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# Treatment-integrated imaging, radiomics, and personalised radiotherapy: the future is at hand

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## ABSTRACT

Since the introduction of computed tomography for planning purposes in the 1970s, we have been observing a continuous development of different imaging methods in radiotherapy. The current achievements of imaging technologies in radiotherapy enable more than just improvement of accuracy on the planning stage. Through integrating imaging with treatment machines, they allow advanced control methods of dose delivery during the treatment. This article reviews how the integration of existing and novel forms of imaging changes radiotherapy and how these advances can allow a more individualised approach to cancer therapy.

We believe that the significant challenge for the next decade is the continued integration of a range of different imaging devices into linear accelerators. These imaging modalities should show intra-fraction changes in body morphology and inter-fraction metabolic changes. As the use of these more advanced, integrated machines grows, radiotherapy delivery will become more accurate, thus resulting in better clinical outcomes: higher cure rates with fewer side effects.

**Key words:** imaging in radiotherapy; SBRT; FLASH; personalised radiotherapy; radiomics

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## Current imaging techniques for radiotherapy planning, simulation, and dose delivery — advantages and limitations

### Current radiotherapy methods: general view

The use of medical imaging for radiotherapy planning and visualization to help achieve accurate dose delivery has long presented an important challenge for radiation oncologists and medical physicists alike [1, 2]. For clinicians, these challenges include selection of the most appropriate imaging modality (e.g., computed tomography (CT), magnetic resonance (MR) or positron emission tomography (PET)), correct interpretation of the imaging data, and final validation of the procedure. This also applies to volume contouring for treatment planning, verification of patient positioning and target alignment before and during treatment delivery, and to assessing treatment response over time. The appropriate use of imaging requires highly specialised training, as evidenced by reports describing significant interobserver variability in target delineation [3, 4]. The approach utilization of imaging also requires a strong understanding of

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new tools, such as radiomics and artificial intelligence, which can enhance the diagnostic precision and also help to select the most appropriate treatment modality [5–7]. For medical physicists, there are three main challenges. The first is whether the physics involved in producing the image has any effect on the information provided by the image and/or the interpretation of the image; and — if so — the extent of this influence [8]. The second challenge is how to integrate images acquired from different hospital units at different points in time into a single, reliable image. While this is certainly feasible, numerous technical obstacles must be overcome in order to accurately overlay and fuse images from different sources [9–11]. The third challenge is the complex question of how to best visualise moving targets to precisely deliver the radiation dose to the target volume [12, 13].

In the past, medical imaging was based exclusively on ionising X-rays produced by photon beams of varying energy levels. Photoelectric, Compton, and pair effects all influence image quality, and these factors also play a role in how well or poorly different inner structures are visualised. In the last decade, major advancements in medical technologies have opened up myriad new possibilities in imaging and dose delivery [14–16]. Imaging devices are now integrated directly into the linear accelerator so that medical images can be acquired, and treatment delivered in the same accelerator. As a result, the imaging process has become closely integrated with dose delivery in both time and place [17, 18].

## Current radiotherapy methods: planning and simulation

Due to advances in computing power in terms of hardware and dose algorithm calculations, it is now possible to compute dose distributions much more quickly than in the past, even for complicated multiple beams with fluctuating field sizes and intensities. To achieve target coverage and organs at risk (OARs) sparing, the robust optimization or traditional method of target volume determination should be used [19]. Radiation doses can be conformed to closely fit the target volume, allowing for a steep gradient outside the target to protect nearby healthy tissues. However, these steep gradients require a highly precise tumour border and an accurate dose distribution that closely follows the tumour throughout the entire treatment process. Perhaps the greatest challenge involves the need to account for intra- and inter-fraction changes caused by the motion of inner structures, changes in the tumour border, and volume shrinkage or enlargement. Indeed, this partially explains why advanced imaging capabilities are increasingly being incorporated into linear accelerators, as this allows for more precise contouring and thus higher therapeutic doses and better dose distribution in target volumes with complex shapes (e.g., concave) with lower doses to (OAR) [20].

To ensure accurate dose delivery, it is essential to account for internal organ motion, which requires real-time imaging in which the radiation beam is continually adjusted and aligned with the tumour. Real-time imaging can substantially improve the accuracy of radiation delivery, thereby increasing local control while reducing the dose absorbed by surrounding healthy tissues, thus reducing toxicity. Despite the growing interest in understanding and addressing organ motion during radiotherapy delivery, the complexity of synchronising radiation delivery in real time to account for this remains highly challenging [21].

The radiotherapy treatment planning process is highly complex, requiring expertise in a wide range of areas, including clinical medicine, radiobiology, and radiation physics. It also requires a thorough understanding of both the potential advantages and disadvantages of technology. Clear visualisation of the tissues being irradiated is essential, as is the capacity to adjust dose delivery in real time. These capabilities are essential given the movement of both the target and the OARs that occurs during the radiation delivery (intra-fraction) and between fractions (inter-fraction).

Due to advances in computer technology, it is now possible to directly compare images from diagnostic X-rays, CT, MR, and PET by fusing these images into a single image. Indeed, while this approach has not yet become a standard, it is becoming increasingly common. First, the images are overlaid and aligned using the visible internal anatomic structures as a guide in a process known as "image registration". Then, the images are fused together to form a single image ("image fusion") [22].

## Current radiotherapy methods: treatment

In the field of radiotherapy, the first computerized image registration methods were based on

either simple or complex rigid transformation algorithms. Simple algorithms rely on mathematical transformations, such as rotation and translation along each axis of the Cartesian coordinate system, whereas complex algorithms are based on scaling and shearing of an image projected onto a reference point. Despite the value of rigid registration methods, they have an important limitation: specific parts of the input image cannot be "deformed"; thus, the fused image is a superposition of the input and reference images. This limitation prompted researchers to develop other methods that would allow for fully elastic transformations which — apart from re-scaling particular image elements — would enable the images to be non-linearly shifted. This process is referred to as deformable image registration (DIR), and the process based on such transformations is known as deformable registration. Currently, the most common DIR processes used in commercially available radiotherapy software programs are those that employ algorithms based on elastic transformations in which voxel intensity in the referred image is compared to the reference image ("demon" registration), and on the analysis of B-spline functions [23].

After the development of DIR, another advance was to move pre-treatment verification of geometrical accuracy of dose delivery from conventional X-ray simulators to CT units, where virtual simulation is available [24]. The virtual CT simulation in conjunction with accelerator-based CT imaging fully replaces conventional X-ray simulation. This important advance was a necessary response to the introduction of advanced radiotherapy techniques.

## Major unresolved challenges

### Fractionation: towards shorter course radiotherapy

The current approach to radiotherapy delivery is based on decades of clinical experience and *in vitro* radiobiology studies. In the conventional approach — known as long-course radiotherapy (LCRT) — dose delivery is fractionated over the course of several weeks (up to seven weeks), with a daily dose administered from Monday to Friday. LCRT is based on radiobiological research showing that most healthy tissues and organs are better able to recover from radiation doses delivered over a longer period than cancerous tissues (which regrow more slowly), thus allowing clinicians to deliver a higher dose to the tumour. However, this approach relies on particular properties of many — but not all — tissues and organs and, thus, it is only appropriate for some tumour types. Certainly, some tissues and organs benefit from prolonged fractionation schedules. However, an observation gathered for certain tumours led to the concept of fewer but larger doses per fraction. For example, prostate cancer (which are increasingly common compared to past decades) do not benefit from LCRT and, therefore, shorter courses of radiotherapy are appropriate. The reason lays on radiobiological properties of prostate tumours and the surrounding tissue, all of which have been confirmed in clinical setting. Patients with prostate cancer are, therefore, mainly treated with fewer but larger dose fractions, which neither negatively impacts treatment outcomes nor increases side effects, provided the total dose has been calculated in accordance with the radiobiological and clinical reports.

Prolonged fractionation schedules have another important drawback: the extended treatment duration, which is less than ideal due to the anatomical changes that occur over the long course of radiotherapy and due to quality assurance issues — including proper set up — associated with radiotherapy administered on a daily basis for multiple weeks. Finally, most patients prefer shorter courses of treatment.

This shift towards fewer fractions at higher doses eventually led to the development stereotactic body radiotherapy (SBRT), also known as stereotactic ablative body radiotherapy (SABR). This treatment has become the non-surgical treatment of choice for patients with non-small-cell lung cancer (NSCLC) who are not considered surgical candidates for medical reasons (e.g., heart disease, etc.). In patients with operable stage I NSCLC, pooled data from phase 3 randomized trials comparing SBRT to surgery indicate that the two treatment modalities are equally effective in local control [25]. The excellent results obtained with SBRT in lung cancer (and other tumours) are due to the improved precision, high doses, and the anti-tumour immune response triggered by SBRT. This immune response is stimulated through multiple mechanisms, most importantly by activation of T lymphocytes [26]. Localized radiotherapy has

also been shown to induce abscopal effects in several types of cancer, including melanoma [27], metastatic NSCLC [28], and other tumours (lymphoma and renal cell carcinoma). SBRT is most commonly used to treat lung cancer. Depending on the location and size of the pulmonary lesions, SBRT can be used with volumetric modulated arcs with photon beam energies ranging from 6-10 MV. Several radiotherapy protocols have been proposed for NSCLC based on tumour size and location: (*a*) 34 Gy in a single fraction (distance to chest wall > 1 cm, tumour size < 2 cm, and distance to the main bronchus > 2 cm; (*b*) 54 Gy (18 Gy in 3 fractions) (distance to chest wall > 1 cm, tumour size between 2 and 5 cm, and distance to the main bronchus > 2 cm); (*c*) 60 Gy (12 Gy in 5 fractions) (distance to chest wall < 1 cm, tumour size < 5 cm, and distance to main bronchus > 2 cm); and (*d*) 60 Gy (7.5 Gy in 8 fractions (tumour size < 5 cm and distance to the main bronchus < 2 cm). [29].

Flash therapy is a new concept based on the observation that doses delivered at an ultra-high dose-rate (short pulses of less than 200 milliseconds) improve the therapeutic index (tumour - normal tissue response). The benefit of this approach is based on the response of normal tissues (i.e., critical organs) which show an increased tolerance to radiation with flash therapy; however, the tumour response to this type of therapy requires further study, although the available evidence suggests that the benefits of this therapy for normal tissue are unlikely to be counteracted by some unforeseen negative impact on tumour response.

Compared to conventional radiotherapy dose rates, the use of ultra-high dose rate flash therapy has a much greater impact on radiochemical events, especially these associated with oxygen concentration in the irradiated volume. Normal and tumour tissues differ in the rate at which radiation-induced free radicals' decay and are removed by the body, and ultra-high dose-rates cause oxygen depletion in normal tissues, making them more radio-resistant [30–32].

In terms of the physics involved, flash therapy minimizes the risks associated with intrafraction motion of the critical organs and tumour due to the extremely short time needed to deliver the radiation [31, 33].

Clinically, this approach results in fewer and less severe side effects, thus offering the potential to irradiate structures/sites commonly associated with a high risk of recurrence or toxicity but where only low doses could be delivered. Currently, only electron beams are available at ultra-high dose rates, with works in progress on protons. Lack of suitable megavoltage photons limits clinical application of this technology to skin tumours or those laying on depths up to few centimetres, thus precluding today treatment of majority of tumours [30-34].

## Radiomics: how to obtain clinically relevant data from images

Radiomics is a new, powerful tool that has recently become available in the field of radiation oncology. Radiomics allows mineable data to be extracted from radiographic medical images. This non-invasive process can be used to identify the tumour characteristics while simultaneously accounting for temporal and spatial heterogeneity. The value of radiomics in radiation oncology is that it could be used to develop imaging-based biomarkers to predict treatment response. The technique is based on high throughput extraction of quantitative features from standard imaging modalities, such as CT, MR, and PET, which are then analysed in relation to biologic and clinical endpoints [35].

Radiomics can identify imaging phenotypes, which could reveal tumour characteristics at the cellular level. For this reason, this tool has real potential to be a potent approach to developing customized clinical decision-making algorithms. Moreover, the radiomics model could also be used for personalized cancer diagnosis, risk profiling, and treatment by analysing imaging features that are undetectable to the human eye, as has already been demonstrated in lung cancer [36].

By combining radiomics with artificial intelligence, it may be possible to create an even more powerful tool that also considers other inputs, such as molecular, metabolic, and microenvironmental tumour analytics, opening up the potential for a new generation of personalized oncology diagnosis and treatment [7].

## Technical possibilities of image registration and fusion in radiotherapy planning

Rigid and deformable registration methods both have important advantages, and these techniques, together with recent technological ad-

vances, have improved the quality and precision of radiation delivery. Ling et al. [37] was the first to propose the concept of integrating physical and biological data to define and delineate the target volume. In that approach, the aim is to incorporate data from functional images — which provide additional information on metabolism, physiology, and/or genotype — into the treatment planning process. One common example of this approach is the integration of data obtained from molecular imaging (e.g., PET scans) with anatomical data (CT scans) in order to identify radiation-resistant regions within the tumour; this combined information is then used to create a heterogeneous dose distribution to improve tumour control [38–40]. Image registration also plays a crucial role in the delivery of radiotherapy. For example, rigid registration is indispensable to optimize patient positioning before administering the fractional dose. Irradiation based on regular image-based control is known as image-guided radiation therapy (IGRT) [41]. The simplest case is rigid registration between digitally reconstructed radiographs (DRR) based on diagnostic/planning CT images and two-dimensional kilo- or megavoltage images (2D-kV or 2D-MV) generated on the linear accelerator. This type of image registration allows for accurate patient positioning based on bony anatomy. To adjust patient positioning based on soft tissues, the diagnostic CT images must be matched to the images obtained on the linear accelerator.

Two kinds of accelerator-based CT are available. The first type is known as megavoltage computed tomography (MVCT), which is generated on helical tomotherapy (HT) machines. Dose delivery in HT differs technically from dose delivery in conventional (C-Arm based) accelerators. In HT-based dose delivery, the gantry rotates with the treatment table such that the radiation source rotates around the patient along a helical path (similar to CT). The ionizing radiation source is a linear accelerator (nominal voltage, 6 MV). The emitted photon beam is fan-shaped, measuring 40 cm in width and 1, 2.5, or 5 cm in thickness (isocentre). MVCT images are generated by applying the matrix of detectors located on the opposite side of the ring. For better quality MVCT images, the nominal voltage in the imaging mode is decreased from 6 MV to 3.5 MV [42, 43]. The use of MVCT allows for daily verification of the patient's position on the treatment table by comparing data from the MVCT scans to the CT images used for radiotherapy planning. By contrast with the helical scanning in HT-based radiotherapy, cone-beam CT (CBCT) on conventional accelerators requires only a single rotation to generate a set of images [15]. However, due to the fixed field size during imaging on conventional accelerators, the set of CBCT images is currently limited to 17 cm in the craniocaudal (CC) direction; by contrast, for HT, the size is practically unlimited, ranging from a single image to image sets covering > 140 cm in the CC direction. The diameter of the in-plane view (field of view; FOV) on conventional accelerators depends on the imaging geometry, which is 26.6 cm for full-fan geometry and 48 cm for half-fan geometry. MVCT has a fixed FOV (diameter, 40 cm). For MVCT imaging, 3.5 MV photon beams are used; by contrast, CBCT images can be generated using kV photon beams (kV-CBCT) when an imaging system is used, or by MV beams (MV-CBCT) directly through the therapeutic beam (6 MV photons).

Despite technical differences between MVCT and CBCT, both can be used for patient positioning. Importantly, the distribution of the delivered dose can be adjusted to account for changes in tumour biology (e.g., hypoxia) detected on functional imaging performed over the course of treatment [44]. However, this technique requires a treatment planning system (TPS) capable of performing DIR to account for changes in the target volume and/or surrounding OARs and also capable of mapping the doses based on those changes. The TPS must also be able to accumulate the mapped doses to calculate the dose distribution on each imaging set (CBCT or MVCT) and then calculate the delivered dose distribution as the accumulation of the individual treatment plans [18]. To mitigate the effects of respiration-related tumour motion on image quality and registration uncertainty, CBCT can be acquired using breath-hold strategies [45] or a four-dimensional (4D) respiratory triggered approach (4D-CBCT) [46].

## Emerging technologies and imaging approaches

The quality of accelerator-based images (e.g., iterative CBCT) can be improved by implementing new reconstruction algorithms [47]. Nevertheless, the quality of accelerator-based CT images is objec-

tively inferior to high-quality diagnostic CT images (such as those from dual-energy imaging) used in radiation therapy planning [48, 49]. It is important to keep in mind that CT imaging deposits radiation in the imaged volume, which explains why numerous authors have recommended using non-radiation-based imaging techniques, such as MRI, for this purpose. In fact, one of the most important advances in recent years is MRI-based patient repositioning on the treatment bed.

MRI provides superb soft tissue visualisation and also has several imaging modalities to identify movement, function, and physiology without delivering any additional radiation dose to the patient. Various integrated MRI-guided radiation therapy (MRIgRT) systems have been developed, including the Unity MR-linac system (Elekta AB, Stockholm, Sweden) equipped with a Philips Marlin 1.5T MR scanner (Philips Healthcare, Best, the Netherlands) [50]; the MRIdian: 0.35T MR-Linac system (ViewRay, Inc., Cleveland Oakwood Village, OH, USA) [51]; and the Aurora RT: 0.6T MR-Linac system (MagnetTx Oncology Solutions Ltd, Edmonton, AL, Canada) [52]. MR-linac systems have only been introduced into clinical practice recently and most studies conducted to date have focused on evaluating the technical possibilities of the system [53, 54], although it is worth noting that one system that integrates MR with a re-designed Cobalt unit has been in clinical use for the last several years. As Henke et al. observed [55], MRIgRT offers improved soft-tissue visualisation, daily imaging, and real-time intra-fraction imaging without added radiation exposure. In addition, MRIgRT also offers the possibility for adaptive radiotherapy (ART) to adjust for anatomical changes. Those authors — based on more than four years of experience with MRIgRT — suggest that the main indications for this technique are applications such as ART for gastrointestinal cancers and accelerated partial breast irradiation for breast cancer.

## Proton therapy: decreased dose deposition in healthy tissues

Protons can be used for radiotherapy at particle kinetic energies close to 250 MeV. At present, however, proton accelerators are substantially more expensive than conventional photon beam accelerators [56, 57]. The two main advantages of proton beams versus photon beams are 1) better dose distribution, with improved sparing of healthy tissues near the target, and lower doses to the whole body (near zero), and 2) a relative biological effectiveness that is clinically estimated to be 10% greater than photon beams [58]. The key characteristic of proton energy is the Bragg peak, the point at which the dose falls nearly to zero after the maximal range of protons is delivered to the target. Photon beams attenuate differently than proton beams in a probabilistic pattern: some photons do not interact with tissues in their path and, thus, a small, but not insignificant dose, is deposited in deeper layers. In addition, protons differ from photons with regard to the biological interaction with the body (due to different physical phenomena), which results in differences in how cellular targets are destroyed (protons having a greater biological effectiveness in terms of cell killing).

Despite the higher cost of proton accelerators and the more complex technology, the number of clinical proton therapy units continues to grow, largely due to their greater effectiveness, but also because both the cost and complexity continue to fall [59]. In the past, most multi-room proton facilities were stand-alone units that were physically separated from the radiotherapy department. However, in recent years the trend has been towards more effective, single room units integrated into the radiotherapy department [60].

In clinical practice, the unique properties of proton radiation allow for better dose distribution, with a sharp dose decrease outside the target volume. Thus, the dose delivered to healthy tissues is lower, with fewer complications and a lower risk of inducing secondary cancers. However, protons are heavy particles and much more difficult to guide than electrons, which requires larger accelerators and the consequent difficulty of integrating imaging devices. For this reason, real-time visualisation during proton irradiation is less advanced and provides less data than available with photon therapy accelerators. That said, newer proton therapy units include image guidance with the gantry [61].

Despite the important theoretical benefits of proton radiotherapy, critics argue that this technology may be unnecessary due to the rapid and continuous improvement in photon beam radiotherapy, achieved through advances in imaging and gating. The latest accelerators are capable of

dose distributions that are close to those obtained with proton radiotherapy in terms of both accuracy and quality [62]. However, manufacturers of proton-based accelerators are developing less expensive and smaller units to better compete with photon-based systems. Likewise, these manufacturers are also working on incorporating new imaging devices, similar to those employed in photon therapy, into the proton accelerators [63].

## Heavy ions: sharper lateral penumbra with the greatest biological effectiveness

Heavy ions have been used in clinical radiotherapy since 1960, when studies were first conducted at the Lawrence Berkeley Laboratory to assess the potential clinical value of helium, followed later by studies of neon and carbon ions [64]. This was a pioneering era in particle therapy, and carbon ions were later adopted due to their more advantageous physical and biological characteristics [65]. These particles have a similar depth dose distribution to protons with Bragg peak, but with a more pronounced tail due to nuclei fragmentation. The main potential advantages of carbon ions are related to their sharper lateral penumbra and higher biological effectiveness (RBE) compared to photons and protons. A unique *in vivo* imaging modality can be obtained through carbon fragmentation and the formation of 0.512 MV gamma rays detectable by PET technology. These images show dose deposition related to molecular interactions [66].

The main interest in using ion therapy is the greater RBE compared to photons or protons, which offers the possibility to successfully treat radio-resistant tumour types, such as sarcoma, melanoma, and adenoid-cystic carcinoma. However, ions present important limitations, mainly the complexity of the technology required to produce and accelerate such heavy particles, which would necessarily be quite costly.

## Summary and conclusion

To conclude, we believe that the major challenge for the next decade is to continue the integration of a range of different imaging devices (which employ different physical phenomena) into linear accelerators. These imaging modalities should be capable of showing intra-fraction changes in body morphology as well as inter-fraction metabolic changes. As the use of these more advanced, integrated machines grows, radiotherapy delivery will become more accurate, thus resulting in better clinical outcomes: higher cure rates with fewer side effects.

## One machine for visualization and treatment

Perhaps the most important unresolved issue in medical imaging is the question of whether the integration of imaging and treatment will eventually allow us to use the same machine to visualize body structures and deliver radiotherapy. As discussed above, traditional photon beam accelerators have already begun to include various X-ray imaging modalities, including both kilovoltage and megavoltage X-ray devices. Other solutions include CT on rail. A more recent approach is the use of X-rays with tomotherapy, which allows for smooth image-guided radiotherapy and therapeutic beam delivery integrated with imaging. Importantly, not all structures (e.g., soft tissues) can be visualized with X-rays, particularly with megavoltage beams. However, this can be overcome by using other imaging modalities such as MRI. Linear accelerators that incorporate MRI have been installed in a growing number of clinics, allowing precise irradiation of "dominant lesions" (regions containing the largest number of neoplastic cells).

## Reaching and following targets accurately: adaptation and gating

Matching the dose volume to the target volume, ideally adapted to changes in the target volume over time, reduces radiation-induced side effects. However, this requires more research and further development to improve the technique and ensure reproducibility. Today, it is possible to accurately plan the dose-curve to less than one millimetre, but this assumes a static condition, which is only an approximation of real-life radiotherapy where multiple factors — change and movement of the tumour, OARs, and the patient — must be accounted for.

## Protons & ions: a competitive tool pending further technological advancement

The advantage of protons and heavy ions is that they both permit the use of very simple radiotherapy delivery techniques compared to photons,

achieving better dose distribution with only a few beams. Moreover, newer proton accelerators now offer intensity modulation and proton-guided imaging, matching the technology that has long been available in photon accelerators.

## Shorter radiotherapy course — same clinical results, fewer problems — expected by patients

When appropriate and feasible, short course, high dose radiotherapy such as SBRT is expected to play an increasingly larger role in radiotherapy. In turn, the decreased demand for linear accelerators will allow more sophisticated techniques and longer courses to be applied when necessary. That said, dose elevation requires more study and should be used with caution, primarily in cases in which the dose-effect curves indicate a high probability of achieving a cure.

## Personalised Medicine: how to obtain data to personalise radiotherapy

In the future, it seems likely that the best outcomes will be obtained if we can better define the specific biological properties of each tumour type. Moreover, other factors associated with an individual's phenotype and genotype, overall health status, and comorbidities will all be taken into account to modify the radiotherapy plan to suit the individual patient. However, this requires obtaining the patient's data, if possible, through non-invasive means. Consequently, radiomics may play a key role in tailoring the radiotherapy strategy.

## Flash therapy: a small improvement or a leap forward?

Time, dose, and dose rate modifications have always been considered to have a large influence on radiotherapy outcomes. The emerging concept of ultra-high dose rate radiotherapy has attracted the interest of researchers because technological advances made this approach feasible and possible to administer. While the current body of evidence is limited, ultra-high dose rate radiotherapy has been shown to improve normal tissue sparing. When this option becomes available in conventional linear accelerators as a photon beam, it will add to the growing portfolio of possible treatments, thus further expanding the role of personalized radiotherapy.

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