respondent, and they are next to one another, then a data entry specialist will be responsible for randomly selecting one of them to be entered and will write down on the form which answer was selected. *Note: To randomly select one of two responses, the data entry specialist will flip a coin (heads - higher number will be entered; tails – lower number will be entered).To randomly select one of three (or more) responses, a table of random numbers should be used with a statistician's assistance.*
- If two or more responses are marked, and they are NOT all next to one another, the response will be considered missing.

Q: *What is the minimum change on a PROMIS instrument that represents a clinically meaningful difference?*

This question is related to an area of active research in the PROMIS network, namely the determination of the "minimally important difference" or "MID" for a PROMIS instrument. A manuscript in the *Journal of Clinical Epidemiology* outlines the process for MIDs for adult PROMIS measures and estimates the MIDs for six PROMIS-Cancer scales: Yost, K. J., Eton, D. T., Garcia, S. F., & Cella, D. (2011). Minimally important differences were estimated for six PROMIS-Cancer scales in advanced-stage cancer patients. *Journal of Clinical Epidemiology, 64(5)*, 507-16.

As described in that manuscript, the MID is a tool to enhance the interpretability of patient-reported outcomes and is often defined as the "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management" (Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Controlled Clinical Trials* 1989; 10(4):407-415).

APPENDIX 1-SCORING TABLES

Pain Interference 6b
Short Form Conversion Table

Raw Score	T-score	SE*
6	41.0	6.0
7	48.5	2.6
8	50.8	2.1
9	52.5	1.9
10	53.8	1.8
11	55.0	1.7
12	56.1	1.7
13	57.1	1.7
14	58.1	1.7
15	59.1	1.6
16	60.0	1.6
17	60.9	1.6
18	61.8	1.6
19	62.7	1.6
20	63.6	1.6
21	64.5	1.6
22	65.5	1.6
23	66.4	1.6
24	67.4	1.7
25	68.5	1.7
26	69.6	1.8
27	70.9	1.9
28	72.4	2.1
29	74.4	2.4
30	78.3	3.7

*SE = Standard Error on T-score metric

Adult version

Pain Interference 4a
Short Form Conversion Table

Raw Score	T-score	SE*
4	41.6	6.1
5	49.6	2.5
6	52.0	2.0
7	53.9	1.9
8	55.6	1.9
9	57.1	1.9
10	58.5	1.8
11	59.9	1.8
12	61.2	1.8
13	62.5	1.8
14	63.8	1.8
15	65.2	1.8
16	66.6	1.8
17	68.0	1.8
18	69.7	1.9
19	71.6	2.1
20	75.6	3.7

*SE = Standard Error

Pain Interference 6a
Short Form Conversion Table

Raw Score	T-score	SE*
6	41.1	6.0
7	48.6	2.4
8	50.7	1.8
9	52.2	1.6
10	53.4	1.6
11	54.5	1.6
12	55.6	1.5
13	56.6	1.5
14	57.6	1.5
15	58.6	1.5
16	59.5	1.5
17	60.4	1.4
18	61.2	1.4
19	62.1	1.4
20	63.0	1.5
21	63.8	1.5
22	64.8	1.5
23	65.7	1.5
24	66.7	1.5
25	67.6	1.5
26	68.7	1.5
27	69.8	1.5
28	71.0	1.6
29	72.6	2.0
30	76.3	3.6

*SE = Standard Error

Pain Interference 8a
Short Form Conversion Table

Raw Score	T-score	SE*
8	40.7	5.9
9	47.9	2.4
10	49.9	1.8
11	51.2	1.5
12	52.3	1.4
13	53.2	1.4
14	54.1	1.4
15	55.0	1.4
16	55.8	1.4
17	56.6	1.4
18	57.4	1.3
19	58.1	1.3
20	58.8	1.3
21	59.5	1.3
22	60.2	1.3
23	60.8	1.3
24	61.5	1.3
25	62.1	1.3
26	62.8	1.3
27	63.5	1.3
28	64.1	1.3
29	64.8	1.3
30	65.5	1.3
31	66.2	1.3
32	66.9	1.3
33	67.7	1.3
34	68.4	1.3
35	69.2	1.3
36	70.1	1.4
37	71.0	1.4
38	72.1	1.6
39	73.5	2.0
40	77.0	3.5

*SE = Standard Error

Adult version

Pain Interference 8a *Short Form Conversion Table*		
Raw Score	T-score	SE*
0	34.0	5.6
1	38.7	4.4
2	40.6	4.2
3	42.7	3.8
4	44.3	3.7
5	45.8	3.4
6	47.1	3.3
7	48.4	3.2
8	49.5	3.2
9	50.6	3.1
10	51.7	3.1
11	52.7	3.1
12	53.7	3.0
13	54.7	3.0
14	55.7	3.0
15	56.6	3.0
16	57.6	3.0
17	58.5	3.0
18	59.5	3.0
19	60.4	3.0
20	61.4	3.0
21	62.4	3.0
22	63.4	3.0
23	64.4	3.0
24	65.4	3.1
25	66.5	3.1
26	67.6	3.2
27	68.8	3.2
28	70.1	3.3
29	71.5	3.4
30	73.2	3.7
31	75.0	3.8
32	78.0	4.3
* SE = Standard error		

Pediatric version

Parent Proxy Pain Interference *8-Item Short Form Conversion Table*		
Summed Raw Score	Standard T-Score	SE*
0	38	6
1	44	3
2	46	3
3	48	3
4	49	2
5	50	2
6	51	2
7	52	2
8	53	2
9	54	2
10	55	2
11	56	2
12	57	2
13	58	2
14	58	2
15	59	2
16	60	2
17	61	2
18	62	2
19	62	2
20	63	2
21	64	2
22	65	2
23	66	2
24	67	2
25	67	2
26	68	2
27	69	2
28	70	2
29	71	3
30	73	3
31	74	3
32	78	4

*SE = Standard Error on T-score metric

Parent Proxy version

APPENDIX 2 – ADDITIONAL FIGURES

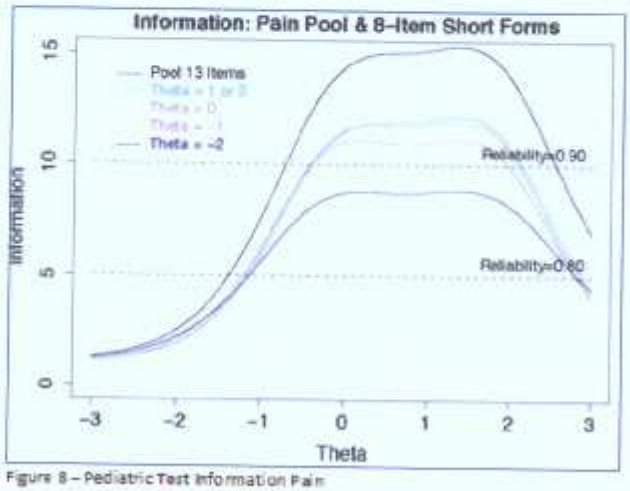


Figure 8 – Pediatric Test Information Pain

Scoring PROMIS Global Short Form

Scoring Global Short Form v1.0 and v1.1

The PROMIS Global Health short form is a 10-item instrument representing multiple domains. It can be scored into a Global Physical Health component and Global Mental Health component using the tables below. Because a scoring table is prepared for a fixed set of items, it can only be used when an examinee responds to all of the items in the set. *One or more missing responses will render such scoring tables unusable.*

The Global scores require re-coding of three items so that high scores reflect better functioning.

Global07	In the past 7 days	How would you rate your pain on average?	5=0 No pain 4=1 4=2 4=3 3=4 3=5 3=6 2=7 2=8 2=9 1=10 Worst pain imaginable
Global08	In the past 7 days	How would you rate your fatigue on average?	5=None 4=Mild 3=Moderate 2=Severe 1=Very severe
Global10	In the past 7 days	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	5=Never 4=Rarely 3=Sometimes 2=Often 1=Always

After recoding, the Global Physical Health score is generated by summing responses to Global03, Global06, Global07rescored, and Global08rescored. The Global Mental Health score is generated by summing responses to Global02, Global04, Global05, and Global10rescored.

Raw Score to T Score Conversion Tables

The following conversion tables allow a user to convert simple summed raw scores from PROMIS global into T-score values on an individual respondent or group of respondents. In all cases, these conversions only work accurately when all questions on the short form have been answered. T-Score distributions are standardized such that a 50 represents the average (mean) for the US general population, and the standard deviation around that mean is 10 points. *A high score always represents more of the concept being measured.* Thus, a person who has T-

scores of 60 for the Global Physical Health or Global Mental Health scales is one standard deviation better (more healthy) than the general population.

Physical *Short Form Conversion Table*		
Raw.Score	**T.Score**	**SE***
4	16.2	4.8
5	19.9	4.7
6	23.5	4.5
7	26.7	4.3
8	29.6	4.2
9	32.4	4.2
10	34.9	4.1
11	37.4	4.1
12	39.8	4.1
13	42.3	4.2
14	44.9	4.3
15	47.7	4.4
16	50.8	4.6
17	54.1	4.7
18	57.7	4.9
19	61.9	5.2
20	67.7	5.9

*SE = Standard Error

Mental *Short Form Conversion Table*		
Raw.Score	**T.Score**	**SE***
4	21.2	4.6
5	25.1	4.1
6	28.4	3.9
7	31.3	3.7
8	33.8	3.7
9	36.3	3.7
10	38.8	3.6
11	41.1	3.6
12	43.5	3.6
13	45.8	3.6
14	48.3	3.7
15	50.8	3.7
16	53.3	3.7
17	56.0	3.8
18	59.0	3.9
19	62.5	4.2
20	67.6	5.3

*SE = Standard Error

- **Conversion Table applies only when ALL questions on the subdomain have been answered**

Hays, R. D., Bjorner, J., Revicki, R. A., Spritzer, K. L., & Cella, D. (2009). Development of physical and mental health summary scores from the Patient Reported Outcomes Measurement Information System (PROMIS) global items. *Quality of Life Research, 18(7)*,873-80. (PMCID: PMC2724630)

Estimating EuroQoL (EQ-5D) Index Scores

Revicki et al (2009) outlined how to use the PROMIS Global Health short form to calculate a EuroQoL (EQ-5D) index score. To begin, use the instructions on page 1 to re-score Global07, Global08, and Global10. Then, use the following formula:

EQ5D score = 0.19123 + (0.00672 * Global2) + (0.00527 * Global3) + (0.00830 * Global4) + (0.04550 * Global6) + (0.02713 * Global7rescored) + (0.01305 * Global8rescored) + (0.00613 * Global9) + (0.02502 * Global10rescored)

Revicki, D. A., Kawata, A., Harnam, N., Chen, W-H., Hays, R. D., & Cella, D. (2009). Predicting EUROQOL (EQ-5D) scores from the Patient Reported Outcomes Measurement Information System (PROMIS) global items and domain item banks in a United States sample. *Quality of Life Research, 18(6)*, 783-91. (PMCID: PMC2704290)