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Review Article

Surgical margin assessment of bone tumours: A systematic review of current and emerging technologies

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HIGHLIGHTS

- The lack of precise intraoperative margin assessment tools for bone cancer is an unmet need to reduce local cancer recurrence.
- New emerging technologies should aim to increase precision in detecting tumour cells while also minimally disrupting the workflow during the operation.
- The use of multimodal spectroscopy technology seems promising for intraoperative margin detection.

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ABSTRACT

Osteosarcoma is the most common malignant tumour of the bone. Complete surgical excision is critical to achieve optimal outcomes and lower recurrence rates. However, accurate assessment of tumour margins remains a challenge and multiple technologies are employed for this purpose. The aim of this study is to highlight current and emerging technologies and their efficacy in detecting clear bone margins intraoperatively, through a systematic review of the literature.

The following databases were searched using the OVID platform: Medline, Embase, Global Health and Google Scholar. Studies were screened using predetermined eligibility criteria. Data was extracted based on study and patient characteristics, modes of detection, and commercial availability, followed by quality assessment.

A total of 17 studies were included. The primary diagnosis varied, with osteosarcoma being reported by 9 studies. Three studies reported relapse, ranging between 17.6%–48%. Twelve studies reported non-invasive imaging as the mode of detection used, while 4 studies reported the use of frozen section. MRI and CT were found to have an accuracy of up to 93 %. Raman spectroscopy was reported to have an accuracy, sensitivity, and specificity of 69%, 58.8% and 83.3% respectively. CT had a sensitivity and specificity up to 83% and 100%, respectively.

In conclusion, there seems to be high potential for the use of multimodal technologies to increase the accuracy of intraoperative margin assessment. Although imaging modalities possess a fair level of accuracy, they carry the risk of radiation exposure, are expensive, and cannot be used in-situ. Future clinical trials are needed to test the effectiveness of these technologies to measure the diagnostic accuracy and overall patient survival.

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Table 1
Medline Database search.

Number	Search terms	Results
1	("Medical device*" or Intervention* or Assess* or Detect* or Technolog* or "image device*" or "imaging device*" or probe*).mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	7,007,565
2	(Intra?operative or monitor or non?invasive or Residual or Retain* or Remain* or "During surgery" or "Real?time" or Boundar* or Edge or "re?excise").mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	2,812,795
3	(Osteosarcoma or "Ewing* Sarcoma" or "Bone cancer" or "Hard tissue cancer" or "Hard tissue tumo?r" or Chondrosarcoma or "Multiple Myeloma" or "Osteochondroma" or "Giant cell tumo?r" or Chondroma).mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	111,805
4	1 and 2 and 3	3833

1. Introduction

Osteosarcoma is the most common primary bone-forming tumour that arises from the malignant transformation of bone building block cells, osteoblasts [1]. The two other types of primary bone tumours are Ewing sarcoma and chondrosarcomas, which are differentiated from osteosarcoma mainly by histological properties and primary localization [2,3]. The incidence of osteosarcoma is higher in adolescents and young adults (Male: Female ratio of 1.4) and is characterised by a bimodal age distribution with a first main peak at 18 years old and the secondary peak at 60 [2]. While it can affect any bone, it mostly arises at long bone extremities with the most proliferative growth plates such as the distal femur (42%), the tibia (19%) and the humerus (10%), followed by the skull or jaw (8%) and pelvis (8%) [4,5]. While the exact cause of osteosarcoma remains unknown, there are several common risk factors such as genetic predispositions, race (proportionally higher in indigenous African and African-American males), other bone diseases (e.g., Paget's disease), and increased radiation exposure [6]. Osteosarcoma tumours are highly heterogeneous, with studies showing more than 80-point mutations with over 80 genes involved [2,7]. They originate mostly from the metaphysis of the long bones causing a large palpable mass with swelling and pain, and as a result, patients usually present with limping, and decreased mobility of the affected limb. The survival rate majorly depends on the metastatic status of the tumour with a 5-year survival rate of 68% for adolescents between ages 15 to 19 [8]. Survival rate significantly drops to around 30% when the tumour metastasizes to the lungs [2]. An Italian study highlighted how patients who did not undergo surgery of recurrence had a 5-year post-relapse survival of 0%, compared to those who do undergo surgery, highlighting the invasive nature of osteosarcoma and the high potential of relapse [9].

2. Diagnosis and treatment

Osteosarcoma is diagnosed through conventional X-ray film and has a "sunburst" pattern of lytic bone lesions, characterised by cortical destruction and a periosteal reaction (Codman triangles) [10].

MRI is used to assess for soft tissue extension and CT scans to assess metastasis, which is often found in the lungs [10]. Osteosarcoma

Table 2
ROBINS-I tool for critical appraisal of the risk of bias in all studies included.

ROBINS-I Tool								
NON-RCTs	Change intervention bias	Classification of Intervention Bias	Measurement Outcome Bias	Missing Data Bias	Reporting Bias	Risk-of-Confounding Bias	Selection Bias	Overall Risk of Bias
L.Cannavò et al.[32]	unclear	low	low	low	low	low	low	low
Anderson et al. [16]	low	low	high	low	low	unclear	low	low
Bajpai et al. [21]	low	low	low	low	low	high	low	low
Aszódi et al. [33]	low	low	high	low	high	high	high	high
Fayad et al. [22]	low	low	low	low	high	high	high	low
Bosma et al. [30]	low	low	high	low	low	high	high	low
Boufettal et al. [35]	low	low	low	low	low	low	low	low
Cates et al. [24]	low	low	high	high	high	unclear	low	unclear
Seong Cho et al. [23]	low	low	low	low	low	unclear	low	low
Evrard et al. [31]	low	low	low	low	low	unclear	low	low
Fujiwara et al. [28]	low	low	low	low	low	unclear	low	low
Hodel et al. [29]	low	low	low	low	low	unclear	low	low
S. Shin et al. [34]	low	low	low	low	low	unclear	low	low
Malek et al. [25]	low	low	low	low	low	unclear	low	low
Meyer et al. [14]	low	low	high	high	low	unclear	high	high
Sakamoto et al. [26]	low	low	low	low	low	high	low	low
Wong et al. [27]	low	low	high	low	low	low	low	low

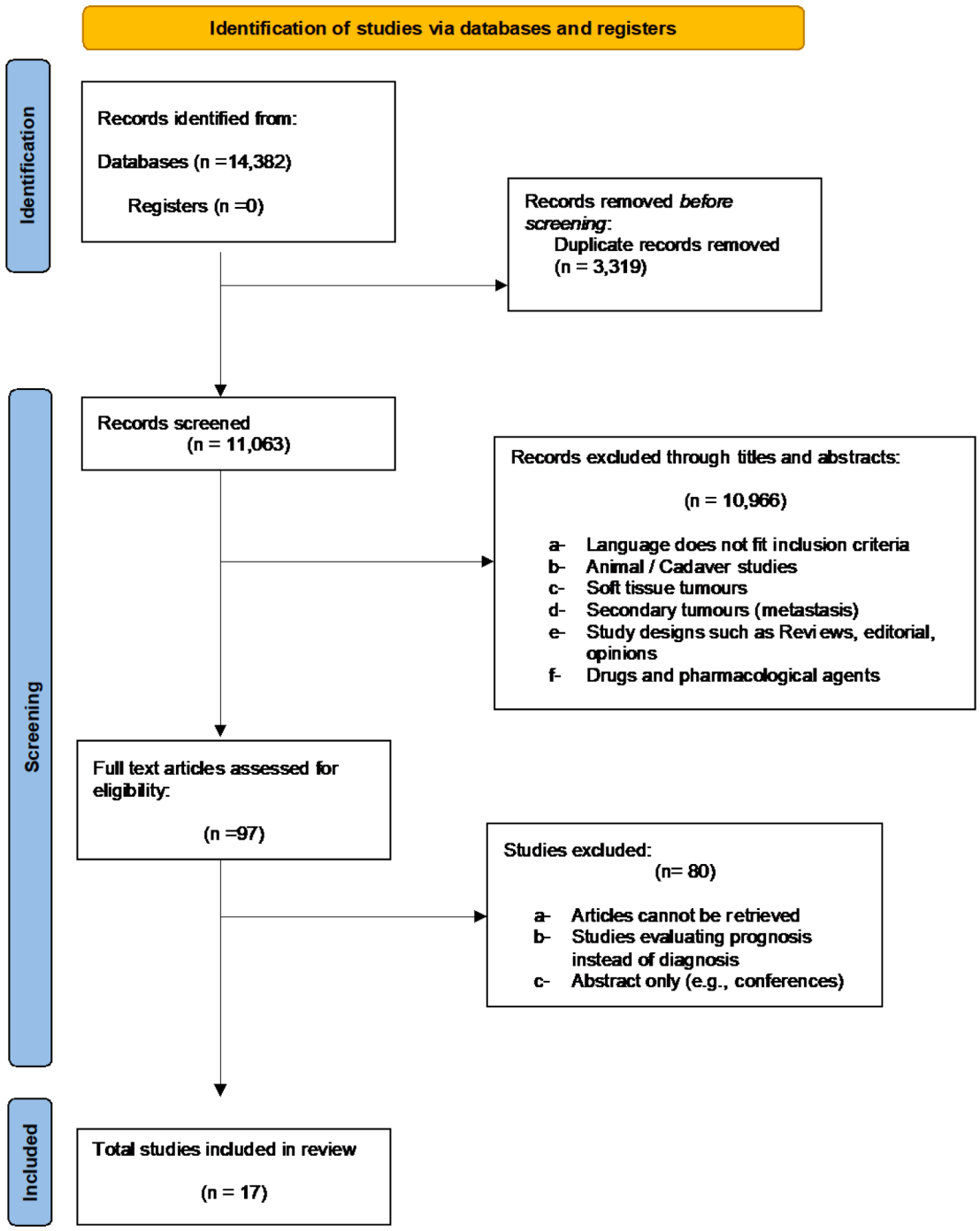

Fig. 1. PRISMA flowchart for results of the literature database search.

treatment includes a complexity of combinations such as disabling surgery (limb amputation), chemotherapy, radiotherapy, and prolonged rehabilitation. These increase the socio-economic and morbidity burden to patients, the community, and the healthcare system. In fact, there are 17 Disability Adjusted Life Years (DALYs) attributed due to osteosarcoma alone compared to 6.5 for bowel, lung, and breast cancers which makes the treatment for osteosarcoma a public health concern [11].

2.1. The importance of intraoperative margin assessment

Complete surgical excision is a critical aspect of the treatment to ensure optimum outcomes and lower rates of recurrence [4]. Patients who suffer from osteosarcoma recurrence currently face less than 20% survival rate in the long term [10]. Orthopaedic surgeons in oncology face challenging decisions as they assess intraoperative margins of resection; While the main goal is to salvage as much functional tissue as possible, they can often be left with no other option but to resect beyond the margin to decrease the risk of recurrence, which can often lead to amputation. These debilitating procedures affect functionality of the limb, cosmetic appearance, and psychological well-being of patients [10]. Furthermore, after primary surgical treatment, patients face up to a 40% chance of cancer recurrence due to local relapse from residual marginal osteosarcoma cells that were not picked up initially by the surgeon [12,13]. This requires the need to undergo additional surgeries, chemotherapy, and radiotherapy exposure. It is also worth mentioning the increased costs on the hospital due to longer stays and adverse

Table 3
Summary of the characteristics of the studies evaluating intraoperative margin assessment.

Author	Study design	Number of patients	Primary diagnosis (number of patients)	Relapse (%)	Technology	Distinguishing factors	Detection mode
L.Cannavò et al.[32]	Retrospective Cohort	46	Primary malignant bone tumours	No	MRI + CT	Bone and soft-tissue margins	Non-invasive
Anderson et al. [16]	Retrospective Cohort	142	Primary bone sarcomas	No	Cryosection + Microscopical analysis	Bone marrow margins	Invasive
Bajpai et al. [21]	Prospective Cohort	31	Osteosarcoma	No	Dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI)	VEGF and Angiogenesis	Non-invasive
Aszodi et al. [33]	Prospective Cohort	13	Primary bone sarcomas	No	Cryosection + Microscopical analysis	Histological examination of malignancy	Invasive
Fayad et al. [22]	Retrospective Cohort	13	Skeletal sarcomas	No	Multivoxel proton magnetic resonance spectroscopic imaging (MRSI)	Markers of malignancy, such as elevated levels of metabolites (choline) that reflect high cell turnover	Non-invasive
Bosma et al. [30]	Case control	70	Pelvic or Sacral sarcomas	No	CT fluoroscopy / intraop. CT	Bone and soft-tissue surgical margins (Enneking system)	Non-invasive
Boufettal et al. [35]	Case series	5	Osteoid osteoma	No	Isotopic tracking probe using HMDP-99mTc probe	99mTc-HMDP tracer fixation on the bone lesion	Minimally invasive
Cates et al. [24]	Retrospective cohort	186	High-grade osteosarcomas	**Yes** (20%)	Musculoskeletal Tumor Society (MSTS) + American Joint Committee on Cancer (AJCC) R system + margin distance method	Pathology reports and operative notes	Margin assessment schemes
Seong Cho et al. [23]	Retrospective cohort	6	High-grade osteosarcoma, chondrosarcoma, and adamantinoma	No	MR images to navigation-assisted bone tumor surgery	Bone and soft-tissue margins	Non-invasive
Evrard et al. [31]	Case-Control	28	Primary pelvic bone sarcomas	No	MRI + CT + Patient-specific instruments (PSIs)	Bony margins and soft-tissue margins	Non-invasive
Fujiwara et al. [28]	Case control	50	Chondrosarcoma	Yes (**48%**)	Oncology-specific navigation surgery (fused with pre-op CT and MR images)	Bone and soft-tissue margins	Non-invasive
Hodel et al. [29]	Retrospective Cohort	68	Chondrosarcoma	Yes (**17.6%**)	CT	Histological grading	Non-invasive
Kseniya S. Shin et al. [34]	Specimen study	16	Skull base tumours	N/A	Stimulated Raman scattering (SRS) imaging technique with a new pseudo-H&E recolouring methodology	Histological examination	Non-invasive
Malek et al. [25]	Case control	32	Osteosarcoma	N/A	Diffusion-weighted (DW) imaging and proton magnetic resonance (MR) spectroscopy	MR Spectroscopy- choline containing compounds. DWI- Restriction of water molecules mobility	Non-invasive
Meyer et al. [14]	Retrospective Cohort	113	High grade osteosarcoma	**Yes ((8.2% (7/85))**	Frozen section with/without pre-operative MRI	Marrow margins	Non-invasive Pre-operative MRI + Invasive (frozen section)
Sakamoto et al. [26]	Specimen study	5	Primary bone sarcomas	N/A	Intra-operative specimen MRI	Marrow margins	Mixed
Wong et al. [27]	Retrospective Cohort	8	High grade osteosarcoma, parosteal osteosarcoma, Low grade chondrosarcoma	No	MRI + CT + 3D software aided visualization for navigation	Transition of marrow signal from abnormal to normal in T1-weighted MR images.	Non-invasive

effects on the patient such as anxiety, increased risk of postoperative infections and poor cosmesis.

The current standard of care to assess intraoperative marginal cells involves examination of the excised tissue by frozen section analysis in the pathology lab [14]. This intraoperative method is labour and resource-intensive, with relatively low sensitivity and specificity [15] and increases surgery time. Additionally, there might be technical challenges with frozen sections due to the amount of fat and the bony aspect of the specimen, which can interfere with the assessment of bone marrow margins [16]. The lack of precise intraoperative margin assessment tools for bone cancer is an unmet need to reduce local cancer recurrence. Sufficient marginal resection is a widely discussed subject and there is no innovative intervention to detect intraoperative margin bone-cancer osteosarcoma cells.

The aim of this study is to highlight the current existing and emerging technologies and their efficacy in detecting clear bone margins during intraoperative bone cancer resection.

3. Material and methods

This systematic review protocol was developed and registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD 42021251826 [17]. The Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) guidelines and flowchart were used for designing this study [18].

3.1. Search strategy

The SPIDER tool (Sample - Phenomenon of Interest - Design - Evaluation - Research type) was adopted and modified to formulate the research question and to establish the eligibility criteria [19]. Search terms were then developed to identify articles from the following databases: Medline, Embase, Global Health and Google Scholar using the OVID platform (Table 1). Key terms that were used in the search were on the relevant technologies, margin assessment intraoperatively for hard

Table 4
Mechanism of Action of the technologies mentioned in the studies.

Technology	Mechanism of action
Magnetic Resonance Imaging (MRI)	Production of a magnetic field to force alignment of H protons found in water of tissues
Computed Tomography (CT) / CT fluoroscopy	Combination of different X-rays taken from different angles in the body – generation cross section images of the body. A combination with fluoroscopy gives real-time imaging that can be useful in interventional procedures
Cryosection + Microscopical analysis	Tissue cut and frozen with the microtome portion of the cryostat and stained for microscopical analysis
Dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI)	Injection of a paramagnetic contrast agent to enhance pattern of tissue – which is seen using MRI
Integrated 18F-FDG PET/CT (F-fluorodeoxyglucose positron emission tomography/computed tomography)	Hybrid imaging approach by the Integration of F-FDG PET and CT. CT data were used for attenuation correction and anatomic localization of PET lesions
Multivoxel proton magnetic resonance spectroscopic imaging (MRSI)	Molecular imaging with MRI – using a map representing signal intensity of metabolites in tissues
Isotopic tracking probe using HMDP-99mTc probe	I.V injection of a tracer (HMDP-99mTc) that will be fixed to the lesion – Radio-detection carried out using gamma camera.
3D-multimodality image (3DMMI-based virtual surgical planning) and 3D-printed patient-specific instruments (PSI)	Assimilating each separate radiographic image into a single 3DMMI revealing all structures in the pelvis
Navigation assisted surgery (3D software). By Stryker	Real-time intraoperative assessments of stability and range of motion
Fast simultaneous two-channel stimulated Raman scattering (SRS) imaging technique and a new pseudo-hematoxylin and eosin (H&E) recolouring methodology	Use of two pulse lasers (pump and Stokes) to excite intrinsic vibrational motions of molecules coherently and detect their unique characteristics on a spectrum
Diffusion-weighted (DW) imaging and proton magnetic resonance (MR)	Measures the Brownian motion of water molecules within a voxel of tissue
Flat-panel volumetric computed tomography	8–16-fold higher image resolution than conventional CTs with shorter acquisition time

tissue tumours and they were combined using Boolean terms (AND/OR). The search was done on articles since inception. Selected articles were then exported to Endnote X9 reference manager software to organise, screen and group articles. After the articles were exported, duplicates were removed manually and electronically.

3.2. Study selection

The review included articles published in English, French, Italian, Urdu and Arabic. Studies included were only those conducted intra-operatively on alive human beings with hard tissue tumours. There were no geographic, gender or ethnic background preferences. Study designs such as randomised control studies (RCTs), cohort, case controls, case series and case report were included. All other languages, animal and cadaver studies articles with soft tissue tumours were excluded. Editorials, reviews, and opinions were also excluded.

3.3. Data extraction and analysis

Five reviewers independently extracted the relevant study data from the final pool of included articles and imported the data on a spreadsheet designed a priori on Microsoft Excel 2013 (Microsoft Corporation, Redmond, Washington, USA). Data was extracted based on the study design, primary diagnosis, relapse, technology used, mode of detection, mechanism of action, distinguishing factors, technology class category, commercial availability, and its patent presence. The quality of all included studies was then analysed using the ROBINS-I tool for critical appraisal of the risk of bias (Table 2) [20].

3.4. Data synthesis

The data found will be grouped into mode of detection categories and will be matched to the primary diagnosis found. The technologies behind the operation of these detection modes will be identified and compared with each other through their distinguishing factors. The percentage of cancer relapse amongst the use of these technologies will be found. The accuracy for detection of cancer cells on the margins will be stated.

4. Results

4.1. Database search results

The results of the database search and screening process are detailed in the PRISMA flow diagram (Fig. 1). A total of 14,382 articles were found in the initial database search, with n = 10,441 from Embase, n = 3,833 articles from Medline, and n = 108 from Global Health. Duplicates were removed (n = 3,319), and the remaining 11, 063 articles were screened. An initial title and abstract screening excluded 10, 966 articles following the above-mentioned inclusion and exclusion criteria. Finally, 97 articles were eligible for full-text review. A total of 80 studies were excluded for the following reasons: a) records could not be retrieved, b) records consisted of abstract only, and c) articles were evaluating prognosis instead of diagnosis. Seventeen studies were included in the final systematic review.

4.2. Study and patient Characteristics:

A total of 17 studies were included in this review (Table 3). These studies ranged from the year 1980, to 2020. Eight were retrospective cohort studies, two were prospective studies, one specimen study, and the rest being case controls/series. The number of patients in each study ranged from 5 to 186, with 5 studies reporting over 50 patients. The primary diagnosis for patients varied across the 20 studies. Eight studies reported osteosarcoma as the primary diagnosis [14,21–27]. Other bone tumours included chondrosarcoma (reported by 5 studies) [22,23,27–29], pelvic/sacral tumours (2 studies) [30,31], primary bone tumours such as malignant giant cell tumours, rhabdomyosarcoma, and plasmacytoma (1 study), osteoid osteoma (2 studies), and skull-base tumours (1 study) (Table 3).

4.3. Relapse and detection modes:

Relapse of the cancer was reported by four studies ranging between 17.6% – 48% [14,24,28,29]. Ten studies reported non-invasive imaging as the mode of detection used [21–23,25,27–32], while 4 studies reported the use of frozen section (invasive) [14,16,29,33]. Other methods of detection included Raman scattering (1 study) [34], Spectroscopy (1 study) [22], and margin assessment schemes (1 study) [24].

Non-invasive imaging modalities involved using Magnetic Resonance Imaging (MRI), Multivoxel proton magnetic resonance spectroscopic imaging (MRSI), Dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI), Computed Tomography (CT), CT-Fluoroscopy. Table 4 refers to the mechanism of action of each of these imaging modalities. Nine studies reported the use of one or several of these non-invasive modalities [14,22,23,26,27,29–32]. MRI, MRSI, CT, and CT-

Table 5
Technical information of the technologies used in the studies.

Author	Technology	Class category	Commercial availability	Patent for the technology	Accuracy	Sensitivity	Specificity
L.Cannavò et al. [32]	MRI + CT	2	Yes	N/A	76% to 83%-Radiologist 68% to 72%-(Orthopaedist)	–	–
Anderson et al. [16]	Frozen section	N/A	Yes	Yes	–	–	–
Bajpai et al. [21]	DCE-MRI	2	Yes	N/A	–	–	–
Aszodi et al. [33]	Frozen section	N/A	Yes	Yes	–	–	–
Fayad et al. [22]	MRSI	–	Yes	Yes	–	–	–
Bosma et al. [30]	CT fluoroscopy / intraop. CT	2	Yes	N/A	–	–	–
Boufettal et al. [35]	Isotopic tracking probe using HMDP-99mTc probe	2	Yes	Yes	–	–	–
Cates et al. [24]	Musculoskeletal Tumor Society (MSTS) + American Joint Committee on Cancer (AJCC) R system + margin distance method	–	–	–	–	–	–
Seong Cho et al. [23]	MR images to navigation-assisted bone tumour surgery	2	Yes	Yes	–	–	–
Evrard et al. [31]	MRI + CT + Patient-specific instruments (PSIs)	2	Yes	Yes	–	–	–
Fujiwara et al. [28]	Navigation assisted surgery	–	Yes	Yes	–	–	–
Hodel et al. [29]	CT	N/A	Yes	N/A	–	–	–
Kseniya S. Shin et al [34]	Stimulated Raman scattering (SRS) imaging technique and a new pseudo-H&E recolouring methodology	–	Yes	Yes	69%	58.80%	83.30%
Malek et al. [25]	DW imaging and proton MR spectroscopy	–	510 (K) clearance by FDA	Not found	87% (92% FS)	–	–
Meyer et al. [14]	Frozen section / MRI	N/A	Yes	Yes	–	–	–
Sakamoto et al. [26]	Intra operative specimen MRI	N/A	Yes	Yes	–	–	–
Wong et al. [27]	MRI + CT + 3D software aided visualization for navigation	N/A	Yes	Yes (software)	–	–	–

Fluoroscopy distinguished cancerous cells from ordinary cells by detecting bone, marrow, and soft tissue margins. DCE-MRI identified angiogenesis and Vascular Endothelial Growth Factor (VEGF) to identify the presence and growth of blood vessels. Invasive imaging modalities included the use of 2-deoxy-2-[fluorine-18] fluoro- D-glucose Computer Tomography (18F-FDG PET/CT), Isotopic tracking probe using HMDP-99mTc probe, cryo/frozen section, Stimulated Raman Scattering (SRS) Microscopy of histology samples, Intraoperative MRI of resected tissue, and Margin Assessment Schemes under Musculoskeletal Tumor Society (MSTS) and American Joint Committee on Cancer (AJCC) with an R system and margin distance method. Six studies reported the use of at least one invasive methodology [14,16,26,29,33,35]. 18F-FDG PET/CT and Isotopic tracking involved intravenous injection of an exogenous reagent/compound. Frozen section, SRS Microscopy, Intraoperative MRI, and Margin Assessment Schemes were performed using resected tissue and biopsies. These methods create pathology reports and histological examination that identify bone, marrow, and soft-tissue margins. Two studies reported the independent use of both invasive and non-invasive modalities in their methods [26,29].

Out of the 17 reported studies, 10 reported entire or partial elements of their methods under patent protection. Seven studies reported Class II medical devices under the Food and Drug Administration's (FDA) device class and regulatory controls, and three studies further reported commercially unavailable methods (Table 5). The different types of technologies used for tumour detection and relapses are presented in Table 6.

4.4. Quality assessment

All the studies reported were non-randomized studies. The Cochrane Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool was used to assess and report the risk of bias [20]. All 17 studies reported were measured against Change Intervention Bias, Classification of Intervention Bias, Measurement Outcome Bias, Missing Data Bias, Reporting Bias, Risk-of-Confounding Bias, and Selection Bias. All seven classifications were used to create an Overall Risk of Bias and each classification was determined using a Low, High and Unclear Bias grading measure. Twelve studies were determined to have a low Overall Risk of Bias, three studies were determined to have a high Overall Risk of Bias, and two studies were determined to have intermediate risk of bias. Fig. 2**a** refers to the risk of bias across all studies. Fig. 2**b** refers to the risk of bias per study.

5. Discussion

This systematic review highlighted the current and emerging technologies for the intraoperative margin assessment of hard tissue/bone tumours. Detection modes of all the technologies used for intraoperative assessment were labelled as invasive, minimally invasive, and non-invasive. Invasive technologies include frozen section since it involves

Table 6
Findings based on the type of bone cancer evaluated in the studies.

	Osteosarcoma	Chondrosarcoma	Ewing Sarcoma
Technologies used for detection	• MRI + CT • Cryosection and Microscopical analysis • DCE-MRI • MRSI • R system and Margin distance method • MR images to navigation-assisted surgery • DW imaging and MR spectroscopy • Frozen section +/- MRI • 3D software navigation	• MRI + CT • Cryosection and microscopical analysis • 3D software navigation • Stimulated Raman scattering • Oncology-specific navigation surgery (fused with pre-op CT and MR images) • MR images to navigation-assisted surgery	• MRI + CT • Cryosection and Microscopical
Invasive methods used	Yes	Yes	No
Relapse - Technology associated	**2 studies** [14,24] -Margin assessment schemes [24] and Frozen section +/- MRI [14]	**2 studies** [28,29] -CT [29] and Oncology specific navigation surgery [28]	No

taking a tissue biopsy from the patient and freezing the microtome of the cryostat. Minimally invasive technologies include F-FDG PET/CT and the I.V tracer injection of HMDP-99 m-Tc for radio-detection. Non-invasive technologies include MRI, MR, MRSI, DCE-MRI CT, and Computer 3D-assisted navigation. When considering technologies to evaluate the margins of tumour, an important criterion to consider is the assessment of the local recurrence that can potentially occur if residual tumour cells were left in the tissue. The highest rate of recurrence was observed in the study that used computer-navigation assisted technology, a minimally invasive detection mode [28].

Relapse of sarcoma was seen in up to 48% of cases where (PET/) CT scan was used to detect cancer cells on hard tissue margins. Comparing this with other studies, this was also seen in similar studies using similar tissue margin detection technologies where cancer recurrence was up to 30% in breast cancer [36–38]. Leaving residual cancer cells in tissues whether they were hard or soft leads to at least three times increased risk of cancer recurrence compared to those with negative tissue margins [38]. Once cancer reoccurs, it mostly leads to repeated surgeries and this is associated with higher surgical risk including poorer cosmetic outcomes, increased economic and psychological burden along with increased risk of infections and morbidity [39]. Hence, achieving microscopically clear margins is extremely crucial to minimise the risk of local recurrence.

The current practice for margin assessment of tissues in most institutions is performing a frozen section or specimen radiography [37]. Frozen section is amongst the most accurate diagnostic tools for margin detection of residual cells with an accuracy of 83% [15] and a sensitivity of 65–78% [15,40]. However, it is still associated with some challenges such as being time consuming, leading to increased operation duration, technically challenging, expensive, and requires an experienced pathologist [15,40].

MRI and CT scanning for marginal assessment in hard tissues showed accuracy of up to 93%. To put this into context with non-hard tumours, this was close to the accuracy found in detecting cancer cells on the margins of excised breast tissues in breast cancer [36]. CT scanning had a sensitivity and specificity up to 83% and 100%, respectively, in marginal detection of hard tissue cancer cells. In breast tissue, however, the sensitivity of CT scanning to detect marginal cancer cells was 56%-83% and specificity between 94.7% – 100% [38,41]. MRI accuracy, sensitivity, and specificity for margin assessment of breast cancer was 92%, 91% and 93%, but it is not yet endorsed for usage inside the operating room because of its high costs, size, and availability [36]. Diffusion weighted Magnetic Resonance has also shown its way in breast cancer margin assessment with sensitivity and specificity of up to 80% and 84%, respectively [37]. This technology was used with the Clear-Sight system, and it showed success for assessment of tumours in freshly excised tissue [37]. The main drawbacks of using imaging technologies include the major disruption to workflow, high costs and increased exposure to radiation.

Raman spectroscopy has shown to have an accuracy, sensitivity, and specificity of 69%, 58.8% and 83.3% respectively. When this technology was used for brain cancer cells detection, it was shown to be more accurate than MRI and was able to detect previously undetectable cancer cells with a sensitivity and specificity of 93% and 91% respectively [42]. The use of Raman Spectroscopy is still at its infancy stages for clinical applications, but its use in *in vivo* models seems promising so far [43]. Raman mainly "reads" the molecular characteristics of tissues and displays the different biomarkers that are pre-programmed through a database on a spectrum in forms of specific peaks. The main advantage of this technology is its capability in being used in situ without disruption to operation workflow and its quick pick up of cancer cells [42].

Research has shown that while intraoperative margin assessment for cancer cells is still a challenge, up to 46% of patients would need a repeat surgery to re-excise residual tumour cells [37]. In situ cancer detection is still a challenge since the interface for interaction between the normal tissue and cancer is hard to visualise [44]. The above-mentioned strategies all involve resection of the pathologic tissue and conducting marginal assessments on the excised tissue while still leaving the normal tissue without assessment. The major drawbacks of these techniques include the disruption of workflow, increased time of operation, high costs and lack of normal tissue marginal assessments. This means that there is still an unmet clinical need for practical and innovative tools to assess margins in situ in real time for an efficient workflow, reduced time and accurate outcomes [44]. Evrard et al., has also recently shown the importance of margin assessment and how using a patient specific instrument for tumour resection with MRI has a synergistic effect in increasing accuracy [45].

The use of multi-modal technologies in one device seems to be the future for increased accuracy. Jermyn et al. showed that using a multimodal spectroscopy that uses Raman spectroscopy, intrinsic fluorescence spectroscopy and diffuse reflectance spectroscopy in situ has maximised cancer cell detection during surgery with accuracy, sensitivity and specificity of 97%, 100% and 93%, respectively [44]. The synergistic effect of these technologies into one innovation have provided maximum cancer detection levels and has the potential to be used for other cancers and tissues.

The limitations that this study encountered included the heterogeneous nature of studies including making it difficult to conduct a *meta*-analysis of the results due to lack of unified measures of associations across the studies. The studies also had a very wide range in the numbers of patients which might not provide a strong sample size for the power of the studies, thereby affecting the external validity. In addition, not all studies reported the accuracy, sensitivity and specificity of the devices used, making it not possible to determine the effectiveness of these technologies. Finally, the included studies were all observational and there were no randomised control trials which are considered to be of higher quality of evidence for diagnostic studies.

6. Conclusions

In conclusion, intraoperative in situ detection of marginal cancer cells in vivo still remains a challenge with the main aim of reducing residual cancer cells and repeat surgeries. There seems to be high potential for the use of multimodal technologies to increase accuracy for cancer detection intraoperatively. Imaging technologies, although posit

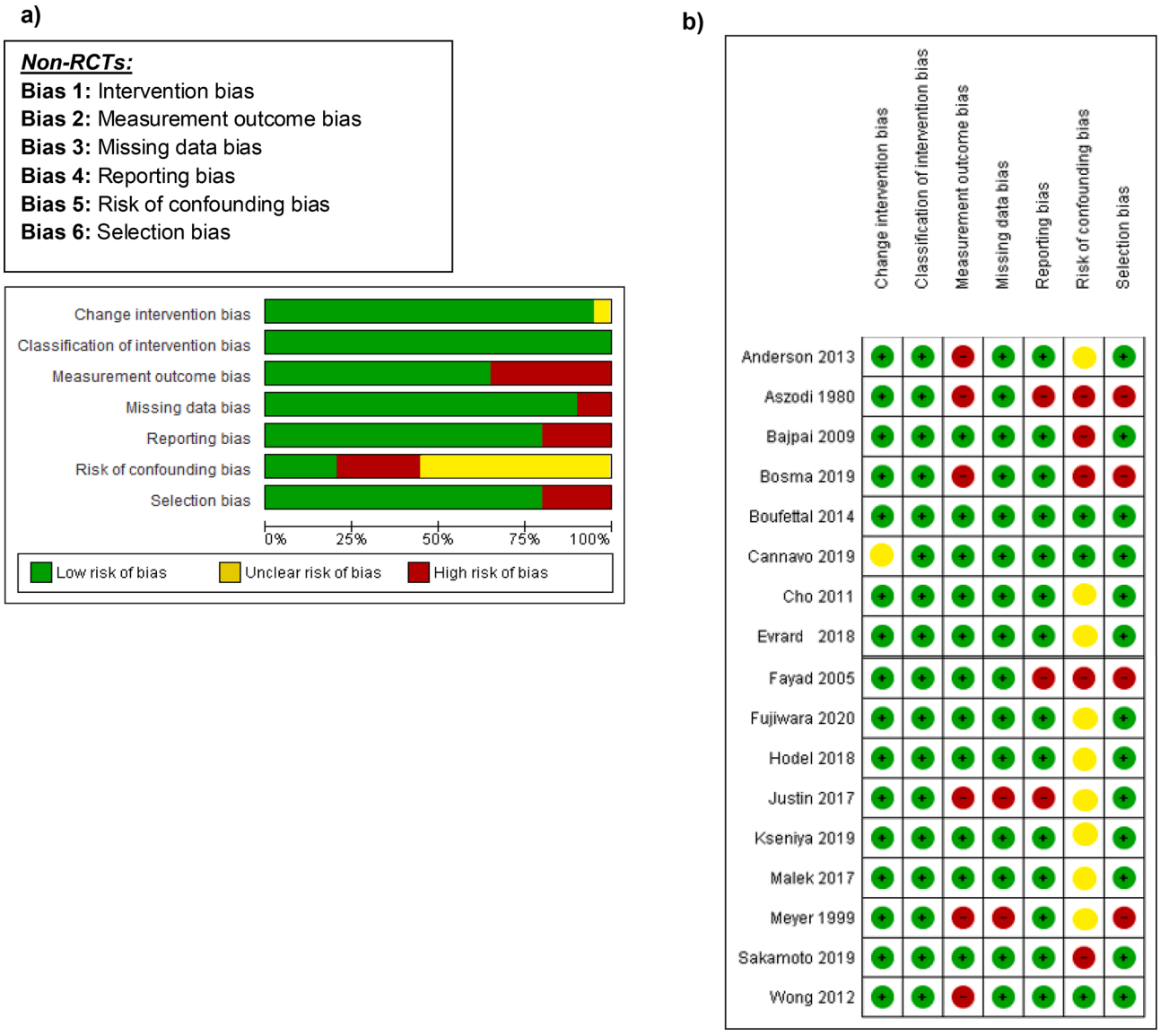

Fig. 2. (a) Cochrane risk of bias graph - assessment of non-randomized studies (b) Cochrane risk of bias summary of all non-randomized studies [14,16,21–35] (Risk of bias graph and summary: review authors' judgements about each risk of bias item presented as percentages across all included studies.).

decent levels of accuracy, still carry risks of radiation, are expensive, and not used in. It would therefore be interesting to explore alternatives to imaging technologies such as Raman. Finally, future clinical trials are needed to test the effectiveness of these technologies to measure the diagnostic accuracy and overall patient survival.

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Declaration of Competing Interest

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