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Review

A systematic review comparing the effective radiation dose of musculoskeletal cone beam computed tomography to other diagnostic imaging modalities

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ABSTRACT

Purpose: Cone-Beam CT (CBCT) is well established in orofacial diagnostic imaging and is currently expanding into musculoskeletal applications. This systematic review sought to update the knowledge base on radiation dose comparisons between imaging modalities in MSK imaging and consider how research studies have reported dose measures.

Methods: This review utilised a database search and an online literature tool. Studies with potential relevance were screened then before full text review, each performed by two independent reviewers, with a third independent reviewer available for conflicts. Data was extracted using a bespoke tool created within the literature tool.

Results: 21 studies were included in the review which compared CBCT with MSCT (13), conventional radiography (1), or both (7). 19 studies concluded that CBCT provided a reduced radiation dose when compared with MSCT: the factor of reduction ranging from 1.71 to 50 with an average of 12. Studies comparing CBCT to DR found DR to have an average dose reduction of 4.55.

Conclusions: The claims that CBCT produces a lower radiation dose than MSCT is borne out with most studies confirming doses less than half that of MSCT. Fewer studies include DR as a comparator but confirm that CBCT results in a higher effective dose on average, with scope for CBCT to provide an equivalent radiation dose. This review highlighted a need for consistency in methodology when conducting studies which compare radiation dose across different technologies. Potential solutions lie outside the scope of this review, likely requiring multi-discipline approach to ensure a cohesive outcome.

1. Introduction

1.1. Rationale

Cone beam CT (CBCT) utilises a conical field through a single rotation with a digital flat panel detector to produce images which can be reconstructed in 3D to appear similar to multislice CT (MSCT). The technology is based on direct digital radiography (DR) and is well established in orofacial practice [1,2]. Over the last decade CBCT has expanded across the musculoskeletal (MSK) applications and is now used for trauma and pathological imaging. Some CBCT devices are similar in appearance to flat-bed MSCT scanners although for some an additional advantage is the smaller size which permits the equipment to be mobile and/or changed in orientation to support weight-bearing acquisition of the ankle and knee [2]. Although initially focussed on the appendicular skeleton, new wide-bore scanners are now able to support pelvic and spinal imaging [2].

The benefits of CBCT over MSCT are purported to also include a smaller footprint, lower power requirement, reduced cost and reduced radiation dose [2–4]. An early prototype of the technology claimed that radiation doses could be 2–3 times less than MSCT [5] and despite the acceptance in practice many papers refer to the dose differences in orofacial imaging rather than in MSK applications [1,6–10]. Musculoskeletal imaging presents different challenges to dental or maxillofacial scan acquisition, particularly in the variation of anatomical tissues and body part size, especially at different ages. There is also the additional

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complication of immobilisation devices such as casts in the context of trauma and larger implants. Limited confirmation of the actual dose reduction opportunities are available in this setting and the one identified systematic review was focussed on non-dental applications and therefore included paranasal sinuses and inner ear examinations [11].

This systematic review sought to update the knowledge base on radiation dose comparisons between imaging modalities in MSK imaging and consider how research studies have reported dose measures. It is also acknowledged that in CBCT there is no single approach to effective dose calculation [12], and therefore it was of interest to consider the methods used by authors for effective dose determination

1.2. *Objectives*

- To identify the published literature regarding CBCT radiation dose for musculoskeletal applications
- To confirm whether CBCT has a lower radiation dose burden to patients than other imaging modalities
- To determine the effective dose reporting metrics as a baseline for future studies

2. Materials and methods

2.1. *Search strategy*

The review protocol was registered on the international Prospective Register of Systematic Reviews (PROSPERO) database [ID CRD42023433648]. A preliminary search was used to guide index terms and keywords to inform the search strategy. Variation in the terminology around musculoskeletal CBCT was identified and therefore the search was widened to include all studies related to CBCT or derivatives. Studies that were published in English from the last ten years and were conducted with human participants, cadavers, or anthropomorphic phantoms were eligible for inclusion. Previous systematic reviews and *meta*-analyses were excluded to prevent double counting of datasets.

2.2. *Inclusion criteria*

The inclusion criteria for this scoping review are summarised within Table 1.

Table 1
Study inclusion criteria.

Inclusion Criteria	
Types of studies	Primary research of qualitative, quantitative, and mixed methodology including cohort studies and service evaluations.
Procedure type	Musculoskeletal examinations (excluding head and neck), arthrogram studies and bone densitometry (using CBCT).
Outcome Types	Limited to radiation dose comparison between imaging modalities (both comparison and effective dose calculations)
Context	Hospital, clinic and research settings

2.3. *Databases*

This systematic review utilised CINAHL, PubMed and MedLine. Specific keywords and MESH headings (Cone-Beam Computed Tomography; Weight-Bearing; tomography, X-Ray Computed) were utilised individually and in combination.

2.4. *Screening and selection*

The search outputs were uploaded into Covidence (https://www.covidence.org), an online literature review tool which enables collaboration and independent scrutiny. Duplicates were automatically removed at the upload stage. Two independent reviewers screened titles and abstracts; conflicts were resolved through joint discussion with a third reviewer until consensus was reached. Those studies which had the potential to be relevant were retrieved and again two independent reviewers then assessed the full text publication and again conflicts were resolved by consensus.

2.5. *Data extraction*

A bespoke data extraction tool was generated within the Covidence platform. Where appropriate (human studies only), the study quality was evaluated using the Quality Assessment Tool for Quantitative Studies [13] concurrently with data extraction. Data extraction and quality assessments were performed by a single reviewer, which was then evaluated by a second reviewer for discrepancies. A third independent reviewer was consulted in situations of conflicting opinion. Once completed, the extracted information was exported to Microsoft Excel for evaluation.

2.6. *Presentation of results*

The extracted data regarding radiation dose comparisons from the included articles is presented and discussed. This review will also discuss implications for future practice and research.

3. Results

Database searches produced 11,396 articles, of which 1152 were automatically removed as duplicates. 10,065 studies were excluded at the screening stage for lack of relevance, predominantly these studies involved a focus on orofacial applications or radiotherapy. 180 articles reached the full text assessment for eligibility and of these 159 were excluded. Reasons for exclusion and specific numbers for each reasoning are displayed in the PRISMA flowchart (Fig. 1). 21 studies were found to be relevant to the topic of radiation dose comparisons between CBCT and other diagnostic imaging modalities.

The study pool consisted of 21 articles from 13 different lead authors with the research undertaken in 5 separate counties (Table 2), with fifteen author teams based in Europe [14–28]. The country of origin had some correlation with the type of equipment used. For instance, the MultiTom Rax, was only used in Germanic studies [17–20], while the CurveBeam CBCT scanners were only used in those performed in the United States (US) [9,29–32], and a single Phion study originated from the Republic of Korea [33]. Four out of the 13 studies compared CBCT to MSCT only, one compared CBCT to DR and the remaining six compared CBCT to both MSCT and DR. Most studies were conducted on cadaver specimens or anthropomorphic phantoms, which were not appropriate for quality assessment. It is acknowledged that cadavers are a suitable proxy to human participants however the quality assessment tool required information regarding participant demographics and consent, along with other information not attainable from cadaveric or phantom based studies. Most of the eligible studies were graded as moderate quality (Table 2).

The dosimetry metric was inconsistent across studies with many not providing an effective dose (ED) calculation. In total; 8 studies calculated ED, 2 studies reported surface skin radiation dose, 8 studies presented data from the imaging modality only and 1 study measured scatter radiation doses (Table 2). Of the studies that calculated ED, the majority reported a tissue weighting calculation using organ dose. Two studies performed an additional calculation to report an age-based weighting while one presented age-weighting without specific tissue data. One study supplied only a total ED, calculated using a conversion co-efficient, which was referenced within the text.

As each study used differing parameters and calculations, it was not possible to perform a *meta*-analysis on the data provided, however summary comparison has been undertaken (Table 3). Of the eight studies which reported effective doses, seven used external dosimetry to record measurements while one utilised the modality dose reports [9].

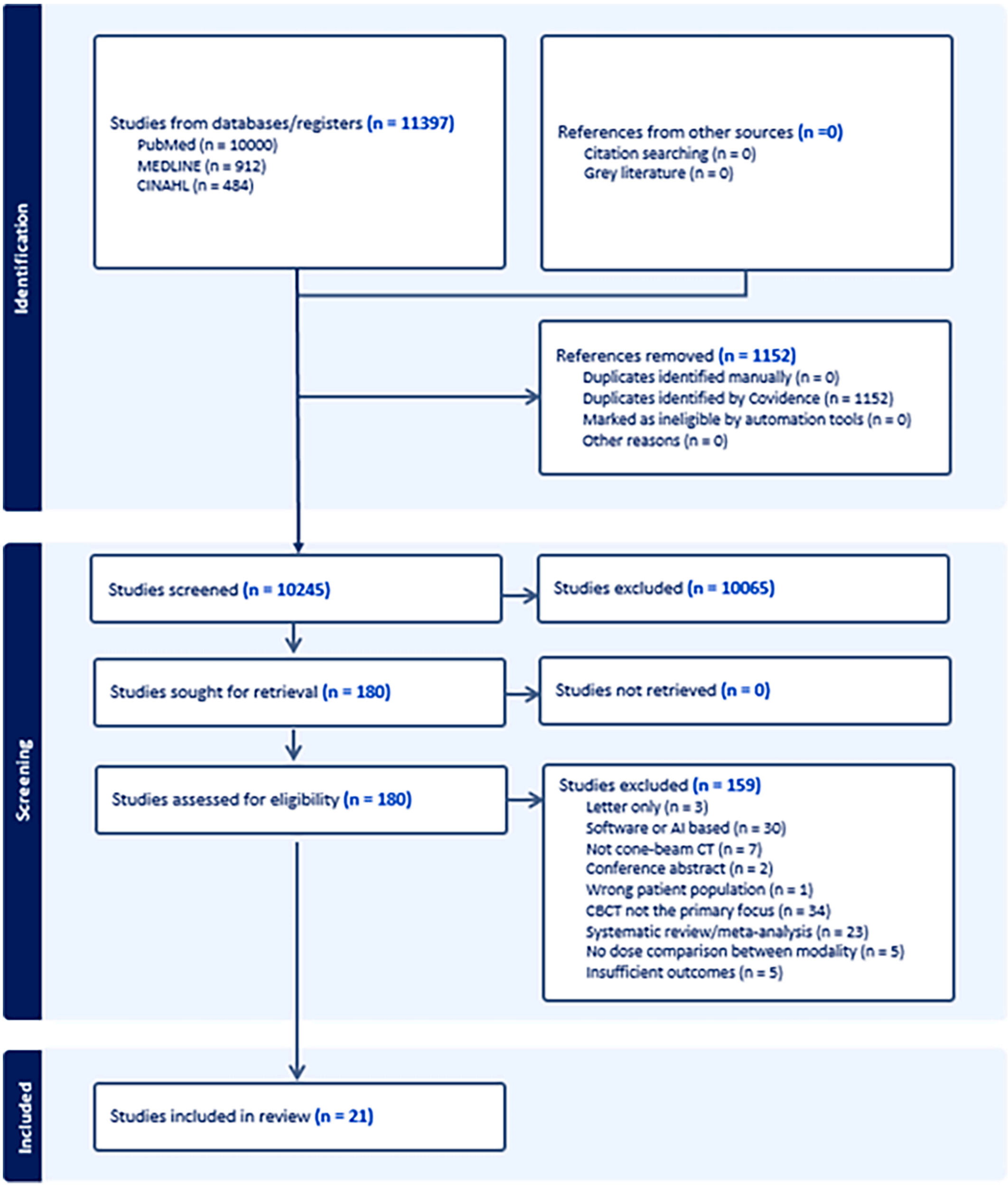

Fig. 1. PRISMA flow chart.

In the majority (87.5 %) of studies optimisation of the CBCT and/or MSCT scanning protocols was confirmed to has been undertaken prior to the research.

In general, the studies that compared the radiation dose impact of CBCT and MSCT were consistent in their findings. This being that often CBCT presented a lower overall quality of images than those provided by the MSCT, but the CBCT images were still diagnostic while providing a reduced radiation dose to the patient. Studies which included radiation doses from DR consistently reported this to be the lowest radiation dose. The reduction in effective dose associated with DR varied, with some optimised CBCT protocols resulting in comparable dose measurements [24–26,29].

Neubauer's study focused on image quality was the exception to this [27]. The study highlighted that for good image depiction of cortical bone and articular surfaces, CBCT could achieve a lower radiation dose than MSCT. However, in overall image quality their optimised MSCT scan produced a statistically significant 20 % reduction in radiation dose when compared to CBCT. To compare the two modalities, this study used absorbed doses measured in mGy rather than effective dose.

In studies which did not calculate effective dose, there was a consistent claim that CBCT resulted in a lower radiation dose. Grunz et al [21] claimed a potential reduction of up to 75 % reduction against MSCT using the twin-head Multitom Rax, while Tschauner et al [28] evidenced a reduction of up to 55 % in mean surface dose between the Planmed Verity and an optimised MSCT. In de Charry et al's study [15], the radiation dose measured from CBCT was twice that of the comparator high-resolution peripheral quantitative computed tomography (HR-pQCT), however less than one-quarter that of the MSCT, 12.6μSv to 52μSv.

4. Discussion

Despite a plethora of publications on the use of CBCT in MSK clinical practice the number of studies comparing the radiation dose with other imaging modalities was relatively small and importantly there were only seven human studies published in the last decade.

Table 2
Overview of the included studies.

Reference	Country	CBCT Make and Model	CBCT Type	Comparator Modality	Subject	Dose Measure	Quality Assessment
Dartus et al, 2021	France	Carestream OnSight 3D	Weightbearing	MSCT	Human	Scan data (CTDIvol)	Moderate
de Charry et al, 2016	France	NewTom 5G	Flatbed	MSCT	Cadaver	Scan data (CTDIvol)	–
Dubreuil et al, 2019	France	Newtom 5G	Flatbed	MSCT	Human	Scan data (CTDIvol)	Moderate
Grunz et al, 2019	Germany	Siemens Multitom Rax	Twin head	MSCT	Cadaver	Scan data (CTDIvol)	–
Grunz et al, 2020a	Germany	Siemens Multitom Rax	Twin head	MSCT	Cadaver	Scan data (CTDIvol)	–
Grunz et al, 2020b	Germany	Siemens Multitom Rax	Twin head	MSCT	Cadaver	Scan data (CTDIvol)	–
Grunz et al, 2021	Germany	Siemens Multitom Rax	Twin head	MSCT	Cadaver; Phantom (Dosimetry)	Scan data (CTDIvol)	–
Hughes et al, 2022	UK	Carestream OnSight 3D	Weightbearing	MSCT; DR	Phantom (Anthropomorphic)	Scatter	–
Jacques et al, 2021	France	Carestream OnSight 3D	Weightbearing	MSCT	Human	Scan data (DLP)	Moderate
Ludlow et al, 2014	USA	CurveBeam PedCAT	Weightbearing	MSCT; DR	Phantom (Anthropomorphic)	Effective dose (organ weighting and age weighting)	–
Ludlow et al, 2018a	USA	CurveBeam InReach	Non-weightbearing	MSCT	Phantom (Anthropomorphic)	Effective dose (organ weighting and age weighting)	–
Ludlow et al, 2018b	USA	CurveBeam InReach	Non-weightbearing	DR	Phantom (Anthropomorphic)	Effective dose (organ weighting and age weighting)	–
Koivisto et al, 2013	Finland	Planmed Verity	Weightbearing	MSCT; DR	Phantom (Anthropomorphic)	Effective dose (organ weighting)	–
Koivisto et al, 2015	Finland	Planmed Verity NewTom 5G	Weightbearing/ Flatbed	MSCT; DR	Phantom (Anthropomorphic)	Effective dose (organ weighting)	–
Koivisto et al, 2018	Finland	Planmed Verity Newtom 5G	Weightbearing/ Flatbed	MSCT; DR	Phantom (Anthropomorphic)	Effective dose (organ weighting)	–
Koivisto et al, 2021	Finland	Planmed Verity Newtom 5G	Weightbearing/ Flatbed	MSCT; DR	Phantom (Anthropomorphic)	Effective dose (organ weighting)	–
Nam et al, 2022	Republic of Korea	Phion Nanofocusray	Non-weightbearing	MSCT	Human	Surface dose +/- Lead Shielding – External Dosimetry (TLD)	Moderate
Neubauer et al, 2016	Germany	Planmed Verity	Weightbearing	MSCT	Cadaver	Monte Carlo Simulation – absorbed dose	–
Pugmire et al, 2016	USA	Planmed Verity	Weightbearing	MSCT	Human	Effective dose (conversation co-efficient)	Weak
Rupp et al, 2021	USA	Carestream Onsight 3D	Weightbearing	MSCT; DR	Cadaver	Scan data (DLP) and External Dosimetry	–
Tschauner et al, 2017	Germany	Planmed Verity	Weightbearing	MSCT	Phantom (Anthropomorphic)	Surface dose – External Dosimetry (TLD)	–

Note: A number of the weightbearing CBCT scanners are also able to be utilised in a vertical orientation non-weightbearing.

4.1. *Dose comparison*

This systematic review aimed to compare the CBCT with other imaging modalities for MSK applications specifically. From a narrative perspective, 19 of the 20 studies comparing CBCT with MSCT supported the hypothesis that CBCT imaging has a reduced radiation dose. The dissenting paper reported that an optimised MSCT could produce an overall lower dose; however, in this context CBCT better depicted the cortical bone and articular surfaces [27]. Of the studies that recorded effective dose, the results showed a significant reduction in radiation dose acquired from CBCT examinations compared to MSCT. The quantification of this radiation dose reduction varied from a factor of 1.71 to 50, averaging a factor of 12. A potential contributing factor to the wide range of averages is the utilisation of FOV in certain CBCT studies. For instance, the Koivisto et al 2015 study reported that the effective dose using an FOV of 18x16 on the Newtom 5G was significantly smaller than the dose measured using an FOV of 15x12 on the same scanner [24] The highest reduction rate was in Ludlow et al, with an effective dose of 0.5 mSv in CBCT to 25 mSv in MSCT [29]. In this instance, CBCT utilised a small FOV while MSCT had a standard adult protocol, which images a significantly larger area.

For studies that included DR data, this was confirmed as having the lowest effective dose of all modalities, the highest reduction being 16.13 times less than CBCT [31]. Overall, the average DR effective dose reduction was 4.55, collating data from the six studies which provided these measures. One study, Koivisto 2018, stated that an optimised CBCT was comparative to DR, with both having an effective dose of 0.9μSv [25]. When comparing CBCT and DR, it is important to consider the additional patient benefits of 3D imaging, particularly in the reduction of repeat follow up imaging [34–36]. Due to the stationary nature of the patient, CBCT images are often less susceptible to distortion when compared with MSCT [37]. Conversely, CBCT may be more susceptible to movement artefacts as the acquisition time is often significantly longer than that of a MSCT scan [38,39]. Patients undergoing MSK imaging relating to trauma are often contending with varying levels of pain and mobility of the affected area, which can increase the difficulty regarding positioning and the likelihood of movement during acquisition [40].

Predominantly, this review found that to date studies are focussed on CBCT dose comparisons for the appendicular skeleton. With emerging wide-bore scanners able to image the spine and pelvis [10] the dose implications require prospective review, alongside diagnostic utility, as the tissue and bone composition together with scatter implications are significantly different in truncal applications.

Table 3
Effective dose comparison between modalities.

Reference	Subject	Mean of Total Effective Dose		
		ConeBeam CT (CBCT)*	**Multi-slice CT (MSCT)***	**Digital Radiography (DR)***
Koivisto, 2013	Knee (Phantom)	12.6 μSv	Somatom – 27.3 μSv Sensation – 48.0 μSv Lightspeed – 32.4 μSv	3.0 μSv
Koivisto, 2015	Ankle (Phantom)	Planmed Verity – 6.0μSv Newtom 5G (High) – 14.3μSv Newtom 5G (Standard 15x12) – 4.0μSv Newtom 5G (Standard 18x16) –1.9μSv	21.4μSv	1.5μSv
Koivisto, 2018	Wrist (Phantom)	Planmed Verity – 2.4μSv Newtom 5G (High) – 1.6μSv Newtom 5G (standard 12x8) – 0.7μSv Newtom 5G (standard 15x12) – 0.9μSv	8.6μSv	0.9μSv
Koivisto, 2021	Elbow (Phantom)	Planmed Verity – 2.6μSv Newtom 5G (High) – 6.7μSv Newtom 5G (standard 12x8) – 2.0μSv Newtom 5G (standard 15x12) – 2.5μSv Newtom 5G (standard 18x16) – 2.1μSv	37.4μSv	1.5μSv
Ludlow, 2014	Foot (Phantom)	Large FOV adult – 2.6–3.8μSv Medium FOV adult – 1.4–2.3μSv Small FOV adult – 0.5–0.9μSv	Care dose Adult – 23μSv Standard Adult – 25μSv	Adult – 0.6μSv
Ludlow, 2018a	Hand – wrist (Phantom)	Standard adult – 1.4μSv Lite adult – 2.7μSv	Standard Adult – 9.8μSv Lite Adult – 8.3μSv	–
	Foot – Ankle (Phantom)	Standard adult – 3.7μSv Lite adult – 1.8μSv	Standard adult – 22.9μSv Lite adult – 20.1μSv	–
	Knee (Phantom)	Standard adult – 2.1μSv Lite adult – 1.2μSv	Standard adult – 32.8μSv Lite adult – 17.9μSv	–
Ludlow, 2018b	Hand (Phantom)	Standard Adult – 0.5μSv Lite Adult – 0.3μSv	–	Standard adult – 0.043μSv Lite adult – 0.031μSv
Pugmire, 2016	Ankle (Paediatric Human)	1.3μSv ± 0.3*	23.0μSv ± 2.3*	–

NB: *Including model and/or protocol where multiple versions used.

4.2. Complications in reporting of radiation dose values

A *meta*-analysis was not possible due to the wide variety of radiation dose measurement methods utilised. While all reported dose comparisons, this was not the primary outcome of many and therefore limited information was provided. In addition, only some authors calculated ED, and these were inconsistent in how the data was presented.

Many studies attempted some degree of radiation dose optimisation; however, this was often not equal amongst all the modalities within a study. Koivisto et al, in their studies containing more than one make and model of CBCT, only optimised one of the CBCT scanners, and did not optimise the comparator modalities [24–26]. One factor that may have affected a research team's ability to conduct optimisation is the ability of the operator to change parameters or protocols and/or the involvement of medical physics professionals.

Seven of the studies that calculated effective dose used anthropomorphic phantoms, while one had living paediatric patients. The phantoms used also varied between studies. Many comprised of human bone surrounded by a synthetic tissue, with most modelled after an adult but some modelled after children. The phantoms also varied in their representative anatomy, with some having a single anatomical area such as hand or knee, while others contained multiple regions such as foot and ankle combined.

Studies that incorporated the use of external dosimetry varied in not only the type of dosimeter used but also the methods of use. In Koivisto et al's studies, MOSFET dosimeters were placed inside anthropomorphic phantoms at levels shown via an annotated x-ray image [23–26]. The phantom itself comprised of human bones with synthetic soft tissue, in which holes were drilled to insert the dosimeters. Ludlow et al also used phantoms made from human bone and synthetic soft tissue; however, they used OSL dosimeters to collect their measurements, with each dosimeter receiving 4 or 5 exposures [29–31]. In contrast, Tschauner measured surface dose only by placing TLDs on the surface of a paediatric phantom, modelled after a 4-year-old child [28]. In studies that imaged the same anatomical region the number of dosimeters used, and their locations, also differed.

Six papers were suitable to undergo quality assessment via the QATQS tool. Of these, one was rated poor [9] while the rest received a moderate rating. No paper was given a strong rating. In these studies, it was found that patient descriptors were often poor, and the samples were small with a considerable risk of bias or confounders. Studies involving diagnostic images are difficult to blind, as a participant will know which scan is being undertaken, and the reporter would be able to differentiate between a CBCT image and that of MSCT or radiography. There are also strong ethical considerations in creating a trial method which would require the same patient to undertake multiple ionising radiation procedures for no additional benefit.

Of the papers which were not suitable for QATQS, the methodologies were often far more robust from a statistical analysis perspective. The dosimetry positioning, calculations used, and type of analysis were often clearly expressed in detail, though only one paper also provided easy access to the dataset as well [28]. Anthropomorphic phantoms provide an alternative in which medical imaging devices can be safely assessed and optimised to find better techniques at lower radiation doses without the need for patients to undergo repeated or additional ionising radiation procedures, although limited trabecular detail does limit their use for bone quality metrics. A specific quality assessment tool for use in studies involving phantoms rather than human participants may allow for better cross-comparison and *meta*-analysis of these studies.

Papers varied in how they collected and collated data. One method involved patients undergoing both CBCT and the comparator within the duration of the study [14]. Another method [9] retrospectively selected paediatric patients who had received a CBCT scan over a 2.5-year period and aged matched these to patients who had undergone a CT in the same period. As this study incorporated images from 15 boys and 19 girls, it is unlikely that the paediatric patients were also matched by gender. The patient ages ranged from 7 to 18 and all examinations were combined to calculate the mean radiation doses. While the anatomical area, foot and ankle, was consistent among the cohort; the age range is broad for a paediatric population and leaves serious limitations to the reliability of the result.

In order to enable a robust comparison of doses across imaging modalities to be made, there needs to be consistency in the reporting of dose metrics. Within the articles that were reviewed there were notable differences in the dose metrics that were presented, and at times a lack of sufficient clarity regarding any calculations that had been performed to enable the presentation of the data. This is not an issue that is unique to the articles reviewed but is rather a more general issue in the published literature. The authors wish to highlight the need for a standardised reporting system for radiation dose metrics in the diagnostic X-ray literature. Production of such a system is beyond the scope of this work as it would require the involvement of medical physicists, radiologists and radiographers to achieve consensus.

When indicating that a proposed piece of equipment or imaging technique will result in a lower radiation dose to patients, it is imperative that the research behind this statement is robust. A key factor in the strength of the radiation dose comparisons within the studies was the inclusion of medical physics within the paper's authorship. This is most clearly demonstrated with the Koivisto papers [23–26], which had detailed and robust methodologies that indicated how the effective dose measurements had been reached. This is also confirmed in Tschaunder's study, which included access to the original raw data through a URL [28].

It was noted that 12 papers involved authorship from radiologists or radiographers but no obvious medical physics involvement, while a further 2 papers [14,32] lacked obvious involvement from the medical physics or radiology professions. Scope of practice within medical and health professions varies from country to country and it is often difficult to discern the professional background of authors in journal articles. For studies that had undertaken radiation dose measurements, this can lower confidence in methods, particularly where the original data is not provided.

4.3. Limitations

This study was limited by the inability to conduct a *meta*-analysis due to lack of cohesion between papers. Future research may benefit from the implementation of a standard procedure to allow for better comparisons between different studies. This study also excluded papers which had not been published in English, to reduce the likelihood of misrepresenting their findings, however it should be acknowledged that many of the papers were from countries where English is not the native language. There were differences in terminology between studies, potentially due to translations or language differences, which negatively impacted the reviewers' ability to form clear comparisons between studies.

5. Conclusions

In conclusion, research into the potential uses of CBCT in MSK applications demonstrates the potential growth in this field. The claims in the literature that the modality produces a lower radiation dose than MSCT is borne out within the literature with most confirming doses less than half that of MSCT. Fewer studies include DR as a comparator but confirm that CBCT results in a higher effective dose on average, although the difference is often small and there is scope for CBCT to provide an equivalent radiation dose.

The MSK applications were predominantly extremity examinations, with no effective dose data available for imaging of the axial skeleton. As emergent technologies, such as wider bore CBCT enter the healthcare systems, robust effective radiation dose comparisons in axial skeleton examinations will be essential to ensuring safe and effective utilisation of CBCT within imaging.

This systematic review has highlighted a need for consistency in methodology when conducting studies which compare radiation dose across different technologies. Potential solutions lie outside the scope of this review and would likely require multi-discipline approach to ensure a cohesive outcome. This is critical in ensuring readers can make clear comparisons in reported data, and particularly can provide an informed explanation to patients and referrers as part of the justification process.

CRediT authorship contribution statement

K. Mason: Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **G. Iball:** Writing – review & editing, Formal analysis. **D. Hinchcliffe:** Investigation, Data curation. **B. Snaith:** Writing – review & editing, Validation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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