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INTERVENTIONAL RADIOLOGY—REVIEW ARTICLE

Voxel-Based Dosimetry as a Means for Treatment Personalisation in Radioembolization: A Systematic Review

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ABSTRACT

Introduction: Radionuclide therapy including ^{90}Y radioembolization is an established form of brachytherapy for treatment of malignancy including hepatocellular carcinoma. Currently, there are several methods available to estimate patient absorbed dose, including voxel-based dosimetry, that can achieve a level of personalisation in the planning and outcome assessments of radioembolization. Despite the advantages of voxel-based dosimetry, it remains a relatively new concept in radioembolization. This study evaluates if voxel-based dosimetry was associated with improved treatment efficacy in radioembolization planning.

Methods: A systematic review was conducted by searching relevant databases (Medline Ovid, PubMed, Embase Ovid, CINAHL Complete, Cochrane Library, CENTRAL, Australian New Zealand Clinical Trials Registry, ClinicalTrials.gov, WHO International Trials Registry, Google Scholar) for literature regarding voxel-based dosimetry in radioembolization.

Results: A total of 41 papers were included for this systematic review. Review of these studies revealed that voxel-based dosimetry can benefit numerous aspects of radioembolization in radionuclide therapy including predicting tumour response, toxicity and patient survival. Numerous studies also indicated that voxel-based dosimetry in radioembolization is a more accurate approach in establishing a dose-effect relationship in targeted radionuclide therapy when compared to other methods. Despite these promising findings, these studies did not investigate or comment on the accuracy of voxel-based dosimetry.

Conclusion: The evidence from this review highlights that voxel-based dosimetry can improve treatment efficacy in radioembolization planning. However, further studies are required to validate the accuracy and feasibility of voxel-based dosimetry in clinical practice.

1 | Introduction

Radionuclide therapy including ^{90}Y radioembolization is an established form of brachytherapy for treatment of malignancy including hepatocellular carcinoma (HCC) [1]. The aim of radionuclide therapy is to deliver tumoricidal doses of radiation to the tumour while limiting radiation exposure to the surrounding healthy parenchyma [2]. Treatment planning is critical in delivering targeted, effective, and safe doses of radiation [3]. Despite the growing role of radioembolization in targeted brachytherapy, further refinements in radiotherapy planning and technique are necessary to improve treatment efficacy and planning [4].

Currently, there are several methods available to estimate patient absorbed dose including single and multi-compartment dosimetry, as well as voxel-based dosimetry. In single-compartment dosimetry, there is no distinction between the tumour and the surrounding normal tissue parenchyma. Multi-compartment

dosimetry can delineate tumour from healthy tissue but does not consider the heterogeneity of the dose distribution in each of these compartments. Furthermore, traditional techniques used in estimating radiation dose and tumour response suffer from considerable degradation caused by noise and resolution limitations (i.e., partial-volume error) limiting the accuracy of dosimetry in radionuclide therapy [5].

Alternatively, voxel-based dosimetry estimates dose for each reconstructed voxel and therefore maps a dose distribution revealing gradients and/or inhomogeneities within tissue parenchyma. Voxel-based dosimetry can therefore be defined as a dose calculation based on SPECT or PET image-derived estimation of spatial radionuclide activity. Voxel-based dosimetry can achieve a level of personalisation in the planning and outcome assessments of radioembolization [6]. This may enhance targeted radionuclide therapy in radioembolization and enable prediction of tumour response, toxicity and patient survival [7].

Despite the advantages of voxel-based dosimetry, it remains a relatively new concept in clinical practice, particularly in radioembolization [4]. Therefore, the objective of this study was to determine if voxel-based dosimetry was associated with improved treatment efficacy in radioembolization planning. This review focused on the indicators supporting clinical use of voxel-based dosimetry for personalised dosimetry rather than the technicalities of the calculation methods themselves.

2 | Methods

A systematic review was conducted by searching relevant databases (Medline Ovid, PubMed, Embase Ovid, CINAHL Complete, Cochrane Library, CENTRAL, Australian New Zealand Clinical Trials Registry, ClinicalTrials.gov, WHO International Trials Registry, Google Scholar) for literature regarding voxel-based dosimetry in radioembolization. No limits were applied to the date range, language or age groups. This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

Databases were searched using the following subject headings and keywords:

Medline (Ovid) Search Strategy –.

(exp Radiotherapy dosage/ OR exp. Radiation dosage/ OR dosage*.mp. OR dose*.mp. OR dosing.mp. OR dosimetry.mp. OR microdos*.mp. OR amount*.mp. OR quantity.mp. OR absor*.mp.)

AND

(exp Radiation dosage/ OR exp. Radioisotopes/ OR exp. Radiotherapy/ OR Radiotherapy planning, computer-assisted/ OR radiation-therapy.mp.)

AND

(Voxel.mp. OR VIDA.mp. OR VDK.mp. OR DVK.mp.)

AND

(exp embolization, therapeutic/ OR exp. carcinoma, hepatocellular/ OR exp. liver neoplasms/ OR embolotherap*.mp. OR embol*.mp. OR radioembol*.mp. OR ((liver.mp. OR hepat*.mp.) AND (neoplas*.mp. OR cancer.mp. OR carcinoma.mp. OR tumo*.mp.)))

The literature search strategy was developed with a Medical Librarian and peer reviewed. by a Research Librarian. Other search strategies have been summarised in Appendix A.

A primary relevance assessment of papers by title and abstract was used to identify studies where the voxel-based dosimetry in radioembolization was the primary focus. All studies chosen for this systematic review were primary research articles that had undergone peer review.

In total, our search strategy (search conducted 3 October 2023) yielded 1628 articles. A total of 278 duplicates were removed. After applying a primary relevance assessment (title and abstract), 1239 papers were excluded, leaving 105 for further analysis. Further assessment for eligibility (e.g., conference abstracts were excluded) yielded a total of 41 papers included for this systematic review (Figure 1).

The PRISMA checklist (2020) was used for data extraction and quality checking of included studies. Retracted publications were excluded from this review. Data extraction was conducted by one reviewer. Participant characteristics, study design and results were extracted. The Critical Appraisal Skills Programme (CASP) was used as a tool for appraisal of the selected studies. A meta-analysis was not possible due to heterogeneity in outcome measures. Ethics approval was not required for this study.

3 | Results

3.1 | Study Characteristics

Characteristics of the 41 included studies have been summarised in Table S1. Included studies ($N = 41$) were published between 2004 and 2023. Overall, a total of 1170 participants were included in this review. The sample sizes of studies ranged from $N = 1$ to $N = 176$. Patient demographics could not be determined for all included studies. The majority of participants included in this study were diagnosed with HCC or liver metastasis and treated with ^{90}Y radioembolization. Numerous patients across several studies also had multiple lesions and/or underwent multiple radioembolization treatments (as summarised in Table S1).

Due to patients undergoing radioembolization treatment for HCC or liver metastasis, the majority of studies were performed and analysed retrospectively. No randomised controlled trials were identified. Outcomes regarding the use of voxel-based dosimetry in radioembolization have been divided into 3 key domains including dose personalisation, patient outcomes and toxicity.

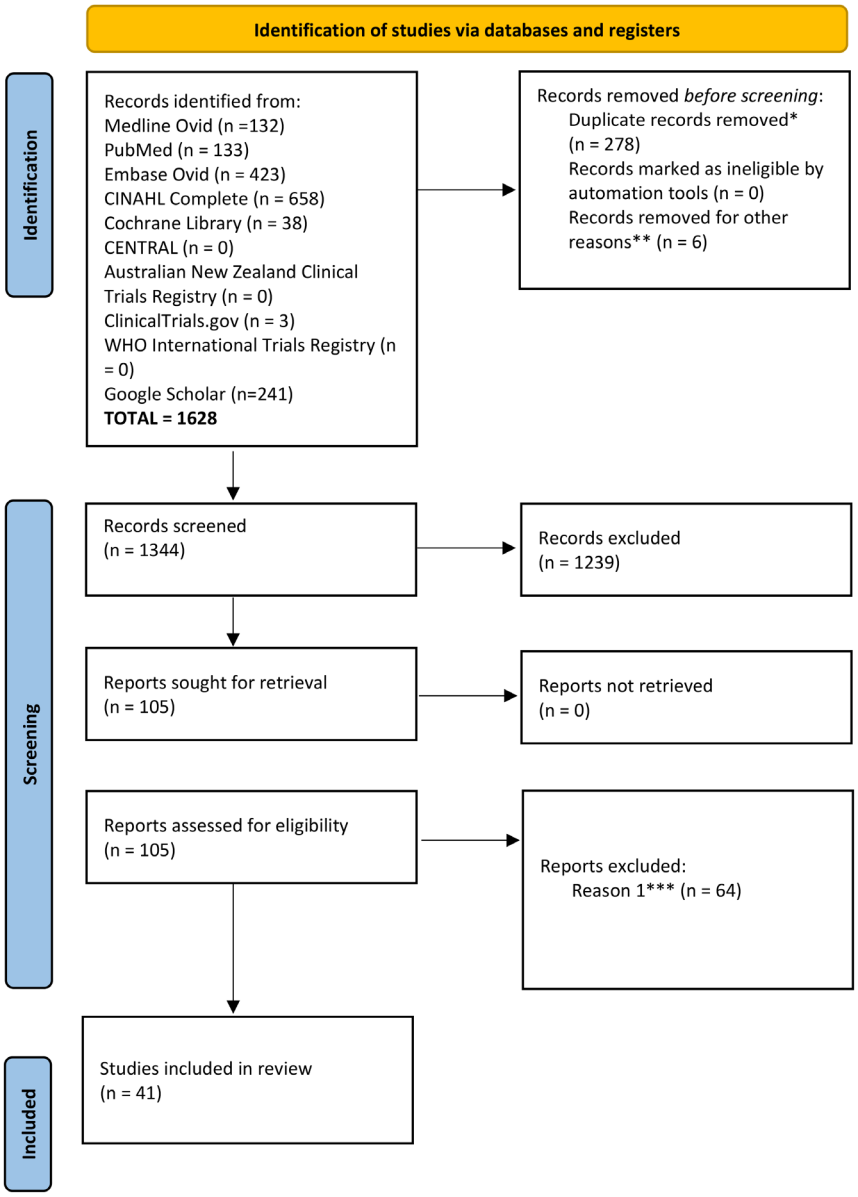

FIGURE 1 | Results summary (pre-screening). *Records de-duplicated in EndNote (using title field only). **Retracted publication. ***Did not meet inclusion criteria (e.g., conference abstract).

3.2 | Dose Personalisation

Accurately quantifying tumoral and non-tumoral absorbed radiation doses is crucial in radioembolization for treatment of HCC and liver metastases. Multiple studies investigated the ability of voxel-based dosimetry to provide a personalised radiation dose estimation following radioembolization. For instance, Sarfaraz et al. suggested that voxel-based dosimetry can differentiate radiation absorbed dose (i.e., dose inhomogeneity) to the liver, tumour and adjacent organs [8]. Chen et al. demonstrated that voxel-based dosimetry could achieve comparable results regarding absorbed dose estimations when compared to other dosimetry methods such as the partition model, and that using a tissue-specific kernel could achieve smaller errors in lung tissue [9, 10]. Similarly, Thomas et al. found that voxel-based dosimetry produced equivalent predictions in normal liver parenchymal dose when compared to the partition model regarding radioembolization treatment for advanced HCC [11]. A study by Bozkurt et al. found that medical internal radiation dose (MIRD) calculations overestimated the absorbed doses by as much as 11% in lungs, 5% in liver and 20% in tumour volumes and suggested that voxel-based dosimetry offered a more precise model of the patients' critical tissues serving as a personalised dosimetric tool for trans-arterial radioembolization treatment planning (noting however, that this is relative to a voxel-based Monte Carlo calculation) [12]. Voxel-based dosimetry was also shown to be superior in estimating absorbed dose and biological effective dose than the American Association of Physicists in Medicine (AAPM) method by Gallio et al. [13]. Furthermore, in addition to heightened accuracy, Plachouris et al. has suggested that by using tissue-specific dose voxel kernels to account for tissue and activity heterogeneity, voxel-based dosimetry can provide rapid and efficient (< 1 min) analyses suitable for everyday clinical practice [14]. Overall, these findings suggest that

voxel-based dosimetry can provide more personalised treatment when compared to other models of dosimetry.

3.3 | Patient Outcomes

The ability to predict tumour response and clinical outcomes following radioembolization are key considerations in optimising individualised treatment planning. Post-therapy monitoring of ^{90}Y activity distribution following hepatic radioembolization has been shown to be reliably quantified using voxel-based dosimetry by Yue et al. [15]. Higher tumour-absorbed doses estimated by voxel-based dosimetry in patients with HCC have been shown by Veenstra et al. to be associated with longer overall survival [16]. D'Arienzo et al. also inferred that voxel-based dosimetry can assess correlations between microsphere distribution, response to treatment and clinical outcomes following radioembolization by showing a case study of complete remission of liver tumour areas which received a high radiation dose [17]. Similarly, Milano et al., Yoo et al. and Orcajo Rincon et al. showed that tumour absorbed dose is a strong predictor of radiological tumour response in voxel-based dosimetry [18–20]. Furthermore, with respect to the now widely used and evidence-based segmentectomy approach in the treatment of HCC, Orcajo Rincon et al. has also demonstrated that voxel-based dosimetry can accurately predict tumour response following radiation segmentectomy [20]. Voxel-based dosimetry has also been shown to accurately predict liver hypertrophy and future liver remnant following lobar/extended-lobar radioembolization in a study by Grisanti et al. [21]. A study by Galizia et al. even demonstrated that outcomes such as HCC necrosis following radioembolization can be quantified more reproducibly by voxel-based dosimetry compared to other methods traditionally used such as two-dimensional analysis [22]. These findings infer that voxel-based dosimetry may play an important role in evaluating and predicting clinical outcomes including patient survival.

3.4 | Toxicity

Localised toxicity to adjacent healthy parenchyma is an important treatment consideration in radioembolization of malignancy including HCC. Chiesa et al. demonstrated that an absorbed dose-effect relationship exists with respect to the radioembolization of HCC with ^{90}Y glass microspheres, and that smaller tumours can be ablated with lower absorbed doses than larger tumours. Chiesa et al. subsequently suggested that a constraint of 70 Gy mean absorbed dose to liver non-tumoral parenchyma corresponds to 15% probability of radio-induced liver decompensation while still achieving an absorbed of several hundreds of Gy to hepatic lesions [23, 24]. Kokabi et al. had a similar finding in that there are dose response and dose toxicity thresholds directly affecting outcomes in patients with HCC undergoing treatment with ^{90}Y resin microspheres in both segmental and non-segmental therapy [25]. This was further evaluated by Watanabe et al. who showed that voxel-based dosimetry may predict hepatotoxicity with greater accuracy than conventional dosimetric methods such as multicompartment dosimetry in HCC patients undergoing radioembolization, and that this could be used to optimise individual patient treatment response [26]. A study by Strigari et al. also illustrated that patient-specific dosimetry could improve therapeutic outcomes with regards to the treatment of HCC, while maintaining an acceptable level of liver toxicity [27]. These findings collectively imply that since smaller tumours can be treated with lower absorbed doses of radiation than larger tumours, pre-treatment planning should be focused more on optimising and minimising the parenchymal dose to prevent toxicity, since tumour response to radiation is strongly dependent on its size.

4 | Discussion

This systematic review has identified potential for voxel-based dosimetry in radioembolization as an effective tool in providing individualised patient treatment planning and prediction of outcomes compared to other forms of dosimetry. However, larger multicentric randomised trials are needed to validate these findings.

There are four major dosimetric models that have been developed for detection and calculation of ^{90}Y levels in radioembolization and radiotherapy. These include the empiric, MIRD, partition and body surface area (BSA) dosimetry models [3]. Although the empiric model is no longer used due to radiation-induced side effects [28], the MIRD, partition and BSA dosimetry models remain widely used in clinical practice; nonetheless, these models also have their limitations. The MIRD model is a single-compartment method of dosimetry, and therefore lacks distinction between the tumour and the surrounding normal tissue parenchyma. This can therefore lead to inaccuracies in ^{90}Y calculations due to the often heterogenous distribution of radioembolization microspheres [3]. The partition model was developed from the MIRD model [29] and is a multi-compartment method of dosimetry and therefore can delineate tumour from healthy tissue (e.g., non-tumoral liver and lung). However, the partition model assumes identical catheter position for dose injections of both ^{90}Y and Tc-MAA, which may not always be feasible in clinical practice (noting that this also remains a limitation of voxel-based dosimetry). Furthermore, as the partition model is derived from the MIRD model of dosimetry, it carries the same assumptions in its mathematical equations (i.e., assumes 100% of the ^{90}Y dose was injected into the patient) [3]. Nonetheless, the partition model attempts to provide a more accurate mathematical model of the heterogenous distribution of microspheres in tumour and normal liver parenchyma than the MIRD model with the use of a tumour: normal (TN) perfusion ratio, but cannot account for intra-lesional and inter-lesional heterogeneity in distribution of microspheres (for instance, due to tumour necrosis), and is difficult to use in practice when dealing with multiple lesions without making assumptions about equal TN ratios of all lesions [3]. The BSA model of dosimetry is derived from the empiric method to calculate patient ^{90}Y dose [30]. However, similar to the MIRD model, the BSA model of dosimetry is a single-compartment method of dosimetry and carries similar assumptions and limitations. However, evolution of the BSA model to the 'modified' BSA approach has attempted to address the heterogeneity of tumour location within the hepatic parenchyma, although remains limited by microsphere distribution (hence dose distribution) in radioembolization [3].

Voxel-based dosimetry is an alternative to overcome the limitations of the aforementioned dosimetry models by estimating

dose gradients and inhomogeneities within tissue parenchyma by calculating absorbed dose for each reconstructed voxel. Voxel-based dosimetry could therefore achieve a level of personalisation in the planning, treatment and outcome assessments of radioembolization, and enhance targeted radionuclide therapy in radioembolization by predicting tumour response, toxicity and patient survival [6, 7].

Despite the numerous advantages of voxel-based dosimetry, there are several limitations. For instance, Hou et al. found that reconstruction algorithms largely overestimate the maximum dose and are therefore not suitable for voxel level dose analysis [31].

While there is a strong case for voxel-based methods in providing more patient-specific dosimetry, future studies may consider broadening the current search strategy to include predictions from other dosimetry models in quantifying treatment efficacy and comparison to voxel-based methods. In addition, studies within this systematic review did not investigate the specific underlying radiation dose distribution or activity distribution. Although this has previously been attempted by Gordon et al. (albeit an ex vivo study) [32], this remains extraordinarily difficult to determine and validate by imaging alone. Patient dose distribution and heterogeneity remains heavily reliant on microscopic scale dosimetry and radiobiological modelling [33]. As such, studies within this review remained focused on correlating clinical outcomes with voxel-based dose estimation and not underlying radiation dose calculations. This therefore remains a limitation of this review. This was exemplified by Yue et al. [15] claiming that ^{90}Y activity distribution following hepatic radioembolization could be reliably quantified using voxel-based dosimetry, with the assumption that they accurately represented the actual activity distribution by showing that SPECT and PET could provide well correlated distributions. Ng et al. recognised that although voxel-based dosimetry is feasible in a clinical setting, there are inhomogeneities in ^{90}Y dose and dose rate throughout the irradiated volume of tissue [34]. Further studies (including phantoms) are required to determine the dose distribution and tumour control probability with greater accuracy. Furthermore, a number of studies had small sample sizes, five of which had as few as $N=1$ [8, 17, 35–37]. There were 26 studies in this review with $<N=30$ (summarised in Table S1). This limitation was recognised by Ferrando et al., who advocated for further studies to be performed on an extended patient cohort to validate the clinical feasibility of voxel-based dosimetry in radioembolization [38]. Although these studies show promising results, such studies should be interpreted with caution, and ideally, larger multi-centric randomised trials are needed to validate these findings.

Furthermore, implementing voxel-based dosimetry for radioembolization comes with additional financial and logistical costs including additional software and licensing, additional computation time and resources, repeated imaging and relatively long acquisition times up to 30 min [39, 40] which could negatively impact existing throughput efficiency and productivity. This may represent a significant hurdle to overcome for clinicians adopting, or transitioning to, voxel-based dosimetry within their institutions.

5 | Conclusion

The evidence from this systematic review highlights that voxel-based dosimetry can improve treatment efficacy in radioembolization planning compared to other forms of dosimetry. However, further studies are required to validate the accuracy and feasibility of voxel-based dosimetry in clinical practice.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Appendix A

Database Search Strategies

Medline (Ovid) –.

(exp Radiotherapy dosage/ OR exp. Radiation dosage/ OR dosage*.mp. OR dose*.mp. OR dosing.mp. OR dosimetry.mp. OR microdos*.mp. OR amount*.mp. OR quantity.mp. OR absor*.mp.)

AND

(exp Radiation dosage/ OR exp. Radioisotopes/ OR exp. Radiotherapy/ OR Radiotherapy planning,

computer-assisted/ OR radiation-therapy.mp.)

AND

(Voxel.mp. OR VIDA.mp. OR VDK.mp. OR DVK.mp.)

AND

(exp embolization, therapeutic/ OR exp. carcinoma, hepatocellular/ OR exp. liver neoplasms/ OR embolotherap*.mp. OR embol*.mp. OR radioembol*.mp. OR ((liver.mp. OR hepat*.mp.) AND (neoplas*.mp. OR cancer.mp. OR carcinoma.mp. OR tumo*.mp.)))

PubMed –.

("Radiotherapy dosage"[Mesh] OR "Radiation dosage"[Mesh] OR dosage*[tw] OR dose*[tw] OR dosing[tw] OR dosimetry[tw] OR microdos*[tw] OR amount*[tw] OR quantity[tw] OR absor*[tw])

AND

("Radiation dosage"[Mesh] OR "Radioisotopes"[Mesh] OR "Radiotherapy"[Mesh] OR "Radiotherapy planning, computer-assisted"[Mesh] OR radiation-therapy[tw])

AND

(Voxel[tw] OR VIDA[tw] OR VDK[tw] OR DVK[tw])

AND

("Embolization, therapeutic"[Mesh] OR "carcinoma, hepatocellular"[Mesh] OR "liver neoplasms"[Mesh] OR embolotherap*[tw] OR embol*[tw] OR radioembol*[tw] OR ((liver[tw] OR hepat*[tw]) AND (neoplas*[tw] OR cancer[tw] OR carcinoma[tw] OR tumo*[tw])))

Embase (Ovid) –.

(exp Radiation dose/ OR dosage*.mp. OR dose*.mp. OR dosing.mp. OR dosimetry.mp. OR microdos*.mp. OR amount*.mp. OR quantity.mp. OR absor*.mp.)

AND

(exp Radiation dose/ OR exp. Radioisotope/ OR exp. Radiotherapy/ OR Radiotherapy planning system/ OR radiation-therapy.mp.)

AND

(Voxel.mp. OR VIDA.mp. OR VDK.mp. OR DVK.mp.)

AND

(exp artificial embolization/ OR exp. liver tumor/ OR embolotherap*.mp. OR embol*.mp. OR radioembol*.mp. OR ((liver.mp. OR hepat*.mp.) AND (neoplas*.mp. OR cancer.mp. OR carcinoma.mp. OR tumo*.mp.)))

CINAHL Complete –.

((MH "Radiation dosage+") OR TX (dosage* OR dose* OR dosing OR dosimetry OR microdos* OR amount* OR quantity OR absor*)

AND

((MH "Radiation dosage+") OR (MH "Radioisotopes+") OR (MH "Radiotherapy+") OR (MH "Radiotherapy, computer-assisted") OR TX (radiation-therapy))

AND

(TX (Voxel OR VIDA OR VDK OR DVK))

AND

((MH "embolization, therapeutic+") OR (MH "liver neoplasms+") OR TX (embolotherap* OR embol* OR radioembol* OR ((liver OR hepat*) AND (neoplas* OR cancer OR carcinoma OR tumo*))))

Cochrane Library and Cochrane Central Register of Controlled Trials (CENTRAL) –.

Advanced Search, Search Manager tab.

1. Radiotherapy dosage [Mesh]
2. Radiation dosage [Mesh]
3. Dosage*
4. Dose*
5. Dosing
6. Dosimetry
7. Microdos*
8. Amount*
9. Quantity
10. Absor*
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. Radiation dosage [Mesh]
13. Radioisotopes [Mesh]
14. Radiotherapy[Mesh]
15. Radiotherapy planning, computer-assisted [Mesh] – single term only (no explode)
16. Radiation NEXT therapy
17. #12 OR #13 OR #14 OR #15 OR #16
18. Voxel
19. VIDA
20. VDK
21. DVK
22. #18 OR #19 OR #20 OR #21
23. embolization, therapeutic [Mesh]
24. carcinoma, hepatocellular [Mesh]
25. liver neoplasms [Mesh]
26. embolotherap*
27. embol*
28. radioembol*
29. Liver NEAR neoplas*
30. Liver NEAR cancer
31. Liver NEAR carcinoma
32. Liver NEAR tumo*
33. Hepat* NEAR neoplas*
34. Hepat* NEAR cancer
35. Hepat* NEAR carcinoma

36. Hepat* NEAR tumo*
37. #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
38. #11 AND #17 AND #22 AND #37

Australian New Zealand Clinical Trials Registry (ANZCTR) –.

Voxel AND dosimetry AND radioembolization.

ClinicalTrials.gov –.

Cancer AND (voxel AND dosimetry) AND (radioembolization OR radioembolisation).

World Health Organization (WHO) International Clinical Trials Registry –.

voxel AND dosimetry AND (radioembolization OR radioembolisation).

Google Scholar –.

(radiotherapy dosage OR radiation dosage OR dosage OR dose OR dosing OR dosimetry OR amount or quantity OR absor) AND (radiation dosage OR radioisotopes OR radiotherapy OR computer assisted radiotherapy planning) AND (radioembol OR embol) AND (Voxel)