

Mini Review

Adult Palliative Oncology and Radiotherapy of Locally Advanced and Metastatic Cancers

Rex Cheung*

275 S Bryn Mawr Ave, K43, Bryn Mawr, PA 19010, USA

***Corresponding author:** Rex Cheung, 275 S Bryn Mawr Ave, K43, Bryn Mawr, PA 19010, USA, Email: cheung.r100@gmail.com**Received:** January 30, 2015; **Accepted:** February 18, 2015; **Published:** February 20, 2015**Abstract**

End of life care is perhaps the most challenging in oncology but a learnable skill. Treating patients with advanced and metastatic disease could provide palliation and sometimes may prolong survival. Palliative care is often complex. This paper does not attempt to be comprehensive but attempts to make choices on the best practices in palliative radiotherapy, and will also discuss other palliative modalities. It discusses how to adapt each step of the radiation oncology clinic flow to meet the needs of palliative patients, pain control and the most appropriate techniques in treatment planning and delivery. This paper discusses the most effective and efficient dose fractions for palliative patients. It also discusses some specific challenging scenarios in palliative oncology in selected details hopefully will enlighten. The radiotherapy in palliative cases is different than the curative cases in the intent of cure versus palliation. When active intervention is futile, palliating the pain and suffering of the cancer patient should be the primary treatment goal.

Introduction

End of life care is perhaps the most challenging in oncology [1-8] but a learnable skill [2]. Hospice care is a top priority of the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology, and National Comprehensive Cancer Network (NCCN) [2,9-11]. Palliative care involves compassionate care and meticulous attention to the psychological needs of the patients and their families [2-8]. Radiotherapy is important in palliative care in oncology patients [12]. About 30% of breast cancer patients are diagnosed with stage IV disease [13]. About 50% of breast cancer patients with distant metastasis have radiotherapy as part of their palliative care [14]. Treating patients with advanced and metastatic disease could provide palliation and sometimes may prolong survival [15]. Palliative care is often complex, a multidisciplinary team may be most appropriate [13,16-18].

This paper does not attempt to be comprehensive but attempts to make choices on the best practices in palliative radiotherapy, and will also discuss other palliative modalities. This paper is part of a series [19-27] discussing current challenges of designing radiation treatment target volumes. This paper includes quite a bit of technical details of radiotherapy and the associated local and systemic treatments because the target volumes needed in radiation treatment are intimately related to the treatment techniques being used, and the other treatments the patients receive.

End of life and aggressive treatment

Performance status [28] is a useful predictor of length of survival of cancer patients receiving palliative radiotherapy [29-32]. Patients with poor performance status (Karnofsky Performance Status (KPS) < 60), non-breast and non-bone metastasis [29] have a median survival of 13 weeks, patients with two out of these three poor prognostic factors have a median survival of 29 weeks, and patients with good prognosis survived for a median of 114 weeks [29].

Use of radiotherapy during the last 30 days of life, regarded by many as inappropriate, was 7.6% for top five most deadly cancers lung, breast, prostate, colorectal and pancreatic cancers [29,33]. In another study, aggressive chemotherapy during the last month of life increased the chance of emergency room visit and intensive care unit admission for stomach cancer patients [34].

Simulation and setup

The goal of simulation is to set up the patient in a way that is comfortable and reproducible especially for palliative cases [35-37]. Cancer pain could be aggravated by the daily radiotherapy process (e.g. simulation, immobilization, transportation) and has been undertreated in about 50% of patients [38-40]. During simulation, the iso-center is set usually at the center of the target volume. However, at the treatment machine, when the simulation film is lined up with the port film for low dose CT using bony landmarks, the iso-center may no longer be at the center of the target volume because the position of the target volume is not representative of the average position of the target volume on daily basis [41] possibly due to discomfort of the patient at simulation. This is called the systemic error in addition to the random error due to internal organ motion secondary to respiratory, bowel or bladder filling [42-45]. When system error is large, re-simulation may be required [36,37,41]. Excessively uncomfortable immobilization, especially in palliative cases, may cause pain and discomfort and cause an excessive systemic error in simulation. No correction level of error (typically a few mm) could be applied so that patients need not be moved daily to adjust for minor systemic setup errors [46,47].

Treatment Planning

Familiar with the CT and MRI characteristics of tumors is very useful for treatment planning. CT number is a measure of the tissue density relative to that of water, it could be negative/dark (e.g. air in lung) if the density is lower than that of water [48]. Tumor necrosis is

a sign of an aggressive tumor [49]. The tumor necrotic center contains largely fluid appears dark on CT [49]. The CT level is usually chosen as the mid value of the CT numbers, and CT window is the range of CT numbers to display [48]. For high resolution imaging, an entire volume of tissue could be imaged to multi-slice CT that acquires all the slices in one revolution as opposed to acquiring each slice one at a time and reconstructs the volume leading to reconstruction artifacts [48]. See [50] for a very useful online reference for tumor imaging.

For brain tumor imaging [50,51], it is useful to note that fat is dark on CT (- 100 HU), bright on both T1 and T2 MRI [50]. Extracranial tumors (about 80% are meningioma and schwannoma) or arise from outside the brain or its coverings, intra-axial tumors are mostly (about 75% are metastasis or astrocytoma) [50]. Extracranial tumors do not have blood brain barrier (BBB) so the contrast enhances homogeneously, with a broad dural base and a dural tail of enhancement [50]. The dural tail is not part of meningioma, and needs not to be treated routinely unless there is a radiographic evidence of invasion [52]. Meningioma, glioblastoma multiforme (GBM) and radiation necrosis (appears similar to GBM) could cross the midline, and multiple sclerosis (MS) could present as single or multifocal masses [50]. Radiation brain necrosis shows finger like edema on T2 MRI and heterogeneous gadolinium enhancement on T1 MRI with contrast after the necrosis liquefies [53,54]. Brain tumors, infarction, infection or demyelinating disease (MS) that destroy the BBB, and pituitary and pineal glands that do not have BBB will enhance with contrast [50]. Pituitary stalk runs at an angle inferiorly to the pituitary gland [50], similar and close to the optic path. The brain tumor and normal tissue interface usually appears differently with different imaging modalities [50,51,55]. The volume of brain tumor imaged by T2/FLAIR could be larger than T1 with contrast MRI [56]. Contrast enhanced CT in the arterial phase clearly delineates the margin of hepatocellular carcinoma [57,58]. Multimodality imaging may be needed for accurate (not under or over covering) target delineation using the composite image [55,56].

Contouring of brain target and normal tissue volumes is best performed in multi-planes. The contouring is not purely anatomical, but also biologic and clinical (considering, for example, the performance status and concurrent chemotherapy). Pre-planning of the treatment volumes (target and normal tissue volumes) is useful.

Dose and fractionation

A protracted course of many weeks may not be the most effective ways for the patients to spend their last few months [35]. A typical hypo-fractionated palliative dose is 3000c Gy in 10 fractions and is highly effective, especially with concurrent chemotherapy [31,59,60]. In this case report, 30 Gy in 10 fractions was used with nedaplatin (80 mg/m² (day 1)) and 5-fluorouracil (800 mg/m² (day 1-4)) [60]. The patient continued with chemotherapy and had 17 months of local control of 3.9 x 3.5 cm lower esophageal squamous carcinoma [60]. In this study, 6 Gy once a week for 5 weeks was used to treat a very advanced squamous cell skin cancer with good pain control [35]. Other dose fractionation could vary from 8 Gy x 1 for a simple bone metastasis, to 4 Gy x 5 fractions for different sites, 8.5 Gy x 2 fractions for lung cancer, and 2 Gy x 23 fractions for many sites [12,31]. Very high dose per fraction has high risk of radiation side effects, for example, 8 Gy x 1 has more risk requiring re-treatment

[61], and injury from the re-irradiation and pathologic fracture [12]. Periosteal edema could happen in about 40% of patients with bone metastases receiving 8 Gy x 1 radiotherapy requiring more analgesic use [62,63]. This could be rescued by 8 mg dexamethasone for 1 to a few days [62-64]. 1700 cGy in two fractions over 3 days provided about 70% relief from hematuria and about 50% relief from pain [65]. The older hypo-fractionated high dose regimens should be used for patient with very limited life expectancy less than one year [12,65,66].

Pain control

Pain control is a very important but sometimes ineffective area in palliative care [67]. In South Korea, it is estimated about 60% of cancer patients experience cancer pain, 90% of cancer pain is controllable, however, cancer pain is undertreated in about 40% of patients [67]. This under-treatment is related to oncologist's poor knowledge of using opioids and alternative pain control methods, exaggerated fear of opioid addition and fear of respiratory suppression [67,68]. World Health Organization (WHO) has published a widely used pain control ladder for pain control in patients with advanced cancers [69,70].

Neuropathic pain includes somatic pain that is sharp (e.g. from cutting) versus visceral pain (e.g. from distention and ischemia) that dull and arching [71]. Radiotherapy and analgesic are important components in cancer pain control [72,73]. Mild pain could be treated with non-steroidal anti-inflammatory drug (NSAID) and paracetamol [72,74], moderate pain could be treated with mild narcotic (e.g. codeine, tramadol, dextropropoxyphene) [72] and severe pain could be treated with morphines [72]. Neuropathic pain could also be treated with anticonvulsant gabapentin and tricyclic anti-depressants [72] and steroid [75].

Bone metastasis

For patients with spinal metastasis, radiotherapy is a standard of care treatment, it provides about partial pain relief in about 60% and complete pain relief in about 30% patients [12]. Patients with spinal metastasis could also be treated with vertebroplasty and kyphoplasty [12]. Bone cortex and marrow have no nerve endings [72,73]. Neuropathic [76] bone pain from metastatic disease could be caused by fracture, irritation of periosteum and endosteum, nerve root compression and muscle spasm [72]. Treatment of bone metastases related event is about US \$28000 and treatment coats about US \$10000 per patient [72,77]. Bone fracture is the most common event related to lytic bone metastasis [77]. CT long bone cortical involvement of more than 30% should be considered for prophylactic fixation prior to radiotherapy [78]. Zoledronic acid was the first bisphosphonate used to treat bone metastasis and strengthen the bones [72]. Bisphosphonates such as Aredia could relieve malignant bone pain in 50% of patients [72,79]. Bisphosphonate inhibits osteoclast activity and could impair bone integrity and bone healing [80]. Bisphosphonate related mandible (maxilla less commonly) necrosis could be confused with metastatic disease that include PET avidity, tissue sclerosis and stranding [80].

Lung cancer

For patients with large lung cancers, radiotherapy is largely palliative [81]. When the tumor is larger than 7 cm, chemotherapy (four courses in 3-week intervals: intravenous carboplatin with area under curve of 5 [81,82] on day 1, oral vinorelbine 0 mg/m² days 1

and 8) and radiotherapy (hypo-fractionated 42 Gy/ 15 fractions) improved overall survival from 9.7 months to 13.4 months compared with chemotherapy alone [81]. The patients received chemotherapy first and needed radiotherapy was treated with 17 Gy over 2 fractions [81].

About a third of lung cancer patients have hypercalcemia especially patients with squamous cell lung cancer [77]. Hydration, diuretics (40 mg furosemide IV every 12 to 24 hours), glucocorticoid (60 prednisone orally daily or 100 mg hydrocortisone IV every 6 hours), IV bisphosphonate normalize malignant hypercalcemia in most patients [77]. Bronchial obstruction could be relieved by endoscopic cryotherapy [83] and radiotherapy.

Triple negative breast cancer

For triple negative (ER (estrogen receptor) negative, PR (progesterone receptor) negative, Her2 (human epidermal receptor) negative), estrogen receptor alpha targeted therapy has been used to treat patients with triple negative metastatic breast cancer [84]. One of its major side effects is cachexia secondary to loss of nutrient sensing and metabolism leading to muscle wasting and fatigue [84].

Stomach cancer

In one study, 30 Gy in 3 Gy fractions provided about 70% relief from blood transfusion from gastric bleeding for more than a month [59], about 50% of the patients developed rebleeding [59]. The median time to rebleeding in the study was 3.3 months [59], and patients received concurrent chemotherapy had lower rebleeding rate [59]. Bleeding from stomach melanoma been treated with more hypofractionated 16 Gy in 4 Gy fractions that provided 4 months of relief, and could be retreated with 9 Gy in 3 Gy fractions in this case report [85]. In this study, a median dose of 35 Gy in 14 fractions to the stomach provided control for bleeding, dysphagia/obstruction and pain in about 70-85% of patients [86], and control for the remaining part of life in about 50% of these patients [86]. A biological equivalent dose (BED) of equal or more than 41 Gy was found to be needed for good control of gastric symptoms [86].

Colorectal cancer

For colorectal cancer patients, obstruction and perforation is usually managed by colonic resection, stoma, lavage, internal bypass or stenting [18]. Bleeding, pain or tenesmus and fullness could be managed by radiotherapy [18].

Brain and brainstem metastasis

Radiotherapy Oncology Group (RTOG) performed a trial comparing whole 5 x 4 Gy versus 15 x 3 Gy or 20 x 2 Gy, the survival was the same using the shorter or the longer courses of radiotherapy [30]. The risk of neurotoxicity was higher with the large dose pre fraction whole brain radiotherapy [30].

Brain stem metastasis is challenging to treat because it is located in the critical area [87-89], brain stem metastasis less than 1 ml may be safely and effectively treated with Gamma Knife stereotactic radiosurgery with a median dose of about 16 – 18 Gy prescribed to 50% [87-89]. For larger brain stem metastases or patient received whole brain radiotherapy, they could be treated with 21 – 30 Gy in 3 -5 fractions [88]. In this study, MRI T1 with gadolinium contrast was used to define the target; no clinical margin was used [88]. Six months

survival after Gamma Knife SRS (minimum of 16 Gy) was 42%, with shorter survival for patients also received whole brain radiotherapy (3750 cGy whole brain followed by 16 Gy or less SRS boost) in this study [89]. Neurocognitive function is worse after whole brain and SRS when compared with SRS [90]. Upfront SRS for solitary or limited brainstem metastasis may be the better treatment saving the whole brain radiotherapy for salvage [91] in palliative cases.

Conclusion

The radiotherapy in palliative cases is different than the curative cases in the intent of cure versus palliation. When active intervention is futile, palliating the pain and suffering of the cancer patient should be the primary treatment goal.

References

1. Cannon C. Death happens every day. *Oncol Nurs Forum*. 2013; 40: 532.
2. Rangachari D, Smith TJ. Integrating palliative care in oncology: the oncologist as a primary palliative care provider. *Cancer J*. 2013; 19: 373-378.
3. Ohnsorge K, Gudat H, Rehmann-Sutter C. What a wish to die can mean: reasons, meanings and functions of wishes to die, reported from 30 qualitative case studies of terminally ill cancer patients in palliative care. *BMC Palliat Care*. 2014; 13: 38.
4. Kondo S, Shimazu T, Morizane C, Hosoi H, Okusaka T, Ueno H. A retrospective analysis of factors associated with selection of end-of-life care and actual place of death for patients with cancer. *BMJ Open*. 2014; 4: e004352.
5. Dy SM, Walling AM, Mack JW, Malin JL, Pantoja P, Lorenz KA, et al. Evaluating the quality of supportive oncology using patient-reported data. *J Oncol Pract*. 2014; 10: e223-230.
6. Wright AA, Zhang B, Keating NL, Weeks JC, Prigerson HG. Associations between palliative chemotherapy and adult cancer patients' end of life care and place of death: prospective cohort study. *BMJ*. 2014; 348: g1219.
7. Hadders H, Paulsen B, Fougner V. Relatives' participation at the time of death: standardisation in pre and post-mortem care in a palliative medical unit. *Eur J Oncol Nurs*. 2014; 18: 159-166.
8. Anquetin L, Rietjens J, van der Heide A, Bruinsma S, Janssens R, Deliens L, et al. Physicians' experiences and perspectives regarding the use of continuous sedation until death for cancer patients in the context of psychological and existential suffering at the end of life. *Psychooncology*. 2014; 23: 539-546.
9. Levy MH, Back A, Benedetti C, Billings JA, Block S, Boston B, et al. NCCN clinical practice guidelines in oncology: palliative care. *J Natl Compr Canc Netw*. 2009; 7: 436-473.
10. Hassett MJ, McNiff KK, Dicker AP, Gilligan T, Hendricks CB, Lennes I, et al. High-priority topics for cancer quality measure development: results of the 2012 American Society of Clinical Oncology Collaborative Cancer Measure Summit. *J Oncol Pract*. 2014; 10: e160-166.
11. Smith TJ, Temin S, Alesi ER, Abernethy AP, Balboni TA, Basch EM, et al. American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. *J Clin Oncol*. 2012; 30: 880-887.
12. Kaloustian PE, Yurter A, Etame AB, Vrionis FD, Sciubba DM, Gokaslan ZL. Palliative strategies for the management of primary and metastatic spinal tumors. *Cancer Control*. 2014; 21: 140-143.
13. Arican A, Bozkurt T, Bozcuk H, Demirkan B, Buyukberber S, Alkis N, et al. A cross-sectional survey of the diagnosis and management of bone metastasis in breast cancer patients in Turkey. *Support Care Cancer*. 2014; 22: 2629-2634.
14. Steinauer K, Gross MW, Huang DJ, Eppenberger-Castori S, G uth U. Radiotherapy in patients with distant metastatic breast cancer. *Radiat Oncol*. 2014; 9: 126.

15. Takeda A, Sanuki N, Kunieda E. Role of stereotactic body radiotherapy for oligometastasis from colorectal cancer. *World J Gastroenterol*. 2014; 20: 4220-4229.
16. Nieder C, Angelo K, Dalhaug A, Pawinski A, Aandahl G, Haukland E, et al. Palliative Radiotherapy with or without Additional Care by a Multidisciplinary Palliative Care Team: A Retrospective Comparison. *ISRN Oncol*. 2014; 2014: 715396.
17. Xu L, Zhang H, Liu J, Chen X. Investigation of the oral infections and manifestations seen in patients with advanced cancer. *Pak J Med Sci*. 2013; 29: 1112-1115.
18. Costi R, Leonardi F, Zanoni D, Violi V, Roncoroni L. Palliative care and end-stage colorectal cancer management: the surgeon meets the oncologist. *World J Gastroenterol*. 2014; 20: 7602-7621.
19. Cheung MR. Target Volumes, Image Fusion and Contouring in Modern Radiotherapy Treatment Planning. *Jacobs Journal of Radiation Oncology*. 2014; 1: 15.
20. Cheung R, Kang J, Yeung V. Using a Robotic Stereotactic Radiation Treatment System for Re-Irradiation may be Safe and Effective. *Jacobs Journal of Radiation Oncology*. 2014; 1: 9.
21. Cheung R. Using a Robotic Stereotactic Radiation Treatment System to Treat Benign Intracranial Tumors and Trigeminal Neuralgia. *Austin J Radiat Oncol & Cancer*. 2014; 1: 2.
22. Cheung R. The Utility of a Robotic Stereotactic Radiation Treatment System to Treat Primary and Metastatic Liver Tumors. *Austin J Cancer Clin Res*. 2014; 1: 2.
23. Cheung R. Using stereotactic radiation systems to irradiate and re-irradiate head and neck cancers. *Journal of Radiation Oncology*. 2015; 1: 7.
24. Cheung R. A light account of challenges to modern radiotherapy: clinics, epidemiology, and public health. Lambert Academic Publishing, Germany. 2015.
25. Cheung R. Challenges in radiotherapy treatment planning in the high-precision radiotherapy era. *Jacobs Journal of Radiation Oncology*. 2015.
26. Cheung MR. Introduction to stereotactic hypofractionated radiotherapy, re-irradiation, and cancer genome research. Austin Publishing Group, Texas. 2015.
27. Cheung MR. Using data from The Cancer Genome Atlas (TCGA) to model outcome of cancer patients to guide oncologic treatment. Introduction to stereotactic hypofractionated radiotherapy, re-irradiation, and cancer genome research: Austin Publishing Group, Austin, Texas. 2015.
28. http://en.wikipedia.org/wiki/Performance_status.
29. Angelo K, Dalhaug A, Pawinski A, Haukland E, Nieder C. Survival prediction score: a simple but age-dependent method predicting prognosis in patients undergoing palliative radiotherapy. *ISRN Oncol*. 2014; 2014: 912865.
30. Rades D, Dunst J, Schild SE. A new scoring system to predicting the survival of patients treated with whole-brain radiotherapy for brain metastases. *Strahlenther Onkol*. 2008; 184: 251-255.
31. Chow E, Abdolell M, Panzarella T, Harris K, Bezjak A, Warde P, et al. Predictive model for survival in patients with advanced cancer. *J Clin Oncol*. 2008; 26: 5863-5869.
32. Nieder C, Andratschke N, Angelo K, Haukland E, Grosu AL. Development of a score predicting survival after palliative reirradiation. *J Oncol*. 2014; 2014: 128240.
33. Guadagnolo BA, Liao KP, Elting L, Giordano S, Buchholz TA, Shih YC. Use of radiation therapy in the last 30 days of life among a large population-based cohort of elderly patients in the United States. *J Clin Oncol*. 2013; 31: 80-87.
34. Hong JH, Rho SY, Hong YS. Trends in the Aggressiveness of End-of-Life Care for Advanced Stomach Cancer Patients. *Cancer Res Treat*. 2013; 45: 270-275.
35. McKay MJ. Advanced skin squamous cell carcinoma: role of radiotherapy. *Aust Fam Physician*. 2014; 43: 33-35.
36. de Boer HC, Heijmen BJ. A protocol for the reduction of systematic patient setup errors with minimal portal imaging workload. *Int J Radiat Oncol Biol Phys*. 2001; 50: 1350-1365.
37. de Boer HC, van Sörnsen de Koste JR, Senan S, Visser AG, Heijmen BJ. Analysis and reduction of 3D systematic and random setup errors during the simulation and treatment of lung cancer patients with CT-based external beam radiotherapy dose planning. *Int J Radiat Oncol Biol Phys*. 2001; 49: 857-868.
38. Pignon T, Fernandez L, Ayasso S, Durand MA, Badinand D, Cowen D. Impact of radiation oncology practice on pain: a cross-sectional survey. *Int J Radiat Oncol Biol Phys*. 2004; 60: 1204-1210.
39. Janjan N. Do we need to improve pain management in the radiation oncology department? *Nat Clin Pract Oncol*. 2005; 2: 130-131.
40. Bell BC, Butler EB. Management of predictable pain using fentanyl pectin nasal spray in patients undergoing radiotherapy. *J Pain Res*. 2013; 6: 843-848.
41. Wang J, Lin SH, Dong L, Balter P, Mohan R, Komaki R, et al. Quantifying the interfractional displacement of the gastroesophageal junction during radiation therapy for esophageal cancer. *Int J Radiat Oncol Biol Phys*. 2012; 83: e273-280.
42. Melancon AD, O'Daniel JC, Zhang L, Kudchadker RJ, Kuban DA, Lee AK, et al. Is a 3-mm intrafractional margin sufficient for daily image-guided intensity-modulated radiation therapy of prostate cancer? *Radiother Oncol*. 2007; 85: 251-259.
43. Yeo UA, Taylor ML, Supple JR, Siva S, Kron T, Pham D, et al. Evaluation of dosimetric misrepresentations from 3D conventional planning of liver SBRT using 4D deformable dose integration. *J Appl Clin Med Phys*. 2014; 15: 4978.
44. Knybel L, Cvek J, Otahal B, Jonszta T, Molenda L, Czerny D, et al. The analysis of respiration-induced pancreatic tumor motion based on reference measurement. *Radiat Oncol*. 2014; 9: 192.
45. Akino Y, Oh RJ, Masai N, Shiomi H, Inoue T. Evaluation of potential internal target volume of liver tumors using cine-MRI. *Med Phys*. 2014; 41: 111704.
46. de Boer HC, van Os MJ, Jansen PP, Heijmen BJ. Application of the No Action Level (NAL) protocol to correct for prostate motion based on electronic portal imaging of implanted markers. *Int J Radiat Oncol Biol Phys*. 2005; 61: 969-983.
47. de Boer HC, Heijmen BJ. eNAL: an extension of the NAL setup correction protocol for effective use of weekly follow-up measurements. *Int J Radiat Oncol Biol Phys*. 2007; 67: 1586-1595.
48. http://en.wikibooks.org/wiki/Basic_Physics_of_Nuclear_Medicine/X-Ray_CT_in_Nuclear_Medicine
49. Cha S. Update on brain tumor imaging: from anatomy to physiology. *AJNR Am J Neuroradiol*. 2006; 27: 475-487.
50. http://gistsupport.medshelf.org/Marina_on_Tumor_Necrosis
51. Bulthuis VJ, Hanssens PE, Lie ST, van Overbeeke JJ. Gamma Knife radiosurgery for intracranial meningiomas: Do we need to treat the dural tail? A single-center retrospective analysis and an overview of the literature. *Surg Neurol Int*. 2014; 5: S391-395.
52. <http://www.radiologyassistant.nl/en/p47f86aa182b3a/brain-tumor-systematic-approach.html>
53. Wang YX, King AD, Zhou H, Leung SF, Abrigo J, Chan YL, et al. Evolution of radiation-induced brain injury: MR imaging-based study. *Radiology*. 2010; 254: 210-218.
54. Wu X, Gu M, Zhou G, Xu X, Wu M, Huang H. Cognitive and neuropsychiatric impairment in cerebral radionecrosis patients after radiotherapy of nasopharyngeal carcinoma. *BMC Neurol*. 2014; 14: 10.
55. Guo L, Shen S, Harris E, Wang Z, Jiang W, Guo Y, et al. A tri-modality image fusion method for target delineation of brain tumors in radiotherapy. *PLoS One*. 2014; 9: e112187.
56. Corwin D, Holdsworth C, Rockne RC, Trister AD, Mrugala MM, Rockhill JK, et

- al. Toward patient-specific, biologically optimized radiation therapy plans for the treatment of glioblastoma. *PLoS One*. 2013; 8: e79115.
57. Xu H, Gong G, Wei H, Chen L, Chen J, Lu J, et al. Feasibility and potential benefits of defining the internal gross tumor volume of hepatocellular carcinoma using contrast-enhanced 4D CT images obtained by deformable registration. *Radiat Oncol*. 2014; 9: 221.
58. Choi BI, Han JK, Cho JM, Choi DS, Han MC, Lee HS, et al. Characterization of focal hepatic tumors. Value of two-phase scanning with spiral computed tomography. *Cancer*. 1995; 76: 2434-2442.
59. Asakura H, Hashimoto T, Harada H, Mizumoto M, Furutani K, Hasuike N, et al. Palliative radiotherapy for bleeding from advanced gastric cancer: is a schedule of 30 Gy in 10 fractions adequate? *J Cancer Res Clin Oncol*. 2011; 137: 125-130.
60. Yamashita H, Okuma K, Nomoto A, Yamashita M, Igaki H, Nakagawa K, et al. Extended cancer-free survival after palliative chemoradiation for metastatic esophageal cancer. *World J Gastrointest Oncol*. 2014; 6: 52-54.
61. Mithal NP, Needham PR, Hoskin PJ. Retreatment with radiotherapy for painful bone metastases. *Int J Radiat Oncol Biol Phys*. 1994; 29: 1011-1014.
62. Westhoff PG, de Graeff A, Geerling JI, Reyners AK, van der Linden YM. Dexamethasone for the prevention of a pain flare after palliative radiotherapy for painful bone metastases: a multicenter double-blind placebo-controlled randomized trial. *BMC Cancer*. 2014; 14: 347.
63. Chow E, Ling A, Davis L, Panzarella T, Danjoux C. Pain flare following external beam radiotherapy and meaningful change in pain scores in the treatment of bone metastases. *Radiother Oncol*. 2005; 75: 64-69.
64. Chiang A, Zeng L, Zhang L, Lochray F, Korol R, Loblaw A. Pain flare is a common adverse event in steroid-naïve patients after spine stereotactic body radiation therapy: a prospective clinical trial. *Int J Radiat Oncol Biol Phys*. 2013; 86: 638-642.
65. Srinivasan V, Brown CH, Turner AG. A comparison of two radiotherapy regimens for the treatment of symptoms from advanced bladder cancer. *Clin Oncol (R Coll Radiol)*. 1994; 6: 11-13.
66. Pal S, Dutta S, Adhikary SS, Bhattacharya B, Ghosh B, Patra NB. Hemi body irradiation: An economical way of palliation of pain in bone metastasis in advanced cancer. *South Asian J Cancer*. 2014; 3: 28-32.
67. Jho HJ, Kim Y, Kong KA, Kim DH, Choi JY, Nam EJ, et al. Knowledge, practices, and perceived barriers regarding cancer pain management among physicians and nurses in Korea: a nationwide multicenter survey. *PLoS One*. 2014; 9: e105900.
68. Kim MH, Park H, Park EC, Park K. Attitude and knowledge of physicians about cancer pain management: young doctors of South Korea in their early career. *Jpn J Clin Oncol*. 2011; 41: 783-791.
69. Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. *Cancer*. 1987; 59: 850-856.
70. Marinangeli F, Ciccozzi A, Leonardi M, Aloisio L, Mazzei A, Paladini Am, et al. Use of strong opioids in advanced cancer pain: a randomized trial. *J Pain Symptom Manage*. 2004; 27: 409-416.
71. http://en.wikipedia.org/wiki/Visceral_pain
72. Delea TE, McKiernan J, Brandman J, Edelsberg J, Sung J, Raut M, et al. Impact of skeletal complications on total medical care costs among patients with bone metastases of lung cancer. *J Thorac Oncol*. 2006; 1: 571-576.
73. Ripamonti C, Fulfarò F. Malignant bone pain: pathophysiology and treatments. *Curr Rev Pain*. 2000; 4: 187-196.
74. McCormack K. Non-steroidal anti-inflammatory drugs and spinal nociceptive processing. *Pain*. 1994; 59: 9-43.
75. Watanabe S, Bruera E. Corticosteroids as adjuvant analgesics. *J Pain Symptom Manage*. 1994; 9: 442-445.
76. http://en.wikipedia.org/wiki/Neuropathic_pain
77. D'Antonio C, Passaro A, Gori B, Del Signore E, Migliorino MR, Ricciardi S, et al. Bone and brain metastasis in lung cancer: recent advances in therapeutic strategies. *Ther Adv Med Oncol*. 2014; 6: 101-114.
78. Tatar Z, Soubrier M, Dillies A, Verrelle P, Boisgard S, Lapeyre M. Assessment of the risk factors for impending fractures following radiotherapy for long bone metastases using CT scan-based virtual simulation: a retrospective study. *Radiat Oncol*. 2014; 9: 227.
79. Coleman RE. How can we improve the treatment of bone metastases further? *Curr Opin Oncol*. 1998; 10 Suppl 1: S7-13.
80. Bhatt G, Bhatt A, Dragun AE, Li XF, Civelek AC. Bisphosphonate-related osteonecrosis of the jaw mimicking bone metastasis. *Case Rep Oncol Med*. 2014; 2014: 281812.
81. Strøm HH, Bremnes RM, Sundstrøm SH, Helbekkmo N, Aasebø U. Poor prognosis patients with inoperable locally advanced NSCLC and large tumors benefit from palliative chemoradiotherapy: a subset analysis from a randomized clinical phase III trial. *J Thorac Oncol*. 2014; 9: 825-833.
82. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol*. 1989; 7: 1748-1756.
83. Fitzmaurice GJ, Redmond KC, Fitzpatrick DA, Bartosik W. Endobronchial cryotherapy facilitates end-stage treatment options in patients with bronchial stenosis: A case series. *Ann Thorac Med*. 2014; 9: 120-123.
84. May FE. Novel drugs that target the estrogen-related receptor alpha: their therapeutic potential in breast cancer. *Cancer Manag Res*. 2014; 6: 225-252.
85. Slater JM, Ling TC, Slater JD, Yang GY. Palliative radiation therapy for primary gastric melanoma. *J Gastrointest Oncol*. 2014; 5: E22-26.
86. Kim MM, Rana V, Janjan NA, Das P, Phan AT, Delclos ME, et al. Clinical benefit of palliative radiation therapy in advanced gastric cancer. *Acta Oncol*. 2008; 47: 421-427.
87. Kased N, Huang K, Nakamura JL, Sahgal A, Larson DA, McDermott MW, et al. Gamma knife radiosurgery for brainstem metastases: the UCSF experience. *J Neurooncol*. 2008; 86: 195-205.
88. Kilburn JM, Ellis TL, Lovato JF, Urbanic JJ, Daniel Bourland J, et al. Local control and toxicity outcomes in brainstem metastases treated with single fraction radiosurgery: is there a volume threshold for toxicity? *J Neurooncol*. 2014; 117: 167-174.
89. Peterson HE, Larson EW, Fairbanks RK, MacKay AR, Lamoreaux WT, Call JA, et al. Gamma knife treatment of brainstem metastases. *Int J Mol Sci*. 2014; 15: 9748-9761.
90. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 2009; 10: 1037-1044.