Has the Scottish Managed Clinical Network for Sarcoma influenced the survival outcomes for primary malignant bone tumours?

F. MacDonald*, S. Gupta

NHS Greater Glasgow and Clyde, UK

ABSTRACT

Primary malignant bone tumours (PMBT) are rare. We have reviewed patient outcomes in Scotland over a 20 year period and provided an update on the principles of current management strategies for the non-specialist practitioner.

The Scottish Managed Clinical Network for Sarcoma (MCN) connects the three main management centres for sarcoma in Scotland: Glasgow, Aberdeen and Edinburgh. Prior to the formation of the MCN, all centres were connected via the Scottish Bone Tumour Registry (SBTR), where they would meet on a quarterly basis and all the bone/soft tissue tumour cases were discussed retrospectively.

The MCN was introduced in 2006. Our primary aims were to assess the impact of the MCN on patient outcomes and to update clinicians on the recognition, assessment and staging of PMBT. A secondary aim was to compare results from the Scottish centres with other UK sites.

The patient information was gathered from the Scottish Bone Tumour Registry, held at the Queen Elizabeth University Hospital in Glasgow. All patients with diagnoses of Osteosarcoma, Chondrosarcoma and Ewing Sarcoma between 1994 and 2014 were included.

Results showed that there was no significant change in outcome following the formation of the Scottish Managed Clinical Network for Sarcoma, and that there were little differences in outcome amongst the three major management centres in Scotland. Findings also show Scotland to have similar outcomes to that of the rest of the UK following diagnosis of a primary malignant bone tumour.

1. Introduction

Primary malignant bone tumours (PMBT) are rare, accounting for less than 1% of primary malignancies^{1,2} and only 0.5% of all cancer deaths.³ In Scotland this equates to approximately five or six people being diagnosed with a PMBT each year. There are three dominating types of PMBT, accounting for approximately 76% of all PMBTs.² These are Osteosarcomas, Chondrosarcomas and Ewing Sarcoma.

2. Osteosarcoma

2.1. Epidemiology

The most common primary malignant bone tumour is an Osteosarcoma.^{2,3,7,9,10} Osteogenic tumours by definition produce osteoid or bony matrix and can be both benign and malignant.⁹ The malignant variety, Osteosarcoma is often aggressive, with symptoms usually developing over a period of weeks to months.^{1,9} Osteosarcoma has six subtypes; Conventional Osteosarcoma, Telangiectatic, Small Cell, Low Grade Central, Secondary Osteosarcomas due to pre-existing abnormalities e.g. Paget's, and Parosteal.⁹ This tumour is mostly found in adolescents (ages 10–25), however 30% occurs in those over 40 so it should not be discounted in adults and the elderly.^{1–5,7,9,10} As with all

malignant bone tumours, males are more commonly affected with an M:F ratio of between 1.4 and 2:1.^{1,9} This gender gap lessens with increasing age (Picture 1).⁹

2.2. Sites affected

The long bones of the appendicular skeleton are usually involved, the majority found in the distal femur, proximal tibia and proximal humerus, with 50% occurrence around the knee.^{1–3,7,9,11} Osteosarcoma is most often a disease of the metaphysis, with approximately 91% of occurrence here.^{2,7,9} It is extremely rare to have an Osteosarcoma of the epiphysis.^{2,9} As age at onset increases, there is greater incidence of short, flat bones being affected such as the jaw, skull, pelvis and spine.^{2,7,9}

2.3. Aetiology

Osteosarcomas are idiopathic, however some risk factors have been identified.^{7,9} Risk factors include previous radiation therapy and Paget's disease of bone, however less than 1% of people with Paget's will develop osteosarcoma.^{1,9,13} These risk factors are therefore associated with development in older adults rather than adolescents. Other notable links are to familial neoplastic disorders such as Retinoblastoma

* Corresponding author.

E-mail address: f.macdona1d3@nhs.net (F. MacDonald).

<https://doi.org/10.1016/j.jor.2019.02.027>

Received 13 September 2018; Accepted 17 February 2019

Available online 07 March 2019

0972-978X/ Crown Copyright © 2019 Published by Elsevier, a division of RELX India, Pvt. Ltd on behalf of Prof. PK Surendran Memorial Education Foundation. All rights reserved.

Picture 1. Osteosarcoma, with classic bone forming matrix.

and Li-Fraumeni syndrome.^{1,7,12} However, the rarity of occurrence leaves doubts as to its true relationship.^{9,14}

2.4. Symptoms and signs

Osteosarcomas are highly malignant, therefore symptoms develop over the course of a few weeks to months and can be non-specific.^{7,9} General symptoms may include exhaustion, unexplained weight loss and fevers.⁹ Pain is the dominating symptom in most malignant bone tumours. The pain at first may be non-specific, but this can soon change to a persistent deep bone pain^{6,7,9,15}. Red flags include non-mechanical bone pain, night pain and pain that is increasing or persistent.^{7,15}

Physical examination may find no abnormality if the patient has presented early enough which can be misleading.⁹ Swelling over the affected area or a palpable mass may be apparent, which is another red flag.^{7,9,15} Decreased range of motion in the closest joint can occur which can make the diagnosis challenging.⁹

Pathological fracture occurs in approximately 5–10% of patients, especially in advanced Osteosarcoma. It has been documented as a first presentation to secondary care, where the patient would usually experience pain and other symptoms prior to fracture but diagnosis had not been made.⁹

2.5. Investigation

Following a detailed history and careful examination, the following investigations should be carried out.

Investigation	Findings
Plain film x ray	Effect of lesion on bone? ie Bony destruction or formation Periosteal reaction? Soft tissue swelling? Matrix?
Blood tests	Screen for other causes of bone pain (eg pagets, myeloma) FBC CRP/ESR Bone profile
MRI	Local staging
CT chest, abdomen and pelvis	Systemic staging
Bone scan	Systemic staging
Biopsy	Confirm subtype

2.6. Investigation Table^{7–10,15,16}

Both plain film x-ray and blood tests can be easily completed in primary care. Part of the investigation should involve the GP referring the patient with suspicious bone symptoms to secondary care^{4,6–10,15,16} where more detailed investigations may take place.

2.7. Treatment

An untreated Osteosarcoma will be fatal.⁹ Opioid analgesia is usually required for pain and can be issued in primary care.⁹ Curative treatment is available, and should be carried out at specialist centres.^{4–10,15–17} Routine modern treatment involves both neo-adjuvant and adjuvant chemotherapy with surgery.^{2,7,10} Neo-adjuvant therapy aims to treat the micro-metastases which may be undetectable at diagnosis – the lung being a common site of deposition.^{2,9} In addition, the tumour may shrink, but more commonly any associated soft tissue component ossifies and pain is reduced. Osteosarcoma is known to be resistant to radiotherapy, and therefore it tends to be used only for local control during palliative care.^{7,10} The aim would be for limb salvage and reconstructive surgery however amputation can be considered if it serves to increase patient function,^{7,10} or if the tumour is deemed otherwise unresectable.

2.8. Outcomes

The treatment available can be curative.^{7,9,10} The prognosis of Osteosarcoma is estimated on a number of factors, the most important one being response to chemotherapy.^{2,7,9,10,18} The differences between chemotherapy responders and non-responders is huge, with 5 year survival for a responder (tumour necrosis of more than 90%) being 80–90% and a non-responder (tumour necrosis less than 90%) being less than 15%⁹ which is what the survival rate of osteosarcoma was in the 1970's.¹⁸ Type of Osteosarcoma is important, for example the Conventional Osteosarcoma five year survival is noted to be between 40 and 80% where the typically lower grade Parosteal group has excellent outcomes with 91% at five years.^{1,2,7,9,10,16,18} Other factors to predict outcome include size of tumour^{2,18} and stage at presentation.^{2,7,9,10,18}

3. Chondrosarcoma

3.1. Epidemiology

Chondrosarcoma is a malignant bone tumour that arises from chondroblasts, laying down hyaline cartilage.^{2,9} It is the second most common type of primary malignant bone tumour, accounting for approximately 20%.^{1,7,9,10} These types of tumours tend to be slow growing, with symptoms evolving over months and years.^{1,7,9} There are six subgroups of Chondrosarcoma; Conventional type (90%), Periosteal, Secondary, Dedifferentiated, Mesenchymal, and Clear Cell.^{2,7,9,19} All Chondrosarcomas have been grouped together for the purposes of further discussion. Males are affected slightly more than females, with the M:F being < 2:1.^{2,9,10} Chondrosarcomas occur in adults, with an age range of 45–60, the majority being over 50 years.^{1,7,9,10,15} It is rare in a person under the age of 30 years.²

3.2. Sites affected

The ilium is the most commonly involved bone, followed by the proximal femur, proximal humerus, distal femur, and then the ribs.^{1,2,7,9,19} It is very rare to find Chondrosarcoma in the spine or skull, if found these would more commonly be the Mesenchymal type of Chondrosarcoma.⁹

Picture 2. Chondrosarcoma, with classic 'Popcorn' Stippled appearance.

3.3. Aetiology

As with Osteosarcoma, the aetiology is unknown.⁹ There are links to benign tumours such as Osteochondroma and Multiple Hereditary Exostosis (MHE), but the risk is low (malignant transformation risk for solitary osteochondroma being < 1% and for MHE ~5%).^{9,19,47,48} Patients who have multiple enchondromas such as Ollier's disease or Maffucci syndrome carry a higher risk of developing Chondrosarcoma (25–30%). These conditions in themselves are very rare with, 1/100 000 being affected by Ollier's disease and less than 200 reported presentations on Maffucci syndrome since its description in 1881,²⁰ so their contribution to risk is limited.

3.4. Symptoms and signs

Chondrosarcoma can present with local swelling/mass and pain, either one symptom or both.^{9,10} The symptoms will have developed over the course of months, or even years. Pathological fracture is still a risk, however as it can be slow growing, this is less likely to happen (Picture 2).⁹

3.5. Investigation

As with any path to diagnosis, a careful history and examination should be carried out prior to investigations. These patients tend to be over 40 years old, where incidence of bone metastases (mostly lung, breast, thyroid, kidney and prostate) are more common than primary malignant bone tumour so initial care should take this into consideration.⁷ Investigation pathway should follow as described in the Osteosarcoma section, a plain film X-Ray and blood tests as a minimum in primary care.^{7–10,15,16}

3.6. Treatment

Chondrosarcomas are in general highly resistant to both chemotherapy and radiotherapy.^{1,2,7,19} Treatment is based on surgical excision of the tumour with wide margins, if this cannot be achieved using limb salvage and reconstructive methods then amputation is required.^{2,19} Even with successful clearance of the primary Chondrosarcoma, the metastases remain problematic in the higher grades of tumour.^{7,10} There is evidence for using chemotherapy with some success in certain subtypes such as Mesenchymal Chondrosarcomas,^{7,10,21,22} but this is limited. Radiotherapy may be used in a palliative setting for local control.¹⁰

3.7. Outcomes

Prognosis largely depends on the histological grade of Chondrosarcoma.^{7,9,10} Grading has been noted to be challenging, with differing opinions of specimens between specialists.^{7,10} It is based on a scale of 1–3, looking at nuclear size, staining and cellularity.⁹ The majority of Chondrosarcomas are grade 1 (61%) which brings a 5 year survival rate of 89%.^{9,23} Grade 2 accounts for 36% and the grade 3 for only 3%, both of which share a 5 year survival of 53%.^{9,23} The low grade Chondrosarcomas are less likely to metastasize, where high grade tumours such as the Dedifferentiated type, can be aggressive and frequently metastasize.¹⁰ Chondrosarcomas of all types and grades can recur locally,^{7,9,10} and if they do recur there is a risk of approximately 10% that it will be of a higher grade of malignancy.^{9,19}

4. Ewing Sarcoma

4.1. Epidemiology

Ewing Sarcoma is a small round blue cell malignancy, and shares the same characteristic chromosomal translocations (t(11; 22) (q24; q12)) as a primitive neuroectodermal tumour (PNET).^{1,9,10} It is therefore described by the World Health Organisation as a tumour of neuroectodermal derivation.⁹ Ewing Sarcoma is the third most common primary malignant bone tumour, accounting for approximately 7% of all primary malignant bone tumours.^{1,9} It is a disease of children and adolescents, being the second most common cause of primary bone malignancy in young people after Osteosarcoma.^{1,7,9,10} The age range at diagnosis is 10–18 years¹⁵ with a median age of 15 years, 80% of patients are less than 20 years old.^{7,9,10} It is very rare to find a Ewing Sarcoma in a patient over the age of 30 years, or in a patient of Asian or African descent.^{7,9,10} The male to female ratio is 1.5:1.^{1,2,7,9,10}

4.2. Sites affected

Ewing Sarcoma is mostly found in the diaphysis or metaphysis of long bones, the pelvis and the ribs.^{1,2,7,9,20} The bones of the skull, spine, scapula, hands and feet are less likely to be involved.⁹ All Ewing Sarcomas are high grade, and at the time of presentation approximately 20–25% of patients have radiologically visible metastasis (mainly lung, bone and bone marrow).^{7,10,24}

4.3. Aetiology

As with Osteosarcoma and Chondrosarcoma, Ewing Sarcoma is idiopathic.^{2,9} It does not appear to have links with any other condition.

4.4. Symptoms and signs

The most common presenting complaint is pain, with or without mass.⁹ Ewing Sarcoma does sometimes display symptoms and signs that other primary malignant bone tumours do not, such as a remittent fever (of about 38°), a raised ESR, anaemia and leucocytosis.⁹ Again, pathological fracture can be a rare feature if there has been missed diagnosis (for example Osgood schlatter disease) (Picture 3).⁹

4.5. Investigation

Should follow the same pattern as described in the Osteosarcoma section, and in addition bone marrow aspirate and a serum LDH can be included as a prognostic tool. These patients will be younger, and so metastatic deposits are less likely.^{7–10,15,16} Care should be taken during the history to determine the nature of the pain, onset, duration etc as the younger patient may find it very difficult to describe what they are feeling.²⁵ This in combination with a lack of clinical suspicion for Ewing Sarcoma can lead to diagnostic delay.^{16,26}

Picture 3. Ewings Sarcoma with pathological fracture and large soft tissue mass clearly seen on the lateral view.

4.6. Treatment

Current treatment usually involves 3–6 cycles of neo-adjuvant chemotherapy followed by surgical excision and reconstruction, then 6–10 cycles of adjuvant chemotherapy.^{7,10} Radiotherapy can be used post operatively if resection margins have been inadequate and can be useful in treatment of lung metastases.^{7,10,27} Radiotherapy can also be used as the definitive treatment in the axial skeleton where adequate margins may be difficult to achieve because of anatomical constraints.

4.7. Outcomes

The outcome of Ewing Sarcoma has a number of influencing factors, including stage, size of tumour and locality (pelvic tumours have a worse outcome).^{7,9,10} As Ewing Sarcoma is chemosensitive, since its introduction, five year survival rates have increased from less than 10%, to approximately 65%.^{7,9,10} This is reduced in those who present with metastatic disease, where five year survival is up to 40%.⁷

5. Summary Table^{1,2,7,9}

Type of tumour	Incidence	Age affected	Sites	Treatment	Average survival rate
Osteosarcoma	30%	10–25	Metaphysis of long bones, 50% at knee, Ilium, proximal long bones, ribs.	Chemotherapy and surgery.	40–60%
Chondrosarcoma	20%	45–60		Surgery	53–89%
Ewing Sarcoma	7%	10–18	Diaphysis/metaphysis of long bones	Chemotherapy, surgery and radiotherapy.	40–70%

6. Treatment and management changes in Scotland

From the treatment methods discussed above, since the introduction of chemotherapy there has been a huge increase in the five year survival rates for both Osteosarcoma and Ewing Sarcoma. This has not been the case for Chondrosarcoma, where the outcomes have not changed significantly in the last 20 years. Research suggests various reasons for chemo-resistance such as the volume of extracellular matrix surrounding the tumour, blocking target access of the chemotherapy drugs, or that due to chemotherapy targeting rapidly dividing cells, it is

essentially useless against the slow growing Chondrosarcoma.¹⁹ Further research is being carried out in an attempt to find a molecular target for treatment of Chondrosarcoma.

From 1992 Glasgow has had meetings regarding management of Sarcoma. In around 2004 the Aberdeen centre joined, forming the Scottish Managed Clinical Network for Sarcoma (MCN). Dundee followed in 2005, Inverness in 2006 and Edinburgh moved in and out of the MCN, before joining in 2007. Prior to the formation of the MCN, all centres were connected via the Scottish Bone Tumour Registry (SBTR), where they would meet on a quarterly basis and all the bone/soft tissue tumour cases were discussed retrospectively. These quarterly meetings were replaced by weekly MCN meetings. For the purposes of this paper we shall regard 2006 to be the beginning of the MCN, and we shall look at patient outcome for each of the centres and as Scotland as a whole from 1994 to 2014 for Primary malignant bone tumour.

The aim of this paper is to explore patient outcome following diagnosis of PMBT in Scotland from 1994 until 2014, using 2006 as the introduction of the MCN, to see if its formation influenced patient outcome. A breakdown of the outcomes for the 3 management centres in Scotland will be also be included. Finally Scottish outcomes will be compared with other UK centres.

7. Method

The patient information was gathered solely from the Scottish Bone Tumour Registry, held at Glasgow's Queen Elizabeth University Hospital. Only patients with diagnoses of Osteosarcoma, Chondrosarcoma and Ewing Sarcoma were included, and the tumour must have been diagnosed in the 20 years between 1994 and 2014.

A review of notes checklist was compiled to standardise questions for all patients. The Questions were as follows:

1. Age and sex of patient
2. Date of presentation
3. Region for treatment.
4. Diagnosis
5. Outcome

No patient identifiers were to be collected as this project is purely a note based observational study.

8. Results

A total of 485 patients were identified. 17 of which were excluded as they died of causes unrelated to their PMBT. A further 145 were excluded for other reasons, such as being lost to SBTR follow up, or that the cause/date of their death was un-documented at the SBTR, leaving a total of 323 patients for inclusion. To allow 5 year outcome for comparison to UK figures, a further 15 patients were excluded as they had not yet had their diagnoses for this duration, leaving 308 patients for 5 year survival comparison. These results can be seen in the [flowchart](#) below (Flowchart 1).

Between 01/01/1994 and 31/12/2005 214 patients were found on the SBTR to have been diagnosed with PMBT, and from 01/01/2006 until 31/12/2014 109 patients were identified, the latest date of diagnosis in 2014 being the end of February.

Of the 214 identified patients diagnosed prior to 2006, 185 were alive at 1 year (86%), 155 were alive at 2 years (72%) and 135 were alive at 3 years (63%) 123 alive at 4 years (58%) and finally 112 alive at 5 years (52%). Of the 109 patients identified from 2006 onwards, 100 were alive at 1 year (91%), 75 were alive at 2 years (69%), at 3 years 58 of the 109 patients had survived (53%). Of the 94 patients identified from 2006 onwards, having been diagnosed for at least 5 years, 46 were alive at 4 years (49%) and 36 were alive at 5 years (38%). The results are tabulated below.

Flowchart 1. Patient inclusion flow.

Survival	Pre MCN	Post MCN
1 year	86%	91%
2 years	72%	69%
3 years	63%	53%
4 years	58%	49%
5 years	52%	38%

Using all 308 patients identified this gives an overall 5 year survival rate for primary malignant bone tumour in Scotland of 48% (55% in England⁴⁴), with males accounting for 57% and females 43%. The 5 year survival rate in Scotland for both males and females is 48%, in comparison to English counterparts 58% and 59% respectively.^{43,44}

Sex	Scottish 5 year survival	English 5 year survival ^{43,44}
Male	48%	58%
Female	48%	59%

To look more closely at the data, firstly comparing 5 year survival for tumour type, Osteosarcoma, Chondrosarcoma and Ewing Sarcoma.

Tumour type	Scottish 5 year survival	English 5 year survival ^{44,45}
Osteosarcoma	45%	45%
Chondrosarcoma	46%	65%
Ewing Sarcoma	51%	50%

A comparison amongst the 3 main centres in Scotland, Glasgow (West) Aberdeen (North) and Edinburgh (East) was then carried out. Glasgow having treated a total of 167 patients in the time period,

Aberdeen 68 patients and Edinburgh 55 patients. The results are tabulated below.

Centre	Overall 5 year survival	5 year survival for Osteosarcoma	5 year survival for Chondrosarcoma	5 year survival for Ewing Sarcoma
Glasgow (West)	49%	46%	46%	52%
Aberdeen (North)	43%	38%	60%	24%
Edinburgh (East)	53%	50%	44%	71%

9. Discussion

The results show that there has been little influence to patient outcome following the formation of the MCN in 2006. Interestingly, also in 2006 the paper “Size matters for sarcomas!” by Grimer⁴⁶ was published, where common objects were used as descriptors of tumour size, a golf ball was used as the benchmark of when one must assume malignant until proven otherwise. This was then used in a pilot campaign by Sarcoma UK in 2012, where 600 GP’s in Birmingham were sent golf ball keyrings with “is it sarcoma?” inscribed in addition to a poster of how to refer to the sarcoma centre. The campaign was then rolled out as the “On the Ball” campaign in 2014 where it received national media coverage. This message could have influenced patient outcome, as both GP’S and patients may have been more inclined to seek expert advice on discovering a mass.

Looking at the 3 management centre outcomes, we can see that there is little difference amongst them. In Aberdeen the 5 year survival for Ewing Sarcoma is less than that of Glasgow or Edinburgh. This can perhaps be explained by the vast area of the highlands and islands the

Aberdeen centre covers, and its patient population. On review of individual cases the majority of these patients delayed seeking GP advice, for reasons such as not wanting to bother the Doctor, or having been too busy with work. Of the Aberdeen group, there were 17 cases of Ewing Sarcoma, and the patients were older than the worldwide data would suggest is typical. It is noted to be a disease of children and adolescents, with an age range of 10–18 years and a median age at diagnosis of 15 years old.^{7,9,10} It is also said to be rare in those over 30 years,^{7,9,10} however in the Aberdeen group the average age at diagnosis of the patient was 30 years old, the oldest being 58. This may mean that the GP would suspect more common conditions such as Osteoarthritis, or muscular injury before thinking of malignancy. This can perhaps explain why for the Aberdeen group, once at the GP, the diagnosis was further delayed for 3 of the patients of whom PMBT was never part of the differential diagnosis. These patients only received plain film x-ray between 56 days and 1 year in secondary care after presenting to their GP. Delay in diagnosis of Ewing Sarcoma significantly increases the mortality rate, and has been shown in several research papers.^{24,26,41,42} It should be noted that once referred to secondary care, all of the patients were seen on average of 23 days which is well in keeping with NICE guidance.⁶

To compare Scottish outcomes with that of our English counterparts, we can see that there is minimal difference between the two. Both Scotland and England have a 45% survival rate for Osteosarcoma, and 51%–50% respectively for Ewing Sarcoma. There is, however, a significant difference in the Chondrosarcoma outcomes, with Scotland having 46% survival and England 65%. Reasons for this could again relate to population diversity, or our comparatively small numbers to treat, however having not been able to compare patients on a case by case basis to further investigate the differences in Chondrosarcoma outcome, it is impossible to account for these differences. A further study could be initiated from these results to find reasons. There is no difference in overall survival rates between males and females. Given our comparably small number of patients to treat this shows Scotland is in keeping with both English and worldwide outcomes.^{1,2,7,9,43–45}

10. Conclusion

Approximately 6 patients per year are diagnosed with a primary malignant bone tumour in Scotland. This paper explored the outcomes of the patients diagnosed with PMBT over the course of 20 years in Scotland. It showed that there was no change in outcome following the formation of the Scottish Managed Clinical Network for Sarcoma, and that there were little differences in outcome amongst the three major management centres for Sarcoma in Scotland. Findings also show Scotland to have similar outcomes to that of England, and that we are in keeping with the worldwide trend in outcome following diagnosis of a primary malignant bone tumour. It would be informative to further explore the differences in Chondrosarcoma outcomes between Scotland and England in a follow up paper, and to introduce the regular review of Scottish PMBT outcomes as is done by the National Cancer Intelligence Network in England.

Conflicts of interest

We would like to declare we have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jor.2019.02.027>.

References

- Underwood J, Cross S. *General and Systematic Pathology*. fifth ed. Sheffield: Churchill Livingstone; 2009.
- Duckworth T, Blundell C. *Orthopaedics and Fractures*. fourth ed. Oxford: Wiley Blackwell; 2009.
- updated 08/09/12 www.cancerresearchuk.org.
- updated march 2010 <http://www.nice.org.uk/nicemedia/live/10903/28934/28934.pdf>.
- updated October 2010 <http://www.britishsarcomagroup.org.uk/#/guidelines/4556224410>.
- updated April 2011 <http://publications.nice.org.uk/referral-guidelines-for-suspected-cancer-cg27>.
- Grimer RJ, Athanasou N, et al. UK guidelines for the management of bone sarcomas. *Sarcoma*. 2010;1:1–14.
- Grimer RJ, Briggs TWR. Earlier diagnosis of bone and soft tissue tumours. *J Bone Joint Surg Br*. 2010;92-b:1489–1492.
- WHO classification of tumours. *Pathology and Genetics of Tumours of Soft Tissue and Bone*. Lyon: IARC Press; 2013.
- Bone sarcomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. European sarcoma Network working group. *Milan. Annals of Oncology*. 2012;23:100–109.
- Dorfman HD, Czerniak B. *Bone Cancers*. *Cancer*. 1995;75:203–210.
- Fuchs B, Pritchard DJ. Etiology of osteosarcoma. *Clin Orthop Relat Res*. 2002;397:40–52.
- Hansen MF, Nellissey MJ, et al. Common mechanisms of osteosarcoma and Paget's disease. *J Bone Miner Res*. 1999;2:39–44.
- Ruggieri P, Sim F, et al. Malignancies in fibrous dysplasia. *Cancer*. 1994;73:1411–1424.
- Scottish Sarcoma MDT, Mahendra A, Jane M, Duncan R. Referral Guidelines for Primary Bone Sarcoma. Updated 03/02/14 http://www.ssn.scot.nhs.uk/images/stories/SSN/nhs_ayrshire_and_arran_bone_sarcoma_referral_poster.pdf.
- Grimer RJ, Sneath RS. Diagnosing malignant bone tumours. *J Bone Jt Surg*. 1990;72-B:754–756.
- National Comprehensive Cancer Network. USA. Clinical Practice Guidelines in Oncology, Bone Cancer. Updated 24/09/13 http://www.nccn.org/professionals/physician_gls/pdf/bone.pdf.
- Bramer JA, Van Linge JH, et al. Prognostic factors in localized extremity osteosarcoma: a systematic review. *Eur J Surg Oncol*. 2009;45:2367–2375.
- Bovee J, Cleton-Jansen A, et al. Emerging pathways in the development of chondrosarcoma of bone and implications for targeted treatment. *Lancet Oncol*. 2005;6:599–607.
- Silve C, Juppner H. Ollier disease. *J Rare Dis*. 2006;22:1–37.
- Dantonello T, Leuschner I, et al. Mesenchymal chondrosarcoma of soft tissues and bone in children, adolescents and young adults: experiences of the CWS and COSS study groups. *Cancer*. 2008;112:2424–2431.
- Cesari M, Bertoni F, et al. Mesenchymal chondrosarcoma. An analysis of patients treated at a single institution. *Tumour*. 2007;93:423–427.
- Bjornsson J, McLeod R, et al. Primary chondrosarcoma of long bones and limb girdles. *Cancer*. 1998;83:2105–2119.
- Philip M, Simpson S, et al. Ewing's sarcoma of the upper extremity: presenting symptoms, diagnostic delay and outcome. *Sarcoma*. 2005;9:15–20.
- Lissauer T, Clayden G. *Illustrated Textbook of Paediatrics*. fourth ed. Edinburgh: Mosby Elsevier; 2012.
- Goyal S, Roscoe J, et al. Symptom interval in young people with bone cancer. *Eur J Cancer*. 2004;40:2280–2286.
- Paulussen M, Ahrens S, et al. Ewing's tumours with primary lung metastases: survival analysis of 114 (European intergroup) cooperative ewing's sarcoma studies patients. *J Clin Oncol*. 1998;16:3044–3052.
- Bacci G, Di Fiore M, Rimondini S, et al. Delayed diagnosis and tumour stage in ewing's sarcoma. *Oncol Rep*. 1999;6:465–466.
- Simpson P, Reid R, Porter D. Ewing's sarcoma of the upper extremity- presenting symptoms, diagnostic delay and outcome. *Sarcoma*. 2005;9:15–20.
- National Cancer Intelligence Network. England: Bone Sarcomas: Incidence and Survival Rates in England – NCIN Data Briefing. September 2010; September 2010 www.NCIN.org.uk/publications/data_briefings/bone_sarcomas_incidence_and_survival.
- National Cancer Intelligence Network. England. Bone Sarcomas Incidence and survival: Tumours Diagnosed between 1985 and 2009. www.NCIN.org.uk/publications/data_briefings/bone_sarcoma_incidence_and_survival_rates_in_england_october_2012.
- National Cancer Intelligence Network. England. Bone Sarcomas, Incidence and Survival Rates in England. www.NCIN.org.uk/publications/data_briefings/bone_sarcoma_incidence_and_survival_rates_england_september_2012.
- Grimer RJ. Size matters for sarcomas!. *Ann R Coll Surg Engl*. 2006 Oct;88(6):519–542.
- Khurana J. *WHO Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone*. Lyon: LARC press; 2002:234–236.
- Steffner R. Benign bone tumours. *Cancer Treat Res*. 2014;162:31–63.