Palliative radiation treatment of bone and spine metastases. In the metastatic cases; the indications for different treatments and fractionations.

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Abstract:
Radiotherapy (RT) for bone metastases with external beam radiotherapy (EBRT) often give pain relief and may help to stop the cancer progression and compression. There are many approches to spinal vertebral bone metastase with EBRT; such as three dimensional conformal RT (3DCRT) with or without wedges, intensity modulated radiotherapy (IMRT), steriotactic body radiotherapy (SBRT), volumetric arc therapy (VMAT) and thomotherapy. Depend on the tissue tolerance the fractionated or single dose EBRT of 3Gyx10fr=30 Gy, 4Gyx6fr=24Gy, 5Gyx4fr=20 Gy, or 8Gyx1fr=8Gy should be given.The fractionated RT has greater and more prolonged relief in spine sites, but acute reactions are longer, and 8% re-treatment (2-2.5 times less then single or SBRT) and the fracture progression rare with conventional EBRT.
For planning single fraction 1x8 Gy radiotherapy and multi-fraction 3x10 Gy radiotherapy, we have made many plans to give EBRT to cervical, torocal, lumbar, sacral and pelvic bone metastasis in patients with metastatic bladder and lung cancer. Single fraction for metastatic bladder cancer and 10 fractions for lung cancer were examined from different angles.
As a result of the evaluation of the plans with dose volume histograms, it was found that conventional three-dimensional conformal radiotherapy planning was good for the treatment of metastatic lesions. Side effects were found to be within normal tissue tolerances. The patients received three-dimensional radiotherapy from the anterior-posterior areas for treatment. Relief and tumor control were achieved in the follow-up.
Many RT planning and applications are tried and the most appropriate treatment can be performed safely within the dose limits of tumor control and normal tissue tolerances.

Key words: Radiotherapy, Bone metastases, Spine

Kemik ve omurga metastazlarında palyatif radyasyon tedavisi.
Metastatik durumlarda; farklı tedaviler ve fraksiyonlar için endikasyonlar.

Özet: Radyoterapi (RT) olarak, kemik metastazları için Eksternal Radyoterapi (EBRT)genellikle ağrıyı keser ve kanserin ilerlemesini ve kompresyonunu durdurmaya yardımcı olabilir. EBRT ile spinal vertebral kemik metastazına yönelik birçok yaklaşım vardır; örneğin kama veya kamasız üç boyutlu konformal RT (3DCRT), yoğunluk modülasyonlu radyoterapi (IMRT), steriotaktik vücut radyoterapisi (SBRT), volumetrik ark tedavisi (VMAT) ve tomoterapi. Doku toleransına bağlı olarak, 3Gyx10fr = 30 Gy, 4Gyx6fr = 24Gy, 5Gyx4fr = 20Gy veya 8Gyx1fr = 8Gy'nin fraksiyone veya tek doz EBRT'si verilmelidir. Tek 8 Gy veya SBRT maliyet etkindir, omurga bölgelerinde hızlı ancak daha kısa ağrı gidericidir ve akut RT reaksiyonları daha azdır, ancak% 20 yeniden tedavi ve % 38 kırılmanın gelişmesi mümkündür. Fraksiyone RT, omurga bölgelerinde daha fazla ve daha uzun süreli bir rahatlamaya sahiptir, ancak geleneksel EBRT ile akut reaksiyonlar daha uzundur ve % 8 tekrar ışınlama (tek veya SBRT'den 2-2.5 kat daha az) gerekebilir ve kırılmanın gelişmesi nadir görülür.
Tek fraksiyon 1x8 Gy radyoterapi ve çok fraksiyon 3x10 Gy radyoterapi planlaması için metastatik mesane ve akciğer kanseri olguları olan hastalarda EBRT'yi servikal, torokal, lomber, sakral ve pelvik kemik metastazına vermek için birçok plan yaptık. Metastatik mesane kanseri için tek fraksiyon, akciğer kanseri için 10 fraksiyon değişik açılardan incelendi.
Planların doz volüm histogramları ile değerlendirilmesi sonucunda konvasiyonel üç boyutlu konformal radyoterapi planlamasının metastatik lezyonları iyi şekilde tedavi ettiği saptandı. Yan

etkilerin normal doku toleransları içinde kaldığı saptandı. Hastalara tedavi için üç boyutlu ön-arka alanlardan radyoterapi uyguladı. Takipte hastalarda rahatlama ve tümör kontrolü sağlandı.
Birçok RT planlama ve uygulaması denenerek en uygun olan tedavi tümör kontrolü ve normal doku toleranslarının doz sınırlarında içinde güvenli olarak yapılabilir.
Anahtar Kelimeler: Radyoterapi, Kemik metastazları, Spinal

Inroduction:

In clinical oncology the solid tumors such as lung, breast, and prostate, the painful bone metastases in spine, pelvis, and extremities are almost seen 80 %. Opioid is the first-line approach for moderate or severe pain and nonsteroidal antiinflammatory agent (NSAID) should be used, if no contraindication.With radiotherapy (RT); the pain relief is 50-85 % and complete pain relief is 15-8 %. The spinal cord, eusophageal tissue and intestinal tissue have serial morphologic behavior and if a small volume or a spot injured with RT more then tolerance dose the signal and functions can not pass or not work behind the injured site. But the liver, kidney and lung has parallel morphologic behavior and if a small volume or spot injured with RT more then tolerance dose the signal and functions can pass orwork behind the injured site through the parallel structures.

The spinal cord tolerance dose is 46 Gy, 2 Gy/fr, spinal cord α/β= 2Gy, and there is relation between irradiated volume and lenght (cm) with the spinal cord side effects (1, 2). (Table 1 and Table 2).If the irradiated spinal cord is short there is probability recover with migrated and recurietment of neuronal stem cells to injured site.

Table 1: The QUANTEC summary for spinal cord (1).

Partial organ	3D-CRT	Myelopathy	Dmax=50 Gy	0.2 (%)	including full cord cross-section
Partial organ	3D-CRT	Myelopathy	Dmax=60 Gy	6 (%)	
Partial organ	3D-CRT	Myelopathy	Dmax=69 Gy	50 (%)	
Partial organ	SRS (1 fr)	Myelopathy	Dmax=13 Gy	1 (%)	Partial cord cross-section irradiatted
Partial organ	SRS (hypo)	Myelopathy	Dmax=20 Gy	1 (%)	3 fr, partial cord cross-sectionirradiatted

Table 2: Spinal tissue myelitis tolerance dose with lenght (2).

	TD 5/5 volume			TD 50/5 volume			Selected end point
Spinal cord	5cm: 50	10cm: 50	20cm: 50	5cm: 70	10cm: 70	20cm: (-)	Myelitis necrosis

There is golden 72 hours of emergency for metastatic bone and spinal cord compression, but at present the metastatic spinal cord compressions can be treated with RT after golden 72 emergency with succesfull results (3).

There are some useful RT fractionations with external beam radiotherapy (EBRT) 3Gyx10fr =30 Gy, 4Gyx6fr=24Gy, 5Gyx4fr=20 Gy, or single 8Gyx1fr=8Gy.The RT field is one vertebral body above and below.

Stereotactic Body Radiation Therapy (SBRT) is a new single or hypofractionated application in the radiation oncology practice. The SBRT can be use if persistent or recurrent bone pain after a standard course of EBRT or recurrent tumor in spinal or paraspinal areas after EBRT or newly discovered oligometastatic bone metastases whom the primary is controlled and estimated survival greater than 6

months, but; the highly conformal RT and SBRTmay exclude subclinical disease and may increase a risk for cancer regrowth (4, 5).

Single 8 Gy or SBRT are cost effective, have rapid but inferior short pain relief in spine sites and the acute RT reactions are shorter, but 20% re-treatment and 38% fracture progression. The SBRT has higher risk of vertebral compression fractures with >18 Gy (10%) vs 16-18 Gy (3%) because much doses destroy not only the cancer cells but also the osteoblasts that we need them to use for repair in destroyed spinal bone tissue by cancer cells. The fractionated RT has greater and more prolonged relief in spine sites, but acute reactions are longer, and 8% re-treatment (2-2.5 times less then single or SBRT) and the fracture progression rare with conventional EBRT (6-8).

Side effect of single RT, SBRT and EBRT; the myelopathy risk is 0% with single 8 Gy or 3Gyx10=30 Gy in painful lesions of the spine, the radicular pain is less response with single 8 Gy if compared to 20 Gy in 5 fractions, the flare pain is %35, especially higher in the first 1-2 days with single fraction treatment, but the anti-inflammatory or dexamethasone reduce these effects to use in 1 hour before 8 Gy radiation, with 8 mg daily for five days, also the eusophagitis, pneumonitis and nausea (relief with anti emetics) are less in single or EBRT (9, 10).

If single fraction EBRT was initially used; repeat irradiation with fractionated treatment or SBRT, radiopharmaceuticals, image-guided local thermal ablations such as “radiofrequency ablation (RFA), cryoablation (or cryotherapy), microwave ablation, laser ablation (or laser interstitial thermal therapy” or kyphoplasty/vertebroplasty for vertebral compressionfractures may use (11).

The vertebroplasty is injection of polymethylmethacrylate surgical cement in to the vertebral body but contraindicated in spinal cord compression and in significant extraosseous tumor invasion, the side effects may be extravasation of cement outside of the vertebral bone, pneumothorax, pulmonary and fat emboli,dura mater injury and death of patient. Kyphoplasty is also a vertebroplasty with insertion a balloon to inflate it into vertebral body, then fill with liquide-viscous polymethylmethacrylate cement with less extravasationof cement (11-13).

There is Spinal Instability Neoplastic Score (SINS) to determine the surgery. The score between 0-6 is stable, 7-12 is potentially unstable, 13-18 is unstable (Table 3) (14, 15).

Table 3: Spinal Instability Neoplastic Score (SINS) (14, 15).

Component		Score
Location		
	Junctional (O-C2; C7-T2; T11-L1; L5-S1)	3
	Mobile spine (C3-6; L2-4)	2
	Semigirid (T3-10)	1
	Rigid (S2-5)	0
Mechanical pain		
	Yes	3
	No	2
	Pain free lesion	1
Bone lesion		
	Lytic	2
	Mixed (lytic/blastic)	1
	Blastic	0
Radiographic spinal alignment		
	Subluxation/translation present	4
	Deformity (kyphosis/scoliosis)	2
	Normal	0
Vertebral body collapse		
	>50% collapse	3
	<50% collapse	2
	No collapse with >50% body involved	1
	None of the above	0
Posterolateral involvement		
	Bilateral	3
	Unilateral	1
	None of the above	0

Decompression/stabilization plus RT for patient with single level spinal cord compression and long life expectancy is better compared to radiotherapy alone. After surgery 30 Gy in 10 fractions are common to eradicate microscopic residual disease. Surgery and postop RT compared to RT alone and improvement in overall ambulation rates (84% versus 57%), duration of ambulation (122 days versus 13 days), regaining lost ambulation (62% versus 19%), and survival (126 days versus 100 days) (16).

During RT we can see scattering electrons from metalic topical agents and metalic implants and these may cause increase of side effects. With non-metal containing agents there are less dermal damage compared to zinc oxide ointment and silver sulfadiazine cream (17). With oral dental metalic or gold implants there are 1.4 %-19.3% dose increase with photon radiotherapy techniques (18).

During diagnose and follow up, the titanium paramagnetic material is not affected by the magnetic field of MRI. The risk of implant complications is very low, and MRI is a safe application in patients with titanium implants (19).The spinal titanium implants during RT has effects to decrease 5-7% and increase 5.5% the doses in irradiated fields. These dose differences must be calculate and consider in treatment protocols carefully (20). The anterior, posterior, lateral or oblique positions of the metalic

implants are importand during the RT application that these implants may affect the iso-doses in the irradiated fields (21). The titanium implants have little affect in SBRT but during SBRT planning the metalic implants has impact on RT dose distrubitions and must be calculate correctly and RT team should be sure before RT application (22).

In spinal and bone methastatic cases the use of radiopharmaceuticals and external beam radiotherapy is common, the osteoblastic metastases must be documented by a Technetium-99 bone scan and should be sure the diagnose of malignant pathology. The bone targeting radioisotopes can be administered with RT. The beta (β)radiations range are 0.2 to 3.0 mm. There are β-emitting agents strontium-89, samarium-153, rhenium-186. Also β-emitting lutesium-177 has prostate membran spesific antigene, with 6.65 days half life.

If the multiple bone metastases have diffuse pain are too much and too many lesionssuch as more than 5 lesions to be treated with radioisotope and some local EBRT together (23).

The myelosuppression is low, but after chemotherapy with radiopharmaceuticalsmay be high, the pain relief onset of 2- 3 weeks, the partial response rates of 55-95%, the complete response rates of 5-20%, the mean duration of pain relief of 3-6 months and the pain flare is 10-40% (24).The prophylactic use ofradiopharmaceuticalsare still under investigation.

The α-emitting Ra-223 has 11.4 days half life and approved only for castration-resistant prostate cancer which localize to areas with osteoblastic activity(25). TheRa-223 significantly improved overall survival (median overall survival was 14.1 versus 11 months; p = 0.001) prostate cancer and the dose/schedule for radium-223 dichloride is50 kBq/kg (1.35 microcuries/kg) administered by slowly by the way of IV, over one minute every four weeks for six doses (26, 27).

If access to radiopharmaceuticals are limited the historical hemibody RT should be done with 6Gy in 1 fraction to upper body and then 8 Gy lower body and might be an economical way for palliation on matastatic bone pain (28) (Figure 1).

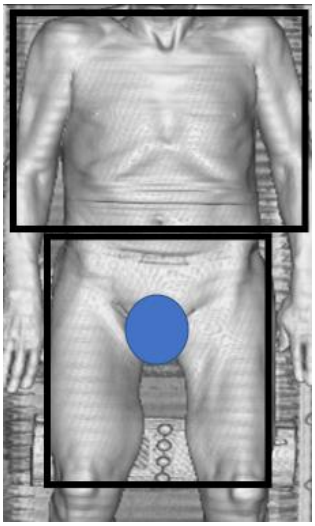

Figure 1: Hemibody RT to upper torso (6Gy) and to lover body (8Gy).

The bisphosphanates are internalized by osteoclasts, causing a decrease in both their activity and viability and also may cause tumor cell death. RT reduces tumor produced osteoclast activating factors (OAF's) and there is synergy between bisphosphonate for osteolytic field and EBRT for tumor

component. But to use bisphosphonates may cause renal impairment and osteonecrosis of the jaw (29).Osteoclast inhibitor denosumab may usufel for castration-resistant prostate cancer (30).

Methods and Results:

There are many approches to spinal vertebral bone metastase with EBRT; such as three dimensional conformal RT (3DCRT) with or without wedges, IMRT, SBRT,volumetric arc therapy (VMAT) and thomotherapy. We made plans for Varian Linear Accelerator with Eclipse Treatment Planning System with the fields or shapes of; peace, three angles, posterior three fields, horseshoe,IMRT and anterior-posterior.(Figure 2).

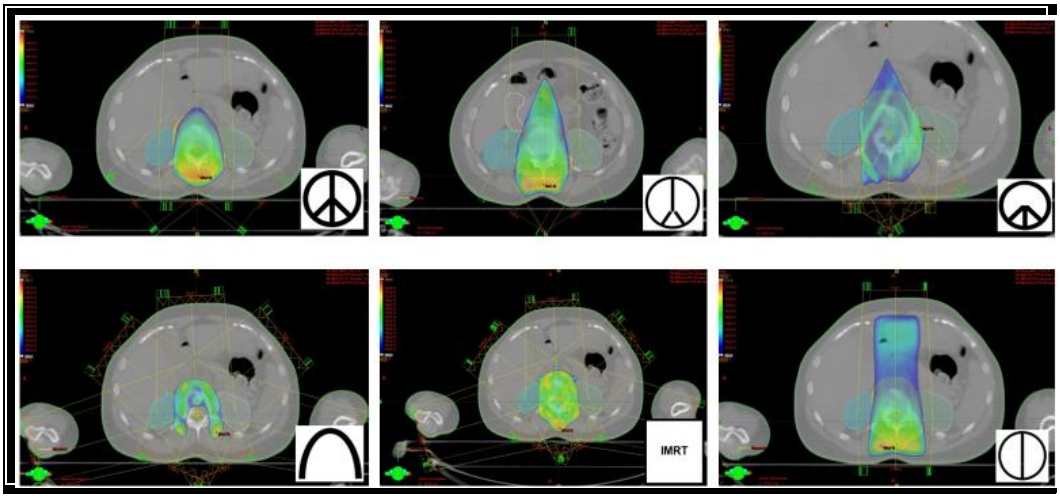

Figure 2. Radiotherapy plans for bone metastases

peace, three angles, posterior three fields, horseshoe, IMRT and anterior-posterior.

In our radiation oncology patients with metastatic bladder and lung cancer cases we followed and made plans to give EBRT to servical, thorocal, lumbar, sacral and pelvic bone metastases.

The bladder cancer patient had servical VII. bone metastasis, thorocal XII. bone metastases and sacral bone metastases (Figure 3). The patient planned tostart a chemotherapy after a single fractionated RT. The dose volume histograms (DVH) of spinal cord, kidneys, lungs, hearth and eusophageal organs were under tolerance doses.After the setup and portal imaging the servical and thorocal bone metastases had been givensingle 1x8 Gy, with anterior-posterior photon EBRT (Figure 4-5). After a short period of RT the patient had flair of pain but resolve with steroid and analgetics very fast.

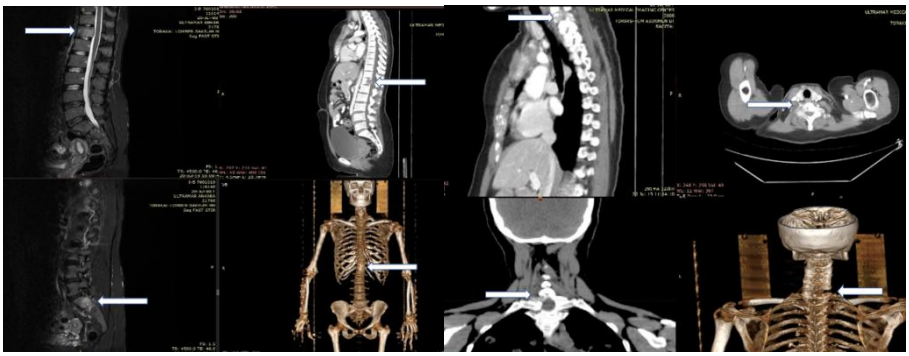

Figure 3: Servical VII., thorocal XII. and sacral bone metastases

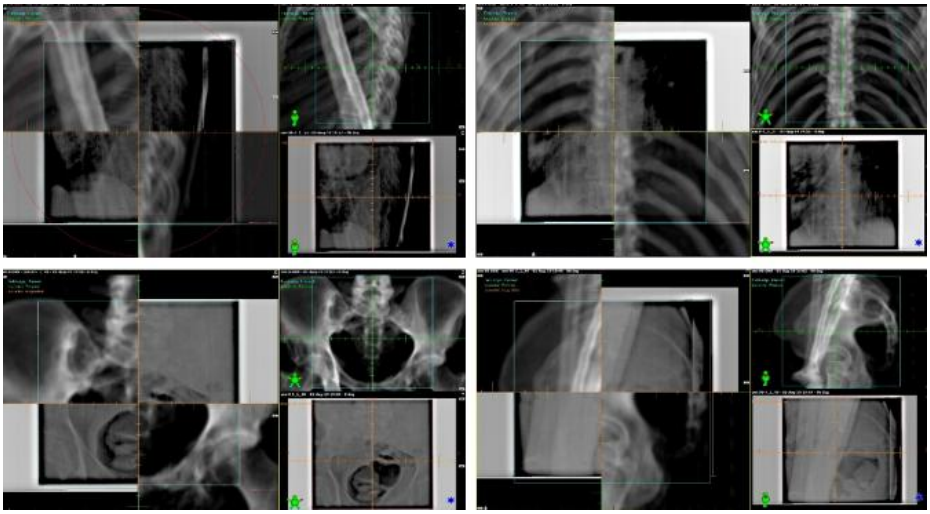

Figure 4: Portal images for servical and thorocal spinal bone metastases

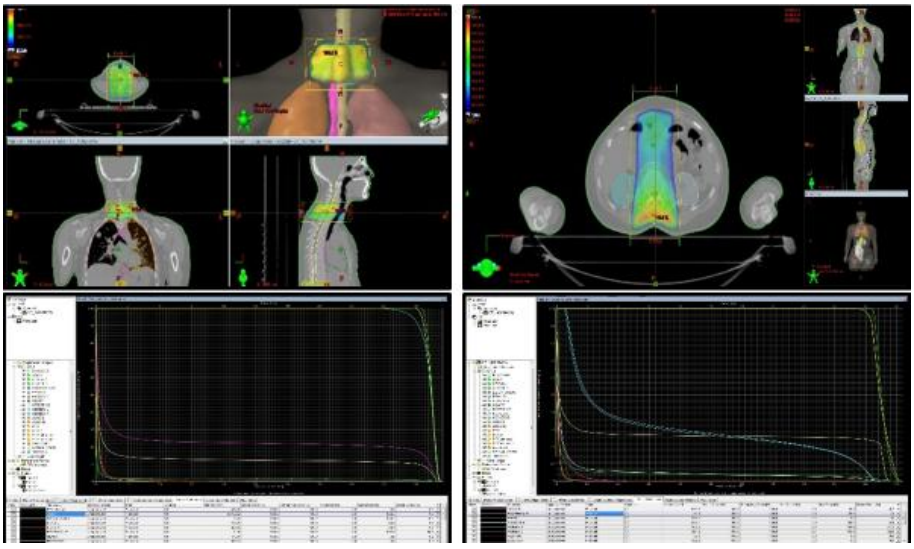

Figure 5: The DVH of spinal cord, kidneys, lungs, hearth and eusophageal and tumours. The servical and thorocal bone metastases took 1x8 Gy, with fields of anterior-posterior EBRT

The lung cancer patient had thorocal V., thorocal XI.,lumber III-IV, sacral and pubic bone metastases (Figure 6). The patient was continuing the chemotherapy,but because of the increase of the pain and compressions, the fractionated RT planned which the DVHs of spinal cord, kidneys, lungs, hearth and eusophageal organs were under tolerance doses.After the setup and portal imaging the servical,

thorocal, lumber, sacral and pubic bone metastases took fractionated 10x3 Gy total 30Gy, with anterior-posterior photon EBRT (Figure 7-8) with good pain reliefs.

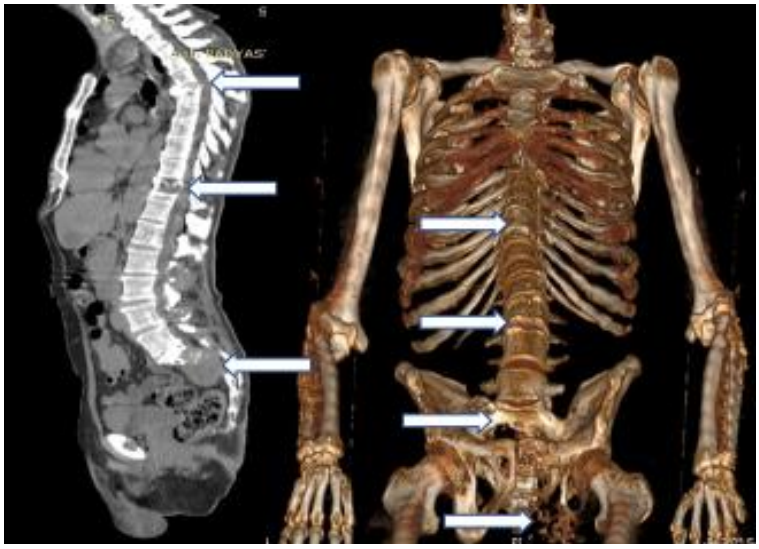

Figure 6: Thorocal V., thorocal XI., lumber III-IV, sacral and pubic bone metastases

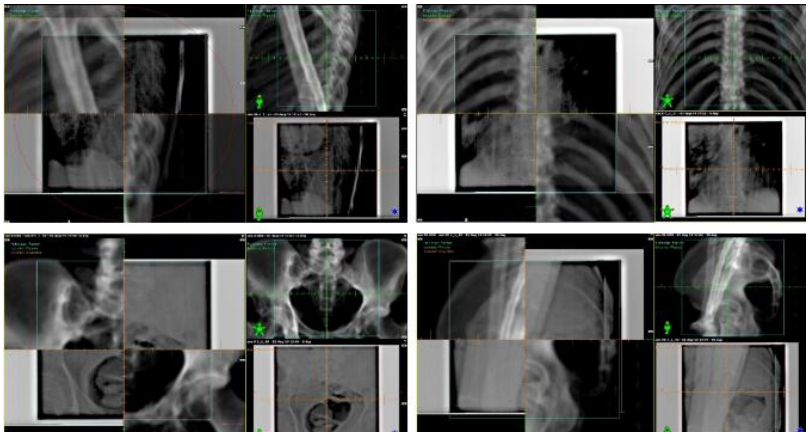

Figure 7: Portal images for thorocal, lumber, sacral and pelvic bone metastases

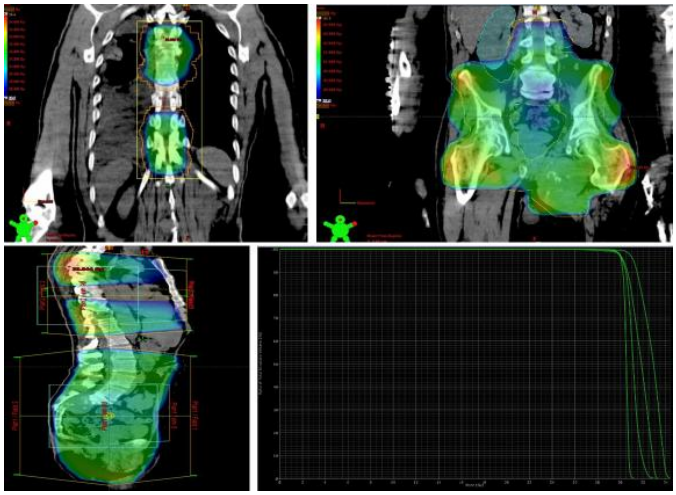

Figure 8: The DVHs of spinal cord, kidneys, lungs, hearth and eusophageal and tumours. The bone metastases took 10x3 Gy, with anterior-posterior EBRT

Discussion:

In solid tumours painful bone metastases in spine, pelvis, and extremities are almost seen 80 %. The nonsteroidal antiinflammatory agent (NSAID) and opioid are usually as the first-line approach for moderate or severe pain, and also the bisphosphanates can be used.

The spinal cord has serial morphologic behavior and if a small volume or spot injured with RT more then tolerance dose the signal and functions can not pass or work behind the injured site. The spinal cord tolerance dose is 46 Gy, 2 Gy/fr, spinal cord α/β= 2Gy, and there is relation between irradiated volume and lenght (cm) with the spinal cord side effects (1, 2). With radiotherapy (RT); we can see50-85 % pain reliefand 5-8 %complete pain relief.

The golden 72 hours emergency for metastatic bone and spinal cord compression can be treated with RT after golden 72 emergency with succesfull outcomes (3).

For external beam radiotherapy (EBRT) there are 3Gyx10fr =30 Gy, 4Gyx6fr=24Gy, 5Gyx4fr=20 Gy, or single 8Gyx1fr=8Gy schedules. Also SBRT is a new single or hypofractionated application EBRT in the Radiation Oncology practice.The single 8 Gy or SBRT are cheaper, have rapid/short pain relief in spine sites, but 20% re-treatment and 38% fracture progression if compare with the fractionated RT there is greater pain relief in spine sites, and 8% re-treatment (2-2.5 times less then single or SBRT) and the fracture progression rare with conventional EBRT (6-8).

The scattering electrons from metalic implants may cause increase or decrease of radiotherapy dose closer to the target volumes. The titanium paramagnetic material is not affected by the magnetic field of MRI and the spinal titanium implants during RT has effects to decrease 5-7% and increase 5.5% the doses in irradiated fields (19, 20). The position of the metalic implants are importand during the RT application that these implants may affect the iso-doses in the irradiated fields (21, 22).

For repeat irradiation with SBRT together with radiopharmaceuticalsradiofrequency ablation (RFA), cryoablation (or cryotherapy), microwave ablation, laser ablation (or laser interstitial thermal therapyor surgery (kyphoplasty/vertebroplasty) for vertebral compressionfractures may use (11-13).

As theradiopharmaceuticals there are β-emitting agents strontium-89, samarium-153, rhenium-186, lutesium-177 and α-emitting Ra-223 in clinical usefor multple bone metastases or historical hemibody RT should be done with 6Gy in 1 fraction to upper body and then 8 Gy lower body might be an economical way (28).

Due to our treatment planning and linear accelerator systems we made five plans for multiple bone metastases in the cases of bladder and lung cancers. After setup and portal imaging of the bone metastasis the patients were treated with photon EBRT with good pain relief and without any unacceptable side effects. The single dose 8 Gy or fractionated 30 Gy should be use to relief bone pain.

Conclusion:

RT planning and applications are a safe and help full with in the normal tissue tolerance dose limits. Single 1x8 Gy and fractionated 10x3Gy EBRT can be usufel applications to decrease the pain on the bone metastases. Also there are many treatments such as surgery, chemotherapy, radioisotopes, bisphosphanates, denosumab. In the case of compression, relaps or to much metastatic lesions there are repeat irradiation with fractionated treatment or SBRT, radiopharmaceuticals, image-guided local thermal ablations such as “radiofrequency ablation (RFA), cryoablation (or cryotherapy), microwave ablation, laser ablation (or laser interstitial thermal therapy” or kyphoplasty/vertebroplasty. The single

dose of 8 Gy, or fractionated 3Gyx10fr=30Gy,4Gyx6fr=24Gy and 5Gyx4fr=20 Gy should be use to relief bone pain.

References;

[1]. The Use of Normal Tissue Complication Probability (NTCP) Models in the Clinic, Lawrence B. q Marks, Ellen D. Yorke, Andrew Jackson, et al., Int J Radiat Oncol Biol Phys. 2010; 76: 1–19

[2]. Tolerance of normal tissue to therapeutic irradiation. Emami B, Lyman J, Brown A, et al., Int J Radiat Oncol Biol Phys 1991;21:109–22

[3]. Golden Hour For Emergency Spinal Cord Compression. RT: Is It Too Late To Do It After 72 Hours? A.I. Saito, M. Nakashiro, H. Kunogi, Int J Radiat Oncol Biol Phys,2011; 81: 650–51

[4]. Stereotactic Ablative Radiation Therapy for the Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET): Results of a Randomized Trial. D.A. Palma, R.A. Olson, S. Harrow, et al., Int J Radiat Oncol Biol Phys., 2018Volume 102: 3–4

[5]. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet, 2019; 393: 2051-58

[6]. Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline. Lutz S, Balboni T, Jones J, et al., Pract Radiat Oncol. 2017; 7: 4-12

[7].Palliative radiotherapy trials for bone metastases: a systematic review. Chow E, Harris K, Fan G, et al. J Clin Oncol. 2007; 25: 1423-36

[8]. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Lutz S, Berk L, Chang E, et al., Int J Radiat Oncol Biol Phys. 2011; 79: 965-76

[9]. Should dexamethasone be standard in the prophylaxis of pain flare after palliative radiotherapy for bone metastases?-a debate. Niglas M, Raman S, Rodin D, et al., Ann Palliat Med. 2018; 7 :279-83

[10]. Palliative radiotherapy. Spencer K, Parrish R, Barton R, Henry A, British Med J. 2018; 360: 1-12

[11]. Percutaneous kyphoplasty for the treatment of spinal metastases. CHEN F,XIA YH, CAO WZ, et al., Oncol Lett. 2016; 11: 1799–1806

[12]. Medium-term results of percutaneous vertebroplasty in multiple myeloma. Ramos L, de las Heras J, Sanchez S, et al., Eur J Haematol. 2006; 77: 7-13

[13]. Balloon kyphoplasty in the treatment of metastatic disease of the spine: a 2-year prospective evaluation. Pflugmacher R, Taylor R, Agarwal A, et al., Eur Spine J. 2008; 17: 1042-48

[14]. Reliability of the Spinal Instability Neoplastic Score (SINS) among radiation oncologists: an assessment of instability secondary to spinal metastases. Fisher CG, Schouten R, Versteeg AL, et al., Radiat Oncol. 2014; 9: 2-7

[15]. Reliability of the Spinal Instability Neoplastic Scale among radiologists: an assessment of instability secondary to spinal metastases. Fisher CG, Versteeg AL, Schouten R, et al.,Am J Roentgenol. 2014; 203: 869-74

[16. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial.Patchell RA, Tibbs PA, Regine WF, et al.,Lancet. 2005; 366: 643-48.

[17. Effect of metal-containing topical agents on surface doses received during external irradiation. Iyama A, Matsuyama T, Matsumoto E, et al., J Radiat Res. 2018; 59: 794-9

[18]. Evaluation of the scatter doses in the direction of the buccal mucosa from dental metals. Shimamoto H, Sumida I, Kakimoto N, et al., J Appl Clin Med Phys. 2015; 16: 233-43

[19]. Are titanium implants actually safe for magnetic resonance imaging examinations? Kim YH, Choi M, Kim JW., Arch Plast Surg. 2019; 46: 96–7

[20]. Spinal implants and radiation therapy: the effect of various configurations of titanium implant systems in a single-level vertebral metastasis model. Pekmezci M, Dirican B, Yapici B, et al., J Bone Joint Surg Am. 2006; 88:1093-100

[21]. Influence of internal fixation systems on radiation therapy for spinal tumor. Li J, Yan L, Wang J, et al., J Appl Clin Med Phys. 2015; 16: 279–89

[22]. The dosimetric impact of implants on the spinal cord dose during stereotactic body radiotherapy. Yazici G, Sari SY, Yedekci FY, et al., Radiat Oncol. 2016; 11: 1-9

[23]. Effectiveness of radioisotope therapy in bone metastases, based on personal experience. Skóra T, Kowalska T, Zawiła K., Contemp Oncol (Pozn). 2012; 16: 201–5

[24]. Radioisotopes for the palliation of metastatic bone cancer: A systematic review. Finlay L, Mason M, Shelley. 2005; 6: 392-400

[25]. Radium-223 in asymptomatic patients with castration-resistant prostate cancer and bone metastases treated in an international early access program.
Heidenreich A, Gillessen S, Heinrich D, et al., BMC Cancer. 2019; 19: 1-10

[26]. Alpha emitter radium-223 and survival in metastatic prostate cancer. Parker C, Nilsson S, Heinrich D, et al. N Engl J Med. 2013; 369: 213-23.

[27]. A randomized, dose-response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. Nilsson S, Strang P, Aksnes AK, et al. Eur J Cancer. 2012; 48: 678-86

[28]. Hemi body irradiation: An economical way of palliation of pain in bone metastasis in advanced cancer. Pal S, Dutta S, Adhikary SS, et al., South Asian J Cancer. 2014; 3: 28–32

[29]. Review: bisphosphonates reduce fractures, radiotherapy, and hypercalcaemia and increase time to a first skeletal related event. Ross JR, Saunders Y, Edmonds PM, et al., British Med J. 2003; 327: 469–72

[30]. Denosumab treatment in the management of patients with advanced prostate cancer: clinical evidence and experience. Hegemann M, Bedke J, Stenzl A, et al., Ther Adv Urol. 2017; 9: 81-8