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Four-Dimensional Computed Tomography (4DCT) in Radiation Oncology: A Practical Overview

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Abstract

Purpose of Review It has been 20 years since four-dimensional computed tomography (4DCT) was adopted in radiation oncology. By acquiring respiratory-correlated CT images, 4DCT allows characterization of tumour motion during radiotherapy target delineation. This technology has improved tumour delineation accuracy, in fact, it is now considered essential for highly conformal, high radiation, and precise radiotherapy treatment delivery. Nevertheless, due to the sampling of irregular patient breathing cycles, 4DCT suffers from image artefacts that can compromise tumour delineation accuracy. Addressing this challenge has been the driving motivation behind the latest advancements in 4DCT implementations. The purpose of this review is to provide a practical overview on 4DCT technology, its developments, and how it is used in radiation oncology.

Recent Findings The most significant hardware advancement in helical CT scanner technology has been the increase of CT-slices from 16 to 256/320-slice, allowing faster scan times. In terms of software developments, reconstruction algorithms have greatly improved, and a multitude of artefact reduction techniques has been demonstrated to be beneficial—though not all are commercially available. Nowadays, it is possible to significantly reduce artefacts to nearly non-discernible levels. This is achievable through recent innovations in 4DCT which merge advanced hardware and software tools to implement patient-specific models that account for breathing irregularities to efficiently acquire high-integrity CT data.

Summary This article provides a practical review of how 4DCT technology has evolved in radiation oncology, from both a technical and logistical point of view.

Keywords 4D computed tomography · 4DCT · Radiation oncology · Radiotherapy · Radiation therapy · SBRT · Review article

Introduction

Radiotherapy treatment planning begins by obtaining a computed tomography (CT) scan of a patient, which is referred to as a treatment simulation CT. The purpose of the simulation CT is to obtain 3D anatomical information of the patient's treatment site and surrounding anatomy, determine a patient's reference position, ensure that the patient is positioned in a reproducible and comfortable setup for treatment, and to use their CT to generate a customized treatment plan. 3DCT simulation is conducted while the patient breathes freely. By using 3DCT simulation, the treatment plan is generated using radiological images that portray a snapshot in time of the tumour's position, size, and location.

Technical advancements have made it possible for radiotherapy deliveries to be shaped and conformed to the treatment target. This allows maximization of radiation dose delivery to the target volume while simultaneously sparing nearby healthy tissue. Treatment targets located near the diaphragm (such as lung and liver tumours) move with patient respiration [1]. For example, depending on which lobe the tumour is in [1], these tumours can move up to 2 cm with the largest magnitude of motion being in the craniocaudal

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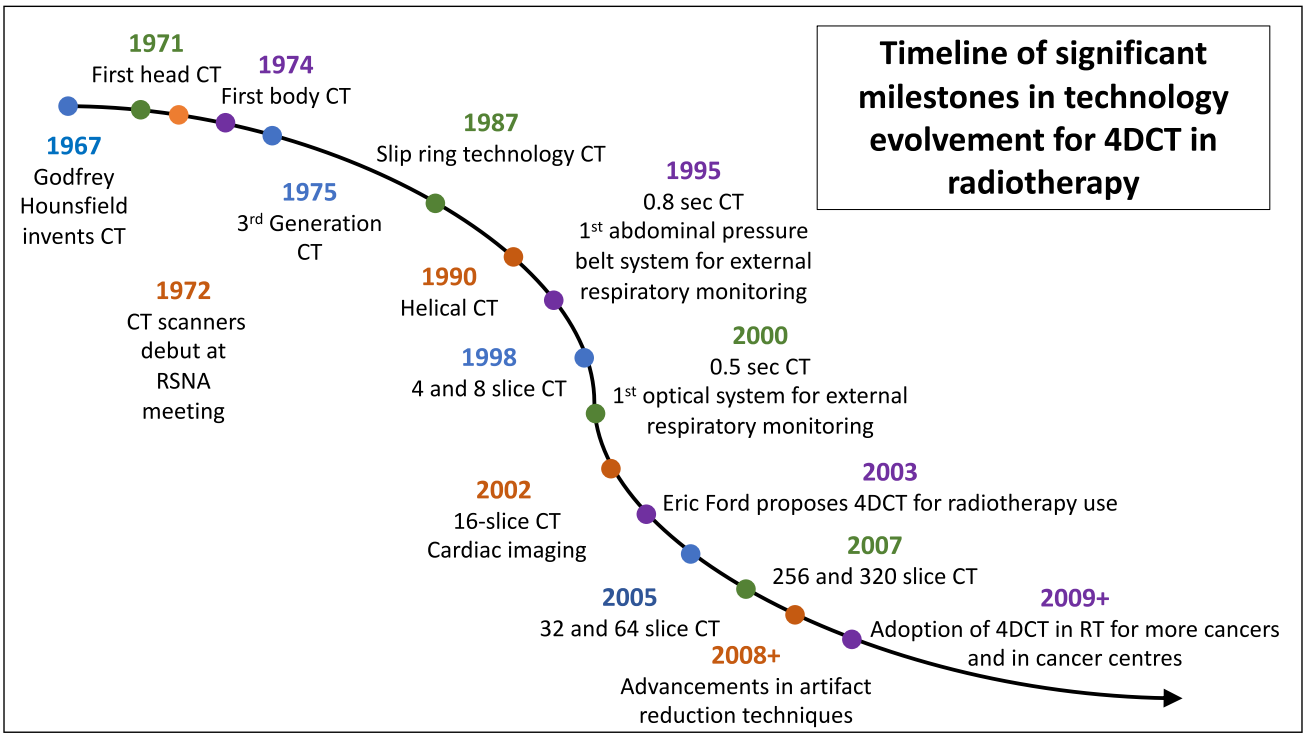

Fig. 1 A summary timeline of significant milestones in technology evolvement for 4DCT in radiation oncology

direction [2]. Radiotherapy treatment plans are traditionally designed for a fixed target, and if the variability in tumour position, volume and size are not well accounted for during treatment planning, then geometric errors can manifest in errors during treatment delivery [3, 4].

Four-dimensional CT (4DCT) provides respiratory-correlated CT scans that can be used to characterize target motion. This is achieved by acquiring CT data during multiple respiratory states. By using 4DCT during radiotherapy treatment planning, it is possible to better visualize and incorporate a moving tumour's position, volume and size, thus, improving radiotherapy planning accuracy.

The aim of this paper is to provide an overview on the use of 4DCT in radiation oncology. First, a summary of the historical development of 4DCT will be presented. This is followed by a review of anatomical sites where the use of 4DCT in radiation oncology is found to be most beneficial. Common 4DCT image acquisition techniques used are then explored, followed by an overview on the typical workflow for acquiring and utilizing 4DCT in radiotherapy. Since radiotherapy requires stringent quality assurance measures, an overview of recommended quality assurance tests for 4DCT is then provided. Typical considerations that arise when using 4DCT in radiotherapy are then discussed, with an emphasis on both technical and logistical considerations. Other modalities utilized for acquiring respiratory-correlated images are then introduced. This review concludes with a review of novel and anticipated developments in the utilization of 4DCT for radiation therapy as well as future directions in radiology.

Historical Development

CT technology has significantly improved since it was first developed in 1972 by Godfrey Hounsfield [5]. This rapid evolvement has paved the way to develop and adopt 4DCT in radiation oncology. As will be reviewed below, scan acquisition time has significantly decreased since the early implementations of CT. It is now possible to acquire 4DCT image sets within the average human respiratory cycle [6], making this technology more practical for routine clinical use.

Below is a summary of 4DCT key historical milestones, which are also graphically presented in Fig. 1.

Early Developments (1970s–1990s)

First-generation CTs were introduced in the early 1970's [5]. Early CTs relied on collimated small pencil beams and a single detector that translated to cover the imaging object before the source was rotated to acquire the next view. The average scan duration for first-generation CTs varied between 30 min and a few hours, with image reconstruction times taking up to several days [7]. Second-generation CT scanners used mini-fan beams and multiple detectors

to minimize translations, reducing scan acquisition times to around 2 min per slice. Third-generation CT scanners were introduced by Essential Medical Imaging (EMI) and were considered a significant improvement. These scanners use fan-beam geometry and multiple detectors to allow full coverage of the field of view by rotating simultaneously, further reducing scan time. In 1976, fourth-generation CTs were introduced. These CT scanners had a fixed ring of detectors and a rotating X-ray source; however, they were found to be expensive and impractical. In general, early CT techniques were limited by slow scan speeds and poor image quality, making them unsuitable for clinical use in radiation oncology.

Advancements and Early Adoption (1990s–2000s)

A major technological leap in CT systems occurred in 1990 when slip-ring technology was introduced. A slip ring is an electromechanical device that allows the transmission of electrical signals from a stationary to a rotating object; thus, continuous gantry rotation became feasible [8]. In 1990, and by employing slip-ring technology, helical CT was introduced by combining a rotating gantry with a translating imaging couch.

Until 1998, CT scanning was performed using a fan beam and a single slice. 4DCT became feasible after multi-slice scanners were introduced, which reduced slice scan time to seconds and decreased heat loading [9]. The first multi-slice scanner was a 4-slice scanner and allowed image acquisition that extended along the patient's craniocaudal direction.

The 1990s and early 2000s witnessed major advancements in technology which paved the way for practical 4DCT applications in radiation oncology. Faster scan speeds, improved image quality, and the introduction of multi-slice CT scanners enabled the acquisition of high-resolution 4DCT images within a tolerable breath-hold time for patients [10].

Clinical Adoption of 4DCT (2000s-Present)

In the early 2000's, and as cardiac CT imaging took the forefront, optimization of CT technology focused on further reducing scan time to enable cardiac imaging within the heart rate timeframe [11]. Multi-slice CT expanded to 16 slices in 2002 [12], 64 slices in 2004 [13], then 256 and 320 slices in 2007 [14]. Finally, it was possible to achieve rapid scan times and extend the field of view to 16 cm along the craniocaudal direction (the long/vertical axis of the heart). Multi-slice CT scan acquisition average times further reduced to approximately 15s, which accommodates 2–3 breathing cycles.

In 2003, Ford et al. [15] proposed the use of 4DCT (respiratory-correlated CT) in radiation oncology. Through experimental validation using a moving phantom, they demonstrated that respiratory-correlated CT is an effective method for reconstructing complete 3DCT datasets at multiple respiratory phases using a single helical 3DCT scan. Vendors promptly realized the potential advantages for radiation oncology and quickly adopted 4DCT technology in commercial solutions [16, 17].

The mid to late 2000s met widespread adoption of 4DCT in radiation oncology clinics, particularly for treating tumours in the thorax and abdomen. As the technology matured, researchers focused on refining 4DCT acquisition methods [18], developing more sophisticated motion modelling algorithms [19•] and utilizing 4DCT for CT simulation

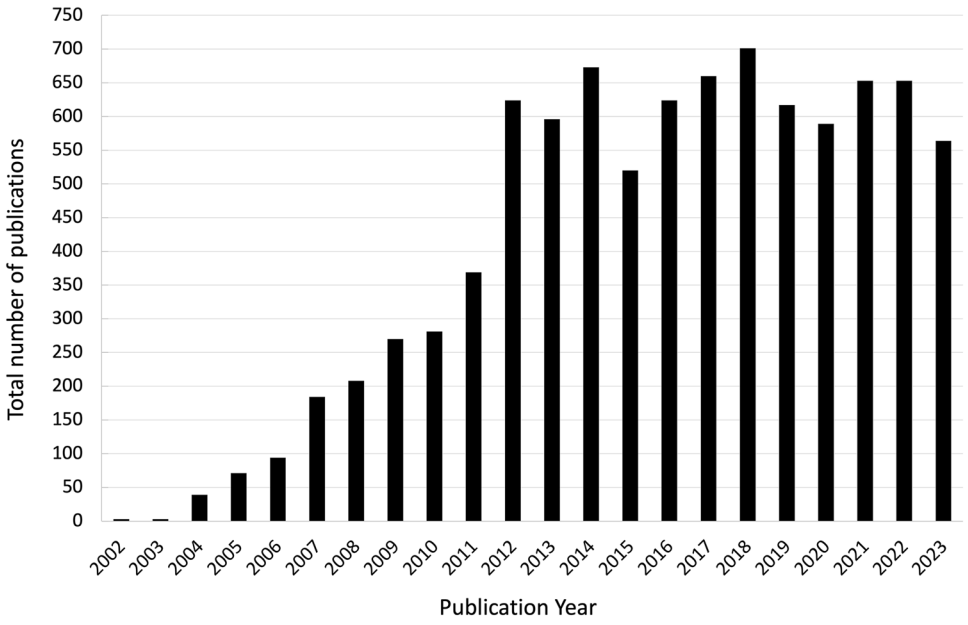

Fig. 2 The number of publications per year related to the use of 4DCT in radiation oncology in the last 20 years. Note that 4DCT in radiation oncology was proposed in 2002 by Ford et al.[15]. This figure was sourced from Dimensions® at https://app.dimensions.ai on November 13, 2023. Search criteria: "4DCT AND radiation oncology OR radiotherapy OR radiation therapy" in full data. 2023 Digital Science and Research Solutions Inc

of different types of cancers [20]. Figure 2 shows the rise in research and published clinical use of 4DCT in radiation oncology since it was first proposed.

Cancer Treatment Sites Benefitting from 4DCT Simulation

As previously mentioned, tumours that reside near the diaphragm tend to move during respiration, with the largest tumour motion usually observed in the craniocaudal direction. Table 1 lists tumour translation motion data reported for lung, liver and pancreatic tumours.

A recent survey was conducted in France to investigate the most common cancer sites that undergo 4DCT image acquisition during radiation therapy simulation [20]. One hundred and fifty-two radiotherapy centres responded to the survey, with a mixed response from private and government centres. Figure 3 shows a summary of their findings, which determined that 4DCT is most widely used in lung, liver (especially with oligometastatic tumours), adrenal, pancreatic and esophageal cancers. Although similar surveys have yet to be conducted in other regions in the world, the cancer sites reported in this study are those commonly encountered in radiation oncology clinics equipped with 4DCT-capable simulators.

In addition to requesting 4DCT radiotherapy simulation services by anatomical sites, there are also certain radiotherapy techniques that benefit from 4DCT simulation. Radiotherapy is conventionally delivered in ≤ 2 Gy dose per fraction. Over the past decade, stereotactic body radiation therapy (SBRT) has been shown to provide increased tumour control probability and lower associated toxicities for many cancer types, such as those of the lung and liver [24]. SBRT delivers high doses localized to the tumour site in fewer fractions. Since 4DCT facilitates accurate tumour targeting which in turn minimizes exposure to healthy tissues, it is considered an essential imaging tool for SBRT [2].

4DCT Acquisition

Although helical CT scanning paved the way for 4DCT technology, nowadays, 4DCT images are often acquired using the "cine" acquisition method. In helical CT acquisition, the patient lays on the table and is translated inside the CT scanner bore while the scanner gantry rotates. This results in

Table 1 Tumour motion data for some anatomical sites known to benefit from 4DCT simulation

Anatomical site	No. of patients in study	Average [mm] (Range) [mm]			Source
		CC	AP	RL	
Lung	25	12.5 ± 7.3 (6 to 34)	9.4 ± 5.2 (5 to 22)	7.3 ± 2.7 (3 to 12)	Erridge et al.[21]
Liver	10	5.3 ± 3.3 (1.5 to 14.8)	2.4 ± 2.2 (1.5 to 14.8)	1.7 ± 0.8 (0.6 to 3.8)	Shimohigashi et al. [22]
Pancreas	15	15 ± 9 (6 to 34)	5 ± 3 (1 to 13)	3 ± 1 (2 to 5)	Heerkens et al. [23]

Tumour motions are reported separately in the craniocaudal (CC), anterio-posterior (AP) and right-left (RL) directions

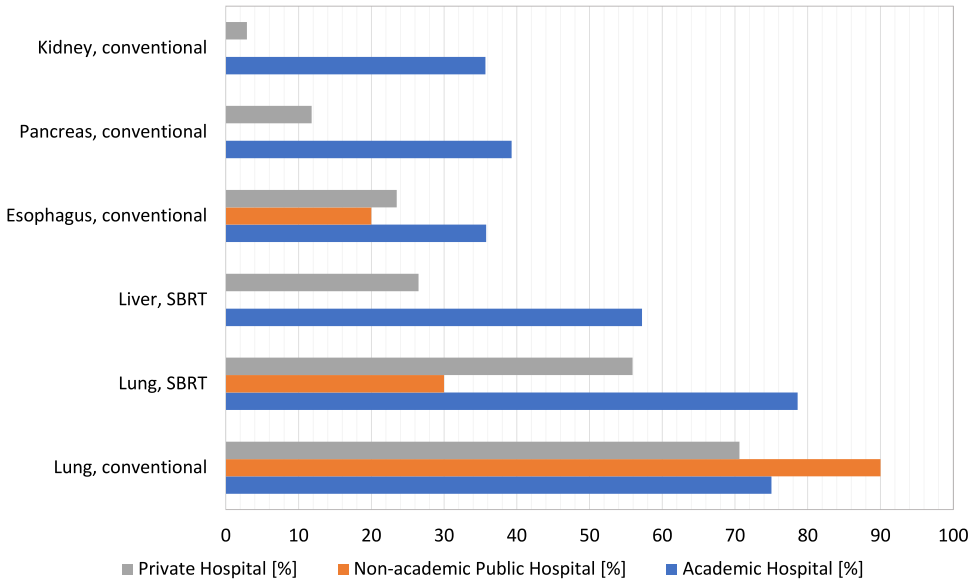

Fig. 3. 4DCT radiotherapy simulation use and frequency for different cancer sites depending on the type of radiation oncology centres. Original data collection was conducted and published in 2019 by Duarte et al.[20] as part of a national survey in France. Cancer sites treated with conventional dose fractionation (*i.e.* in ≤ 2 Gy dose per fraction) are distinguished from those treated with stereotactic body radiotherapy (SBRT), where higher doses per fraction are delivered in fewer fractions

a continuous apple peel-like pattern of the image acquisition trajectory. On the other hand, in cine acquisition, the gantry fully rotates around the patient while the table is fixed, the table then translates to the next position and repeats image acquisition unit the entire volume of interest is imaged. One advantage of cine-4DCT over helical-4DCT is that it is possible to generate a narrower slice sensitivity profile (and thus, a narrower slice thickness) [25]. 4DCT image integrity is primarily achieved by meeting the data sufficiency condition described by Parker [26] and Pan [27], which states that image acquisition must collect data at each location for the duration of a breathing cycle plus the duration of data acquisition for an image reconstruction.

4DCT images are often acquired by "stacking" image slices from each breathing phase to form multiple 3D images that correlate with various breathing states. Stacked image acquisition can be obtained prospectively or retrospectively [10]. In prospective acquisition, the CT scanner only acquires images at a breathing state of interest, such as during full inhalation. In retrospective acquisition, the CT scanner collects images at each couch position. Once the scan is complete, the scanning software correlates each image slice with a breathing state depending on the breathing cycle, and then sorts images belonging to each breathing state in a different bin. Each bin then produces a 3D image set for a particular breathing state. Most radiation oncology departments use 4DCT reconstruction protocols that generate ten breathing phases. In retrospective 4DCT, binning occurs after collecting the image set, so no additional imaging dose is delivered to the patient. However, in prospective 4DCT, imaging dose can increase if more breathing phases are captured, and the risk versus benefit of acquiring more data while increasing image dose becomes an important consideration. In both image acquisition scenarios, increasing the number of phases also means increasing data storage needed and decreasing data transfer speed, which are both an important logistical aspect to consider. Additional 4DCT logistical considerations are discussed in the next section.

Stacked image acquisition relies on using a breathing-signal surrogate to relay a metric that monitors breathing motion and correlates the patient's breathing to corresponding image slices in the image set collected. Breathing signal surrogates can be external, such as by using optical systems [16], abdominal pressure belts [28], or spirometry [29, 30]. Or, alternatively, they can be internal such as by using internal fiducial markers [31, 32] or data-based surrogates that identify internal anatomical features [33–35]. Depending on the application and resource availability in radiation oncology clinics, it is prudent to quantify the differences in image quality and reproducibility of various retrospective signal surrogate 4DCT systems and be confident in the adopted system. For example, Sprouts [36] sought to measured and quantify differences in the tumour volumes defined for lung, pancreas and liver cases obtained on 4DCTs acquired with two commercial systems. He found that both the commercial optical system (Real-Time Position Management RPM, Varian Medical Systems, Palo Alto, CA) and the commercial internal data-based surrogate system (Smart Deviceless 4D, GE HealthCare, General Electric Company, Chicago, IL) produced similar results.

4DCT Artefacts and Logistical Aspects

Seventy-five to ninety per cent of clinical 4DCT scans exhibit artefacts [29, 37, 38]. However, this does not mean these images are clinically unusable.

Image artefacts manifest as artificial spatial features on an image. If uncorrected, 4DCT artefacts can cause uncertainties in tumour volume, size and location, potentially extending to errors in radiotherapy treatment planning accuracy [18]. 4DCT artefacts can also cause inaccurate pixel values, which may lead to inaccurate radiation dose calculation by radiotherapy treatment planning systems [39]. The primary source of artefacts in 4DCT is irregularities in patient breathing motion [38, 40–42], this is because patients do not have a perfect breathing trace. In fact, as presented in Fig. 3, most radiation oncology patients being imaged with 4DCT are lung cancer patients, and their disease can impede their normal breathing ability. Other sources of artefacts are coughing, bin sorting inaccuracies, and inadequate scan settings. Figure 4 shows examples of common 4DCT artefacts as originally categorized by Yamamoto et al.[38], in which artefacts manifest as blurring, duplication of anatomical structures, overlapping structures, and incomplete structures.

There have been several strategies demonstrated to reduce 4DCT artefacts. One practical and simple strategy is to reduce scan pitch for helical-4DCT so that image slice interpolation is reduced [18], thus, minimizing ghosting artefacts. This technique is also effective for slow breathing patients. However, the downside of reducing the scan pitch is that imaging dose will increase, data storage capacity will increase, and the maximum X-ray tube "on" time will limit scan length. To overcome these limitations, two scans can be obtained and registered for radiotherapy planning: one with slow-pitch 4DCT just surrounding the tumour volume, and another free breathing CT with a longer field of view. If slow scans are used, another aspect to keep in mind relates to cases requiring image contrast administration. The timing of intravenous contrast uptake must be considered since long scan times may prevent contrast uptake in the imaging area of interest.

Several other techniques for cine-4DCT artefact reduction have been demonstrated. These are based on retrospectively reducing acquired data associated with breathing

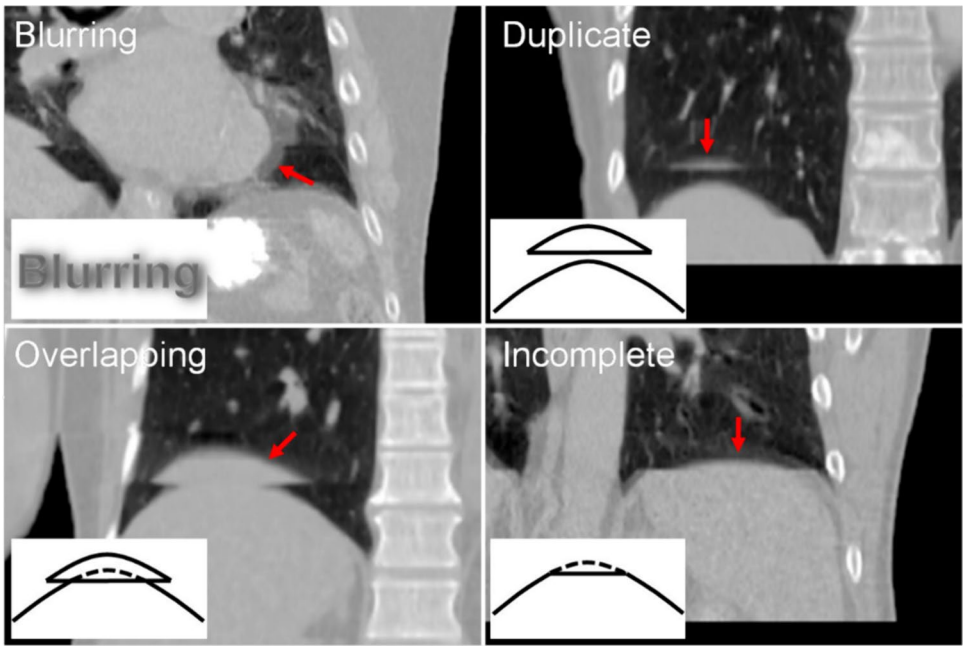

Fig. 4 "Example 4DCT images with schematic diagrams for four types of artefacts: blurring, duplicate structure, overlapping structure and incomplete structure. Corresponding artefacts are indicated by arrows in respective images." Reprinted from Retrospective Analysis of Artifacts in Four-Dimensional CT Images of 50 Abdominal and Thoracic Radiotherapy Patients, 72(4), Tokihiro Yamamoto, Ulrich Langner, Billy W. Loo, John Shen, Paul J. Keall. Pages No. 9, Copyright (Nov 15, 2008), with permission from Elsevier

irregularities from being collected when binning image slices associated with each breathing phase [38, 42, 43]. Prospective 4DCT artefact reduction methods have also been investigated by Keall et al.[29] and Castillo et al. [18], with one established technique being "oversampling" image acquisition.

One widely recognized artefact reduction approach is sorting respiratory-correlated data by amplitudes instead of phases during the data binning process [44]. This has been noted to be effective because as opposed to phase (time), breathing amplitude can be more accurately correlated with a tumour's position [45]. Figure 5 shows how amplitude sorting can reduce breathing artefacts compared with phase sorting. Hugo et al. [10] provide an overview on this technique as well as other 4DCT reduction strategies such as displacement/velocity gating [43], and audio-visual coaching [46, 47]. Both techniques require guiding the patient to achieve a more consistent breathing trace during 4DT simulation, which reduces image artefacts. Despite being beneficial, these approaches can be resource intensive, and sometimes challenging to achieve for ill patients who have laboured breathing. Furthermore, if coaching is used during 4DCT simulation, then it should also be applied during treatment delivery to avoid breathing pattern inconsistencies at the time of simulation compared with the time of treatment.

Other challenges due to patient-related factors can also arise in 4DCT. For example, because visceral and subcutaneous fat can reduce visibility of chest motion, by using breathing-signal surrogates, it may be challenging to obtain a well-defined breathing trace for thin or obese patients [48]. When imaging obese patients, signal amplification can mitigate this issue, but it is not always an effective strategy. The signal surrogate may also be unreliable for thin patients who have a hallow-shaped body at the level of the chest and upper abdomen. In this case, placing the signal surrogate below the umbilical cord may help; however, one must ensure that the signal measured reflects breathing motion and not abdominal motion.

Tumour Definition on 4DCT for Radiation Therapy Planning

Figure 6 shows a general overview of radiotherapy target delineation volumes recommended by the International Commission on Radiation Units and Measurements (ICRU) [3, 4]. In brief, radiotherapy target delineation begins by defining the gross tumour volume (GTV), or tumour extent visible on the treatment planning CT. Then, the GTV is extended by a margin to include suspected microscopic spread to create the clinical target volume (CTV). The CTV is then extended by an additional margin to obtain the planning target volume (PTV), which accounts for all sources of intrafraction motion, interfraction motion, and setup errors. So far, these volumes assume the tumour is static. To account for tumour motion, the ICRU introduced the concept of the internal target volume (ITV) [4], which is an additional margin surrounding the CTV that accounts for geometric uncertainties related to organ motion. If target delineation includes an ITV, then the PTV is created from ITV. The PTV is the volume that will be used as the treatment target.

There are several methods of utilizing 4DCT image sets to aid in defining the ITV, such as by merging phase-by-phase

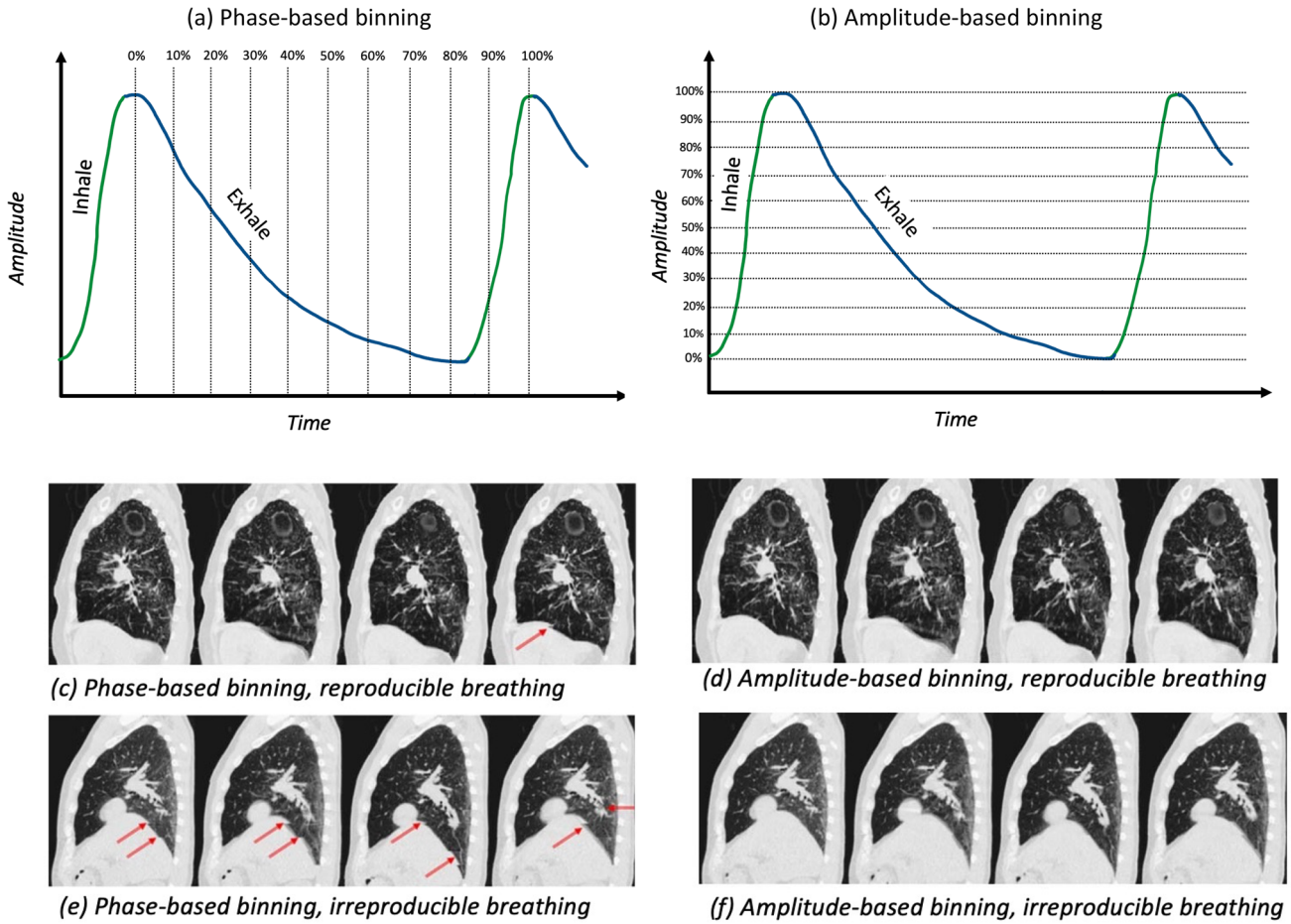

Fig. 5 A graphical representation of phase-based binning (**a**) and amplitude-based binning (**b**) 4DCT image reconstruction techniques. Phase-based binning is prone to 4DCT artefacts, as shown in (**c**) for a patient with relatively reproducible breathing, and (**e**) for a patient with relatively irreproducible breathing. The same patients' 4DCT images were used to reconstruct images using amplitude-based binning for reproducible breathing (**d**) and irreproducible breathing (**e**). Arrows indicate significant 4DCT reconstructing artefacts, which are shown to decrease with amplitude-based binning. Subfigures **c**–**f** are reproduced with permission from "A comparison between amplitude sorting and phase-angle sorting using external respiratory measurement for 4D CT", 33(8), Lu, Wei, Parikh, Parag J., Hubenschmidt, James P., Bradley, Jeffrey D., and Low, Daniel A. Page 2968, Copyright (2006), with permission from Wiley

GTV delineations [49], combining maximum inhale and exhale GTVs [50, 51], defining the GTV on the 4DCT's average intensity projection (AIP) image [52] or on the maximum intensity projection (MIP) image [53]. Recently, the American Association of Physicists in Medicine's (AAPM) Task Group 324's respiratory management in radiation oncology survey reported that in clinical practice of 491 survey respondents, 73% used MIP, 63% used AIP, 18% used both inhale and exhale phases, and 4% used other methods for defining the ITV on 4DCT image sets [54•]. Each method has its own advantages and disadvantages. For example, AIP images can underestimate tumour motion extent (an example is shown in Fig. 6), and MIP images can be unreliable in target delineation for complex or larger tumours such as in the case of non-early stage lung cancers [55]. By far, phase-by-phase GTV delineation is considered to reflect the actual tumour motion; however, since target delineation on more image sets is required, it is time consuming, subject to high levels of variability and inconsistency, and requires more quality assurance by medical physicists [49]. To address this issue, there has been interest in adopting automated tools for 4DCT-based GTV/ITV delineation to improve phase-by-phase target delineation processes [56].

Quality Assurance

4DCT is instrumental in improving radiotherapy target delineation accuracy for moving targets. As with any technology utilized for radiotherapy target delineation, it is, therefore, essential to verify its performance and reliability. 4DCT quality assurance is performed using a programmable

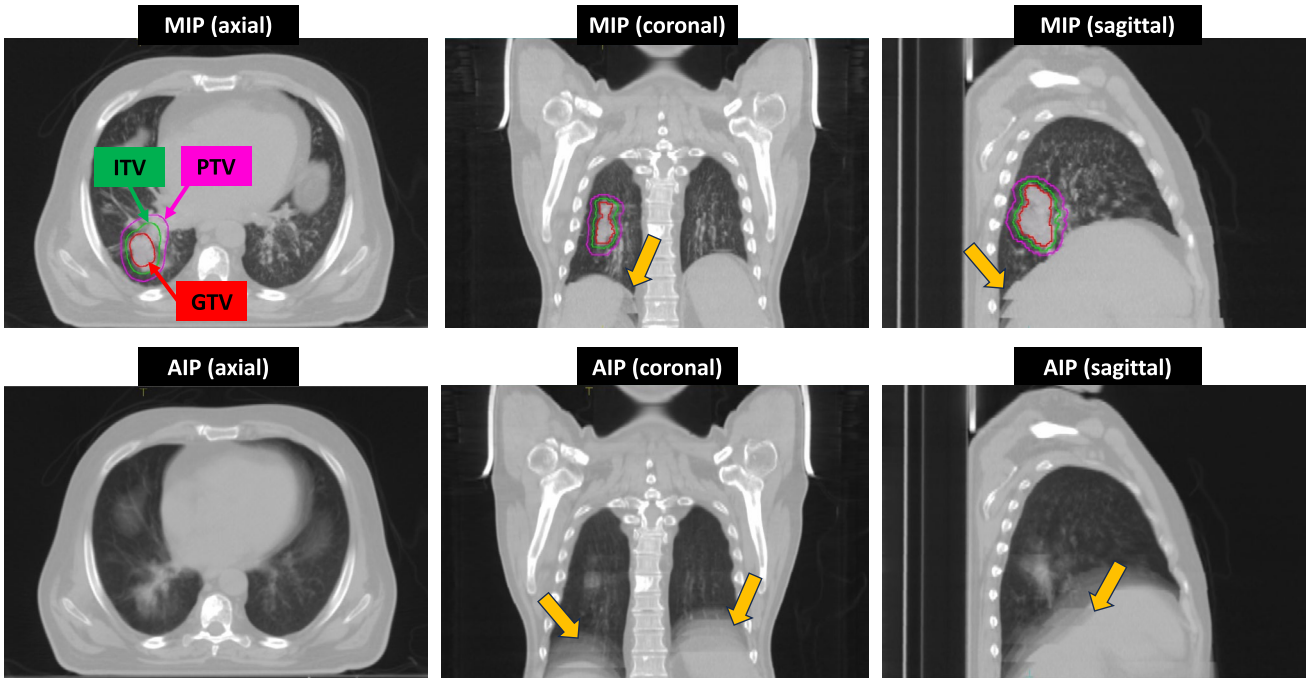

Fig. 6 Sample 4DCT images contrasting the difference between maximum intensity projection (MIP) and average intensity projection (AIP) images for a lung cancer case. In these images, the same x, y, z CT slice coordinate is shown and on different views: axial, coronal and sagittal. Both reconstructed images show visible artefacts (indicated with the yellow arrows). In this example, the MIP was used for radiotherapy target delineation where the gross volume tumour (GTV), or visible tumour is first delineated, followed by the internal target volume (ITV) and then the planning target volume (PTV). *N.B*: Images are viewed using a standard lung window level (W = 1700, L = -300). The longitudinal lines shown along the arms on the coronal images are part of a radiotherapy CT simulation immobilization device, which is made of plastic

Table 2 The Canadian Partnership for Quality Radiotherapy's [56] published guidelines on quarterly and annual quality control tests for 4DCT radiotherapy simulators

Test	Action	Frequency
4DCT reconstruction	Functional	Quarterly
Amplitude of moving target(s) measured with 4DCT	< 2 mm	Quarterly
Spatial integrity and positioning of moving target(s) at each 4D respiratory phase	2 mm (FWHM) difference from baseline measurement (increased for amplitudes larger than 2 cm)	Quarterly
Mean CT number and standard deviation of moving target(s) at each respiratory phase	(± HU) and (± 10%) from baseline measurement (increased for amplitudes larger than 2 cm)	Quarterly
3DCT intensity projection image reconstruction (average, maximum intensity projection, minimum intensity projection)	2 mm (FWHM) difference from baseline measurement (increased for amplitudes larger than 2 cm)	Quarterly
4DCT data import to treatment planning system	Functional	Quarterly
4DCT low contrast resolution at each respiratory phase	Reproducible (set action level at time of acceptance)	Annual
4DCT high contrast spatial resolution at each phase	Reproducible (set action level at time of acceptance)	Annual
4D slice thickness (sensitivity profile) at each respiratory phase)	Reproducible (set action level at time of acceptance)	Annual

respiratory motion phantom, such as the CATPHAN® (The Phantom Laboratory, Salem, USA) CT phantom fixed on a moving platform. The Canadian Partnership for Quality Radiotherapy (CPQR) provides up-to-date guidelines on quality control tests, frequencies, and tolerances for 4DCT devices used in radiotherapy [57], these are summarized in Table 2. The CPQR recommends using one-dimensional phantom motion, along the craniocaudal direction, which is where 4DCT artefacts are mostly observed. Additionally, as with 3DCT, 4DCT quality control test results are dependent on imaging protocols used, and so the recommended tests must be performed for all imaging protocols used clinically (variable kVps, mAs, slice thickness, and pitch, if applicable). Because patients have different breathing pattern

amplitudes and periods, phantom measurements should simulate a range of amplitudes (*e.g.*, static or 0 cm, to 4 cm peak to peak) and a range of periods (*e.g.* 0 cm, or static, to 8s in 1 s intervals [58]. Finally, the CPQR also recommends that the tests should also be repeated for all reconstruction techniques applied, whether phase based, amplitude based, or time based) [57].Given all these data, manual image analysis of 4DCT QA measurements can be tedious, time consuming and error prone. Which is why following a meeting at the 4th ESTRO Physics Workshop (Clinical Translating of CT innovations in Radiation Oncology), Tahiri et al. [59] introduced a comprehensive yet reproducible and automatic 4DCT QA workflow, called QAMotion. QAmotion is an in-house built application that utilizes a Thorax dynamic phantom (CIRS, Sun Nuclear, Norfolk, VA, USA) with a 2-cm-diameter tumour insert to acquire 4DCT images and perform CPQR recommended tests automatically. The research group behind QAMotion has collaborated with MIM Software to provide an online open access to QAMotion. Such tools can improve adoption of CPQR recommended tests for 4DCT QA, streamline routine performance, and facilitate multi-centre 4DCT validation studies [60•]. Automated tools are useful for validating inter-institutional 4DCT performance validation for multi-institutional trials, particularly since it has been found that 4DCT artefacts and poor image quality can compromise radiotherapy treatment planning quality, and have consequently negatively influenced clinical outcome in lung and liver SBRT [61••].

Other 4D-Imaging Modalities

In addition to 4DCT simulation, other 4D-imaging modalities are used during radiotherapy treatment planning, such as 4D magnetic resonance imaging (MRI), 4D cone-beam CT (CBCT), and 4D positron emission tomography (PET).

Due to its superior soft tissue contrast and image slice direction and contrast flexibilities, MRI is often used in radiotherapy simulation [62, 63]. MRI has inherently long image acquisition times and does not rely on ionizing radiation, both of which are advantageous in forming 4D images. As an alternative to 4DCT, 4DMRI has been adopted to characterize respiratory motion in the thoracic and abdominal regions. A recent review article by Stemkens et al.[64] provides an up-to-date summary of various 4DMRI techniques, the safety requirements to consider prior to clinical implementation, and future directions in 4DMRI. It is worth noting that the term "4DMRI" is not only used to describe respiratory-correlated 4DMRI (*i.e.* MRI scans that vary with phase/ amplitude). 4DMRI can also refer physiologically-correlated MRI, such as in the as in the cases of 4D cardiovascular imaging, 4DMR angiography, and 4D flow imaging [64].

Another respiratory-correlated 4D-imaging modality is 4DPET, which is used in lung SBRT to provide functional information that better visualizes standardized uptake volumes (SUVs) with ongoing target motion [65]. An overview on 4DPET's historical development, principles of operation, and current challenges were discussed by Hugo et al.[10]. Since PET suffers from slow image acquisition time (in minutes), average images derived from 3DPET images do not encompass full-target motion. This has been shown by Siva et al. [66], who found that compared with 4DPET/CT, 3DPET/CT can underestimate the full range of motion and cause under-coverage of the target during lung SBRT. Nevertheless, investigative trials have shown how 4DPET can allow personalizing radiotherapy plans based on a patient's lung capacity and function, such that larger doses of radiation can be delivered through areas of poorly functioning lung instead of well-functioning lung volume [67–69].

Advancements and Future Directions

Today, 4DCT is an essential tool in radiation oncology, enabling more precise and effective treatment of tumours that move due to respiration. Since its implementation two decades ago, interest in 4DCT use in radiation oncology significantly increased after 2010 and has steadily continued as shown by the rate of publication presented in Fig. 2. Current research continues to explore new ways to reduce 4DCT artefacts as well as integrate 4DCT into treatment planning and delivery. Although 4DCT technology has improved since its early days, the primary cause of artefacts remains since it stems from irregular patient respiration cycles. Patient coaching and feedback have been shown to reduce breathing irregularities. However, in radiotherapy, there has been debate about the overall benefit of coaching during simulation when the patient's breathing pattern may change without coaching during treatment [46]. Therefore, improvements in 4DCT artefact reduction strategies have pivoted towards better handling of the inevitable, irregular patient breathing.

Respiratory motion model-based techniques have been shown to be effective in reducing, or nearly eliminating, 4DCT artefacts. These models allow surrogate signals to be correlated to internal organ motion directly rather than only using the signal for phase or amplitude-based sorting. One such technique is the "5D" respiratory motion model, which models tissue displacement as a function of five degrees of freedom by using fast-helical CT acquisition to sample the respiratory cycle and applying deformable image registration to a baseline reference geometry to quantify tissue displacement [70]. Pre-clinical validation of this technique has shown promising results [71]. A recently introduced technique, called intelligent-4DCT (i4DCT) uses

patient-specific breathing traces to drive 4DCT data selection, so that breathing irregularities are prospectively filtered out of the projection data, thereby reducing artefacts, maintaining efficient scan times, and reducing patient dose [19, 72]. i4DCT is now commercially available and under further clinical investigation.

As mentioned earlier, oversampling techniques have been shown to reduce 4DCT artefacts; however, more CT acquisition data can mean more radiation dose to patients. Artificial intelligence (AI) can improve oversampling techniques by reducing noise in low-dose projections [73].

Conclusions

4DCT technology has become essential for treatment target delineation of moving tumours in modern radiation oncology practice. In this review article, the technology and acquisition methods of 4DCT were reviewed. Over the last two decades, many improvements have been made in 4DCT technology. However, the primary challenge of 4DCT remains to be the presence of image artefacts caused by irregular patient breathing. Several new mitigating strategies were discussed in this paper. This paper also reviewed how 4DCT images are utilized in radiotherapy target delineation and provided an overview on 4DCT QA guidelines, methods, and tools for commercial 4DCT systems. The advantages and adoption of other 4D-imaging modalities in radiation oncology (e.g. 4DMRI, 4DCBCT and 4DPET) were also described.

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Declarations

Competing Interests The authors declare no competing interests.

Research Involving Human and Animal Rights This article does not contain any studies with human or animal subjects performed by the author.

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- • Of importance
- •• Of major importance

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