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REVIEW

BONE METASTASES FROM COLORECTAL CANCER

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Summary

Colorectal cancer is the third leading cause of cancer-related deaths in the world and death is usually attributed to disease progression with recurrence and metastases. Bone metastases from colorectal cancer is an uncommon event and when occurs, usually as a late manifestation of the disease, is preceded by liver or lungs metastases. The most common sites of osseous metastases are the vertebral column, pelvis and the sacral regions. Early diagnosis is important for improving quality of life in these patients.
Key words: distal metastases, colorectal neoplams, bone metastases, solitary bone metastasis

Résumé

Les métastases osseuses du cancer colorectal

Le cancer colorectal est la troisième principale cause de décès liées au cancer dans le monde, le décès étant généralement attribué à la progression de la maladie, à la récidive et aux métastases. Les métastases osseuses du cancer colorectal sont un événement rare et quand il se produit habituellement comme une manifestation tardive de la maladie, est précédé par les métastases du foie ou du poumon. Les sites les plus communs des métastases osseuses sont la colonne vertébrale, le bassin et les régions du sacrum. Un diagnostic précoce est important pour améliorer la qualité de vie chez ces patients.
Mots clés: métastases distales, néoplasmes colorectaux, métastases osseuses, métastase osseuse solitaire

Introduction

Colorectal cancer is one of the most common malignancies worldwide and continues to be one of the leading causes of cancer-related death globally. In colorectal cancer patients, similar to those with other malignancies, metastases are the main cause of cancer-related mortality. Distant metastatic disease is present in approximately 25% of patients at initial diagnosis and half of colorectal cancer patients will develop metastases in the course of the disease (1).

The recurrence pattern of colon cancer is characterized by a rate of local recurrence of 1 to 19%, a 5-16% rate of local recurrence associated to distant metastasis and a 12-22% rate of systemic recurrence. The recurrence pattern of rectal cancer is: local recurrence rate of 7-33%, local and systemic recurrence rate of 7-30% and systemic recurrence rate of 6-19% (2).

Higher survival rates in colon cancer have led to an increasingly frequent appearance of metastases in locations that were previously rare. Recent studies have revealed that the patients who receive adjuvant or neo-adjuvant therapy show an increased rate of bone metastases Sundermeyer et al., in a review of 1,020 patients, diagnosed with colon cancer, found up to 10% of bone metastases and a 3% of brain metastases, mainly in patients that had been subject to multiple systemic treatments (2).

The most common sites of colorectal cancer metastases are the liver and the lung. The incidence of bone metastasis from colorectal cancer has been reported to be 8.6-27% in autopsy cases and in 3.7-11% in clinical cases (3). Kanthan et al. (4), reviewed 5352 cases of colorectal carcinoma and

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found that 16.9% cases had skeletal metastasis only, whereas in 83.1% cases, skeletal metastasis was combined with liver, lung or brain metastasis.

Rectum cancer had a higher incidence rate of lung (5.6% vs 3.7%) and bone metastasis than colon cancer. From the various histological types, signet ring cell carcinoma showed a high incidence of bone metastasis. (5) The most common sites for metastases include the vertebral column, pelvis, and long bones (6).

Roth et al. (7) used positron emission tomography and /or CT scans in 252 patients with a diagnosis of colorectal cancer and found the incidence of bone metastasis to be 5.5%, with an average time from initial diagnosis to detection of metastatic disease of 9.8 months for liver involvement, significantly shorter than the average times of 23.3 months to detect lung metastasis and 21.2 months to detect bone metastasis. The average time for colon cancer to metastasize from the liver to bone was 8.3 months whereas the time to metastasize from lung to bone was 3.3 months. No cancer metastasized to bone without first metastasizing to the liver or lung in this study. As reported in the literature the colorectal cancer metastasizes first to the liver or lungs, which both contain dense capillary beds that can trap tumor cells and seed them into these organs. The environment of a specific organ and its influence on tumor cell adhesion can also contribute to the efficacy of tumor spread. They concluded that if a colorectal cancer patient has no sign of disease involvement in the liver or lungs, evaluation of a suspicious bone lesion should not be aggressive and more noninvasive data should be obtained from other diagnostic modalities or follow-up. Lung metastasis indicates the potential for cancer to metastasize to bone in the colorectal cancer population better than liver metastasis does.

Different series have shown that the median survival of patients with bone metastases is between 5 to 7 months after detecting the bone metastases Nozue et al. (10) reviewed the treatment and prognosis of patients with colorectal cancer and bone metastases. Out of 928 patients in the study, only 1.3% of the patients presented bone metastases, which were in an advanced stage in all cases. The survival rate for these patients was very poor, with an average of 5 months and a 1-year survival rate of 20%. According to Jimi et al (3), mean survival from the diagnosis of bone metastases is 9.3 months. The serum CEA level at the time of diagnosis of bone metastases, history of pulmonary metastases or metastases in the ribs significantly affected survival. In the few case reports of patients with solitary bone metastasis from colorectal cancer, the use of radiotherapy or surgical resection of the bone metastases has been reported to achieve favorable results (6-10).

Somatic mutation status in metastatic colorectal cancer is becoming increasingly clinically relevant as it may be correlated not only with response to biologic therapies, but also with site-specific pattern of metastatic spread and outcome The presence of a KRAS mutation is associated with a distinct pattern of metastatic spread with decreased liver metastases and increased lung, brain, and bone metastases (11).

Metastatic lesions are usually multiple and tend to appear on the axial skeleton and the proximal segments of the limbs. Their location, in decreasing order, is the following: dorso-lumbar spine, sacrum, pelvis, ribs, sternum, proximal third of the femur, proximal third of the humerus and cranium Acral metastases (located in the hand and foot) are rare (12).

More than 95% of spinal metastases are extradural lesions. Most of the remaining lesions are intradural extramedullary tumors, while intramedullary metastases are rare, comprising about 0.5% of the spinal metastases (13). Metastatic carcinoma has a predilection for the well vascularized bone of the vertebral body in the spine; the neural arch is less frequently involved. The posterior half of the vertebral body is usually involved first, followed by the anterior body, lamina, and pedicles by means of two mechanisms: via arterial emboli to the abundant bone marrow of the vertebral bodies and subsequently into the anterior or posterior extradural space through venous channels, or via retrograde spread through the valve less extradural Batson's venous plexus. Metastases occur most frequently in the lumbar spine followed by the thoracic and cervical spine (14,15).

Pain is the initial symptom in most of the patients. It may be due to medullary compression, distension of the periosteum, peripheral neurovascular involvement or pathological fractures and is usually local, but sometimes can radiate in the distribution of the nerve root of the involved level. Neurologic compromise in the form of weakness, sensory loss, and sphincter disturbance usually occurs after the onset of pain. Sensory or motor deficits are present in 38-76% of the patients. The natural history of spinal metastasis is progression to complete irreversible paraplegia if immediate treatment is not undertaken. Due to the smaller space available for the spinal cord, thoracic lesions are more often symptomatic (70%), followed by lumbar (20%), and cervical lesions (10%) (12-14).

When pain affects a long bone, it is easily located by the patient. Metastases affecting the femur or the tibia generate pain on walking and functional deficit, but the pain usually appears when the bone destruction levels are over 50% and it indicates an imminent fracture, that is a fracture that can appear as a result of a physiological load. In such cases a propylactic fixation is recommended especially in load-bearing bones. When the tumor invades the cortical bone and affects soft tissue, swelling may appear and this may be a sign of lesion aggressiveness (12).

As an example of rare location of the bone metastases, mandible is described in the literature as a potential metastatic site, thus the sign of mental nerve neuropathy should be considered as a significant symptom in patients with colorectal cancer and such cases should be further investigated accordingly (16).

DIAGNOSIS

Osseous metastases from colorectal carcinoma are predominantly osteolytic lesions, while osteoblastic or mixed osteoblastic-osteolytic lesions are rare (6). Bone destruc-

tion secondary to metastasis is not caused by the tumor cells. The tumor cells secrete an osteoclast activating factor and so osteolysis is mediated by osteoclastic resorption (12).

X-rays scans can detect metastatic bone disease if the bone mineral loss is more than 30-50%.

Anteroposterior and lateral plain radiographs of the spine demonstrate abnormal findings in up to 90% of the patients with symptomatic spinal metastasis. The detection or prediction of fracture risk is an advantage of this technique. It requires a detailed assessment of the size and character of the bone destruction. Osteolytic lesions are associated to a higher risk than mixed and osteoblastic lesions, just as lesions that invade more than half of the diameter of the cortical bone, lesions located on the trochanteric region or lesions that affect a load-bearing bone. X-rays scans may evaluate the response to treatment. Osteolytic metastases create a sclerotic edge of reactive bone, followed by an increase in sclerosis, moving from the edges towards the center and finally reduce its size. Comparisons with previous radiographies make it possible to differentiate between progression and a positive response to treatment.However, in view of their low sensitivity, bone X-rays series have largely been replaced by scintigraphy.

Bone scintigraphy-Since the 1961 report by Fleming et al. that administered radiostrontium localized preferentially in areas of diseased bone, the skeletal scintiscanning has proved to be a valuable diagnostic technique.

Tc-99m bone scintigraphy offers certain advantages: high sensitivity, information of the entire skeleton simultaneously, information for the staging of the lesion and the response to treatment.

The isotope is absorbed by areas with increased blood flow and increased exchange of reactive bone. It shows enhanced areas in osteolytic and osteoblastic lesions, due to the bone renewal that takes place at the periphery of the lesion.

A group of randomly dispersed lesions with scintigraphic enhancement on the axial skeleton may be a sign of metastatic disease, but isolated lesions may be difficult to interpret. In order to decrease false positive or false negative results, it must be taken into consideration that: fractures and surgical scars can be enhanced up to 1-3 years; an enhancement following the longitudinal axis of the rib can be a sign of metastases, radiation-induced osteonecrosis or steroid abuse may lead to false negative results, due to an increased enhancement in the entire skeleton. However, it is less sensitive than MRI in detecting bone metastasis, almost 50% of its results are false negative, so it should be assessed in combination with MRI and CT scans (4,7,12,17).

CT scan complements radiographies and provides more information for the diagnosis and the possibility of an imminent fracture. It is useful in the assessment of the vertebral column and the pelvis and a very good technique for guided biopsies of the bone metastatic lesions.

MRI presents high sensitivity for the detection of metastasis and high specificity for the characterization of lesions. Metastatic lesions show low intensity in T1-weighted images and high intensity in T2-weighted images. This technique assesses peritumoral soft tissue, offers a more accurate assessment of neurovascular and medullary compression, provides a better characterization of the bone marrow and the possibility of skip metastases. Multiple lesions, the presence of soft-tissue masses, the involvement of posterior elements, a convex shape and a sharp edge between normal marrow and affected marrow are signs of metastasis.MRI is important for the further treatment planning.Although MRI is useful in the detection of early metastasis that are localized completely in the bone marrow cavity routinely bone, scintigraphy remains that most cost-effective method for examination of the entire skeleton (12,17,18).

Positron emission tomography (PET) is an imaging technique that uses as a tracer the [18F]2-fluoro-2deoxy-Dglucose (FDG), a glucose analog absorbed by malignant tissue with an increased metabolic activity. With a high sensitivity, PET scan is important for the identification of primary lesions and other metastases, being able to differentiate a scar from local recurrence and to assess the response to treatment. PET/CT-based response evaluation has proven to be valuable in chemotherapy and especially in targeted treatment, 2 sets of criteria to quantify anticancer treatment response being currently available: the criteria developed by the European Organization for Research and Treatment of Cancer (EORTC) and PET Response Criteria in Solid Tumors (PERCIST) (17-19).

Some authors report that FDG PET is more sensitive than CT in the clinical assessment of patients with metastatic colorectal cancer. Lai et al. (20) reported that FDG PET showed better results in detecting extrahepatic lesions than the conventional imaging. Ogunbiyi et al. (21) reported that FDG PET was 95%–100% sensitive for detecting liver metastases. These values were superior to those for CT, which had a sensitivity of 74% and a specificity of 85%.

It has even a better sensitivity in detecting liver metastases than the new method of immunoscintigraphy with 99mTc-labeled antibody (Fab8) fragment specific to CEA (22).

Bone metastases usually appear when colorectal cancer is in an advanced stage, when the diagnosis has already been established, thus a histological diagnosis is not usually necessary. When the primary site of bone metastatic cancer is unknown (0.5-7% of the oncologic patients), biopsy is necessary for an accurate diagnosis (23). In the case of an osteolytic lesion without diagnosis of the primary tumor, the differential diagnosis must be performed with conditions like Paget's disease, hyperparathyroidism, myeloma, lymphoma, chondrosarcoma, malignant fibrous histiocytoma, sarcomas (7,10,12).

Treatment

The therapeutic approach for bone metastases, as in any neoplastic pathology, is a multidisciplinary one, joining oncologists, anatomopathologists, interventional radiologists, pain therapeutics and orthopedic surgeons.The treat-

ment of bone metastases derived from colorectal tumors is the same as the treatment for bone metastases with other primary sites.

With the newer treatment regimens, median survival of >20 months has been reported for patients with advanced colorectal cancer. The increase in overall survival in patients with metastatic cancer increases the likelihood that patients develop bone metastases during the course of their disease and the associated bone destruction will manifest within the patient's lifetime, resulting in potentially debilitating sequelae. The acute consequences of bone metastases include skeletal-related events (SRE) - pathological fracture, , spinal cord compression, the need for radiotherapy or surgery to bone and hypercalcemia of malignancy.

The final data of a large Italian multicenter study on the natural history of patients with bone metastases from CRC,analysing positron emission tomography and/or CT scans from 252 patients with colon cancer reported 5.5% of patients having bone metastases at primary diagnosis, all patients with bone lesions also had visceral metastases. The median time between primary diagnosis and diagnosis of bone metastases was 21 months. This evaluation of the natural history of bone metastasis secondary to CRC suggests that there is a very aggressive disease course in bone that can result in potentially debilitating SRE within a short time.The median time to developing the first SRE after diagnosis of bone metastases is only 1 month.

The most commonly reported events includes severe bone pain requiring palliative radiotherapy, pathologic bone fractures and spinal cord compression (6,10,12).

Opioid drugs or other strategies like nerve block and neurostimulation or even surgery are used in moderate or intense pain (10,12).

Bisphosphonates inhibit the osteoclast activity and some authors have suggested that they are not only useful in the treatment of pain and the prevention of osteolytic complications, but they can also modify the natural course of evolution of cancer in some cases, due to the effect they have on some intermediate products, such as growth factors (24).

Radiotherapy is the most widely used palliative treatment for bone metastasis. It is the treatment of choice for painful lytic bone metastases without short-term risk of fracture and it is combined with surgery when there is a fracture or an imminent fracture. It leads to the necrosis of tumor cells, which makes it possible for the bone tissue to regenerate afterwards. The result is pain relief and, later on, a re-calcification of the destroyed areas of the bone, which is important for the functional recovery of the patient and the prevention of pathological fractures. Two different radiation methods are used: external radiation therapy and systemic or metabolic radiation therapy. After external radiation therapy bone re-calcification can be observed 1 to 3 months after radiation in 60-80% of the patients. Systemic radiation with radiopharmaceuticals is recommended for patients with symptomatic diffuse bone involvement. The most common radiopharmaceuticals are strontium-89 and samarium-153. Treatment with systemic radiation therapy shows pain relief in 70-75% of the patients, and it lasts for 2-4 months. In patients with a good clinical response, the treatment can be repeated (1,10,12).

With a few exceptions, curative surgery is not a realistic objective for the patients bone metastases from a colorectal cancer. The surgical approach may vary according to metastasis characteristics, such as location, its size and the affected areas.

Major surgical procedures should be considered only for patients who are expected to survive more than three months. The patient's life expectancy, overall tumor load, quality of life and other treatment options should be assessed before surgical planning (14). Surgical resection of isolated metastatic bone lesion has been shown to be a good treatment option, generally resulting in prolonged survival (25).

In case of spinal involvement, patients with a neurological deficit associated to instability require early decompression and stabilization. In the case of stable lesions, they can benefit from radiotherapy and orthopedic treatment. Surgery is indicated when symptoms are still present in spite of treatment of fractures or instability after treatment, as well as for the post-therapeutic progression of the tumor and medullary compression.Laminectomy provides an excellent improvement of pain in 75-100% of the patients, as well as neurological improvement in 50-75% of the cases. Many practitioners think that patients with a minimum life expectancy of 6-12 weeks are candidates for surgery (25,26). Radiotherapy is indicated in patients with intense pain with no medullary involvement or with a neurological deficit that shows a slow and incomplete onset and progression, whenever osteoarticular spinal instability (which is the key element for the indication of surgery) has been ruled out. In cases in which short-term prognosis is poor or when surgery is contraindicated due to the general condition of the patient, radiotherapy is the only option.

The complex anatomy and approach of the pelvis make surgery a difficult task, and other palliative techniques, such as arterial embolization of the metastasis or radiotherapy may be indicated in the first place. However, the periacetabular area requires surgical reconstruction, an extremely rare and complex technique.

Proximal third of the femur is the most common location for metastases that affect long bones. The most common techniques used are hip arthroplasty, pin osteosynthesis or open osteosynthesis.

In diaphyseal bone metastases, the treatment of choice is an osteosynthesis of the bone as wide and stable as possible. In patients with prolonged survival prospects an intervention on the metastatic site and a resection of the affected bone fragment and subsequent reconstruction are indicated. The reconstruction with bone cement was common during the 80s and 90s, but nowadays bone allografts are more common.

Humerus is the second most commonly affected bone in the limbs after the femur.

The initial symptom is usually a pathological fracture

or pain associated to an imminent fracture. Standard procedures include arthroplasty and osteosynthesis.

Acrometastas is are metastases to the hands or the feet. They are very rare- 0.3% - 3% of all bone metastases. Bone metastases of a colorectal cancer are even rarer and there are few references in the medical literature (27,28).

Acrometastases are difficult to diagnose and are often mistaken for a benign disease, osteomyelitis, rheumatoid arthritis, gout, fractures, synovitis or glomus tumor, among others. Most of the bone metastases located on the hands affect the phalanges and they originate most frequently from a lung or breast cancer. The right hand is more commonly affected than the left hand Acrometastases of colon cancer and urinary tract cancer are usually found on the foot; hand acrometastases in these cases being exceptionally rare (29,30).

Traumatisms, temperature gradients, hormonal factors, local hemodynamic factors or immune factors and the properties inherent to the metastasizing cell are the factors suggested for the accumulation of tumor cells on the limbs. These metastases usually leave the articulations intact (31,32). The third finger is the most common one in the medical literature, and the distal phalange is the most commonly affected. The metacarpus, the proximal phalange and the middle phalange are the next most common locations for acrometastasis. Acrometastasis is more common in men, with a 2:1 ratio, probably due to a higher incidence of lung carcinoma.

The acrometastases usually appear in an advanced stage of the disease. For this reason, the prognosis is poor, and the objective is to alleviate the pain. The therapeutic options include amputation, radiation therapy, curettage, cementation, chemotherapy and wide excision (33).

Conclusions

Bone metastases from colorectal cancer are uncommon, usually present late in the natural history of metastatic disease and are associated with liver or lung metastasis. They are becoming more apparent as more locoregional controls are achieved with aggressive therapy using multiagent chemotherapy and their early detection improves quality of life, as well as survival.

As a result of the loss of bone density, affected bones become prone to fracture and injury.

Therapeutic management of this condition includes chemotherapy, radiotherapy and surgery, but because of survival after onset of bone metastasis is very poor, palliative treatment is the aim. As survival improves for this patient population, clinicians should be aware of the potential for metastases at previously uncommon sites.

Refrences

1. VanCutsem E, Oliveira J. Advanced colorectal cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up.Ann Oncol.2009;20 Suppl 4:61–63.
2. Sundermeyer, M. L; Meropol, N.J; Rogatko, A; Wang, H; Cohen, S.J. (2005).Changing Patterns of Bone and Brain Metastases in Patients with Colorectal Cancer. Clinical Colorrectal Cancer.vol 5, no 2 (July 2005). 108-113
3. S. Jimi, T. Yasui, M. Hotokezaka, K. Shimada. Clinical features and prognostic factors of bone metastases from colorectal cancer. SurgeryToday. July 2013, Volume 43,Issue7,pp 751-756
4. Kanthan R, Loewy J, Kanthan SC. Skeletal metastases in colorectal carcinomas A Saskatchewan profile. Dis Colon Rectum 1999;42:1592-7
5. Qiu M, Hu J, Yang D, Cosgrove DP, Xu R. Pattern of distant metastases in colorectal cancer: a SEER based study. Oncotarget. 2015 Nov 17;6(36):38658-66
6. Santini D, Tampellini M, Vincenzi B, Ibrahim T, Ortega C, Virzi V, et al. Natural history of bone metastasis in colorectal cancer: final results of a large Italian bone metastases study.Ann Oncol.2012;23:2072–2077
7. E. S Roth,D. T Fetzer,B. J Barron,U. A Joseph,I.W Gayed,D. Q Wan. Does colon cancer ever metastasize to bone first? a temporal analysis of colorectal cancer progression. BMC Cancer. 2009; 9: 274
8. Chalkidou AS, Boutis AL, Padelis P. Management of a Solitary Bone Metastasis to the Tibia from Colorectal Cancer. Case Rep Gastroenterol 2009;3:354-359
9. Onesti JK, Mascarenhas CR, Chung MH, Davis AT. Isolated metastasis of colon cancer to the scapula: is surgical resection warranted?World J Surg Oncol.2011;9:137
10. Nozue M, Oshiro Y, Kurata M, Seino K, Koike N, Kawamoto T, Taniguchi H, Todoroki T, Fukao K. Treatment and prognosis in colorectal cancer patients with bone metastasis. Oncol Rep.2002;9:109–112
11. Lipsyc M, Yaeger R.Impact of somatic mutations on patterns of metastasis in colorectal cancer.J Gastrointest Oncol. 2015 Dec;6(6):645-9
12. GermánBorobio León, Asunción García Plaza, Roberto González Alconada, Ignacio GarcíaCepeda, Jorge López Olmedoet.al.Bone Metastasis of Rectal Carcinomawww.intechopen.com
13. Schick U, Marquardt G, Lorenz R. Intradural and extradural spinal metastases. Neurosurg Rev 2001;24:1-5
14. E. Demirçay, E. Civelek,E. Demiralay.Solitaryspinous process metastasis: a case report Joint Diseases and Related Surgery 2013;24(1):58-61
15. Batson OV. The function of the vertebral veins and theır role in the spread of metastases. Ann Surg 1940;112:138-49
16. Colella G, Giudice A, Siniscalchi G, et al.Chin numbness: a symptom that should not be underestimated: a review of 12 cases.Am J Med Sci2009;337:407–10
17. Galasko CS. Diagnosis of skeletal metastases and assessment of response to treatment.ClinOrthopRelat Res. 1995Mar;(312): 64-75
18. Chiewvit P, Danchaivijitr N, Sirivitmaitrie K, Chiewvit S, Thephamongkhol K. Does magnetic resonance imaging give value-added than bone scintigraphy in the detection of vertebral metastasis?J Med Assoc Thai. 2009 Jun;92(6):818-29
19. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med. 2009;50(suppl 1):122S–150S
20. Lai DT, Fulham M, Stephen MS, Chu KM, Solomon M, Thompson JF, Sheldon DM, Storey DW. The role of whole-body positron emission tomography with [18F]fluorodeoxyglucose in identifying operable colorectal cancer metastases to the liver.Arch Surg. 1996 Jul;131(7):703-7.
21. Ogunbiyi OA, Flanagan FL, Dehdashti F, Siegel BA, Trask DD, Birnbaum EH, Fleshman JW, Read TE, Philpott GW, Kodner IJ. Detection of recurrent and metastatic colorectal cancer: comparison of positron emission tomography and computed tomography.AnnSurgOncol. 1997 Dec;4(8):613-20.
22. P.Willkomm, H. Bender, M. Bangard, P. Decker, F. Grunwald,Hans. Biersack FDG PET and Immunoscintigraphy with 99mTc-Labeled Antibody Fragments for Detection of the Recurrence of Colorectal Carcinoma J Nucl Med 2000; 41:1657–1663

23. O.Buyukbebeci,G.Karakurum,E.Tutar,A. Gulec,O.Arpacioglu. Biopsy of vertebral tumour metastasis for diagnosing unknown primaries Journal of Orthopaedic Surgery 2010;18(3):361-3
24. Ross, J.R; Saunders ,Y; Edmonds, P.M; Patel, S; Wonderling, D; Normand, C. A systematic review of the role of bisphosphonates in metastatic disease.Health Technol Assess. vol 8. August 2004. 1-176
25. Gallagher DJ, Kemeny N. Metastatic colorectal cancer: from improved survival to potential cure.Oncology.2010;78:237–248
26. George R, Jeba J, Ramkumar G, Chacko AG, Leng M, Tharyan P. Interventions for the treatment of metastatic extradural spinal cord compression in adults. Cochrane Database Syst Rev 2008;
27. Ben Abdelghani K, Chekili S, Hajri R, Laater A, Zakraoui L. Colic adenocarcinoma and talus acrometastasis:a case report.GastroenterolClin Biol. 2008 Oct;32(10):835-7
28. Flynn CJ, Danjoux C, Wong J, Christakis M, Rubenstein J, Yee A, Yip D, Chow E.Two cases of acrometastasis to the hands and review of the literature.Curr Oncol.2008 Oct;15(5):51-8.
29. Méndez López JM, García Mas R, SalvàColl G. Metastasis of an adenocarcinoma of the colon to the 1st metacarpal bone.AnnChir Main Memb Super.1997;16(2):134-7
30. R. Wijayaratna, Joyce Wing Yin Ng Metatarsal metastasis as the presenting feature of occult colorectal carcinoma BMJ Case Rep. 2013
31. Chang, H.C; Lew, K.H; Low, C.O. Metastasis of an adenocarcinoma of the stomach to the 4th metacarpal bone. Hand Surgery 2001 December; 6(2): 239-242.
32. Healey JH, Turnbull AD, Miedema B, Lane JM. Acrometastases.A study of twenty-nine patients with osseous involvement of the hands and feet.J Bone Joint Surg Am. 1986 Jun;68(5):743-6.
33. Spiteri, V; Bibra, A; Ashwood, N; Cobb, J. Managing acrometastases treatment strategy with a case illustration. Ann R CollSurgEngl 2008 October; 90(7): 8-11.