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A systematic review examining clinical markers and biomarkers of analgesic response to radiotherapy for cancer-induced bone pain

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ABSTRACT

Introduction: Cancer frequently spreads to bone, causing cancer-induced bone pain (CIBP) which affects quality of life. The best treatment is radiotherapy (XRT), but response is variable. The aim of this systematic review was to identify factors that predict analgesic response.

Materials and methods: Using PRISMA guidelines, Medline (1946–2018), Embase Classic + Embase (1947–2018) and Cochrane (setup-2018) databases were searched. Eligible studies examined adult patients receiving external beam XRT for CIBP with clinical marker and/or biomarkers evaluated.

Results: Twenty-one studies (n = 4490) were included: Urinary markers in three studies (n = 357), genomic biomarkers in one study (n = 107), imaging techniques in five studies (n = 231) and demographics and disease parameters in eight studies (n = 4572). Quantitative sensory testing (n = 23) and physical activity and/or gait (n = 42) have been examined in one study each, while two studies have evaluated grade of spinal instability (n = 276).

Conclusion: No predictors of analgesic response from XRT in CIBP were identified but several show promise.

1. Introduction

A consequence of the increasing number of patients being diagnosed and living with cancer is that more patients also live with disseminated disease. These patients will often need palliative care input at some point in their disease trajectory, resulting in an increased burden on palliative care services. Of all organs primary cancers spread to, bone is one of the most common. Bone metastases are associated with pain in up to 50% of patients, termed cancer-induced bone pain (CIBP). (Coleman, 1997, 2006; Mercadante, 1997) CIBP adversely affects quality of life, therefore treatment of CIBP is of great importance. (Cramarossa et al., 2013)

The gold standard treatment for CIBP is radiotherapy (XRT) (Colvin and Fallon, 2008), however only up to 24% of patients treated with XRT for CIBP experience complete pain relief. (Rich et al., 2018) The remaining 76% of patients will get some or no pain relief. The ability to stratify patients likely to experience a pain relieving effect from XRT may have implications for clinical practice. Patients who are likely to benefit from XRT could be prioritised, whereas those less likely to benefit, could have additional support from palliative care specialists to improve their pain management in other ways, and avoid unnecessary side-effects and the additional hospital visits that XRT can involve.

Different factors for predicting what patients respond to XRT for CIBP have been explored, but these have not been compared. Therefore the aim of this systematic review was to identify and compare clinical markers and biomarkers which predict analgesic response to XRT for CIBP.

2. Materials and methods

Ethical approval was not required for this study. A comprehensive systematic review using the PRISMA guidelines was conducted. (Moher et al., 2009) Detailed searches were carried out in Medline (1946 - April Week 2 2018), Embase Classic + Embase (1947–2018 week 15) and Cochrane (setup – 16.04.18). Keywords and subject headings used were “neoplasms”, “cancer”, “tumour”, “bone neoplasms”, “bone metastases”, “pain”, “radiotherapy”, “biomarkers” and “predictor”. The full search strategy is outlined in Appendix A. In addition, reference lists were manually searched for relevant publications.

Following the literature search, the titles of all studies were reviewed and studies deemed not relevant were excluded. Eligible studies reported on adult patients with cancer and bone metastases, receiving external beam XRT for CIBP, clinical marker and/or biomarker that was assessed in relation to analgesic response to XRT. Studies examining pain response after different radiation doses were not included, as this topic has been thoroughly discussed elsewhere. (Rich et al., 2018)

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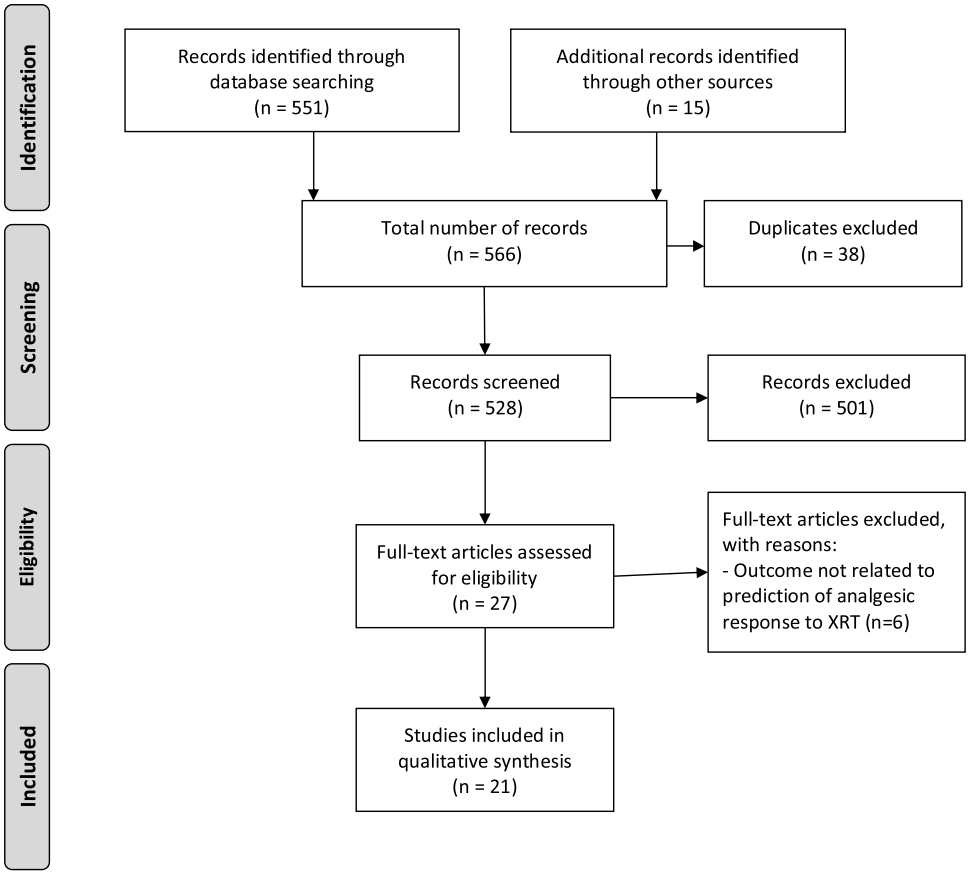

Fig. 1. PRISMA flow diagram.

Studies not in the English language, studies on hemi-body-, radiopharmaceutical- or stereotactic radiation therapy, and case reports were also excluded.

The abstracts of all remaining studies were then reviewed, and again non-relevant studies were excluded. Subsequently full text studies were retrieved and evaluated. The content and quality of the included studies were assessed by two authors independently (KG and TS). Factors evaluated included study design; possible study limitations; participants; setting and results. A formal meta-analysis was not feasible because of the heterogeneity of patient cohorts and outcome definitions.

3. Results

The literature search and appraisal process are shown in Fig. 1. A total of 551 studies were retrieved. The additional hand-searching of papers from reference lists revealed another 15 studies, making 566 studies in total. Removal of 38 duplicates left 528 studies for further evaluation. Table 1 details the twenty-one studies that were included after abstracts and full texts had been evaluated. (Hoskin et al., 2000; Chow et al., 2009, 2015; Adli et al., 2013; Zhao et al., 2015; Reginelli et al., 2016; Westhoff et al., 2014; Scott et al., 2012; Sande et al., 2014; Furfari et al., 2017; van der Velden et al., 2017a; Tahara et al., 2016; Kirou-Mauro et al., 2008; Nguyen et al., 2011; Zeng et al., 2012; Gallizia et al., 2017; van der Velden et al., 2017b; Mitera et al., 2010; Hird et al., 2008; Arcangeli et al., 1998; Nakamura et al., 2016) The most common causes for exclusion were that the XRT was not for CIBP, that the intention was to study marker(s) that could be used for monitoring disease after XRT rather than for predicting analgesic response to XRT, and that the studies were case reports. Herein a narrative of included studies is presented.

3.1. Urinary markers

Three studies assessed the use of urinary markers of osteoclast activity as a predictor of response to XRT. Hoskin et al. explored the effects of XRT on levels of pyridinoline (PYD) and deoxypyridinoline (DPD) in urine of 22 patients with breast or prostate cancer. (Hoskin et al., 2000) The urine samples were collected before (baseline) and one month post-XRT (follow-up). Pain was assessed using a 4-point scale (none, mild, moderated and severe). Eight patients had a complete response (patient reported 'none' on the pain scale), nine had a partial response (a one point decrease on the pain scale) and five were non-responders. A relationship was found between patients with a good response to the treatment and a low concentration of the urine markers in their baseline samples. These patients also had no significant changes in the concentration of urine markers from baseline to follow-up (p-values not reported). In non-responders, there were relatively high concentrations of urine markers at baseline, which then increased significantly from baseline to follow-up.

Chow et al. evaluated the use of urinary markers (PYD, Calcium, Creatinine, Magnesium, Phosphate and N-telopeptide), in a prospective study of 125 participants receiving XRT for CIBP. (Chow et al., 2009) Urine samples were collected before the treatment started (baseline) and one month post treatment (follow-up). Pain was assessed at baseline and follow-up, using the Brief Pain Inventory (BPI), and analgesic use was also recorded. Patients were grouped into XRT responders (n = 68) and non-responders (n = 57), according to the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases". (Chow et al., 2002, 2012) "Responder" covered complete and partial response as per guideline definitions: Complete response is a pain score of 0 at the treated site with no concomitant increase in analgesic intake (stable or reducing analgesics, calculated into daily oral morphine equivalent doses [OMED]). A partial response

Table 1
Selection of relevant papers.

Author / Year	n	Design	Setting	Primary outcome	Secondary outcome	Method for prediction studied	Summary, main findings
Hoskin et al. / 2000	22	Letter to Editor, prospective study Urine collected pre-XRT (baseline) and 1 month post-XRT (follow-up) Pain assessed by 4-point scale (none, mild, moderate, severe)	Conventional external beam XRT (8 Gy x 1 or 4 Gy x 5) Breast and prostate cancer patients	Levels of urinary markers at follow-up compared to baseline in responders versus non-responders. Complete response was defined as reporting 'none' on the pain scale. Partial response was defined as reporting a one point decrease on the pain scale from baseline to follow-up.		Urinary markers -Pyridinoline (PYD) -Deoxypyridinoline (DPD)	Higher baseline levels in XRT non-responders compared to responders (p-values not reported).
Chow et al. / 2009	166 participated 125 evaluable	Prospective study Urine collected pre-XRT (baseline) and 1 month post-XRT (follow-up) Pain evaluated using the BPI at baseline and follow-up. Analgesic use also recorded.	Conventional external beam XRT	Change in levels of urinary markers from baseline to follow-up in responders versus non-responders. "Responder" was defined according to the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases".		Urinary markers -Pyridinoline (PYD) -Calcium -Creatinine -Magnesium -Phosphate -N-telopeptide (NTX)	No difference in baseline levels in XRT non-responders versus responders ($0.3412 \leq p \leq 0.9112$ for different markers).
Chow et al. / 2015	169 participated 109 evaluable	Prospective study Urine samples collected pre- and one month post re-irradiation. Pain evaluated using Brief Pain Inventory (BPI). Analgesic use also recorded.	Conventional external beam XRT	Levels of urinary markers at follow-up compared to baseline in responders versus non-responders. "Responder" was defined according to the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases".		Urinary markers -Pyridinoline (PYD) -Deoxypyridinoline (DPD) -N-telopeptide (NTX) -Alpha and Beta cross-laps of C-telopeptide (CTX)	Non-responders had a slightly increased level of urinary markers compared to responders at baseline (PYD $p = 0.03$; DPD $p = 0.04$).
Furfari et al. / 2017	107	Prospective study Saliva samples were collected pre-XRT (baseline). Pain evaluated using the BPI. Analgesic use also recorded.	Conventional external beam XRT (8 Gy x 1)	Association between response to XRT and known disease-causing variants from inflammation, radiation response and DNA damage pathways. "Responder" was defined according to the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases".		Genetic biomarkers Saliva samples sequenced to identify single-nucleotide variants in genes with known disease-causing variants from inflammation, radiation response and DNA damage pathways. Identified variants were incorporated into a prognostic score, which then was compared to patients' XRT responder status.	Single-nucleotide variants involved in mechanisms including DNA repair, inflammation, cellular adhesion and cell signalling have significant associations with radiation response. A high prognostic score corresponded with a higher chance of response to XRT, with 89% of patients in the high prognostic group responding to XRT ($p < 0.0001$).
Adli et al. / 2013	31	Prospective study. Baseline assessment done pre-XRT, follow-up assessments at weeks 2, 4, 8, 12, 16, 20 and 24. All patients had undergone pre-XRT FDG PET/CT scanning for staging purposes. FDG PET SUV_{max} for the index site was recorded. Pain assessed using the VAS or the faces pain rating scale. Analgesic use also recorded.	Conventional external beam XRT (8 Gy x 1)	Levels of FDG PET SUV_{max} pre-XRT in responders versus non-responders. "Responder" was defined according to the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases".		^{18}FDG PET uptake	Patients with bone metastases with a lower SUV_{max} had a better XRT response compared to bone metastases with a higher SUV_{max} ($p \leq 0.04$).

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Table 1 (*continued*)

Author / Year	n	Design	Setting	Primary outcome	Secondary outcome	Method for prediction studied	Summary, main findings
Zhao et al. / 2015	74 patients, 185 bone lesions	Retrospective study. Assessments pre-XRT (baseline) and one month post-XRT (follow-up). XRT FDG PET/CT scan at baseline and follow-up. FDG PET SUV_{max} was recorded. Pain assessed by an 11-point NRS (0-10). Analgesic use also recorded.	Conventional external beam XRT (3 Gy x 10; 2.5 Gy x 14; 2 Gy x 20; 8 Gy x 1) Patients with non-small cell lung cancer (NSCLC)	Interval to radiographic progression (progression free survival, defined as the interval from the first XRT-session to in-field progressive disease) and the interval to an in-field event (event-free survival, defined as the interval from the first XRT-session to an in-field skeletal-related event). "Responder" was defined according to the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases".	Association between levels of FDG PET SUV_{max} pre-XRT and pain response post-XRT.	^{18}FDG PET SUV_{max}	No association between the FDG PET SUV_{max} pre-XRT and the pain response to XRT ($p = 0.175$). However, the change in FDG PET SUV_{max} from before to after XRT was associated with the pain response ($p < 0.001$). No prediction up-front.
Tahara et al. / 2015	31 patients, 40 bone lesions	Prospective study. Assessments pre-XRT (baseline) and 4 weeks post-XRT (follow-up). XRT FDG PET/CT scan at baseline and follow-up. FDG PET SUV_{max} was recorded. Pain assessed by an 11-point NRS (0-10). Analgesic use also recorded.	Conventional external beam XRT	Correlation between the SUV_{max} of the painful bone metastases and the pain response to XRT 4 weeks post-XRT. "Responder" was defined according to the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases".	The relationship between the SUV_{max} of the painful bone metastases and the incidence of pain relapse of the bone metastases at the index site.	^{18}FDG PET SUV_{max}	Changes in the SUV_{max} differed significantly between the responder and non-responder groups ($p < 0.03$). No relationship was observed between the pre-XRT and post-XRT SUV_{max} relative to the pain response.
Mitera et al. / 2011	33 patients, 40 spinal vertebrae	Retrospective analysis of prospectively collected data. Assessments were done before XRT (baseline) and at 1, 2 and 3 months post-XRT (follow-up). Pain was assessed using an NRS, 0-10. Analgesic use was also recorded. A spinal assessment scoring system was used to capture the following CT features of the spinal metastases at baseline: osseous and soft tissue tumor extent, pathologic fracture, severity of vertebral height loss and kyphosis.	Conventional external beam XRT. Vertebral metastases only.	Correlation between CT imaging features of spinal metastases with pain relief after XRT. "Responder" was defined according to the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases".		CT imaging features of spinal metastases	There were no significant differences in pain response after XRT in patients with and without any of the CT features of the spinal metastases ($p > 0.05$)
Reginelli et al. / 2016	62	Prospective study. Assessments done pre-XRT (baseline) and 30 and 60 days post-XRT (follow-up). MRI diffusion weighted imaging (DWI) sequences ("DWI pattern") evaluated at baseline and the follow-up assessments, graded I-III. Pain assessed at follow-up assessments, using a 4-point scale comparing the pain to the baseline level (unchanged,	Conventional external beam XRT (3 Gy x 10) Vertebral (cervical, thoracic and lumbar) metastases only	Difference in "predictive index" at follow-up compared to baseline. No comparison done between responders and non-responders.		MRI DWI sequences Incorporated into a "predictive index" combining: -MRI-DWI sequences ("DWI pattern") -KPS -Number of metastases -Change in pain	Evaluated "predictive index" 30 days and 60 days after XRT – no prediction up-front. Concludes that the index can be useful in monitoring patients at follow-up (no results from statistical analysis reported).

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Table 1 (*continued*)

Author / Year	n	Design	Setting	Primary outcome	Secondary outcome	Method for prediction studied	Summary, main findings
		worsened, slightly better, much better). KPS assessed at follow-up assessments, using a 4 point scale comparing the KPS to the baseline level (much better, slightly better, unchanged, worse). Number of bone metastases assessed at baseline and follow-up assessments.					
Arcangeli et al. / 1998	205 patients, 255 bone lesions	Prospective study Assessments done pre-XRT (baseline) and post-XRT (follow up). Pain assessed using a VAS, 0-10. Analgesic use recorded by using a 5-point scale, scoring both analgesic strength and frequency.	Conventional external beam XRT	Association between primary diagnosis and response from XRT. Complete pain relief: Score ≤ 2 in the pain scale or 0 in the analgesic requirement scale. Partial pain relief: Score of 3-4 in the pain scale or 1-2 in the analgesic requirement scale.		Primary diagnosis	Significantly less patients with complete pain response after XRT among lung cancer compared to breast cancer ($p = 0.04$) and prostate cancer ($p = 0.002$).
Hird et al. / 2008	548	Secondary analysis of prospectively collected data. Assessment pre-XRT (baseline) and at 1, 2 and 3 months post-XRT (follow-up). Pain assessed by an NRS, 0-10. Analgesic use was also recorded.	Conventional external beam XRT	Difference in pain response after XRT between patients with gastrointestinal cancer and patients with other types of primary cancers. "Responder" was defined according to the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases".		Primary diagnoses	No statistically significant differrences were observed in XRT response rates in patients with gastrointestinal cancer compared to patients with other types of primary cancers.
Westhoff et al. / 2014	1157	Secondary analysis of prospectively collected data. Assessment pre-XRT (baseline) and weekly for 12 weeks post-XRT (follow-up). Pain assessed using an 11-point NRS. Analgesic use also recorded.	Conventional external beam XRT	Difference in pre-defined patient characteristics between responders and non-responders. "Responder" was defined according to the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases".		Characteristics of patients and disease -Age -Type of primary cancer -Absence/presence of visceral metastases	Breast cancer as the primary tumour site and absence of visceral metastases were associated with a good XRT response (breast cancer compared to lung cancer: multivariable adjusted hazard ratio (HR) 0.74 [95% CI 0.62–0.90]; compared to "other types of cancer": multivariable adjusted HR 0.72 [95% CI 0.57–0.91]); no visceral metastases compared to visceral metastases present: multivariable adjusted HR 0.88 [95% CI 0.74–1.03]). Age was not found to be a predictor of response (<65 years compared to 65-74 years: univariate HR 0.94 [95% CI 0.81–1.10]; compared to ≥ 75 years: univariate HR 0.84 [95% CI 0.69–1.02]).
van der Velden et al. / 2017	1027	Secondary analysis of prospectively collected data. Pain assessed pre-XRT (baseline) and at 1-, 2- and 3 months post-XRT (follow-up).	Conventional external beam XRT	Relationship between pre-defined patient characteristics and response to XRT. "Responder" was defined according to the "International		Clinical determinants evaluated: -Type of primary cancer -Interval between diagnosis of primary cancer and diagnosis of first bone metastasis	Primary tumor site, performance status and baseline pain predicted XRT response, with a corrected concordance statistic (*c*-statistic) of 0.63. The predicted response rates after XRT

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Table 1 (*continued*)

Author / Year	n	Design	Setting	Primary outcome	Secondary outcome	Method for prediction studied	Summary, main findings
				consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases".		-KPS -Gender -Age -XRT dose -Localisation of metastatic bone pain -XRT preceded by surgery -Absence/presence of visceral metastases at time of XRT -Previous systemic treatment -Baseline pain score -Use of opioid pain medication Clinical determinantes identified as predictors were incorporated into a prediction model to calculate a "Clinical Risk Score"	increased from 37.5% for patients with the highest "Clinical Risk Score" to 79.8% for patients with the lowest score, and were in good agreement with the observed response rates.
Zeng et al. / 2011	386	Secondary analysis of prospectively collected data. Assessments done before XRT (baseline) and monthly for 6 months post-XRT (follow-up). Pain assessed by the BPI. Analgesic use also recorded.	Conventional external beam XRT	Compare pain and functional outcomes in patients with spinal versus non-spinal metastases. "Responder" was defined according to the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases".		Location of bone metastases (spinal versus non-spinal)	Location of bone metastases (spinal versus non-spinal) was not a predictive factor of pain response after XRT ($p > 0.05$). Normal work ($p = 0.0164$) at month 5, and sleeping problems ($p = 0.0423$) at month 6 were better in patients initially exhibiting spinal bone metastases.
Nguyen et al. / 2011	109	Secondary analysis of prospectively collected data. Assessments done before XRT (baseline) and at 1, 2 and 3 months post-XRT (follow-up). Pain assessed by the BPI. Analgesic use also recorded.	Conventional external beam XRT Only patients with spine metastases	Association between XRT response and location of the bone metastases within the spine. "Responder" was defined according to the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases".	The secondary objectives were to search for BPI functional item change over time, and to compare responders versus non-responders according to location within the spine and BPI function interference items at follow-up intervals.	Location of the bone metastases within the spine.	Location of the bone metastases within the spine (lumbar/lumbosacral spine, $p = 0.91$; thoracic/thoraco-lumbar spine, $p = 0.05$; cervical/cervical thoracic spine, $p = 0.38$) was not a predictor of XRT response.
Kirou-Mauro et al. / 2008	1053	Secondary analysis of prospectively collected data. Assessment pre-XRT and at 1, 2 and 3 months post-XRT (follow-up). Pain assessed by the BPI. Analgesic use also recroded.	Conventional external beam XRT	The proportion of patients who experienced mild (score, 1-4), moderate (score, 5-6), or severe (score, 7-10) pain at baseline and who went on to achieve a complete response, partial response or progression. "Responder" was defined according to the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases".		Severity of pain before XRT.	No significant difference in the proportion of responders and non-responders in patients with mild pain at baseline compared with those with moderate or severe pain at 1, 2 and 3 months post-XRT ($p = 0.41$, $p = 0.50$ and $p = 0.81$, respectively).
Nakamura et al. / 2016	87	Prospective study. Assessments done pre-XRT (baseline) and 2 months post-XRT (follow-up). Pain assessed using an NRS, 0-10. Analgesig use was also recorded. Neuropathic pain was assessed using a screening questionnaire	Conventional external beam XRT	Association between neuropathic pain features and response after XRT. "Responder" was defined according to the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases".		Neuropathic pain features.	Overall response rate: -Patients with neuropathic features: 59% (95% CI 33-82%) -Patients without neuropathic features: 55% (95% CI 40-70%) (No p-value reported)

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Table 1 (*continued*)

Author / Year	n	Design	Setting	Primary outcome	Secondary outcome	Method for prediction studied	Summary, main findings
		validated to identify neuropathic pain components in Japanese patients.					
Scott et al. / 2012	23	Assessment pre-XRT (baseline) and 4-6 weeks post-XRT (follow-up). Pain assessed using the BPI. Quantitative Sensory Testing (QST) carried out on the skin overlying the index site.	Conventional external beam XRT	Change in QST assessment from baseline to follow-up in responders versus non-responders. "Responder" was defined as a decrease of at least 30% in BPI score.		QST (dynamic mechanical allodynia, mechanical detection threshold, mechanical pain threshold, hyperalgesia and thermal sensation)	Normalisation of abnormal thermal sensation (warm) in XRT responders (but no prediction up-front) (no p-value reported).
Sande et al. / 2014	60	Secondary analysis of prospectively collected data. Assessment pre-XRT (baseline) and 6-8 weeks post-XRT (follow-up). Pain assessed using the BPI. Analgesic use also recorded. Activity assessed for 14 days from baseline, using an ambulatory physical activity meter (*activ*PAL). Gait assessed at baseline and follow-up, using an electronic walkway (GAITRite).	Conventional external beam XRT	Change in parameters of physical activity or gait from baseline to follow-up in responders versus non-responders. "Responder" was defined according to the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases".		Characteristics of physical activity and gait	No association was found between XRT response and physical activity or gait ($p > 0.05$).
Gallizia et al. / 2017	121	Prospective study. Assessments done pre-XRT (baseline) and 2-8 weeks post-XRT (follow-up). Pain assessed using an 11-point VAS. Analgesic use also recorded. CT- and/or MRI scans collected at baseline + at follow-up if available.	Conventional external beam XRT Only patients with spine metastases	Correlation between the Spine Instability Neoplastic Score (SINS) and pain at baseline, and between SINS and pain response from XRT. Comparison done between patients with pain classified as "stable", "increased" and "decreased".		The SINS classification system.	No significant correlation was found between SINS and pain at balseline ($p \geq 0.4$). A statistically significant correlation was demonstrated between SINS and pain response post-XRT ($p < 0.05$).
van der Velden et al./ 2017	155	Prospective study. Pain assessed by an 11-point NRS (0-10). Analgesic use was also recorded.	Conventional external beam XRT Only patients with spinal metastases	The relationship between the degree of spinal (in)stability as measured by the Spine Instability Neoplastic Score (SINS) and response to XRT. "Responder" was defined according to the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases".		The SINS. This is a recent classification system for diagnosis of spinal instability caused by vertebral metastases.	Significant association between SINS and XRT response (adjusted odds ratio 0.78 [95% CI 0.62-0.98]). No association between SINS and an overall pain response (adjusted OR 0.94 [95% CI 0.81-1.10]).

Abbreviations: BPI – Brief Pain Inventory CI – Confidence interval CT – Computed tomography ^{18}FDG - Fluorine 18 fluorodeoxyglucose HR – Hazard ratio KPS - Karnofsky performance scale MRI – Magnetic resonance imaging NRS – Numerical rating scale OR – Odds ratio PET - Positron emission tomography SUV_{max} - Maximum standardized uptake value VAS – Visual analogue scale XRT – Radiotherapy.

is pain reduction of two or more at the treated site on a scale of 0 to 10 without analgesic increase, or analgesic reduction of 25% or more from baseline without an increase in pain. “Non-responder” covered pain progression and indeterminate response: Pain progression: Increase in pain score of two or more above baseline at the treated site with stable OMED, or an increase of 25% or more in OMED compared with baseline with the pain score stable or one point above baseline. Indeterminate response: Any response that is not captured by the complete response, partial response, or pain progression definitions. (Chow et al., 2002, 2012) Chow et al. did not find any significant difference in urinary markers between responders and non-responders ($0.3412 \leq p \leq 0.9112$ for different markers).

In 2015 Chow et al published another prospective study further exploring urinary markers as XRT predictor. (Chow et al., 2015) Urinary markers (PYD and DPD) were analysed at baseline (before XRT) and follow-up (one month post-XRT) in 109 patients receiving re-irradiation to a previously radiated bone metastasis. Pain was assessed recording BPI and analgesic use. Patients were grouped into “responders” and “non-responders” according to the consensus guidelines. (Chow et al., 2002, 2012) Non-responders were found to have a slightly increased level of urinary markers compared to responders at baseline (PYD $p = 0.03$; DPD $p = 0.04$).

3.2. Genetic biomarkers

In 2016 Furfari et al. published a secondary analysis of the data from the study by Chow et al. from 2015, discussed previously. It included 107 patients with cancer receiving XRT (8 Gy x 1) for painful bone metastases. (Furfari et al., 2017) Saliva samples were collected pre-XRT (baseline) and sequenced to identify single-nucleotide variants in genes with known disease-causing variants from inflammation, radiation response and DNA damage pathways. Pain was assessed using BPI and analgesic use. Patients were grouped into “responders” and “non-responders” according to the consensus guidelines. (Chow et al., 2002, 2012) Single-nucleotide variants involved in mechanisms including DNA repair, inflammation, cellular adhesion and cell signalling were significantly associated with radiation response. The identified variants were then incorporated into a prognostic score, which was compared to patients’ XRT responder status. A high prognostic score corresponded with a higher chance of response to XRT, with 89% of patients in the high prognostic group responding to XRT ($p < 0.0001$).

3.3. Imaging techniques

Five of the included studies focused on different imaging techniques as a method to predict XRT response, which of three evaluated whether levels of fluorine 18-fluorodeoxyglucose (^{18}FDG) positron emission tomography (PET) maximum standardized uptake value (SUV_{max}) could be used to predict a good XRT response. The first study was published by Adli et al. in 2013, and was a prospective study including 31 patients with CIBP. (Adli et al., 2013) All patients had a ^{18}FDG PET scan taken before their XRT. Pain was assessed at baseline (before XRT), and at follow-up (week 2, 4, 8, 12, 16, 20 and 24), using a visual analogue scale or the faces pain rating scale. XRT response was defined according to the consensus guidelines. (Chow et al., 2002, 2012) The authors found that patients with bone metastases with a lower SUV_{max} had a better XRT response compared to bone metastases with a higher SUV_{max} ($p \leq 0.04$). The location of the bone metastasis did not play a role in the response to the treatment (p-value not reported).

The second study was a retrospective study published by Zhao et al. in 2015. (Zhao et al., 2015) The authors evaluated the levels of fluorine ^{18}FDG PET SUV_{max} in 74 patients with non-small cell lung cancer (NSCLC), before and after XRT. Patients were assessed before their XRT (baseline) and one month after XRT (follow-up). Pain was assessed using an 11-point numerical rating scale (NRS), and analgesic use was also recorded. XRT response was defined in accordance with the consensus guidelines. (Chow et al., 2002, 2012) The study did not demonstrate any association between the ^{18}FDG PET SUV_{max} pre-XRT and the pain response to XRT ($p = 0.175$). However, an association was found between the change in FDG PET SUV_{max} from before to after XRT and the pain response to XRT ($p < 0.001$).

The third study was a prospective study by Tahara et al. published in 2015. (Tahara et al., 2016) ^{18}FDG PET SUV_{max} was evaluated in 31 patients with a total of 40 bone lesions, before and after XRT. Patients were assessed before XRT (baseline) and four weeks post-XRT. Pain was assessed using an 11-point NRS in addition to recording of analgesic use. XRT response was defined in accordance with the consensus guidelines. (Chow et al., 2002, 2012) Changes in the SUV_{max} differed significantly between XRT responders and non-responders ($p < 0.03$).

Mitera et al. published a retrospective study in 2011, evaluating the relationship between computed tomography (CT) features of the spinal metastases at baseline (osseous and soft tissue tumor extent, pathologic fracture, severity of vertebral height loss and kyphosis) and the pain relief after XRT. (Mitera et al., 2010) Thirty-three patients with a total of 40 vertebral metastases were included. Assessments were done before XRT (baseline) and at one, two and three months post-XRT (follow-up). Pain was assessed using an 11-point NRS. Analgesic use was also recorded. XRT response was defined in accordance with the consensus guidelines. (Chow et al., 2002, 2012) No significant differences were found in pain response after XRT in patients with and without any of the CT features of the spinal metastases ($p > 0.05$).

In 2016 Reginelli et al. explored the use of diffusion weighted imaging (DWI) in a prospective study in 62 patients with CIBP from spinal metastases. (Reginelli et al., 2016) Assessments were carried out before XRT (baseline) and at 30 and 60 days post-XRT (follow-up). A four-component “predictive index” was calculated at each assessment, amalgamating the number of bone metastases, variations in Karnofsky Performance Scale (KPS), changes in pain and DWI pattern. The index was found to be potentially useful in monitoring patients at follow-up (no results from statistical analysis reported).

3.4. Patient demographics and disease related parameters

Eight studies had explored different demographics and disease related parameters as potential predictors of XRT response. The first publication was a prospective study by Arcangeli et al., published in 1998, examining primary diagnosis as predictor of XRT response. (Arcangeli et al., 1998) This was a prospective study including 205 patients with a total of 255 bone metastases. Pain had been assessed using a visual analogue scale (VAS), 0–10. Analgesic use had been recorded by using a 5-point scale, scoring both analgesic strength and frequency. Complete pain relief was defined as a score ≤ 2 in the pain scale or 0 in the analgesic requirement scale. Partial pain relief was defined as a score of 3–4 in the pain scale or 1–2 in the analgesic requirement scale. Significantly less patients with lung cancer experienced a complete pain response compared to breast cancer ($p = 0.04$) and prostate cancer ($p = 0.002$).

In 2008 Hird et al. published a study comparing pain response after XRT in patients with gastrointestinal cancer with patients with other types of primary cancer. (Hird et al., 2008) This was secondary analysis of prospectively collected data of 548 patients. Assessments were carried out pre-XRT (baseline) and at one, two and three months post-XRT (follow-up). Pain was assessed using an 11-point NRS. XRT response was defined according to the consensus guidelines. (Chow et al., 2002, 2012) No statistically significant differences were observed in XRT response rates in patients with gastrointestinal cancer compared to

patients with other types of primary cancers.

A study of 1157 patients was published by Westhoff et al. in 2014. (Westhoff et al., 2014) This was a secondary analysis of prospectively collected data, and it explored whether patient age, type of primary cancer and the absence/presence of visceral metastases influence the response from XRT for CIBP. Pain was assessed before XRT (baseline) and weekly for 12 weeks post-XRT (follow-up) using an 11-point numerical rating scale. XRT response was defined according to the consensus guidelines. (Chow et al., 2002, 2012) Breast cancer as the primary tumour site and absence of visceral metastases were associated with a good XRT response (breast cancer compared to lung cancer: multivariable adjusted hazard ratio (HR) 0.74 [95% CI 0.62–0.90]; compared to "other types of cancer": multivariable adjusted HR 0.72 [95% CI 0.57–0.91]); no visceral metastases compared to visceral metastases present: multivariable adjusted HR 0.88 [95% CI 0.74–1.03]). Age was not found to be a predictor of response (< 65 years compared to 65–74 years: univariate HR 0.94 [95% CI 0.81–1.10]; compared to ≥75 years: univariate HR 0.84 [95% CI 0.69–1.02]).

Another large study (n = 1027) was published by van der Velden et al. in 2017. (van der Velden et al., 2017c) This was also a secondary analysis of prospectively collected data. Pain was assessed pre-XRT (baseline) and at one, two and three months post-XRT (follow-up). XRT response was defined according to the consensus guidelines. (Chow et al., 2002, 2012) The following clinical characteristics were evaluated as predictors of XRT response: type of primary cancer, interval between diagnosis of primary cancer and diagnosis of first bone metastasis, Karnofsky performance status, gender, age, XRT dose, localisation of metastatic bone pain, XRT preceded by surgery, absence/presence of visceral metastases at time of XRT, previous systemic treatment, baseline pain score and use of opioid pain medication. Primary tumor site, performance status and baseline pain score predicted XRT response, with a corrected concordance statistic (*c*-statistic) of 0.63. The clinical characteristics identified as predictors were then incorporated into a prediction model to calculate a "Clinical Risk Score". A moderate model performance was demonstrated with predicted response rate after XRT of 37.5% for patients with the highest "Clinical Risk Score", increasing to 79.8% for patients with the lowest score. The predicted response rates were in good agreement with the observed response rates.

Zeng et al published a study of 386 patients in 2011. (Zeng et al., 2012) This was secondary analysis of prospectively collected data, and evaluated whether bone metastases located to the spine compared to other locations affected the response (pain and functional outcomes) after XRT. Patients had been assessed before XRT (baseline) and monthly for six months after XRT (follow-up). Pain was assessed using the BPI. Analgesic use was also recorded. Patients were grouped into "responders" and "non-responders" according to the consensus guidelines. (Chow et al., 2002, 2012) Location of bone metastases (spinal versus non-spinal) was not a predictive factor of pain response after XRT ($p > 0.05$). However, normal work ($p = 0.0164$) at month five, and sleeping problems ($p = 0.0423$) at month six were better in patients initially exhibiting spinal bone metastases.

Nguyen et al. published a retrospective study in 2011, evaluating the location of bone metastases within the spine as a predictor of XRT response (pain and functional interference). (Nguyen et al., 2011) A total of 109 patients with spinal metastases had been included. Patients were assessed before XRT (baseline) and at one, two and three months after XRT (follow-up). Pain was assessed using the BPI in addition to recording of analgesic use. "Responder" was defined according to the consensus guidelines. (Chow et al., 2002, 2012) The location of the bone metastases within the spine was not a significant predictor of response to XRT (lumbar/lumbosacral spine, $p = 0.91$; thoracic/thoraco-lumbar spine, $p = 0.05$; cervical/cervical thoracic spine, $p = 0.38$).

Two studies had explored pain characteristics in relation to response to XRT. Kirou-Mauro et al. published a study in 2008 evaluating the severity of pain before XRT as a predictor of XRT response. (Kirou-Mauro et al., 2008) This was secondary analysis of prospectively collected data, and a total of 1053 patients were included. Patients were assessed pre-XRT (baseline) and at one, two, and three months post-XRT (follow-up). BPI had been used to assess the pain in addition to recording of analgesic use. "Responder" was defined according to the consensus guidelines. (Chow et al., 2002, 2012) No significant difference was found in the proportion of XRT responders and non-responders in patients with mild pain at baseline compared with those with moderate or severe pain at one, two and three months post-XRT ($p = 0.41$, $p = 0.50$ and $p = 0.81$, respectively).

In 2016 Nakamura et al. published a prospective study comparing pain response after XRT in patients with neuropathic pain features compared to patients without these features. (Nakamura et al., 2016) Eighty-seven patients were included, and the patients were assessed before XRT (baseline) and at two months post-XRT (follow-up). Neuropathic pain was assessed using a screening questionnaire validated to identify neuropathic pain components in Japanese patients. Patients were grouped into "responders" and "non-responders" according to the consensus guidelines. (Chow et al., 2002, 2012) Overall response rate was 59% (95% CI 33–82%) in patients with neuropathic features compared to 55% (95% CI 40–70%) in patients without neuropathic features (no p-value reported).

3.5. Thermal sensation

Scott et al. assessed the use of Quantitative Sensory Testing (QTS) as a predictor of XRT response in a prospective study published in 2012. (Scott et al., 2012) A total of 23 patients with CIBP were included. Assessments were carried out before XRT (baseline) and at 4–6 weeks post-XRT (follow-up). The QST included mechanical detection threshold (MDT); mechanical pain threshold (MPT); mechanical pain sensitivity (i.e. hyperalgesia) and responses to warm and cool sensations, and was carried out on the skin overlying the area of CIBP. Pain was also assessed, using the BPI. An XRT response was defined as a decrease of at least 30% in BPI score. The authors demonstrated a pattern in the XRT responders, where an abnormal thermal sensation (warm) at baseline was normalised after the XRT, while this did not happen in the non-responders (p-value not reported).

3.6. Physical activity and gait

Sande et al. explored the use of assessment of physical activity and/or gait as a predictor of response to XRT in CIBP conducting secondary analysis of prospectively collected data. (Sande et al., 2014) Forty-two patients were assessed before XRT (baseline) and at 6–8 weeks after XRT (follow-up). Pain was assessed using the BPI. Physical activity and gait were assessed using an activity meter (*ativPAL*™) and an electronic walkway (GAITRite). Patients were grouped into "responders" and "non-responders" according to the consensus guidelines. (Chow et al., 2002, 2012) No association was found between XRT response and physical activity or gait ($p > 0.05$).

3.7. Spinal (in)stability

Two studies published in 2017 evaluated spinal (in)stability as a predictor of pain response after XRT. Gallizia et al. had included 121 patients with spinal metastases in a prospective study. (Gallizia et al., 2017) Patients were assessed pre-XRT (baseline) and 2–8 weeks post-XRT (follow-up). CT and/or magnetic resonance imaging (MRI) scans were collected at baseline and at follow-up if available. The Spine

Instability Neoplastic Score (SINS) was calculated for the painful bone metastases. This is a new classification system for diagnosis of spinal instability caused by vertebral metastases, and is based on six factors; spine location, pain, bone lesion quality, spinal alignment, vertebral body collapse, and posterolateral involvement of spinal elements. A low score indicates spinal stability, while a high score indicates instability. Pain was assessed using an 11-point VAS and analgesic use was recorded. Patients were grouped into XRT "responders" and "non-responders" according to the consensus guidelines. (Chow et al., 2002, 2012) A statistically significant correlation was found between SINS and pain response post-XRT ($p < 0.05$).

The second study on spinal (in) stability was published by (van der Velden et al. (2017b)) This was a prospective study, including 155 patients with spinal metastases. This study also evaluated the relationship between the classification system SINS and pain response to XRT. Pain was assessed using an 11-point NRS in addition to recording of analgesic use. XRT "Responder" was defined according to the consensus guidelines. (Chow et al., 2002, 2012) The authors found a significant association between SINS and XRT response (adjusted odds ratio 0.78 [95% CI 0.62-0.98]). No association was found between SINS and an overall pain response (adjusted odds ratio 0.94 [95% CI 0.81–1.10]).

4. Discussion

Clinical markers and biomarkers that have been explored as predictors of pain response to XRT include urinary markers (Hoskin et al., 2000; Chow et al., 2009, 2015), genetic biomarkers (Furfari et al., 2017), different imaging techniques (Adli et al., 2013; Zhao et al., 2015; Reginelli et al., 2016; Tahara et al., 2016; Mitera et al., 2010), patient demographics related parameters (Westhoff et al., 2014; Kirou-Mauro et al., 2008; Nguyen et al., 2011; Zeng et al., 2012; Hird et al., 2008; Arcangeli et al., 1998; Nakamura et al., 2016; van der Velden et al., 2017c), QST (Scott et al., 2012), assessment of physical activity and/or gait (Sande et al., 2014) and classification of spinal instability. (Gallizia et al., 2017; van der Velden et al., 2017b) No marker was identified as a predictor that at present can be used in clinical practice. Urinary markers as well as imaging techniques had been explored in several studies with the intention to verify previously positive results, however the studies had divergent results. Age was not found to influence the outcome from XRT for CIBP, while good performance status might be associated with a better pain relief from XRT. Patients with breast and prostate cancer might experience a better pain relief compared to patients with lung cancer. Whether pain score at baseline influence the outcome from XRT is unclear, with the study by van der Velden et al. finding an association between high pain score at baseline and a good pain response, while Kirou-Mauro et al. did not found any such relationship. Neither QST nor assessment of physical activity and/or gait were shown to predict pain response from XRT. For spinal metastases, it does not seem to be an association between where in the spine the metastases is located and the pain relieving effect from XRT. For the two studies examining the relationship between spinal (in)stability and response from XRT, the study by Gallizia et al. was negative, while van der Velden et al. found an association, and it is therefore unclear whether this influences the XRT outcome or not.

In UK alone more than 23,000 episodes of XRT are delivered for the treatment of CIBP yearly, involving approximately 70,000 patient attendances. (Specialised Commissioning Team, 2016) With 24% of treatments not resulting in the patients experiencing any pain relief, more than 5700 episodes of treatment are delivered each year with no effect, and about 17,500 hospital visits are made in vain. Patients that do not experience pain relief from the first treatment with XRT, or who experience relapse of the pain after some time, can get re-treatment with a further treatment of XRT. The efficacy of re-irradiation is comparable to initial radiation treatment. (Wong et al., 2014) However, there are still many patients who will never experience pain relief from XRT. A way to identify the patients that would benefit from XRT for CIBP may have implications for patients and health care resources. Patients likely to experience a benefit from XRT could be prioritised. Those less likely to benefit, could have additional support from palliative care specialists to improve their pain management in other ways. This would also save these patients from experiencing unnecessary side-effects, as nausea, fatigue and even a temporary worsening of pain (pain flare). (Hird et al., 2009) In this frail group of patients avoiding unnecessary hospital visits, which can be burdensome and distressful, is also of importance. (Yarnold, 1999)

Certain limitations are present with this systematic review. It only included papers in the English language, thereby potentially missing eligible studies published in other languages. The exclusion criteria can potentially have left out relevant studies, and publication bias can be present.

With the implications that a predictor of pain response to XRT for CIBP could have both for patients and health service utilisation more work in this area would be of interest. The present systematic review highlights certain areas for improvement in future trials. The number of patients has been low in most studies, which limits the possibilities to carry out any sub-analysis. Further, outcomes have been defined in different ways; pain has been assessed using different assessment tools and XRT "responder" and "non-responder" has been defined in various ways. This makes it challenging to compare the trials. Some of the findings regarding both urinary markers, genetic biomarkers, use of imaging techniques and QST are promising, and further work in these areas is of great interest.

5. Conclusions

Currently there is no robust clinical marker or biomarker which predicts response to XRT for CIBP. Several factors show promise, however larger studies which are prospective in nature are needed to explore these. If a clinical marker or biomarker was identified which could predict analgesic response, this could be employed in treatment stratification.

Conflict of interest statement

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Appendix A

XRT for CIBP, Embase Classic + Embase, 1947-2018 week 15 (n = 474)

1. exp Neoplasms/
2. Neoplasms.mp.
3. Cancer.mp.
4. Tumour.mp.
5. exp Bone Neoplasms/
6. bone neoplasms.mp.
7. bone metastases.mp.
8. exp Pain/
9. pain.mp.
10. cancer induced bone pain.mp.
11. bone pain.mp.
12. exp Radiotherapy/
13. radiotherapy.mp.
14. exp Biomarkers, Tumor/
15. exp Biomarkers/
16. biomarkers.mp.
17. predictor.mp.
18. 1 or 2 or 3 or 4
19. 5 or 6 or 7
20. 8 or 9 or 10 or 11
21. 12 or 13
22. 14 or 15 or 16 or 17
23. 18 and 19 and 20 and 21 and
24. limit 46 to (human and english language and (adult < 18 to 64 years > or aged < 65+ years >))

XRT for CIBP, Medline, 1946 - April Week 2 2018 (n = 43)

1. exp Neoplasms/
2. Neoplasms.mp.
3. Cancer.mp.
4. Tumour.mp.
5. exp Bone Neoplasms/
6. bone neoplasms.mp.
7. bone metastases.mp.
8. exp Pain/
9. pain.mp.
10. cancer induced bone pain.mp.
11. bone pain.mp.
12. exp Radiotherapy/
13. radiotherapy.mp.
14. exp Biomarkers, Tumor/
15. exp Biomarkers/
16. biomarkers.mp.
17. predictor.mp.
18. 1 or 2 or 3 or 4
19. 5 or 6 or 7
20. 8 or 9 or 10 or 11
21. 12 or 13
22. 14 or 15 or 16 or 17
23. 18 and 19 and 20 and 21 and 22
24. limit 23 to (english language and humans and "all adult (19 plus years)")

XRT for CIBP, Cochrane, Setup – 16.04.18 (n = 34)

#1MeSH descriptor: [Neoplasms] explode all trees
#2Neoplasms*
#3Cancer*:ti,ab,kw (Word variations have been searched)
#4Tumour*
#5MeSH descriptor: [Bone Neoplasms] explode all trees
#6Bone neoplasms*
#7Bone metastases*
#8MeSH descriptor: [Pain] explode all trees
#9Pain*
#10Cancer induced bone pain*
#11Bone pain*
#12MeSH descriptor: [Radiotherapy] explode all trees
#13Radiotherapy*

#14MeSH descriptor: [Biomarkers, Tumor] explode all trees
#15MeSH descriptor: [Biomarkers] explode all trees
#16Biomarkers*
#17Predictor*
#18#1 or #2 or #3 or #4
#19#5 or #6 or #7
#20#8 or #9 or #10 or #11
#21#12 or #13
#22#14 or #15 or #16 or #17
#23#18 and #19 and #20 and #21 and #22

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