Journal of Research and Practice on the Musculoskeletal System
JRPMS

Mini Review

RANK, RANK-L and OPG system as a prognostic and severity indicator for metastatic bone disease

Anna-Louiza Chaliasou[1], **Christos Zafeiris**[1,2]

[1]*Postgraduate Program "Metabolic Bone Diseases", National and Kapodistrian University of Athens, Medical School, Athens, Greece;*
[2]*Laboratory for the Research of the Musculoskeletal System "Th. Garofalidis", National and Kapodistrian University of Athens, Medical School, Athens, Greece*

Abstract

Bones represent the third most common location of metastatic tumors in patients with generalized malignancy. A percentage of 83% of the patients with bone metastases will experience pain due to them and many of them will not receive adequate therapy, which will result in a decrease in their life quality. The system that is composed by the receptor activator of nuclear factor (NF)-kB-ligand (RANK-L), the receptor activator of nuclear factor kB (RANK) and the receptor osteoprotegerin (OPG) play a key role in the migration and growth of neoplastic cells, especially in metastatic bone disease. The aim of this review is to process the contemporary knowledge of the role of the RANK/RANK-L/OPG system in carcinogenesis and to evaluate the potential use of the system or parts of it as biomarkers and indicators of the severity and the prognosis of metastatic bone disease. Finally, a suggestion is made for further investigation between the association of serum RANK, RANK-L and OPG levels and the severity of pain patients with metastatic bone disease endure.

Keywords: Biomarker, Metastatic bone disease, RANK/RANK-L/OPG system

Introduction

Bones represent the third most common location of metastatic tumors in patients with generalized malignancy, after the liver and the lung. Bone metastasis rates, vary depending on the primary tumor site. Specifically, the percentage of bone metastases in generalized breast or prostate cancer, ranges between 65 and 75%, 30-40% in lung cancer, 14-45% in melanoma, 20-25% in kidney cancer, 60% in thyroid cancer and 40% in bladder cancer[1].

Bone metastases are divided into osteolytic, osteoblastic and mixed depending on how they interact with the bone remodeling system. Osteolytic metastasis causes the destruction (or lysis) of the affected bone and this is principally due to increased osteoclastic activity. This type of bone metastasis is mainly encountered in breast, lung, kidney, thyroid and gastrointestinal malignancies, and is also very characteristic of multiple myeloma, melanoma, non-Hodgkin lymphoma and of Langerhans-cell histiocytosis. Also, in more advanced stages of malignancies, bone ischemia as a result of vascular compression can result in osteolytic bone metastasis. Osteoblastic or sclerotic bone metastases is typically found in prostate cancer and is defined by the production of new bone. The main representative of mixed bone metastasis is breast cancer[2]. In this case, the patients may have bone metastasis that have both osteolytic and osteoblastic parts in a single lesion or they could have multiple osteolytic and osteoblastic lesions on their bones. It is estimated that 15 to 20% of the women with breast cancer and bone metastasis belong in this latter category.

The authors have no conflict of interest.

Corresponding author: *Anna-Louiza Chaliasou, Anapiron Polemou 20, 11521, Athens, Greece*

E-mail: *annalouisachaliasou@gmail.com*

Edited by: *Konstantinos Stathopoulos*

Accepted *10 February 2022*

Pain as a severe complication in metastatic bone disease

The main complications of bone metastases are hypercalcemia, pathological fractures, spinal cord compression and pain. These complications are directly correlated with increased morbidity, reduced mobility and decrease of life quality, which is a great concern for these patients, as they slowly get incapable of participating in their daily activities and they become dependent on other people.

Pain is the most frequent symptom of the metastatic bone disease. A percentage of 83% of the patients with bone metastases will experience pain due to them. The severity, the frequency and the place of the pain will differ[3,4], while 23 to 45% of these patients will not receive an adequate treatment to manage the pain[5]. These numbers should be considered as very dissatisfying if we take into account the availability of the many different types of treatment that we can provide to patients to manage their pain.

The physiology of metastatic disease includes four main stages. First, angiogenesis consists an essential prerequisite for tumor growth and at the same time the main pathway that tumor cells use to migrate in distant organs, such as bones. Secondly, cancer cells filtrate the cell membrane locally and then adhere to the endothelium of the tissue that are going to filtrate, resulting in organ invasion and metastatic hearth creation[6]. It is important to mention that bones consist a very fertile environment for the filtration and the development of metastatic disease. This is due to the high concentration of cytokines that are released during bone remodeling, while osteoclastic activity during bone resorption creates a suitable microenvironment for the adhesion and growth of cancer cells. Furthermore, the rich bone vascularization aids the transportation of the tumor cells[7].

The pathophysiology of the pain that is occurred due to bone metastases is complex and involves both neuropathic and inflammatory pathways. Tumors beyond cancer cells, are also composed of inflammatory cells which secrete transmitters and cytokines. These chemical factors activate the nerve endings of pain in the bones and lead to increased osteoclast activity, which results in the destruction of nerve endings. Also, inflammation causes the decrease of microenvironmental pH, which results in the activation of pain nerve endings, sensitive in a lower ph. A third mechanism is the direct filtration of bone nerves by tumor cells, while the enlargement of the periosteum, due to metastatic mass, can cause pain in the area. Finally, complications of bone metastases, such as abnormal fractures and spinal cord compression are a cause of pain in patients who suffer from metastatic skeletal neoplasia[8].

There are drugs that target the osteoclastic activity which gets upregulated by the cancer cells and their spreading to the bone. In this category, the prime example are bisphosphonates that have been used for more than fifteen years in the treatment of tumor induced hypercalcemia and has been proven to diminish the incidence of cancer events of the skeleton. Bisphosphonate inhibit specifically the osteoclasts by preventing tumor cells to bind to the bone matrix, by stopping the activation of the adenosine triphosphate-dependent proton pump which disrupts the dissolvement of the bone mineral matrix by not letting protons to secret, by the destruction of the osteoclast cytoskeleton and by promoting the apoptosis of the osteoclasts[9,10]. Also, bisphosphonates inhibit the recruitment and the differentiation of the cells that will evolve into osteoclasts[11] and promote the inhibition of matrix metalloproteinases[12] and finally, they have a direct role in the destruction of the cancer cells by activating proapoptotic roads[13,14].

Denosumab is a human monoclonal antibody that specifically binds and inactivates RANKL, the receptor activator of NF-kB ligand, which has an especially important role in the stimulation of osteoclastic differentiation[15]. Many studies have compared the efficiency between denosumab and bisphosphonates in the treatment of patients with metastatic bone disease[16]. The results were very positive for denosumab as a first-line treatment in cancer patients with solid tumors, as well as a second-line treatment for patients with solid tumors and hematological malignancies that had previously used bisphosphonates as a therapy and had not seen a decrease in bone markers, so their risk for skeletal-related events was still high[17,18].

Furthermore, chemotherapeutic agents, aiming to reduce the total cancer burden and hormone therapy, for sensitive to hormones malignancies, are used to treat systemic bone metastatic disease. In addition, the analgetic treatment of patients with both opioid and non-opioid drugs, does not cure but relieves the pain and improves the quality of life in such patients. Steroids are also being used because of their anti-inflammatory ability and their efficiency in decreasing the swelling that is associated with bone metastases. Alternative non-pharmaceutical methods should also be mentioned, with radiotherapy being the main representative, while in some cases surgical treatment or intravenous radiation, which is a form of radiation that uses radiopharmaceuticals, molecules of radioactive material that are given intravenously and have a strong attraction to bones, are indicated[19,20].

The RANK, RANK-L and osteoprotegerin system

The system that is composed by the receptor activator of nuclear factor (NF)-kB-ligand (RANK-L), the receptor activator of nuclear factor kB (RANK) and the receptor osteoprotegerin (OPG), was identified in the late 1990s, while trying to isolate factors that regulate osteoclastogenesis[21]. Since then, it has been discovered that this system does not just have a role in the regulation of bone resorption but holds a critical spot in bone modeling and remodeling. Furthermore, the main components of the RANK/RANK-L/OPG system have been found in multiple organs through the body and research has proved its contribution to the development of mammary glands and lactation, as well as,

to cancer cell proliferation and metastasis in breast, prostate and primary bone cancer. It should also be mentioned that the RANK/RANKL system is one of the signaling pathways, that through the dendritic cells, lead to the development and adaptability of the immune system[22].

Osteoclastogenesis and thus bone resorption is promoted by a paracrine signaling through the interaction of the osteoclast receptor RANK and its ligand RANK-L, which is part of the tumor necrosis factor family and is detected either as a transmembrane protein on the surface of osteoblasts and stromal cells, or in its soluble form after the action of proteinases on the transmembrane protein. It should be noted that the production of RANK-L by B and T lymphocytes is also considerable, especially, in case of inflammatory conditions[23,24]. Osteoprotegerin, a soluble glycoprotein of the TNFR family, binds to RANK, thereby preventing RANK activation and practically inhibits osteoclastogenesis and bone resorption. Osteoprotegerin is produced by osteoblastic cells in the bones, but also by the gastrointestinal, lung, breast and skin epithelial cells, as well as by vascular endothelial cells, B lymphocytes and dendritic cells[25,26].

RANK/RANK-L/OPG and its role in carcinogenesis

RANK and RANK-L factors play a key role in the migration and growth of neoplastic cells[27]. Neoplastic cells produce the parathyroid hormone peptide (PTHrP), which augments osteoclastogenesis by increasing the RANK-L expression on the osteoblasts surface. Particularly, RANK-L binds to its receptor (RANK), which is located on the surface of precursor osteoclasts, resulting in their maturation and activation. Increased osteoclastogenesis can lead to osteolysis and consequently to the release of minerals and growth factors which consist a factor that favors the proliferation of cancer cells, along with the increased PTHrP production[28].

In breast cancer, growth factors released by the lysis of the bone, such as IGF-1 and TGF-β, reinforce in their own way the development of neoplastic disease. Specifically, IGF-1 activates sequential signaling pathways that lead to cancer cell proliferation and chemotaxis, by directing them to the bones for filtration, thereby increasing the metastatic load. As regards TGF-β reinforces bone resorption by inducing the expression of PTHrP and Il-11, which suppresses osteoblastogenesis. Integrins release favors the adhesion of tumor cells to bone, whereas Prostaglandin E2 increases RANK-L expression. Factors that stimulate osteoclastogenesis with concomitant osteoblastogenesis suppression are interleukins 6 and 11 (IL-6, IL-11), macrophage colony stimulating factor (M-CSF) and tumor necrosis factor-1(TNF-a)[29].

Osteoblastic metastases are characteristic in prostate cancer. Endothelin-1 (ET-1) consists a cancer cell derivative that leads to osteoblast proliferation, that induces however osteoclastogenesis through its interaction with multiple cytokines (RANK-L, CTFG, PTHrP). In fact, increased expression of PTHrP, in combination with the inactivation of the osteolytic action of the peptide by Prostate-Specific Antigen (PSA) is according to studies, the main pathway for the generation of osteoblastic metastases[30]. In addition, platelet-derived growth factor (PDGF) stimulates osteoblast proliferation and leads to bone formation, whereas insulin-like growth factor type 1 (IGF-1) acts chemotactically on cancer cells by directing them to the bones and by stimulating their migration and development of bone metastases, and subsequently induces the proliferation of tumor cells in the bones. Finally, we should mention the proteases, adrenomedullin, bone morphogenetic proteins (BMP's) and TGF-beta factors that are involved in the creation and development of osteoblastic metastases of prostate cancer[31].

As interaction of RANK/RANK-L does not only affect bone homeostasis but also plays an important role in multiple processes of human body, a considerable number of studies have been carried out, aiming to determine the possible association of RANK-L blockade with antitumor activity. Studies are focusing specifically on the blockade of RANK/RANK-L axis with denosumab, in patients with an increased risk of developing primary breast carcinoma. Particularly, a decrease has been observed in the proliferation of breast cells, in women treated with denosumab, which is the monoclonal antibody associated with RANK/RANK-L, inhibiting RANK/RANK-L interaction and consequently inhibiting osteoclast formation, function and survival[32].

RANK/RANK-L/OPG system as biomarkers

According to the National Cancer Institute (NCI) a biomarker is "a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease and may, also, be used to see how well the body responds to a treatment for a disease or condition".

The role of RANK/RANK-L/OPG as biomarkers has been under investigation for nearly two decades now. In the beginning, the researchers were focused solely on bone associated processes and diseases and especially in bone absorption and bone remodeling[33]. Nowadays, the significance of the system in multiple organs and systemic body functions has expanded the research for its suitability as a biomarker in many diseases of the cardiovascular system such as atherosclerosis, coronary artery calcification[34,35], acute coronary syndrome[36], ischemic stroke[37], abdominal aortic aneurysm progression[38], as well as, in more systemic procedures an example of which is thermal regulation[39].

The importance of the system on metabolic bone diseases led to wider investigation on the use of RANK/RANK-L and OPG as biomarkers on illnesses of the joint, such as osteoarthritis[40], rheumatoid arthritis[41], diabetic Charcot arthropathy[42] and periprosthetic joint infection and aseptic prosthesis loosening[43]. Naturally, research on its significance

on dental diseases followed and by now the system has been proved as an accurate biomarker for the occurrence of periodontitis[44], for the bone loss that is associated with peri-implantitis[45] and for the bisphosphonate-related osteonecrosis of the jaw[46].

In malignant diseases with bone involvement the role of the RANK/RANK-L/OPG system has been thoroughly established. Its value has not been completely measured as more and more research is being conducted for its use as a disease related, prognostic and treatment efficiency biomarker. In the matter of the later reference, studies have been already conducted both on the utility of these indictors in monitoring the response of metastatic bone disease to zoledronic acid treatment[47], by measuring them in the blood of patients, and in women with breast cancer who have been treated with anthracycline-based chemotherapy for their predictive value for metastatic bone disease[48].

The ability to measure RANK, RANK-L and osteoprotegerin was made possible by immunohistochemistry, the polymerase chain reaction and the Western blot method. The calculation of RANK, RANK-L and osteoprotegerin can be performed after cell collection and tissue biopsy, while the measurement of RANK-L and osteoprotegerin is now possible in the blood by ELISA (Enzyme-Linked Immunosorbent Assay). However, all the above methods are not widely available and, so far, there have not been large clinical trials to determine the actual value of the soluble RANK-L and OPG as biomarkers[49].

Conclusion and future directions

In conclusion, the RANK/RANK-L/OPG system appears to be involved in many intracellular pathways that are associated with survival, proliferation and bone metastasis. Nevertheless, there is still insufficient bibliography, whereby one of these factors can be used safely as a biomarker, for the diagnosis, prognosis and evaluation of metastatic bone disease.

Considering that most of the patients with metastatic bone disease will experience pain that decrease their life quality and that many of them will not receive adequate treatment for this symptom, we suggest further investigation into the prospect that the levels of the serum RANK, RANK-L and OPG molecules could be associated with the severity of the pain these patients suffer from.

References

1. Coleman R. Bisphosphonates: clinical experience. Oncologist 2004; 9:14–27.
2. Papachristou D, Basdra E, Papavassiliou A. Bone metastases: Molecular mechanisms and novel therapeutic interventions. Med Res Rev 2012;32(3):611-36.
3. Delaney A, Fleetwood-Walker SM, Colvin LA, Fallon M. Translational medicine: Cancer pain mechanisms and management. Br J Anaesth 2008;101:8794.
4. Walley J, Colvin LA, Fallon MT, Murray G, Clausen E. Characterisation of cancer-induced bone pain. In Proceedings of The British Pain Society 2006;A45.
5. O'Toole GC, Boland P. Metastatic bone cancer pain: etiology and treatment options. Curr Pain Headache Rep 2006;10(4):288-292.
6. Bussard K, Gay C, Mastro A. The bone microenvironment in metastasis; what is special about the bone? Cancer Metastasis Rev 2008;27:41-55.
7. Chambers A, Groom A, MacDonald I. Dissemination and growth of cancer cells in metastatic sites. Nat Rev Cancer 2002;2:563-572.
8. Von Moos R, Costa L, Ida Ripamonti C, Niepel D, Santini D. Improving quality of life in patients with advanced cancer: Targeting metastatic bone pain. European Journal of Cancer 2017;71:80-94.
9. Van der Pluijm G, Vloedgraven H, vanBeek E, et al: Bisphosphonates inhibit theadhesion of breast cancer cells to bone matrices in vitro. J Clin Invest 1996;98:698-705.
10. Boissier S, Magneto S, Frappart L, et al: Bisphosphonates inhibit prostate and breastcarcinoma cell adhesion to unmineralized andmineralized bone extracellular matrices. CancerRes 1997; 57:3890-3894.
11. Rogers MJ, Gordon S, Benford HL, etal: Cellular and molecular mechanisms of action of bisphosphonates. Cancer 2000;88:2961-2978.
12. Teronen O, Heikkila P, Konttinen YJ, etal: MMP downregulation and inhibition bybisphosphonates. Ann N Y Acad Sci 1999;878:453-465.
13. Fromigue O, Lagneaux L, Body JJ: Bisphosphonates induce breast cancer cell deathin vitro. J Bone Miner Res 2000;15:2211-2221.
14. Green JR: Antitumor effects of bisphosphonates. Cancer 2003; 97:840-847.
15. Bekker PJ, Holloway DL, Rasmussen AS, et al. A single dose placebo-controlled study of AM. 162, a fully human monoclonal antibody to RANKL, in postmenopausal women, 2004. J Bone Miner Res 2005; 20:2275–2282.
16. Body JJ, Lipton A, Gralow J, Steger GG, Gao G, Yeh H, Fizazi K. Effects of denosumab in patients with bone metastases with and without previous bisphosphonate exposure. J Bone Miner Res 2010; 25:440-446.
17. Coleman R, Brown J, Terpos E, et al. Bone markers and their prognostic value in metastatic bone disease: clinical evidence and future directions. Cancer Treat Rev 2008;34:629–639.
18. Lipton A, Steger GG, Figueroa J, et al. Extended efficacy and safety of denosumab in breast cancer patients with bone metastases not receiving prior bisphosphonate therapy. Clin Cancer Res 2008; 14:6690–6696.
19. Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. A review of published literature. Ann Oncol 2008;19:1985–1991.
20. Patrick D, Cleeland C, von Moos R, Fallowfield L, Wei R, Öhrling K, Qian Y. Pain outcomes in patients with bone metastases from advanced cancer: assessment and management with bone-targeting agents. Support Care Cancer 2015;23:1157–1168.
21. Liu W, Zhang X. Receptor of nuclear factor-κB ligand (RANKL)/RANK/osteoprotegerin system in bone and other tissues (Review). Molecular Medicine Reports 2015;11:3212-3218.
22. Mekonnen S, Getnet M, Dumessa E. The RANK/RANKL/OPG system in tumorigenesis and metastasis of cancer stem cell: potential targets for anticancer therapy. OncoTargets and Therapy 2017;10:3801-3810.
23. Lum L, Wong B, Josien R, Becherer J, Erdjument-Bromage H, Schlondorff. Evidence for a role of a tumor necrosis factor-alpha (TNF-alpha)-converting enzyme-like protease in shedding of TRANCE, a TNF family member involved in osteoclastogenesis and dendritic cell

survival. Biol Chem 1999;274:13613-8.
24. O'Brien C. Control of RANKL gene expression. Bone 2010;46:911-919.
25. Lacey D. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 1998; 93:165-176.
26. Roodman G. Regulation of Osteoclast Differentiation. Ann NY Acad Sci. 2006; 1068: 100-109.
27. Schmiedel B, Scheible C, Nuebling T. RANKL expression, function, and therapeutic targetiong in multiple myeloma and chronic lymphocytic leukemia. Cancer Res 2013;73:683-694.
28. Wegelt B, Peterse J, van't Veer L. Breast cancer metastasis: markers and models. Nat Rev Cancer 2005;5:591-602.
29. Lorenzo J, Horowitz M, Choi Y. Osteoimmunology: interractions of the bone and immune system. Endocr Rev 2008;29:403-440.
30. Clines G, Guise T. Molecular mechanisms and treatment of bone metastasis. Expert Rev Mol Med 2008;10: e7.
31. Lu Y, Zhang J, Dai J, Dehne L, Mizokami A, Yao Z, Keller E. Osteoblasts induce prostate cancer proliferation and PSA expression through interleukin-6-mediated activation of the androgen receptor. Clin Exp Metastasis 2004;21:399–408.
32. De Groot AF, Appelman-Dijkstra NM, Van der Burg SH, Kroep JR. The anti-tumor effect of RANK-L inhibition in malignant solid tumors – A systemic review. Cancer treatment reviews 2018;62:18-28.
33. Boyce B, Xing L. Functions of RANKL/RANK/OPG in bone modeling and remodeling. Arch Biochem Biophys 2008;473(2):139-46.
34. Maser R, Lenhard J, Sneider M, Pohlig R. Osteoprotegerin is a Better Serum Biomarker of Coronary Artery Calcification than Osteocalcin in Type 2 Diabetes. Endocr Pract 2015;21(1):14–22.
35. Kiechl S, Schett G, Wenning G, Redlich K, Oberhollenzer M, Mayr A, Santer P, Smolen J, Poewe W, Willeit J. Osteoprotegerin is a risk factor for progressive atherosclerosis and cardiovascular disease. Circulation 2004;109:2175–2180.
36. Sandberg WJ, Yndestad A, Oie E, Smith C, Ueland T, Ovchinnikova O, Robertson AK, Muller F, Semb AG, Scholz H, Andreassen AK, Gullestad L, Damas JK, Froland SS, Hansson GK, Halvorsen B, Aukrust P. Enhanced t-cell expression of rank ligand in acute coronary syndrome: possible role in plaque destabilization. Arterioscler Thromb Vasc Biol 2006;26:857–863.
37. Jensen JK, Ueland T, Atar D, Gullestad L, Mickley H, Aukrust P, Januzzi JL. Osteoprotegerin concentrations and prognosis in acute ischaemic stroke. J Intern Med 2010;267:410–417.
38. Moran CS, McCann M, Karan M, Norman P, Ketheesan N, Golledge J. Association of osteoprotegerin with human abdominal aortic aneurysm progression. Circulation 2005;111:3119–3125.
39. Hanada R, Leibbrandt A, Hanada T, Kitaoka S, Furuyashiki T, Fujihara H, Trichereau J, Paolino M, Qadri F, Plehm R, Klaere S, Komnenovic V, Mimata H, Yoshimatsu H, Takahashi N, von Haeseler A, Bader M, Kilic SS, Ueta Y, Pifl C, Narumiya S, Penninger JM. Central control of fever and female body temperature by rankl/rank. Nature 2009; 462:505–509
40. Răduţ R, Crăciun AM, Silaghi CN. Bone Markers in Arthropathies. Acta Clin Croat 2019;58(4):716-725.
41. Fardellone P, Séjourné A, Paccou J, Goëb V. Bone Remodelling Markers in Rheumatoid Arthritis. Mediators Inflamm 2014; 2014:484280.
42. Folestad A, Alund M, Asteberg S, Fowelin J, Aurell Y, Göthlin J, Cassuto J. Role of Wnt/β-catenin and RANKL/OPG in bone healing of diabetic Charcot arthropathy patients. A prospective study in 24 patients followed for 2 years. Acta Orthop 2015;86(4):415–425.
43. Friedrich M, Wimmer M, Schmolders J, Strauss A, Ploeger M, Kohlhof H, Wirtz D, Gravius S, Randau T. RANK-ligand and osteoprotegerin as biomarkers in the differentiation between periprosthetic joint infection and aseptic prosthesis loosening. World J Orthop 2017; 8(4):342–349.
44. Belibasakis G, Bostanci N. The RANKL-OPG system in clinical periodontology. Journal of Clinical Periodontol 2012;39(3):239-48.
45. Rakic, M, Lekovic V, Nikolic-Jakoba N, Vojvodic D, Petkovic-Curcin A, Sanz M. Bone loss biomarkers associated with peri-implantitis. A cross-sectional study. Clin Oral Implant Res 2013;24:1110–1116.
46. Bagan L, Jimenez Y, Leopoldo M, Rubert A, Bagan J. Serum levels of RANKL and OPG, and the RANKL/OPG ratio in bisphosphonate-related osteonecrosis of the jaw: Are they useful biomarkers for the advanced stages of osteonecrosis? Med Oral Patol Oral Cir Bucal 2017;22(5):e542–e547.
47. Ibrahim T, Ricci M, Scarpi E, Bongiovanni A, Ricci R, Riva N, Liverani C, De Vita A, La Manna F, Oboldi D, Serra P, Foca F, Cecconetto L, Amadori D, Mercatall L. RANKL: A promising circulating marker for bone metastasis response. Oncology letters 2016;12(4):2970-2975.
48. Timotheadatou E, Kalogeras K, Koliou GA, Wirtz R, Zagouri F, Koutras A, Veltrup E, Christodoulou C, Pentheroudakis G, Tsiftsoglou A, Papakostas P, Aravantinos G, Venizelos V, Pectasides D, Kosmidis P, Karanikiotis C, Markopoulos C, Gogas H, Fountzilas G. Evaluation of the prognostic value of RANK, OPG, RANKL mRna expression in early breast cancer patients with Anthracycline-Based adjuvant chemotherapy. Transl Oncol 2017;10(4):589-598.
49. Peng X, Guo W, Ren T, Lou Z, Lu X, Zhang S, Lu Q, Sun Y. Differential Expression of the RANKL/RANK/OPG System Is Associated with Bone Metastasis in Human Non-Small Cell Lung Cancer. PLOS ONE 2013;8(3):e58361.