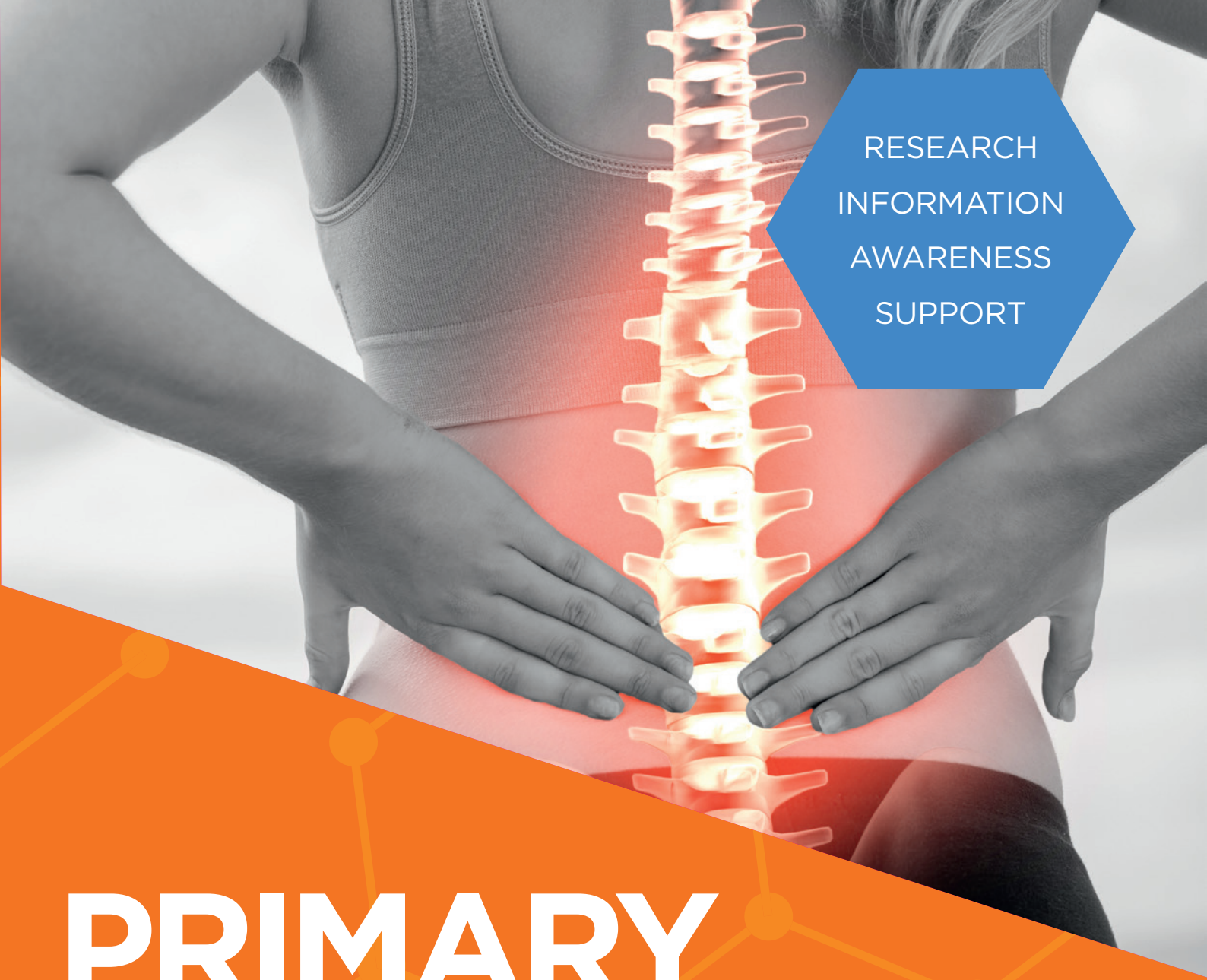

RESEARCH
INFORMATION
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PRIMARY BONE CANCER

CHORDOMA

BONE CANCER RESEARCH TRUST
UNTIL THERE'S A CURE

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CONTENTS

Chordoma is a very rare form of primary bone cancer - accounting for less than 5% of all primary tumours arising in the bone. This cancer most commonly occurs in the spine and the skull, affecting patients aged around 40 to 60 years old.

WHAT IS IT?

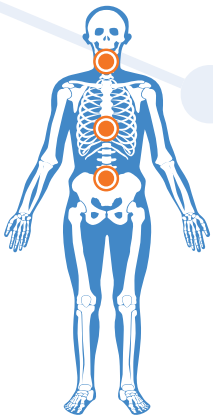
Chordomas grow slowly and are referred to as 'low-grade tumours'. This tumour type develops from tissue known as the **notochord**. The notochord is required during embryonic development to form the template of the spinal tissue while the baby is in the womb. Over time, this spinal tissue is replaced with bone and there is no use for the notochord – though small amounts of the notochord can remain into adulthood with no effect. However, like any other cell type, the remaining notochord cells are capable of being transformed into cancerous cells which grow uncontrollably to form a chordoma tumour. Chordomas most commonly arise in the spine or the skull.

- **50% of chordomas are reported in the sacrococcygeal region of the spine - which is the very base of the spine where it connects to the pelvis**
- **35% of chordomas occur in the base of the skull where the skull meets the spine**
- **15% of chordomas present in the vertebral column - which includes all areas along the main length of the spine**

WHO DOES IT AFFECT?

The yearly incidence of chordoma is approximately **1 case in every 800,000 people**, with approximately 35 people being diagnosed with chordoma each year in the UK and Ireland. There is a slightly higher frequency of chordoma in males than in females and reports state that this tumour type is more common in Caucasian individuals.

Chordomas can develop in anyone, at any age, though are far more commonly diagnosed in adult individuals around the age of **40 to 75 years old**. Children and adolescents are rarely diagnosed with chordoma and make up just 5% of all cases.



50% OF CASES IN THE BASE OF THE SPINE

35% OF CASES IN THE BASE OF THE SKULL

15% OF CASES IN THE MAIN LENGTH OF THE SPINE

WHAT ARE THE SYMPTOMS?

Chordomas located in the spine and the skull frequently present close to major nerves. Therefore, some of the first symptoms chordoma patients experience may be caused by the tumour pressing on these nerves, causing nerve-based symptoms - known as **neurological effects**. These effects include numbness and weakness in the limbs, a sensation of pins and needles and pain in the back, neck or head.

A chordoma can present with many different symptoms and signs depending on its location.

The varying locations of a chordoma and their relative symptoms are:

TUMOURS IN THE BASE OF THE SPINE

LOWER BACK PAIN
which is often dull and becomes worse when sitting

A SMALL LUMP ON THE LOWER BACK

WEAKNESS, NUMBNESS OR PAIN IN THE LOWER BACK OR LEGS

CONSTIPATION

LOSS OF BLADDER CONTROL

TUMOURS IN THE MAIN PART OF THE SPINE

- PAIN
- SWELLING

TUMOURS IN THE NECK

- NECK PAIN
- BREATHING OBSTRUCTION
- DIFFICULTY SWALLOWING

TUMOURS IN THE BASE OF THE SKULL

- SEVERE HEADACHES
- DISTURBANCES TO VISION
  such as double vision, difficulty focusing the eyes or rapid eye movements
- PARALYSIS OF FACIAL NERVES
  causing swallowing, speech and eye movement abnormalities
- PAIN

TYPES OF CHORDOMA

There are **three** known types of chordoma, which are classified due to tumours appearance on imaging tests and under the microscope.

The three known types of chordoma are:

- **CLASSIC/CONVENTIONAL CHORDOMA**
  this is the most common type of chordoma and accounts for around **80-90%** of all cases.

- **CHONDROID CHORDOMA**
  these make up between **5-15%** of all chordoma cases and most frequently arise in the base of the skull.

- **DEDIFFERENTIATED CHORDOMA**
  these account for less than **5%** of all chordoma cases. Although they can arise in all areas of the spine or skull, they are most commonly reported in the base of the spine in an area known as the sacrum.

CAUSES AND RISK FACTORS

Almost all cases of chordoma have been known to occur randomly with no identified cause. However, there is some evidence to suggest that specific genes may be involved in the development of a chordoma. In extremely rare cases, chordoma can develop in multiple members of the same family – which is known as **familial chordoma**.

Some causes and risk factors that increase the likelihood of an individual developing a chordoma are:

• THE BRACHYURY GENE –

Chordomas have unusually high levels of a gene called **brachyury** - which is normally found in the cells of the notochord. Recent research has shown that many chordoma patients have a gene irregularity, known as a mutation, in this brachyury gene which may be associated with chordoma development.

• TUBEROUS SCLEROSIS COMPLEX (TSC)

TSC is a **rare syndrome** causing abnormal tissue growth in major organs. It is caused by mutations in genes known as '**TSC1**' or '**TSC2**'. These mutations result in a lack of control over the cells growth and proliferation and it is this uncontrolled cell growth that causes cancer, and in this case, a chordoma.

• RECEPTOR TYROSINE KINASES (RTK)

RTK are a class of molecules which are well known to be highly expressed in various cancer types - including chordoma. Due to this high expression they are a desirable target for drugs to help combat cancer.

RTK that are expressed highly in chordoma are the **platelet-derived growth factor receptor** (PDGFR) and the **epidermal growth factor receptor** (EGFR). Both molecules receive signals from the blood stream and neighbouring cells to activate the growth and division of cells - which ultimately leads to the uncontrolled growth of cancerous chordoma cells.

• SIGNAL TRANSDUCERS AND ACTIVATORS OF TRANSCRIPTION 3 (STAT3)

STAT3 activation leads to the **uncontrolled growth** and **prolonged survival** of tumour cells in various cancers. It does so by increasing the expression of proteins which prevent abnormal, cancerous, cells from dying. Preventing the function of STAT3 is seen to inhibit the growth of cancerous chordoma cells. Therefore, STAT3 may not only be involved in chordoma development but may also be a useful target for treating chordoma.

DIAGNOSING CHORDOMA

Further tests to confirm a chordoma diagnosis include:

- **A CT SCAN**
- **AN MRI SCAN**
- **A BIOPSY OF THE BONE**
- **BLOOD TESTS**

The first step in diagnosing any primary bone cancer is a trip to the doctor, where a **clinical examination** and an **X-ray** will be carried out. X-rays, CT (computerised tomography) scans and MRI (magnetic resonance imaging) scans cannot definitively diagnose a chordoma. However, these scans can provide important information on the location of the tumour, the stage of the tumour and can determine if the chordoma has spread elsewhere in the body.

Unfortunately, chordoma tumours can occasionally be overlooked on these imaging techniques and therefore the most appropriate way of confirming the diagnosis of a chordoma is by taking a biopsy of the bone to analyse alongside these scans. A biopsy is a specialist procedure that takes a small sample of the tumour so it can be examined under a microscope.

Results from a biopsy can take up to two weeks to analyse but they enable doctors to confirm the presence and specific type of chordoma

AN ALTERNATIVE DIAGNOSIS?

When diagnosing a chordoma, it is important to eliminate the presence of various other health conditions which may have similar signs and symptoms to chordoma. It is important that the correct diagnosis is made to ensure the treatment provided is suitable.

Diseases with similar symptoms or signs are known as '**differential diagnoses**'. There are numerous conditions which present in a similar way to chordoma. Just a few examples are listed here:

- **BENIGN NOTOCHORDAL CELL TUMOUR**
- **METASTATIC CARCINOMA**
- **CHONDROSARCOMA**
- **OSTEOSARCOMA**
- **GIANT CELL TUMOUR OF THE BONE**
- **AN INFECTION**

TREATING CHORDOMA

If the presence of chordoma is confirmed the patient will be referred to the nearest Bone Cancer Centre where the specialist medical team will design the best possible treatment plan for the individual patient.

The main treatment for chordoma patients involves surgery followed by radiotherapy. This cancer type is one which has received a lot of research attention, and scientists are working to develop advanced radiotherapy techniques and targeted drugs to improve chordoma treatment.

SURGERY

The slow-growing nature of this tumour, and its low risk of spreading to other areas of the body, makes the surgical removal of the tumour the most beneficial method of treatment.
The surgical removal of the tumour requires '**wide surgical margins**'. This means the tumour is removed alongside a small amount of healthy tissue to ensure all tumour cells are removed and there is a lower risk of the tumour returning at a later date.

Unfortunately, the location of the chordoma can often make the planning of surgery difficult. Chordomas present on the spine and the skull and are therefore frequently located nearby to major nerves, structures and critical organs. Therefore, the benefit of surgery must be assessed alongside any possible risks or side-effects before being carried out.

RADIOTHERAPY

Radiotherapy is often carried out after surgery to destroy any remaining cancer cells in the area. This offers the best possible control of the chordoma and lowers the risk of the tumour returning at a later date. Radiotherapy may also be used on its own to treat chordoma in cases where the tumour is located in an inoperable position. Additionally, radiotherapy may be given to individuals who require further symptom and pain management – this form of treatment is known as '**palliative radiotherapy**'.

PROTON BEAM RADIOTHERAPY

Proton beam therapy is a newly developed and advanced form of radiotherapy that aims to provide better control of the tumour and reduce the side-effects of radiotherapy.

Unlike conventional radiotherapy, proton beam therapy deposits the full dose of radiation at the specific location of the tumour. This ensures that the tumour receives the full, optimal, radiation dose while protecting surrounding, healthy, tissues from the effect of radiotherapy. Proton beam therapy has shown success in chordoma patients - particularly when tumours are located nearby to critical structures or major nerves. Proton beam therapy is not currently available in the UK. However, the government have committed £250 million into developing centres in London and Manchester. At present, the NHS will fund for selected patients who require proton beam therapy to receive this treatment abroad, in the USA or in Switzerland.

CHEMOTHERAPY

Chemotherapy tends to only be used in the treatment of **dedifferentiated chordoma** - which make up just 5% of chordoma cases.

TARGETED THERAPY

There is ongoing research into the development of targeted drug therapies, which target a specific molecule that may be overexpressed or mutated in this cancer type and not in healthy cells. Development of targeted drug treatments may help improve survival for chordoma patients. Researchers have identified specific genes which show increased expression levels and activity in chordoma. These specific genes may become '**molecular targets**' for targeted drug treatments which have the potential to be safer and more specific than conventional chemotherapy agents.

The main molecular targets of chordoma that have been identified are:

PLATELET-DERIVED GROWTH FACTOR RECEPTOR (PDGFR):

PDGFR is a protein receptor initiating the growth and progression of many cancer types. **70-75%** of chordomas express PDGFR in high levels. PDGFR has been targeted with a drug known as **Imatinib**. Clinical trials using Imatinib have shown success in treating patients and reducing the size of the chordoma tumour. However, the response to Imatinib is often short-lived and varies in each patient, and so clinical trials are continuing in this area.

EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR):

EGFR is a protein receptor initiating the growth and progression of many cancer types. **70%** of chordomas express EGFR in high levels. EGFR can be directly targeted with various drugs, including Erlotinib, Cetuximab and Gefitinib. **Erlotinib** has shown some promising results in stabilising the disease when tested in a small amount of chordoma patients. However, more clinical trials are required to determine if Erlotinib could be used as a treatment for chordoma in the future. Clinical trials are set to test the effect of a drug known as **Afatinib** in treating chordoma patients, due to its ability to inhibit and prevent the functioning of EGFR. These trials will begin at the end of 2016.

Ultimately, targeted therapies are in the early stages of development and although further experiments are required, the results seen so far are promising.

FOLLOW-UP CARE

After finishing treatment, many patients will require follow-up care.

Follow-up care at the hospital will allow healthcare professionals to keep an eye on a patient's general health and ensure the patient hasn't suffered any **'LATE EFFECTS'** from their treatment. Late effects of a patient's treatment include effects on the patient's kidney function, fertility or risk of developing a secondary cancer

Follow-up care can continue for months, or even years, and allows patients to discuss any concerns they may have with their doctor. Tests may be carried out during these appointments to ensure the patient is healthy and the cancer is not at risk of returning.

REHABILITATION AND SUPPORT

Following treatment, many patients benefit from further support and rehabilitation services.

Rehabilitation is a form of therapy that enables patients to regain strength, tackle day-to-day activities and return to normal life as quickly as possible following a disease. These services are available both during and after treatment and include:

- **PHYSIOTHERAPISTS:** help patients return back to an active lifestyle as quickly as possible to restore strength, movement and function
- **OCCUPATIONAL THERAPISTS:** help patients to complete day-to-day activities in order to regain their independence
- **DIETICIAN:** offer advice on the most appropriate nutrition for patients during and after their treatment
- **PROSTHETISTS:** specialists who design and create prostheses following amputations to match as closely as possible to the individual patients removed limb
- **ORTHOTISTS:** specialists who provide aids for patients following surgery, such as splints or special footwear

Patients, or their family and friends, may benefit from discussing any feelings of anxiety or concerns they may have following a cancer diagnosis or treatment. Many services are available for this form of support, such as:

- **PSYCHOLOGICAL SUPPORT AND SERVICES:** psychologists will support patients through any feelings of anxiety or depression to overcome the concerns that often come with a cancer diagnosis
- **LOCAL SUPPORT GROUPS:** many support groups are organised and ran locally. It is best to ask your clinical nurse specialist for information on these local services

THE BONE CANCER RESEARCH TRUST IS THE LEADING CHARITY DEDICATED TO FIGHTING PRIMARY BONE CANCER.

OUR MISSION IS TO SAVE LIVES AND IMPROVE OUTCOMES FOR PEOPLE AFFECTED BY PRIMARY BONE CANCER THROUGH RESEARCH, INFORMATION, AWARENESS AND SUPPORT.

WE RECEIVE NO GOVERNMENTAL FUNDING, SO RELY ENTIRELY ON THE SUPPORT OF THE PUBLIC TO CONTINUE OUR LIFE SAVING WORK.

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OR VISIT BCRT.ORG.UK

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