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Radiotherapy

Current Awareness Bulletin

February 2017

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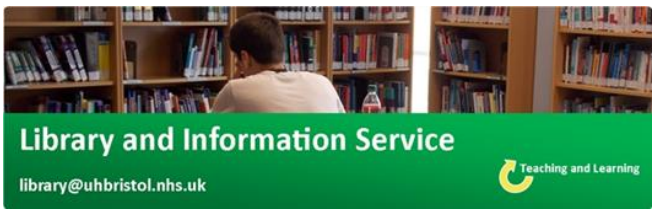

Lunchtime Drop-in Sessions

All sessions last one hour

March (1pm - 2pm)	
Thurs 2nd	**Critical Appraisal**
Fri 10th	**Interpreting Statistics**
Mon 13th	**Literature Searching**
Tues 21st	**Critical Appraisal**
Weds 29th	**Interpreting Statistics**
April	(12pm - 1pm)
Thurs 6th	**Literature searching**
Mon 10th	**Critical Appraisal**
Tues 18th	**Interpreting Statistics**
Thurs 27th	**Literature Searching**

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Contents

Current Journals: Tables of Contents

Click on journal title (+ Ctrl) for hyperlink

Journal	Month	Volume	Issue
Radiotherapy and Oncology	February 2017	122	2
International Journal of Radiation Biology and Physics	March 2017	97	4
Clinical Oncology	April 2017	29	4

If you require full articles please email: library@uhbristol.nhs.uk

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Latest Evidence

NICE National Institute for Health and Care Excellence

NICE recommends controlled use of targeted breast cancer radiotherapy treatment alongside further research
NICE has recommended the Intrabeam Radiotherapy System for people with early breast cancer in limited circumstances with additional data collection.
https://www.nice.org.uk/news/article/nice-recommends-controlled-use-of-targeted-breast-cancer-radiotherapy-treatment-alongside-further-research

Radiation therapy for early Dupuytren's disease. Interventional procedures guidance [IPG573].
NICE: December 2016
https://www.nice.org.uk/guidance/IPG573

Cochrane Library

Lawrie TA, Green JT, Beresford M, Burden S, Lal S, Davidson SE, Henson CC, Andreyev HJN. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy (Protocol). Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD012529. DOI: 10.1002/14651858.CD012529.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012529/full

Eastment JG, Burke JP, Fong KM, Yang IA, Bowman RV. Radiation therapy for preventing instrumentation track metastases in malignant pleural mesothelioma (Protocol). Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD012541. DOI: 10.1002/14651858.CD012541.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012541/full

Burdett S, Rydzewska L, Tierney J, Fisher D, Parmar MKB, Arriagada R, Pignon JP, Le Pechoux C, on behalf of the PORT Meta-analysis Trialists Group. Postoperative radiotherapy for non-small cell lung cancer. Cochrane Database of Systematic Reviews 2016, Issue 10. Art. No.: CD002142. DOI: 10.1002/14651858.CD002142.pub4.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002142.pub4/full

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Radiation therapy techniques for newly diagnosed, non-metastatic breast cancer
Author: Lori J Pierce, MD; Section Editor: David E Wazer, MD; Deputy Editor: Sadhna R Vora, MD
Literature review current through: Jan 2017. | **This topic last updated:** Dec 05, 2016.

INTRODUCTION — Radiation therapy (RT) is a critical component of therapy for women with newly diagnosed, non-metastatic breast cancer. RT techniques for women with newly diagnosed, non-metastatic invasive breast cancer will be reviewed here. An overview of RT techniques in cancer treatment is discussed separately. (See "Radiation therapy techniques in cancer treatment".)

https://www.uptodate.com/contents/radiation-therapy-techniques-for-newly-diagnosed-non-metastatic-breast-cancer?source=search_result&search=radiation%20therapy&selectedTitle=5~150

Radiation therapy in the management of melanoma
Author: Anand Mahadevan, MD; Section Editor: Michael B Atkins, MD; Deputy Editor: Michael E Ross, MD
Literature review current through: Jan 2017. | **This topic last updated:** Jan 16, 2017.
https://www.uptodate.com/contents/radiation-therapy-in-the-management-of-melanoma?source=search_result&search=radiation%20therapy&selectedTitle=9~150

Radiation therapy for the management of painful bone metastases
Authors: Lisa A Kachnic, MD; Steven J DiBiase, MD; Section Editor:Steven E Schild, MD
Deputy Editor: Diane MF Savarese, MD
Literature review current through: Jan 2017. | **This topic last updated:** Oct 06, 2016.
INTRODUCTION — Bone metastases are a common manifestation of distant relapse from many types of solid cancers, especially those arising in the lung, breast, and prostate. As many as 80 percent of patients with solid tumors will develop painful bone metastases to the spine, pelvis, and extremities during the course of their illness [1].
https://www.uptodate.com/contents/radiation-therapy-for-the-management-of-painful-bone-metastases?source=related_link

Guidelines

Royal College of Radiologists

Radiotherapy dose fractionation. 2nd edition. Royal College of Radiologists, 2016.

https://www.rcr.ac.uk/system/files/publication/field_publication_files/bfco163_radiotherapy_dose_fractionation_2nd_ed.pdf

Postoperative radiotherapy for breast cancer: UK consensus statements. Royal College of Radiologists, 2016
https://www.rcr.ac.uk/system/files/publication/field_publication_files/bfco2016_breast-consensus-guidelines.pdf

Institute of Physics and Engineering in Medicine

The Design of Radiotherapy Treatment Room Facilities
Expected: Summer 2017
Update of Report 75

Physics Aspects of Quality Control in Radiotherapy (update of Report 81)
Expected: 2017

https://www.ipem.ac.uk/Publications/IPEMReportSeries/ForthcomingPublications.aspx

Current Awareness Database Articles

Below is a selection of articles recently added to the healthcare databases, grouped in the categories:

- Liver SABR
- Radium-223 treatment – Prostate and breast metastases

If you would like any of the articles in full text, or if you would like a more focused search on your own topic, please contact us: library@bristol.nhs.uk

Liver SABR (Stereotactic Ablative Body Radiotherapy)

1. Stereotactic ablative radiotherapy for patients with unresectable or medically inoperable cholangiocarcinoma.

Author(s): Liu, Ming-Yueh; Lo, Cheng-Hsiang; Lin, Chun-Shu; Chao, Hsing-Lung; Yang, Jen-Fu; Lin, Kuen-Tze; Fan, Chao-Yueh; Su, Yu-Fu; Huang, Wen-Yen

Source: Tumori; Jan 2017 ; p. 0

Publication Type(s): Journal Article

Abstract:PURPOSEThe role of stereotactic ablative radiotherapy (SABR) in patients with unresectable or medically inoperable cholangiocarcinoma remains unclear. We examined the efficacy and safety of SABR in this group of patients.METHODSFrom January 2008 to December 2014, 15 patients with 17 lesions were included in this study. The lesions included 14 intrahepatic, 1 hilar, and 2 distal bile duct tumors. Three patients were classified as medically inoperable because of old age or multiple comorbidities. Tumors measured 0.8-13 cm (median, 3.6 cm). The median prescribed dose was 45 Gy delivered in 5 fractions over 5 consecutive days.RESULTSThe median follow-up period for surviving patients was 29.9 months. Objective responses were observed for 10 of 17 tumors (58.8%), including 3 complete responses (17.6%). The median survival duration was 12.6 months, and the 1- and 2-year overall survival rates were 50.3% and 14.4%, respectively. The 1- and 2-year in-field failure-free rates were 61.5% and 30.8%, respectively. For patients with biologically effective doses (BEDs) exceeding 75 Gy10, the 1- and 2-year overall survival rates were 58.3% and 33.3%, respectively, compared to 20.0% and 0%, respectively for those with BEDs lower than 75 Gy10. Radiation-induced liver disease did not develop in any patient. Acute toxicities were generally mild and tolerable.CONCLUSIONSStereotactic ablative radiotherapy could be an alternative treatment for unresectable or medically inoperable cholangiocarcinoma. Further dose escalation may be considered to optimize local control.

2. Predicting the PTV margin for liver SABR treatment

Author(s): Foo J.; Yau S.

Source: Australasian Physical and Engineering Sciences in Medicine; Dec 2016; vol. 39 (no. 4); p. 1098-1099

Publication Type(s): Journal: Conference Abstract

Abstract: Introduction Stereotactic ablative body radiotherapy (SABR) of the liver has many challenges mainly attributed to organ deformation, respiratory motion and poor cone beam CT (CBCT) contrast in the liver. This causes difficulty in choosing a PTV margin. A PTV margin that is too small may not adequately cover the target because of treatment setup errors thus leading to undesired replanning with larger margins. In this study, CBCT data was acquired during treatment for position verification and the adequacy of the current PTV margin was assessed. The setup data was also put in a margin recipe calculation to help predict a PTV margin for future patients. Method Five patients were treated using a breath-hold technique with the Elekta ABC system. Each patient was planned for five fractions. Initial PTV margins of 5 mm were set by the oncologist. For each fraction, the patient typically receives four CBCTs. The positional error during treatment was analysed. The van Herk1 margin recipe formula was applied to determine the appropriate PTV margin using the systematic and random error from the setup. Results The positional error was plotted against time from the first CBCT. An example is shown in Fig. 1 for one patient in the S-I direction. Fig. 1 shows a steady increase in intrafraction motion as the treatment time increased. It is clear that a 5 mm margin is inadequate; this resulted in replanning with the margin increased to 10 mm. The PTV margin was also validated against the margin recipe calculation. As liver SABR patients are less common, the predictive power of this margin recipe calculation can be improved as patient numbers increase. Conclusion Intrafraction motion of liver SABR patients has shown to exceed initial PTV margins even with breath-hold. CBCT data was used to predict the appropriate margin required for future patients to improve target delivery accuracy.

3. Is Individual patient QA of 4DCTs used for SABR planning warranted?

Author(s): Antony R.; Ungureanu E.; Lonski P.; Kron T.

Source: Australasian Physical and Engineering Sciences in Medicine; Dec 2016; vol. 39 (no. 4); p. 1178

Publication Type(s): Journal: Conference Abstract

Abstract: Introduction 4DCT is an important tool in radiotherapy planning of moving structures to inform margins for the target volumes that vary depending on the patient's breathing pattern. In our institution 4DCT is acquired for all stereotactic ablative body radiotherapy (SABR) patients having lung, kidney or liver lesions. We report our experience of the impact of medical physics 4DCT reviews prior to planning based on data from 51 consecutive patients. Method Patients were immobilized using the Elekta Body fix system and 4DCT images acquired with 140 kVp in helical mode on a Phillips Brilliance wide bore CT scanner. Breathing tracks were recorded using the Philips bellows system. Depending on the breathing frequency, the pitch factor is adjusted by the operator for each patient. The images were reconstructed for 10 equidistant breathing phases and a full review of the scan was done by a radiation oncology medical physicist. Results 4DCT scans of 51 patients with different treatment sites and breathing patterns were reviewed. Their impact on treatment volumes with different breathing patterns was assessed and advice on margin and contouring provided where deemed appropriate. In several cases a rescan was recommended by the physicist due to excessive artefacts or lack of recorded tumour motion. The results of the reviews are shown in the figure. It can be seen that irregular breathing predicts for more interventions. Conclusion This study confirms that physics 4DCT reviews have an impact on SABR cases where dose is delivered with tight margins. It improves the accuracy of target delineation and reduces the uncertainties in treatment delivery.

4. Clinical Outcomes for Stereotactic Ablative Radiotherapy in Oligometastatic and Oligoprogressive Gynecological Malignancies.

Author(s): Mesko, Shane; Sandler, Kiri; Cohen, Joshua; Konecny, Gottfried; Steinberg, Michael; Kamrava, Mitchell

Source: International journal of gynecological cancer : official journal of the International Gynecological Cancer Society; Nov 2016

Publication Type(s): Journal Article

Abstract:OBJECTIVESWe report single-institution clinical outcomes of women treated with stereotactic ablative radiotherapy (SABR) for oligometastatic or progressive gynecological malignancies.MATERIALS AND METHODSFrom 2009 to 2015, 47 lesions from 28 patients were treated with SABR and retrospectively analyzed. All patients had oligometastatic (93%) or oligoprogressive (7%) disease. Primary cancer diagnoses were 15 ovarian, 8 endometrial, 2 cervical, 2 vaginal, and 1 uterine carcinosarcoma. Treatment was delivered using a median of 5 fractions to a median total dose of 40 Gy. Targets were grouped by treatment site and assessed for response using Response Evaluation Criteria in Solid Tumors v1.1. Mean biologically effective

dose and pre-SABR tumor size were compared with response. Progression-free survival (PFS) was determined using Kaplan-Meier analysis, and toxicity outcomes were graded using Common Terminology Criteria for Adverse Events version 4.03.RESULTSMedian follow-up was 12.8 months. Target locations were 17% liver, 21% lung, 17% paraaortic node, 26% other node, and 19% pelvic soft tissue. After treatment, 34% of targets were stable (SD), 32% had a partial response (PR), 17% had a complete response (CR), and 17% had progressive disease (PD). No failures occurred in lung or nodal targets. Mean ± standard deviation pre-SABR tumor diameter was 24 ± 22 mm. There was a significant difference in mean size between lesions that had a favorable (SD, PR, and CR) versus unfavorable response (PD) (17.2 vs 57.6 mm, P = 0.0044). Lesions that responded favorably were also more likely to have received a higher biologically effective dose (79.0 vs 59.6 Gy, P = 0.027). Median PFS was 10.8 months, and 1 patient experienced grade 3 toxicity.CONCLUSIONSThe SABR is a safe and effective local treatment modality in patients with oligometastatic gynecological disease. Distant progression remains the primary mode of failure in this patient population. In carefully selected patients, a combination of systemic treatment and SABR may offer long-term PFS.

5. Robotic intrafractional US guidance for liver SABR: System design, beam avoidance, and clinical imaging.

Author(s): Schlosser, Jeffrey; Gong, Ren Hui; Bruder, Ralf; Schweikard, Achim; Jang, Sungjune; Henrie, John; Kamaya, Aya; Koong, Albert; Chang, Daniel T; Hristov, Dimitre

Source: Medical physics; Nov 2016; vol. 43 (no. 11); p. 5951

Publication Type(s): Journal Article

Abstract:PURPOSE To present a system for robotic 4D ultrasound (US) imaging concurrent with radiotherapy beam delivery and estimate the proportion of liver stereotactic ablative body radiotherapy (SABR) cases in which robotic US image guidance can be deployed without interfering with clinically used VMAT beam configurations. METHODS The image guidance hardware comprises a 4D US machine, an optical tracking system for measuring US probe pose, and a custom-designed robot for acquiring hands-free US volumes. In software, a simulation environment incorporating the LINAC, couch, planning CT, and robotic US guidance hardware was developed. Placement of the robotic US hardware was guided by a target visibility map rendered on the CT surface by using the planning CT to simulate US propagation. The visibility map was validated in a prostate phantom and evaluated in patients by capturing live US from imaging positions suggested by the visibility map. In 20 liver SABR patients treated with VMAT, the simulation environment was used to virtually place the robotic hardware and US probe. Imaging targets were either planning target volumes (PTVs, range 5.9-679.5 ml) or gross tumor volumes (GTVs, range 0.9-343.4 ml). Presence or absence of mechanical interference with LINAC, couch, and patient body as well as interferences with treated beams was recorded. RESULTS For PTV targets, robotic US guidance without mechanical interference was possible in 80% of the cases and guidance without beam interference was possible in 60% of the cases. For the smaller GTV targets, these proportions were 95% and 85%, respectively. GTV size (1/20), elongated shape (1/20), and depth (1/20) were the main factors limiting the availability of noninterfering imaging positions. The robotic US imaging system was deployed in two liver SABR patients during CT simulation with successful acquisition of 4D US sequences in different imaging positions. CONCLUSIONS This study indicates that for VMAT liver SABR, robotic US imaging of a relevant internal target may be possible in 85% of the cases while using treatment plans currently deployed in the clinic. With beam replanning to account for the presence of robotic US guidance, intrafractional US may be an option for 95% of the liver SABR cases.

6. Stereotactic ablative radiation therapy prior to liver transplantation in hepatocellular carcinoma.

Author(s): Guarneri, Alessia; Franco, Pierfrancesco; Romagnoli, Renato; Trino, Elisabetta; Mirabella, Stefano; Molinaro, Luca; Rizza, Giorgia; Filippi, Andrea Riccardo; Carucci, Patrizia; Salizzoni, Mauro; Ricardi, Umberto

Source: La Radiologia medica; Nov 2016; vol. 121 (no. 11); p. 873-881

Publication Type(s): Journal Article

Abstract:OBJECTIVEStereotactic ablative radiotherapy (SABR) is a safe treatment approach for hepatocellular carcinoma (HCC) with comparable effectiveness to other local therapies. Only scant information is available concerning the role of SABR prior to liver transplantation (LT) for HCC. We present a consecutive case series investigating the role of SABR as a bridge or downstaging option in HCC patients subsequently submitted to LT.MATERIALS AND METHODSBetween September 2012 and May 2014, 8 patients for a total of 13 lesions underwent SABR prior to LT. Inclusion criteria were a pathological or radiological diagnosis of HCC, lesion size ≤6 cm or lesion number ≤3 with a total diameter ≤6 cm, no extrahepatic metastases, Child-Pugh class A-B, ECOG performance status ≤1. Patients were prescribed 36-48 Gy in 3-5 fractions (8 Gy × 5 fractions or

16 Gy × 3 fractions), in 3-5 consecutive days according to clinical and dosimetric decision making. Radiological response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Pathological response was assessed through the rate of tumor necrosis relative to the total tumor volume. Acute and late toxicities were scored using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (CTCAE v 4.0).RESULTSAmong the 13 pathologically evaluated lesions, 8 (61.5 %) lesions had a complete response 2 (15.3 %) had a minimal pathological response and other 2 (15.3 %) showed stable disease. The remaining lesion had a significant pathological response. Maximum detected toxicity included a G2 GGT increase in two patients (at 1 and 3 months respectively). One patient developed a non-classic RILD with a fivefold increase in transaminase enzymes level and a shift in Child-Pugh category from B7 to C10 due to bilirubin increase. Only one modification in the surgical strategy was needed during LT.CONCLUSIONSSABR proved to be a safe and effective local therapy prior to LT in HCC patients. Prospective controlled clinical trials are needed to evaluate its efficacy compared to other local therapies in this setting.

7. Stereotactic ablative radiotherapy in the treatment of hepatocellular carcinoma >3 cm.

Author(s): Guarneri, Alessia; Franco, Pierfrancesco; Trino, Elisabetta; Campion, Daniela; Faletti, Riccardo; Mirabella, Stefano; Gaia, Silvia; Ragona, Riccardo; Diotallevi, Margherita; Saracco, Giorgio; Salizzoni, Mauro; Ricardi, Umberto; Carucci, Patrizia

Source: Medical oncology (Northwood, London, England); Oct 2016; vol. 33 (no. 10); p. 104

Publication Type(s): Journal Article

Abstract: Stereotactic ablative radiotherapy (SABR) is a safe treatment approach for hepatocellular carcinoma (HCC) with comparable results to other local therapies. For lesions larger than 3 cm, no definitive standard treatment is present and several options are available. We retrospectively review local control (LC) and survival results of SABR in patients with HCC lesions >3 cm. Between 2012 and 2015, we treated 29 patients (39 lesions) having histological or radiological diagnosis of HCC and at least one lesion sized >3 cm. Patients were prescribed 36-48 Gy in 3-5 fractions (mainly 16 Gy × 3 fractions or 8 Gy × 5 fractions), in 3-5 consecutive days. A total of 15 lesions (52 %) had complete, while 10 (34 %) had partial remission; 3 (11 %) had a stable disease. Mean time for CR achievement was 5.8 months (range 1-17). One- and two-year actuarial LC was 100 %. Moreover, 1- and 2-year progression-free (PFS), cancer-specific and overall survival were 57.9 % [standard error (SE) 0.09; 95 % CI 36.9-74.2] and 41.2 % (SE 0.12; 95 % CI 17.7-63.5), 80.7 % (SE 0.08; 95 % CI 59.6-91.5) and 63.3 % (SE 0.11; 95 % CI 38.4-80.3), 71.7 % (SE 0.08; 95 % CI 51.2-84.7) and 56.2 % (SE 0.10; 95 % CI 33.8-73.6). On multivariate analysis, achieving a CR within the target lesion had a borderline significance with respect to PFS (HR 0.83; SE = 0.014; z -1.15; p = 0.095; 95 % CI 0.71-7.45). Time between HCC diagnosis and SABR delivery (12 months) was significantly correlated with OS (HR 16.5; SE 21.5; z = 2.14; p = 0.032; 95 % CI 1.27-213.3) as CLIP score (score: 0-1 vs 2) (HR 5.6; SE 4.6; z = 2.10; p = 0.036; 95 % CI 1.11-27.8). A total of 6 major toxic events (G3-G4) were recorded (20 %). In 2 patients (6 %), a radiation-induced liver disease was seen. In conclusion, SABR provided LC and survival rates comparable to other local therapies for patients with HCC lesion sized >3 cm, with acceptable toxicity profile.

8. Ipilimumab with stereotactic ablative radiation therapy: Phase I results and immunologic correlates from peripheral T-cells.

Author(s): Tang, Chad; Welsh, James W; de Groot, Patricia; Massarelli, Erminia; Chang, Joe Y; Hess, Kenneth R; Basu, Sreyashi; Curran, Michael A; Cabanillas, Maria E; Subbiah, Vivek; Fu, Siqing; Tsimberidou, Apostolia M; Karp, Daniel; Gomez, Daniel R; Diab, Adi; Komaki, Ritsuko; Heymach, John V; Sharma, Padmanee; Naing, Aung; Hong, David S

Source: Clinical cancer research : an official journal of the American Association for Cancer Research; Sep 2016

Publication Type(s): Journal Article

Available in full text at Clinical Cancer Research - from Highwire Press

Abstract:PURPOSELittle prospective data is available on clinical outcomes and immune correlates from combination radiation and immunotherapy. We conducted a phase I trial (NCT02239900) testing stereotactic ablative radiation therapy (SABR) with ipilimumab.EXPERIMENTAL DESIGNSABR was given either concurrently (1 day after the first dose) or sequentially (1 week after the second dose) with ipilimumab (3 mg/kg every 3 weeks for 4 doses) to 5 treatment groups: concurrent 50 Gy (in 4 fractions) to liver; sequential 50 Gy (in 4 fractions) to liver; concurrent 50 Gy (in 4 fractions) to lung; sequential 50 Gy (in 4 fractions) to lung; and sequential 60 Gy (in 10 fractions) to lung or liver. Maximum tolerated dose was determined with a 3+3 dose de-escalation design. Immune marker expression was assessed by flow cytometry.RESULTSAmong 35 patients

who initiated ipilimumab, 2 experienced dose-limiting toxicity and 12 (34%) grade 3 toxicity. Response outside the radiation field was assessable in 31 patients. Three patients (10%) exhibited partial response and 7 (23%) experienced clinical benefit (defined as partial response or stable disease lasting {greater than or equal to}6 months). Clinical benefit was associated with increases in peripheral CD8+ T-cells; CD8+/CD4+ T-cell ratio; and proportion of CD8+ T-cells expressing 4-1BB and PD1. Liver (vs. lung) irradiation produced greater T-cell activation, reflected as increases in the proportions of peripheral T-cells expressing ICOS, GITR, and 4-1BB.CONCLUSIONSCombining SABR and ipilimumab was safe with signs of efficacy; peripheral T-cell markers may predict clinical benefit; and systemic immune activation was greater after liver irradiation.

9. Systematic review of patient reported quality of life following stereotactic ablative body radiotherapy for primary and metastatic liver cancer

Author(s): Mutsaers A.; Greenspoon J.; Walker-Dilks C.; Swaminath A.

Source: Radiotherapy and Oncology; Sep 2016; vol. 120

Publication Type(s): Journal: Conference Abstract

Abstract: Purpose: Stereotactic ablative body radiotherapy (SABR) is an emerging modality in patients with liver cancer who are ineligible for other local therapies. It has been shown to be effective with respect to long-term tumour control with minimal toxicity. However SABR for liver cancer is not current standard of practice despite its potential promise. In order to validate increased offering of this promising therapy, objective systematic data regarding impact on quality of life (QOL) is required. No systematic reviews to date have been performed to analyze QOL for primary or metastatic liver cancers. QOL metrics are a critical part of therapy evaluation, particularly in disease states with short life expectancy. The purpose of this study was to conduct a systematic review of evidence surrounding QOL for liver SABR. Methods and Materials: MEDLINE and EMBASE databases from 1996 to October 2015 were queried to obtain English language studies analysing QOL following SABR for liver cancers. Included studies involved patient-reported QOL as either a primary or secondary endpoint, along with analysis of QOL change over time. Studies were screened by three reviewers, while relevant data were abstracted and analyzed by a single reviewer. Results: Of 2181 initially screened studies, five met all inclusion criteria and were analyzed. Extracted study dates ranged from 2008 to 2015, included a total of 388 eligible patients, and 4/5 studies were prospective in design. All were published studies, with the exception of one conference abstract. Studies included patients with hepatocellular carcinoma, liver metastases and intrahepatic cholangiocarcinoma. Extracted studies were heterogeneous in dose prescription used (11-70 Gy in 3 - 30 fractions), as well as in QOL metrics (EORTC QLQ C-15 PAL,/C- 30/LM-21, Euroqol 5D, FACT-Hep, FLIC) and final endpoints (range: six weeks to 12 months). Despite this there were few clinically or statistically significant declines in QOL scores following SABR. Four studies demonstrated increased fatigue transiently in the first 1-4 weeks, while two studies showed transient worsening of appetite at one month; both metrics returned to insignificant difference from baseline by the final endpoints. All studies showed no significant decline in QOL at their respective endpoints. In studies with overlapping QOL tools, estimates of three-month post-SABR global QOL were similar. Conclusions: Results of this systematic review demonstrate wellpreserved post SABR QOL in patients with otherwise untreatable liver cancer, despite heterogeneity amongst the individual studies themselves. These findings merit further research to increase data collection, to validate QOL tools specific to SABR for liver cancers, and to support comparative effectiveness trials of SABR with other local modalities in liver cancer including surgery, chemoembolization and radiofrequency ablation, with a focus on QOL outcomes as an important endpoint.

Radium-223 treatment – prostate & breast metastases

1. An exploratory analysis of alkaline phosphatase, lactate dehydrogenase, and prostate-specific antigen dynamics in the phase 3 ALSYMPCA trial with radium-223.

Author(s): Sartor, O; Coleman, R E; Nilsson, S; Heinrich, D; Helle, S I; O'Sullivan, J M; Vogelzang, N J; Bruland, Ø; Kobina, S; Wilhelm, S; Xu, L; Shan, M; Kattan, M W; Parker, C

Source: Annals of oncology : official journal of the European Society for Medical Oncology; Feb 2017

Publication Type(s): Journal Article

2. Evaluation of bone metastases by 18F-choline PET/CT in a patient with castration-resistant prostate cancer treated with radium-223.

Author(s): Scalzi, Piera; Baiocco, Cinzia; Genovese, Sabrina; Trevisan, Antonella; Sirotova, Zuzana; Poti, Carlo

Source: Urologia; Feb 2017; vol. 84 (no. 1); p. 61-64

Publication Type(s): Journal Article

Abstract:BACKGROUND To date, bone metastases remain the main cause of morbidity and mortality in

patients with metastatic castration-resistant prostate cancer (mCRPC). Therefore, the combination of accurate early detection of bony disease and effective treatment of these lesions is crucial in the management of mCRPC patients, but clinical trials specifically designed to test novel approaches are currently lacking. CASE DESCRIPTION This report describes the case of a 74-year-old male with bone mCRPC and symptomatic and biochemical progression, who underwent radium-223 therapy, following previous treatment failure. 18F-choline positron emission tomography (PET)/computed tomography (CT) was used to assess changes in skeletal tumor activity before and after radium-223. Changes in prostate-specific antigen and alkaline phosphatase were also determined. 18F-choline PET/CT showed that treatment with radium-223 was able to effectively reduce bone metastatic disease, and this was accompanied by an excellent metabolic response. CONCLUSIONS In clinical practice, metabolic assessment of lesions by 18F-choline PET/CT following radium-223 seems a valid approach to monitor treatment response. Until results from clinical trials become available, reporting of single cases relating to data on the use of this technique remains paramount.

3. Bone Health and Bone-targeted Therapies for Prostate Cancer: a Programme in Evidence-based Care - Cancer Care Ontario Clinical Practice Guideline.

Author(s): Alibhai, S M H; Zukotynski, K; Walker-Dilks, C; Emmenegger, U; Finelli, A; Morgan, S C; Hotte, S J; Winquist, E; Cancer Care Ontario Genitourinary Cancer Disease Site Group

Source: Clinical oncology (Royal College of Radiologists (Great Britain)); Feb 2017

Publication Type(s): Journal Article

Abstract:AIMS To make recommendations with respect to bone health and bone-targeted therapies in men with prostate cancer. MATERIALS AND METHODS A systematic review was carried out by searching MEDLINE, EMBASE and the Cochrane Library from inception to January 2016. Systematic reviews and randomised-controlled trials were considered for inclusion if they involved therapies directed at improving bone health or outcomes such as skeletal-related events, pain and quality of life in patients with prostate cancer either with or without metastases to bone. Therapies included medications, supplements or lifestyle modifications alone or in combination and were compared with placebo, no treatment or other agents. Disease-targeted agents such as androgen receptor-targeted and chemotherapeutic agents were excluded. Recommendations were reviewed by internal and external review groups. RESULTS In men with prostate cancer receiving androgen deprivation therapy, baseline bone mineral density testing is encouraged. Denosumab should be considered for reducing the risk of fracture in men on androgen deprivation therapy with an increased fracture risk. Bisphosphonates were effective in improving bone mineral density, but the effect on fracture was inconclusive. No medication is recommended to prevent the development of first bone metastasis. Denosumab and zoledronic acid are recommended for preventing or delaying skeletal-related events in men with metastatic castration-resistant prostate cancer. Radium-223 is recommended for reducing symptomatic skeletal events and prolonging survival in men with symptomatic metastatic castration-resistant prostate cancer. CONCLUSIONS The recommendations represent a current standard of care that is feasible to implement, with outcomes valued by clinicians and patients.

4. Meeting Report From the Prostate Cancer Foundation Scientific Working Group on Radium-223.

Author(s): Miyahira, Andrea K; Morris, Michael; Soule, Howard R; PCF Radium-223 Scientific Working Group

Source: The Prostate; Feb 2017; vol. 77 (no. 3); p. 245-254

Publication Type(s): Journal Article Review

Abstract: The Prostate Cancer Foundation (PCF) convened a Scientific Working Group Meeting on Radium-223 on September 8, 2016, at The Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan Kettering Cancer Center. The meeting was attended by 18 investigators with expertise in radium-223, bone biology, molecular imaging, biomarkers, and prostate cancer clinical trials. The goal of this meeting was to discuss the known and unknown surroundings the therapeutic effects of the bone targeting agent radium-223, in bone metastatic prostate cancer therapy, and to outline the most critical studies needed to improve the clinical use of this agent. Three major topic areas were discussed: (1) the basic science of radium; (2) immuno-adjuvant properties of radium therapy; and (3) high impact clinical trials and correlative science. This article reviews the major topics discussed at the meeting for the purpose of accelerating studies that will improve the use of radium-223 in the treatment of prostate cancer patients.

5. Lymphocyte function following radium-223 therapy in patients with metastasized, castration-resistant prostate cancer

Author(s): Barsegian V.; Mockel D.; Muller S.P.; Bockisch A.; Horn P.A.; Lindemann M.

Source: European Journal of Nuclear Medicine and Molecular Imaging; Feb 2017; vol. 44 (no. 2); p. 242-246

Publication Type(s): Journal: Article

Abstract: Purpose: Therapy with the alpha-emitter radium-223 chloride (223Ra) is an innovative therapeutic option in patients with metastasized, castration-resistant prostate cancer. However, radiotherapy can lead to hematopoietic toxicity. The aim of this study was to determine if 223Ra therapy induces an impairment of cellular antimicrobial immune responses. Methods: In 11 patients receiving 223Ra treatment, lymphocyte proliferation and the production of pro- and anti-inflammatory cytokines (interferon-gamma and interleukin-10) were determined, using lymphocyte transformation testing and ELISpot, respectively. Lymphocyte function after stimulation with mitogens and microbial antigens was assessed prior to therapy and at day 1, 7 and 28 after therapy. Results: Lymphocyte proliferation and the production of interferon-gamma and interleukin-10 towards mitogens and antigens remained unchanged after therapy. Consistent with these in vitro data, we did not observe infectious complications after treatment. Conclusions: The results argue against an impairment of lymphocyte function after 223Ra therapy. Thus, immune responses against pathogens should remain unaffected.

6. A Retrospective Analysis of the First 41 mCRPC Patients with Bone Pain Treated with Radium-223 at the National Institute of Oncology in Hungary.

Author(s): Küronya, Zs; Sinkovics, I; Ágoston, P; Bíró, K; Bodrogi, I; Böde, I; Dank, M; Gyergyay, F; Vajdics, T; Kolonics, Zs; Nagyiványi, K; Rúzsa, Á; Géczi, L

Source: Pathology oncology research : POR; Jan 2017

Publication Type(s): Journal Article

Abstract: Radium-223 dichloride is an alpha-emitting radiopharmaceutical which significantly prolongs overall survival in patients with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases. This was a retrospective analysis of the efficacy and safety of Radium-223 in the first 41 patients treated at a single center in Hungary. Radium-223 was given at a dose of 50 kBq/kg intravenously every 4 weeks for up to 6 cycles. Between 23rd July 2014 and 23rd February 2016, 41 patients were treated. Patient demographics, laboratory values, treatment outcomes and adverse events were collected from medical records. The mean age was 72.2 years (SD: 7.1). 24 patients received Radium-223 as first-line treatment (58%), 7 patients as second (17%), 3 as third (7.3%), 6 as (14.6%), and 1 as fifth-line therapy (2.4%). The mean number of cycles administered was 5.5 (SD: 1.1). The most common side effects were anemia (32% grade 1-3), nausea (28%, grade 1), diarrhea (4%, grade 2), thrombocytopenia (4%, grade 3). The mean baseline PSA level was 307.2 ng/ml (SD: 525.7), which increased to a mean value of 728.5 ng/ml (SD: 1277) by the end of treatment. The baseline mean ALP of 521.1 U/L (SD: 728) decreased to 245.1 U/L (SD: 283.5). The majority of patients experienced a decrease (37%) or complete cessation (43%) of bone pain intensity. In our symptomatic prostate cancer patient population, Radium-223 proved to be efficient in terms of pain relief, with moderate side effects. No PSA response was detected, while alkaline phosphatase levels significantly decreased.

7. Effect of radium-223 dichloride (Ra-223) on hospitalisation: An analysis from the phase 3 randomised Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial.

Author(s): Parker, Christopher; Zhan, Lin; Cislo, Paul; Reuning-Scherer, Jonathan; Vogelzang, Nicholas J; Nilsson, Sten; Sartor, Oliver; O'Sullivan, Joe M; Coleman, Robert E

Source: European journal of cancer (Oxford, England : 1990); Jan 2017; vol. 71 ; p. 1-6

Publication Type(s): Journal Article

Abstract: Symptomatic skeletal events (SSEs) commonly occur in patients with bone metastases, often leading to hospitalisations and decreased quality-of-life. In the ALSYMPCA trial, radium-223 significantly improved overall survival (hazard ratio 0.70, 95% confidence interval [CI] 0.58-0.83, P < 0.001) and prolonged time to first SSE (hazard ratio 0.66, 95% CI 0.52-0.83, P = 0.00037) and subsequent SSE (hazard ratio 0.65, 95% CI 0.51-0.83, P = 0.00039) versus placebo in patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastases. Health care resource use (HCRU), including hospitalisation events and days, were prospectively collected in ALSYMPCA. We assessed health care resource use for the first 12 months post-randomisation. Significantly fewer radium-223 (218/589; 37.0%) versus placebo patients (133/292; 45.5%) had at least one hospitalisation event (P = 0.016). However, mean number of hospitalisation events per patient was similar (radium-223 0.69 versus placebo 0.79, P = 0.226), likely due to the significantly longer follow-up time for radium-223 (7.82 months versus 6.92 months for placebo; P < 0.001). There were significantly fewer hospitalisation days per patient for radium-223 (4.44 versus 6.68, respectively, P = 0.004). The reduction in hospitalisation days with radium-223 was observed both before first SSE (2.35 days

versus 3.36 days, respectively) and after SSE (7.74 days versus 9.19 days, respectively). Our data suggest that this reduced hospital days along with the survival benefit and reduction in time to SSEs with radium-223 treatment may contribute to improvements in health-related quality-of-life in patients with castration-resistant prostate cancer with symptomatic bone metastases (ALSYMPCA ClinicalTrials.gov number, NCT00699751

8. Radium-223 re-treatment from an international, prospective, open-label study in patients with castration-resistant prostate cancer and bone metastases

Author(s): Sartor O.; Heinrich D.; Mariados N.; Mendez Vidal M.J.; Keizman D.; Thellenberg Karlsson C.; Peer A.; Procopio G.; Frank S.J.; Pulkkanen K.J.; Rosenbaum E.; Severi S.; Trigo Perez J.M.; Wagner V.; Garcia-Vargas J.; Li R.; Nordquist L.T.

Source: Annals of Oncology; 2016; vol. 27

Publication Type(s): Journal: Conference Abstract

Available in full text at Annals of Oncology - from Highwire Press

Abstract: Background: Radium-223 (Ra-223) 50 kBq/kg IV (55 kBq/kg after NIST update) every 4 wk x 6 injections (inj) is indicated in symptomatic bone-metastatic castration-resistant prostate cancer (mCRPC) patients (pts) with no visceral metastases (mets). In an international prospective trial in mCRPC pts (NCT01934790), Ra-223 re-treatment (re-tx) after initial 6 inj was well tolerated, with very low radiologic bone progression rates (Sartor. ASCO GU 2016). Reported are safety and total alkaline phosphatase (ALP) and prostate-specific antigen (PSA) dynamics. Methods: All pts had CRPC with bone mets and completed 6 Ra-223 inj with no bone progression during that initial tx. Pts had radiologic or clinical progression after initial Ra-223 tx, and adequate hematologic (heme) values. Pts who started subsequent anticancer tx must have progressed on the last anticancer tx. Concomitant agents (except cytotoxic) were allowed at investigator discretion. Addition of abiraterone and enzalutamide was not allowed during Ra-223 re-tx. Primary end point was safety; exploratory efficacy end points included times to ALP and PSA progression, and ALP and PSA response rates (>30% decline from baseline). Results: Of 44 Ra-223 re-tx pts, 29 (66%) received all 6 inj. Median time from last inj of initial Ra-223 tx was 6 mo. There were no marked alterations in tx-emergent adverse event (TEAE) incidence vs ALSYMPCA (Table) and no grade 4 or 5 heme TEAEs; 3 (7%) re-tx pts had grade 3 or 4 tx-related TEAEs. Maximum follow-up times for ALP and PSA progression were 12.8 and 11.4 mo, respectively. Median time to ALP progression was not reached. Median time to PSA progression was 2 mo. ALP and PSA response rates at wk 12, 24, and any time before database cutoff are reported (Table). ALP, PSA, and heme lab values will be reported. Conclusions: Ra-223 re-tx was well tolerated, with minimal heme toxicity and ALP and PSA profiles similar to those of ALSYMPCA.

9. Radium-223 with concomitant bone-targeting agents in metastatic castration-resistant prostate cancer (CRPC) patients treated in an international early access program (EAP)

Author(s): Saad F.; Heidenreich A.; Heinrich D.; Keizman D.; O'Sullivan J.M.; Carles J.; Wirth M.; Miller K.; Gratt J.; Seger-Van Tol M.; Nilsson S.; Gillessen S.

Source: Annals of Oncology; 2016; vol. 27

Publication Type(s): Journal: Conference Abstract

Available in full text at Annals of Oncology - from Highwire Press

Abstract: Background: The bone-targeting agents (BTAs) denosumab and bisphosphonates (BPs) are widely used in the supportive care of patients (pts) with CRPC and bone metastases.We present data on pts treated with radium-223 dichloride (Ra-223) with or without a concomitant BTA in an international EAP. Methods: This was a prospective single-arm phase IIIb study of CRPC pts with symptomatic or asymptomatic bone metastases (no visceral disease) recruited from 14 countries. Pts received Ra-223 50 kBq/kg [55 kBq/kg after NIST update] (iv injection) every 4 weeks for 6 cycles. Co-primary endpoints were safety and overall survival (OS). Exploratory analyses investigated the effects of concomitant denosumab (no BPs) or BPs (no denosumab) on OS and symptomatic skeletal events (SSE). Results: 696 pts received at least one Ra-223 cycle. Of those, 127 (18%) pts were treated with concomitant denosumab (no BPs) and 435 (63%) without concomitant BTAs. Key baseline characteristics are reported in pts treated with Ra-223 with or without a concomitant BTA (Table). Median OS (mOS) and median time to first SSE (mSSE) were longer in pts treated with Ra-223 and denosumab versus pts without a concomitant BTA (Table). While key baseline characteristics in pts treated with Ra-223 and denosumab were similar to pts treated with Ra-223 and BPs (no denosumab, 125 [18%] of 696), adding BPs to Ra-223 did not appear to improve mOS. However, mSSE was prolonged in pts receiving Ra-223 and BPs versus pts who received Ra-223 without a concomitant BTA (Table). Conclusions: In this EAP, pts treated with Ra-223 and a concomitant BTA appeared to have longer time to first SSE than those treated without a concomitant

BTA. However, improvement in OS with a BTA was observed with denosumab but not with BPs. Prospective randomized controlled studies are required to confirm the benefit of this specific treatment combination in metastatic CRPC.

10. Changes in alkaline phosphatase (ALP) dynamics and overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC) patients treated with radium-223 in an international early access program (EAP)

Author(s): Heinrich D.; Gillessen S.; Heidenreich A.; Keizman D.; O'Sullivan J.M.; Carles J.; Wirth M.; Miller K.; Procopio G.; Gratt J.; Seger-Van Tol M.; Nilsson S.; Saad F.

Source: Annals of Oncology; 2016; vol. 27

Publication Type(s): Journal: Conference Abstract

Available in full text at Annals of Oncology - from Highwire Press

Abstract: Background: Identifying a reliable marker of efficacy for radium-223 dichloride (Ra-223) would aid in the clinical management of mCRPC patients (pts). In exploratory analyses of mCRPC pts with symptomatic bone metastases treated with Ra-223 in the ALSYMPCA trial, OS was significantly longer in pts with a confirmed decline in ALP levels from baseline at week 12, compared with pts without a confirmed ALP decline. Here, we present data on ALP dynamics and OS and time to first symptomatic skeletal event (SSE) in pts treated with Ra-223 in an international EAP. Methods: This was a prospective single-arm phase IIIb study of CRPC pts with symptomatic or asymptomatic bone metastases (no visceral disease) recruited from 14 countries. Pts received Ra-223 50 kBq/kg (55 kBq/kg after NIST update) iv, every 4 weeks for up to 6 cycles. Co-primary endpoints were safety and OS. Exploratory analyses investigated whether a confirmed decline (any magnitude) in ALP levels was associated with OS and time to first SSE. Results: 696 pts received at least one Ra-223 cycle. Of those, 398 (57%) pts had a confirmed decline in ALP and 298 (43%) had no confirmed ALP decline. Key baseline characteristics are shown (Table). More pts with a confirmed ALP decline (374, 94%) received 5-6 Ra-223 injections than those with no ALP decline (99, 33%). Hazard ratios (HR) for confirmed ALP decline at week 12 vs no decline suggest a strong association of ALP decline with both longer OS (HR 0.299, 95% CI 0.227-0.395) and longer time to first SSE (HR 0.474, 95% CI 0.340-0.662) (Table). Conclusions: In this EAP, which is relevant for pts currently treated in clinical practice, decline in ALP was associated with longer OS and time to first SSE.

11. A phase 2 randomized, double-blind, placebo-controlled trial of radium-223 dichloride with exemestane and everolimus in patients with HER2-negative hormone receptor-positive breast cancer and bone metastases

Author(s): Rugo H.; Petrenciuc O.; Zhang A.; Li R.; Coleman R.E.

Source: Annals of Oncology; 2016; vol. 27

Publication Type(s): Journal: Conference Abstract

Available in full text at Annals of Oncology - from Highwire Press

Abstract: Background: Treatment options for bone-dominant metastatic breast cancer (MBC) are limited. Radium-223 (Ra-223), a first-in-class alpha emitter with a targeted antitumor effect on bone metastases (mets), was well tolerated and reduced bone biomarker levels in a phase 2 study in patients with bone-dominant MBC (Coleman et al. Breast Cancer Res Treat 2014). In patients with HER2- estrogen receptor+ (ER+) bone-dominant MBC, everolimus + exemestane (EVE + EXE) improved progression-free survival (PFS) versus EXE alone. Ra-223 plus EVE + EXE may improve outcomes in patients with HER2- ER+ bone-dominant MBC; this trial will evaluate efficacy and safety of Ra-223 versus placebo in these patients (NCT02258451). Trial design: Eligible patients are pre- or postmenopausal with HER2- ER+ MBC and > 2 bone or soft tissue mets. Patients must have measurable disease per RECIST v1.1, > 1 prior line of hormone therapy for MBC, and 1-2 prior skeletal-related events; be on bisphosphonates or denosumab; and have an ECOG score of 0-1. Patients must have had no past or current need for chemotherapy for MBC, no unresolved spinal cord compression, and no prior EVE treatment. Patients are randomized to receive (1:1) Ra-223 (50 kBq/kg [55 kBq/kg after National Institute of Standards and Technology update] IV) or placebo x 6 cycles q 4 wk plus EXE (25 mg PO q d) + EVE (10 mg PO q d) plus best supportive care. EXE + EVE continues until disease progression or unacceptable toxicity. Stratification is by geographic region (EU/N Amer vs Asia), prior hormone therapy (1 vs > 2), and presence of visceral disease (yes vs no). Safety and efficacy are assessed every 4 weeks. Long-term safety is assessed until study termination. The primary end point is symptomatic skeletal event-free survival (SSE-FS). Secondary end points are overall survival; times to opiate use, pain progression, and chemotherapy; radiologic PFS; and safety. Assuming a 1-sided alpha of 0.1, 90% power, ~ 160 SSE-FS events will be required for the

analysis. Efficacy will be analyzed by a stratified log-rank test. Safety analysis will be descriptive.

12. Radium-223 Therapy for Patients with Metastatic Castrate-Resistant Prostate Cancer: An Update on Literature with Case Presentation

Author(s): Nguyen N.C.; Shah M.; Mountz J.M.; Appleman L.J.; Parikh R.

Source: International Journal of Molecular Imaging; 2016; vol. 2016

Publication Type(s): Journal: Review

Available in full text at International Journal of Molecular Imaging - from ProQuest

Abstract: Background and Purpose. Radium-223 dichloride (Xofigo, Bayer HealthCare Pharmaceuticals Inc.) is the first alpha-particle emitter therapeutic agent approved by the FDA, with benefits in overall survival and delay in symptomatic skeletal event for patients with metastatic castrate-resistant prostate cancer (CRPC). Recent post hoc analyses of the phase III ALSYMPCA trial support the previously established safety profile as well as therapeutic effect and clinical outcome of Radium-223. Currently, Radium-223 is approved as a single agent therapy for metastatic CRPC. Clinical trials are currently investigating Radium-223 in additional clinical settings such as earlier asymptomatic disease and in combination with other agents including hormonal therapeutic agents and immunotherapeutic as well as chemotherapeutic agents. Trials are also ongoing in patients with other primary cancers such as breast cancer, thyroid cancer, and renal cancer metastatic to bone. In this article, the physics and radiobiology, as well as a literature update on the use of Radium-223, are provided along with case presentations, aiming at a better appreciation of research data as well as the assimilation of research data into clinical practice.

13. Sublethal exposure to alpha radiation (223Ra dichloride) enhances various carcinomas' sensitivity to lysis by antigen-specific cytotoxic T lymphocytes through calreticulin-mediated immunogenic modulation.

Author(s): Malamas, Anthony S; Gameiro, Sofia R; Knudson, Karin M; Hodge, James W

Source: Oncotarget; Dec 2016; vol. 7 (no. 52); p. 86937-86947

Publication Type(s): Journal Article

Abstract: Radium-223 dichloride (Xofigo®; 223Ra) is an alpha-emitting radiopharmaceutical FDA-approved for the treatment of bone metastases in patients with advanced castration-resistant prostate cancer. It is also being examined clinically in patients with breast and lung carcinoma and patients with multiple myeloma. As with other forms of radiation, the aim of 223Ra is to reduce tumor burden by directly killing tumor cells. External beam (photon) and proton radiation have been shown to augment tumor sensitivity to antigen-specific CD8+ cytotoxic T lymphocytes (CTLs). However, little is known about whether treatment with 223Ra can also induce such immunogenic modulation in tumor cells that survive irradiation. We examined these effects in vitro by exposing human prostate, breast, and lung carcinoma cells to sublethal doses of 223Ra. 223Ra significantly enhanced T cell-mediated lysis of each tumor type by CD8+ CTLs specific for MUC-1, brachyury, and CEA tumor antigens. Immunofluorescence analysis revealed that the increase in CTL killing was accompanied by augmented protein expression of MHC-I and calreticulin in each tumor type, molecules that are essential for efficient antigen presentation. Enhanced tumor-cell lysis was facilitated by calreticulin surface translocation following 223Ra exposure. The phenotypic changes observed after treatment appear to be mediated by induction of the endoplasmic reticulum stress response pathway. By rendering tumor cells more susceptible to T cell-mediated lysis, 223Ra may potentially be effective in combination with various immunotherapies, particularly cancer vaccines that are designed to generate and expand patients' endogenous antigen-specific T-cell populations against specific tumor antigens.

14. Clinical Correlates of Benefit From Radium-223 Therapy in Metastatic Castration Resistant Prostate Cancer.

Author(s): Alva, Ajjai; Nordquist, Luke; Daignault, Stephanie; George, Saby; Ramos, Jorge; Albany, Costantine; Isharwal, Sudhir; McDonald, Matthew; Campbell, Gregory; Danchaivijitr, Pongwut; Yentz, Sarah; Anand, Aseem; Yu, Evan Y

Source: The Prostate; Dec 2016

Publication Type(s): Journal Article

Abstract:BACKGROUND We sought to identify potential clinical variables associated with outcomes after radium-223 therapy in routine practice. METHODS Consecutive non-trial mCRPC patients who received ≥1 dose of radium dichloride-223 at four academic and one community urology-specific cancer centers from May 2013 to June 2014 were retrospectively identified. Association of baseline and on-therapy clinical variables with

number of radium doses received and clinical outcomes including overall survival were analyzed using chi-square statistics, cox proportional hazards, and Kaplan-Meier methods. Bone Scan Index (BSI) was derived from available bone scans using EXINI software. RESULTS One hundred and forty-five patients were included. Radium-223 was administered for six cycles in 74 patients (51%). One-year survival in this heavily pre-treated population was 64% (95%CI: 54-73%). In univariate and multivariate analysis, survival was highly associated with receiving all six doses of Radium-223. Receipt of six doses was associated with ECOG PS of 0-1, lower baseline PSA & pain level, no prior abiraterone/enzalutamide, <5 BSI value, and normal alkaline phosphatase. In patients who reported baseline pain (n = 72), pain declined in 51% after one dose and increased in 7%. PSA declined ≥50% in 16% (18/110). Alkaline phosphatase declined ≥25% in 48% (33/69) and ≥50% in 16/69 patients. BSI declined in 17 (68%) of the 25 patients who had bone scan available at treatment follow-up. Grade ≥3 neutropenia, anemia, and thrombocytopenia occurred in 4% (n = 114), 4% (n = 125), and 5% (n = 123), respectively. CONCLUSIONS Patients earlier in their disease course with <5 BSI, low pain score, and good ECOG performance status are optimal candidates for radium-223. Radium-223 therapy is well tolerated with most patients reporting declines in pain scores and BSI.

15. Acute Promyelocytic Leukemia After Treatment of Metastatic Castration-Resistant Prostate Cancer With Radium-223

Author(s): Odo U.; Vasudevamurthy A.K.; Sartor O.

Source: Clinical Genitourinary Cancer; Dec 2016

Publication Type(s): Journal: Article In Press

16. Radium-223 Therapy of Bone Metastases in Prostate Cancer.

Author(s): Nilsson, Sten

Source: Seminars in nuclear medicine; Nov 2016; vol. 46 (no. 6); p. 544-556

Publication Type(s): Journal Article Review

Abstract: Metastatic castration-resistant prostate cancer frequently metastasizes to the bone, often resulting in painful skeletal events, reduced quality of life, and reduced survival. Radium-223 is a first-in-class alpha-emitting radiopharmaceutical that has proven to prolong overall survival, delay time to symptomatic skeletal events, and improve quality of life in patients with castration-resistant prostate cancer and symptomatic bone metastases and no visceral metastases. Radium-223 provides survival benefit to patients with castration-resistant prostate cancer and symptomatic bone metastases, regardless of prior docetaxel use. This article gives an overview of the development of radium-223 from the first-in-human trial to current status.

17. Efficacy and Safety of Radium-223 Dichloride in Symptomatic Castration-resistant Prostate Cancer Patients With or Without Baseline Opioid Use From the Phase 3 ALSYMPCA Trial.

Author(s): Parker, Christopher; Finkelstein, Steven E; Michalski, Jeff M; O'Sullivan, Joe M; Bruland, Øyvind; Vogelzang, Nicholas J; Coleman, Robert E; Nilsson, Sten; Sartor, Oliver; Li, Rui; Seger, Monica A; Bottomley, David

Source: European urology; Nov 2016; vol. 70 (no. 5); p. 875-883

Publication Type(s): Journal Article

Abstract: The phase 3 ALSYMPCA trial enrolled metastatic castration-resistant prostate cancer patients with or without baseline opioid use. To assess the efficacy and safety of radium-223 dichloride (radium-223) versus placebo in ALSYMPCA patients by baseline opioid use. Nine hundred and twenty one patients enrolled at 136 centers globally. Radium-223 (50 kBq/kg, intravenous injection) every 4 wk for six cycles or matching placebo, each plus best standard of care. Primary endpoint (overall survival [OS]), main secondary efficacy endpoints, and safety were evaluated by baseline opioid use. Additional analyses included time to first opioid use, time to first external beam radiation therapy for bone pain, and safety of concomitant external beam radiation therapy. At baseline, 408 (44%) patients had no pain and no analgesic use or mild pain with nonopioid therapy (World Health Organization ladder pain score 0-1 [nonopioid subgroup]), and 513 (56%) had moderate pain with occasional opioids or severe pain with regular daily opioids (World Health Organization ladder pain score 2-3 [opioid subgroup]). Radium-223 significantly prolonged OS versus placebo in nonopioid (hazard ratio [HR]=0.70; 95% confidence interval [CI]: 0.52-0.93; p=0.013) and opioid (HR=0.68; 95% CI: 0.54-0.86; p=0.001) subgroups, and significantly reduced risk of symptomatic skeletal events versus placebo, regardless of baseline opioid use (nonopioid subgroup: HR=0.56, 95% CI: 0.39-0.82, p=0.002; opioid subgroup: HR=0.72, 95% CI: 0.53-0.98, p=0.038). Time to first opioid use for bone pain was significantly delayed with radium-223

versus placebo (HR=0.62, 95% CI: 0.46-0.85, p=0.002). Adverse event incidences were similar between opioid subgroups. Radium-223 versus placebo significantly prolonged OS and reduced symptomatic skeletal event risk with a favorable safety profile in castration-resistant prostate cancer patients with symptomatic bone metastases, regardless of baseline opioid use. In this ALSYMPCA opioid subgroup analysis, baseline symptom levels did not appear to impact radium-223 dichloride efficacy or safety.

18. Radium-223: Insight and perspectives in bone-metastatic castration-resistant prostate cancer

Author(s): Buroni F.E.; Persico M.G.; Lodola L.; Aprile C.; Pasi F.; Nano R.

Source: Anticancer Research; Nov 2016; vol. 36 (no. 11); p. 5719-5730

Publication Type(s): Journal: Review

Abstract:223Ra prolongs overall survival in symptomatic patients affected by multiple bone-metastatic castration-resistant prostatic cancer, without visceral or nodal involvement. However, many questions remain about its mechanisms of action, and its use in clinical practice is still unresolved. First of all, what is the main target of alpha-particle emission, that is, in what way does it influences the tumor microenvironment? When is the best timing in the course of the disease, extending its use to asymptomatic low-volume or even to the micrometastatic phase? What are suitable biomarkers to be employed as prognostic factors and response indicators? Which associations with other drugs and their sequence can offer the best results, and is their effect additive or synergistic? Ultimately, in the current climate of spending review, what is the optimal cost and benefit ratio regarding available treatments? In this review, we tried to answer these questions by analyzing the available scientific literature.

19. Radium-223 and metastatic castration-resistant prostate cancer: All that glitters is not gold.

Author(s): Aprile, Carlo; Persico, Marco G; Lodola, Lorenzo; Buroni, Federica E

Source: World journal of radiology; Oct 2016; vol. 8 (no. 10); p. 816-818

Publication Type(s): Journal Article Review

Available in full text at World Journal of Radiology - from National Library of Medicine

Abstract: After being approved by the National Drug Agency in several countries, Radium-223 (Ra-223) is gaining wide acceptance in the treatment of bone metastatic castration resistant prostate cancer. The exact mechanism of action remain unclear: The established model of direct alpha-particle irradiation from the remodelling bone surface, where Ra-223 accumulates, surrounding the tumor foci can explain a lethal effect only on metastatic microdeposits, but not on higher tumor burden. According to the "pre-metastatic niche model", it is likely that Ra-223 targets several non-tumoral cell types of the tumor microenvironment involved in the complex mechanism of cancer bone homing and colonization. A deeper insight into this hypothetical mechanism will lead to a more accurate dosimetric approach and to find optimal sequencing and/or combination with the other therapeutic options.

20. Radium-223 in Heavily Pretreated Metastatic Castrate-Resistant Prostate Cancer.

Author(s): Modi, Dipenkumar; Hwang, Clara; Mamdani, Hirva; Kim, Seongho; Gayar, Hesham; Vaishampayan, Ulka; Joyrich, Richard; Heath, Elisabeth I

Source: Clinical genitourinary cancer; Oct 2016; vol. 14 (no. 5); p. 373

Publication Type(s): Journal Article

Abstract: Radium-223 is a bone-targeting radiopharmaceutical that extends survival in mCRPC. Postapproval data are limited, and the value of biochemical and radiologic monitoring during radium therapy is unknown. We conducted a retrospective study of 29 patients with mCRPC who received radium-223 at 1 of 3 participating institutions between August 2013 and December 2014. Trend of PSA, radiographic changes, and association of biochemical and clinical variables with PSA trend were measured. The median age of patients was 70 years, 79% of patients (N = 23) were European Americans, and 17% of patients (N = 5) were African Americans. Twenty patients (69%) had received at least 3 lines of prior therapies. Some 38% of patients (N = 11) received all 6 cycles of radium-223. Twenty patients (69%) had an increase in PSA during radium therapy, and 4 patients (14%) had a decline in PSA levels. Five patients had visceral metastases on computed tomography imaging performed during the course of radium-223. Radium therapy in mCRPC was associated with an increase in PSA in the majority of these heavily pretreated patients. The development of visceral disease was not uncommon, suggesting a need for follow-up computed tomography monitoring during radium-223 therapy. The significance of early increases in PSA and pain with radium-223 is still uncertain. Although pain and PSA flare have been reported in patients who subsequently have a dramatic response to therapy, we observed that a PSA increase or

pain flare correlates to an improvement in bone scans only in a minority of patients.

21. 68Ga-PSMA-11 PET as a gate-keeper for the treatment of metastatic prostate cancer with radium-223: proof of concept.

Author(s): Ahmadzadehfar, Hojjat; Azgomi, Kambiz; Hauser, Stefan; Wei, Xiao; Yordanova, Anna; Gaertner, Florian; Kürpig, Stefan; Strunk, Holger; Essler, Markus

Source: Journal of nuclear medicine : official publication, Society of Nuclear Medicine; Sep 2016

Publication Type(s): Journal Article

Abstract: We retrospectively evaluated the utility of 68Ga-PSMA-11 PET for planning 223RaCl2 therapy of patients with metastatic prostate cancer and its impact on the therapeutic response as determined by PSA and ALP, as well as the correlation of PSA changes with the results of PSMA-PET, follow-up scans. Sixty-three patients with a median age of 73 years who underwent a total of 307 cycles of therapy with 223RaCl2 were analyzed. In thirty-one patients bone scans and radiological imaging was performed for pre therapeutic imaging (group 1). In 32 patients bone scans and PSMA-PET were performed before therapy (group 2). Patients with small lymph node metastases as well as local recurrence were not excluded from treatment consistent with current guidelines. PSA and ALP were measured prior to each treatment cycle and 4 weeks after the final cycle. Thirteen patients from group 2, who received a second PSMA-PET as a follow-up scan, were evaluated to determine the significance of PSA changes as a follow-up marker. In group 1, four patients (12.9%) showed a PSA decline, of whom 2 patients and 1 patient showed a PSA decline > 30% and > 50%, respectively. In contrast, in group 2, 14 patients (43.8%) showed a PSA decline, of whom 10 and 8 patients showed a decline > 30% and > 50%; respectively (P = 0.007). Thirty-seven patients had a high ALP level (19 from group 1 and 18 from group 2). Twelve (63.2%) and 16 (88.9%) patients of group A and B, respectively, showed an ALP decline. This difference was not significant; however, 7 (36%) and 13 (72.2%) patients in group 1 and 2, respectively, showed an ALP decline > 30% (P = 0.04). Considering any ALP decline as a response, no patient with increasing ALP showed a PSA response (P = 0.036). There was a significant correlation between the PSA changes and the therapeutic response according to follow-up PSMA-PET. Using PSMA-PET as the gatekeeper, radionuclide therapy with 223Ra may be more effective and have more success regarding changes in the PSA. An increase in PSA during therapy cycles occurs due to disease progression.

22. Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial.

Author(s): Saad, Fred; Carles, Joan; Gillessen, Silke; Heidenreich, Axel; Heinrich, Daniel; Gratt, Jeremy; Lévy, Jérémy; Miller, Kurt; Nilsson, Sten; Petrenciuc, Oana; Tucci, Marcello; Wirth, Manfred; Federhofer, Judith; O'Sullivan, Joe M; Radium-223 International Early Access Program Investigators

Source: The Lancet. Oncology; Sep 2016; vol. 17 (no. 9); p. 1306-1316

Publication Type(s): Journal Article

Abstract: In the previously reported ALSYMPCA trial in patients with castration-resistant prostate cancer and symptomatic bone metastases, overall survival was significantly longer in patients treated with radium-223 dichloride (radium-223) than in patients treated with placebo. In this study, we investigated safety and overall survival in radium-223 treated patients in an early access programme done after the ALSYMPCA study and before regulatory approval of radium-223. We did an international, prospective, interventional, open-label, single-arm, phase 3b study. Enrolled patients were aged 18 years or older with histologically or cytologically confirmed progressive bone-predominant metastatic castration-resistant prostate cancer with two or more skeletal metastases on imaging (with no restriction as to whether they were symptomatic or asymptomatic; without visceral disease but lymph node metastases were allowed). Patients received intravenous injections of radium-223, 50 kBq/kg (current recommendation 55 kBq/kg after implementation of National Institute of Standards and Technology update on April 18, 2016) every 4 weeks for up to six injections. Other concomitant anticancer therapies were allowed. Primary endpoints were safety and overall survival. The safety and efficacy analyses were done on all patients who received at least one dose of the study drug. The study has been completed, and we report the final analysis here. This study is registered with ClinicalTrials.gov, number NCT01618370, and the European Union Clinical Trials Register, EudraCT number 2012-000075-16. Between July 22, 2012, and Dec 19, 2013, 839 patients were enrolled from 113 sites in 14 countries. 696 patients received one or more doses of radium-223; 403 (58%) of these patients had all six planned injections. Any-grade treatment-emergent adverse events occurred in 523 (75%) of 696 patients; any-grade treatment-emergent adverse events deemed to be related to treatment were reported in 281 (40%) patients. The most common grade

3 or worse treatment-related treatment-emergent adverse events were anaemia in 32 (5%) patients, thrombocytopenia in 15 (2%) patients, neutropenia in ten (1%) patients, and leucopenia in nine (1%) patients. Any grade of serious adverse events were reported in 243 (35%) patients. Median follow-up was 7·5 months (IQR 5-11) and 210 deaths were reported; median overall survival was 16 months (95% CI 13-not available [NA]). In an exploratory analysis of overall survival with predefined factors, median overall survival was longer for: patients with baseline alkaline phosphatase concentration less than the upper limit of normal (ULN; median NA, 95% CI 16 months-NA) than for patients with an alkaline phosphatase concentration equal to or greater than the ULN (median 12 months, 11-15); patients with baseline haemoglobin levels 10 g/dL or greater (median 17 months, 14-NA) than for patients with haemoglobin levels less than 10 g/dL (median 10 months, 8-14); patients with a baseline Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 (median NA, 17 months-NA) than for patients with an ECOG PS of 1 (median 13 months, 11-NA) or an ECOG PS of 2 or more (median 7 months, 5-11); and for patients with no reported baseline pain (median NA, 16 months-NA) than for those with mild pain (median 14 months, 13-NA) or moderate-severe pain (median 11 months, 9-13). Median overall survival was also longer in patients who received radium-223 plus abiraterone, enzalutamide, or both (median NA, 95% CI 16 months-NA) than in those who did not receive these agents (median 13 months, 12-16), and in patients who received radium-223 plus denosumab (median NA, 15 months-NA) than in patients who received radium-223 without denosumab (median 13 months, 12-NA). Our findings show that radium-223 can be safely combined with abiraterone or enzalutamide, which are now both part of the standard of care for patients with metastatic castration-resistant prostate cancer. Furthermore, our findings extend to patients who were asymptomatic at baseline, unlike those enrolled in the pivotal ALSYMPCA study. The findings of prolonged survival in patients treated with concomitant abiraterone, enzalutamide, or denosumab require confirmation in prospective randomised trials.

23. The safety and efficacy of radium-223 dichloride for the treatment of advanced prostate cancer.

Author(s): Wilson, James M; Parker, Christopher

Source: Expert review of anticancer therapy; Sep 2016; vol. 16 (no. 9); p. 911-918

Publication Type(s): Journal Article

Abstract:A number of drugs have been shown to extend life expectancy in castration-resistant prostate cancer (CRPC). Skeletal related events (SREs) secondary to bone metastases cause significant morbidity for men with CRPC. The α-emitting radiopharmaceutical radium-223 dichloride has been shown to improve overall survival, time to symptomatic skeletal events (SSEs) and quality of life in CRPC. The development of radium-223 from pre-clinical studies to the evidence of efficacy and safety from a phase 3 trial is discussed as well as its pharmacokinetics and metabolism. The integration of radium-223 into routine care for patients with advanced prostate cancer is included including a comparison with other agents in this setting. Expert commentary: The risk/benefit ratio for radium-223 is very similar to that of other agents used in the CRPC setting and is a treatment option for men unsuitable for cytotoxic chemotherapy because of comorbidities. The ALSYMPCA trial demonstrated an improvement in SSEs with radium-223. This is a clinically relevant end-point as not all radiologically-detected SREs are apparent to patients. The correct sequencing of the life-prolonging treatments available to men with CRPC is subject to debate. Radium-223 therapy should be considered before the development of visceral metastases. Drug-combination studies are underway.

24. Radium-223 dichloride in clinical practice: a review.

Author(s): Florimonte, Luigia; Dellavedova, Luca; Maffioli, Lorenzo Stefano

Source: European journal of nuclear medicine and molecular imaging; Sep 2016; vol. 43 (no. 10); p. 1896-1909

Publication Type(s): Journal Article Review

Abstract: The onset of skeletal metastases is typical of advanced-stage prostate cancer and requires a multidisciplinary approach to alleviate bone pain and try to delay disease progression. The current therapeutic armamentarium includes conventional analgesics, chemotherapeutic agents, immunotherapy, androgen-deprivation therapy, osteoclast inhibitors (bisphosphonates, denosumab), surgical interventions, external-beam radiotherapy and radionuclide metabolic therapy. Many studies in recent decades have demonstrated the efficacy of various radiopharmaceuticals, including strontium-89 and samarium-153, for palliation of pain from diffuse skeletal metastases, but no significant benefit in terms of disease progression and overall survival has been shown. The therapeutic landscape of metastatic skeletal cancer significantly changed after the introduction of radium-223, the first bone-homing radiopharmaceutical with disease-modifying properties. In this paper we extensively review the literature on the use of radium-223 dichloride in metastatic castration-resistant prostate cancer.

Exercise: Sensitivity and Specificity

Sensitivity:
If a person has a disease, how often will the test be positive (true positive rate)?

If the test is highly sensitive and the test result is negative you can be nearly certain that they don't have disease.

Specificity:
If a person does not have the disease how often will the test be negative (true negative rate)?

If the test result for a highly specific test is positive you can be nearly certain that they actually have the disease.

Quick Quiz:

1. **A very sensitive test, when negative, helps you:**
   a: Rule-in disease
   b: Rule-out disease
   c: Confuse medical students
   d: Save money

2. **A test which is highly specific, when positive, helps you:**
   a: Rule-in disease
   b: Rule-out disease
   c: Confuse medical students
   d: Save money

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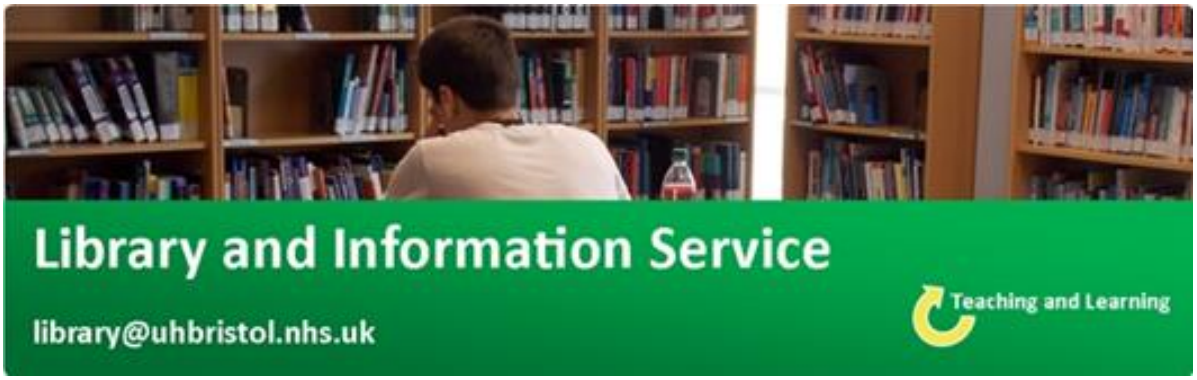
Answers: 1b; 2a



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