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Review article

Electron radiation therapy: Back to the future?

Radiothérapie par électrons : retour vers le futur ?

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ABSTRACT

Electron radiotherapy has long been preferred to photons for the treatment of superficial lesions because of its physical characteristics (high dose at the surface, rapid decrease in depth). Other characteristics (penumbra, heterogeneity on an oblique or irregular surface) make them difficult to use. In most indications (skin cancers, head and neck, medulloblastoma), with technical progress, in some cases they have been replaced by intensity-modulated conformal radiotherapy, brachytherapy and contact therapy. Other indications (drainage of mesotheliomas or irradiation of benign lesions) have disappeared. The low frequency of use leads to problems of safety and cost-effectiveness. However, modern photon radiotherapy techniques are still less effective than electrons in specific indications such as total skin irradiation (mycosis fungoides) or certain thin chest wall irradiations after total mastectomy, reirradiation or paediatric treatments without protons. Flash therapy, initiated by electrons, has been developed over the last 10 years, providing high-dose irradiation in an extremely short time. Initial results show good efficacy, with fewer side effects than with conventional radiotherapy. These results are leading to clinical technological developments on a larger scale. Although it has been replaced in most indications by more modern techniques, electron radiotherapy remains essential for targeted indications in specialised centres. The emergence of flash therapy will lead to new indications, on machines equipped with this new technology, which have yet to be defined and are currently the responsibility of specialised teams.

RÉSUMÉ

La radiothérapie par électrons a longtemps été préférée à celle par photons pour le traitement des lésions superficielles du fait de leurs caractéristiques physiques (forte dose en surface, décroissance rapide en profondeur). D'autres caractéristiques (pénombre, hétérogénéité sur surface oblique ou irrégulière) les rendent difficiles à utiliser. Pour la plupart des indications (cancers cutanés, ORL, médulloblastome), avec les progrès techniques, dans certains cas, ils ont été remplacés par la radiothérapie conformationnelle avec modulation d'intensité, la curiethérapie et la contacthérapie. D'autres indications (drainage des mésothéliomes, ou des irradiations de lésions bénignes) ont disparu. La faible fréquence d'utilisation conduit à des problèmes de sécurité et de rentabilité. Toutefois, les techniques modernes de radiothérapie par photons restent moins performantes que celles par électrons pour des indications particulières comme les irradiations cutanées totales (mycosis fongoïde) ou certaines irradiations de paroi thoracique

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fine après une mastectomie totale, des réirradiations ou des traitements pédiatriques n'utilisant pas les protons. Depuis 10 ans la thérapie flash a été développée, initialisée par les électrons ; elle permet une irradiation à haute dose dans un temps extrêmement court. Les premiers résultats montrent une bonne efficacité avec moins d'effets secondaires qu'avec la radiothérapie classique. Ces résultats conduisent à des développements technologiques cliniques à plus grande échelle. Bien que remplacée pour la majorité des indications par les techniques plus modernes, la radiothérapie par électrons reste indispensable pour des indications ciblées dans des centres spécialisés. L'émergence de la thérapie flash conduira à de nouvelles indications, sur des machines équipées de cette nouvelle technologie, qui restent à définir et sont pour l'instant du ressort d'équipes spécialisées.

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1. Strengths and weaknesses of electron radiation therapy: the medical physicist point of view

Electron energy in radiation therapy ranges from 4 to 22 MeV [1]. Electrons used to be favoured over photons to treat superficial lesions because of their high surface dose (70 to 90% of the maximum dose) and the rapid fall-off of the dose (e.g., for a 6 MeV field, the practical range R_P, corresponding to the maximum depth at which the incident electrons penetrate the medium, is 2.9 cm) [1]. However, several physical drawbacks have limited their use: a field side lower than the R_P value results in a lack of lateral electronic equilibrium, therefore, a limitation in the smallest usable field size, depending on the energy, exists. Furthermore, the penumbra width increases with energy and depth, with a bulging of the low dose value as a direct result of the increase in electron scattering angle, with decreasing electron energy, which results in a dose spread largely beyond the field opening.

In patients, surface obliquities and heterogeneities strongly affect dose distributions. Obliquities affect the penumbra shape while creating hot and cold spots. The depth dose curve is also modified. A depression (e.g., ear canal) increases the dose below it, while decreasing the dose around its periphery. On the other hand, a protrusion (e.g. nose) decreases the dose below it, while increasing the dose around its periphery.

The effect of heterogeneities will depend on their type. Bone shifts the dose towards the surface due to the increased stopping power while air cavities introduce hot and cold spots similar to the effect of surface irregularities due to the loss of side-scatter equilibrium. Obliquities and heterogeneities make thus electrons less attractive for precise radiation therapy distribution.

It is common practice to use a bolus material to increase the dose surface while sparing distal structures. Flexible water-equivalent bolus is not always adequate for irregular surfaces, creating air gaps at surface irregularities. Heat-deformable bolus allows molding hard-to-bolus areas and, more recently, 3D-printed bolus with variable thickness allows optimizing planning target volume (PTV) coverage [2,3].

Electron usage peaked in the 1990s and decreased ever since. There has been very little technological development for some time until the recent development of ultra-high dose rate (flash therapy) and very high energy electron radiotherapy [4,5]. Nevertheless, one can mention niche indications, such as total skin electron therapy or intraoperative electron radiotherapy, and technological developments, such as arc electron therapy, multileaf collimators or scattering foils for modulated electron therapy but, in both cases, their clinical use remained marginal [6–10].

Competing technologies for superficial lesions are brachytherapy (including electronic brachytherapy), superficial or orthovoltage radiotherapy (50 to 320 kV X-rays) and photon volumetric modulated arc therapy (VMAT) [11–13]. The latter technique, performed on linear accelerators typically available in most radiotherapy departments, allows treating target lesions with a better control of the penumbra, especially for those near organs at risk, while being less sensitive to surface obliquities. VMAT dose painting, including integrated boosts, provides better dose distributions within a given volume and has practically eradicated the need for electrons in some frequent radiotherapy indications (e.g., adjuvant radiotherapy for breast cancer). When needed to treat the skin, photon VMAT combined with 3D-printed bolus or new high-density shapeable bolus result in high surface dose and accounts for surface irregularities, therefore still remain preferable to electrons (Fig. 1) [14].

From a logistic point of view, maintaining operational one or several electron energies has a fixed cost, independent of the actual number of treated patients, due to the machine time and human resources necessary for maintenance, quality control and treatment modelling.

Given that professional skills need to be maintained through application into a given number of treatments and that the demand for electron treatments is nowadays considerably decreased, many radiation oncology departments have made the choice of an electron-free environment.

2. Abandoned or decreased indications for electrons in modern radiotherapy and brachytherapy

The most common indication for electrons has been treatment of superficial lesions, with flat, regular surfaces.

2.1. Indications replaced with advances in external-beam radiotherapy

Several "classical" electron indications have been recently replaced by external-beam radiotherapy (EBRT).

2.1.1. Paediatric tumours

For medulloblastoma, a combination of photons and electrons has been replaced by photons alone, mainly to reduce skin toxicity, then by the intensity-modulated radiation therapy (IMRT) [15].

2.1.2. Head and neck cancers

Spinal lymph node irradiation used to be treated with mixed photon-electron radiation, but head and neck cancers were the first to be treated with IMRT, given the complexity of volumes to treat and spare. The primary objective of IMRT was to improve saliva quality, by sparing parotids and submandibular glands, but it has also reduced skin toxicity, particularly in the spinal lymph nodes and rapidly replaced the use of electrons in this setting [16].

2.1.3. Breast cancer

Regional irradiation, including the internal mammary chain lymph nodes, involved anterior beams with junction zones

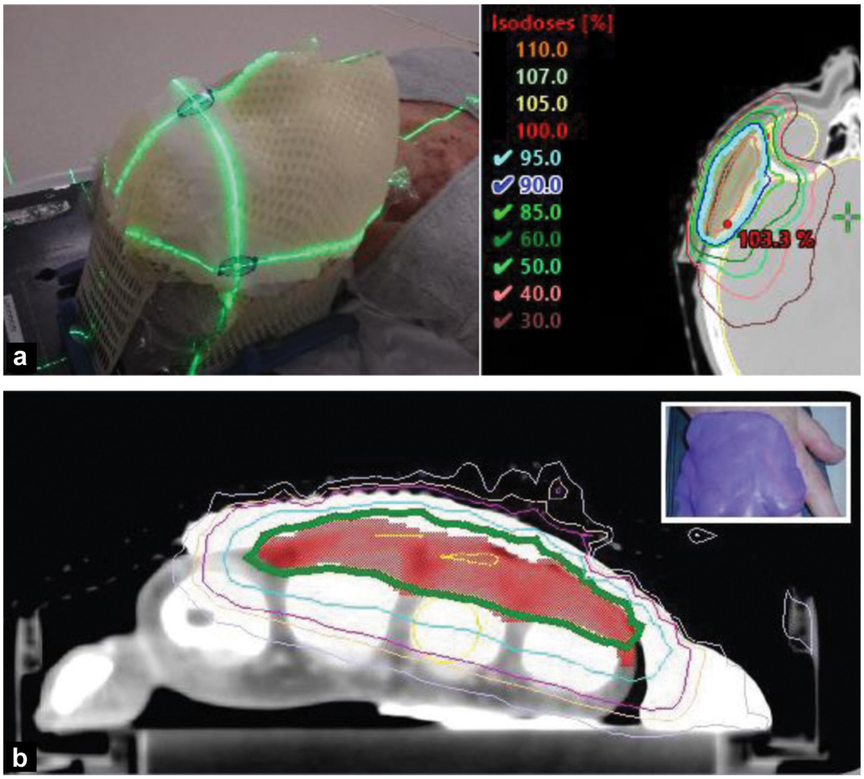

Fig. 1. Photon radiotherapy. a: example of temporal treatment with 3D-printed bolus; b: example of hand treatment with high-density shapeable bolus (Gimeds® ExaSkin commercial documentation).

(resulting often to overdosing). The photon/electron mix used produced quite significant coverage heterogeneities. Studies with IMRT have shown a reduction in hot spots, an improvement in conformity and homogeneity indices and a better coverage of volumes, especially in complex cases. High doses to the homolateral lung and heart are reduced, at the cost of an increase of the lung and heart volume receiving low doses. Cosmetic results are better [17].

2.2. *Indications that have disappeared or decreased*

Electrons were used for preventive irradiation of mesothelioma drainage tracts. However, a phase III trial showed that EBRT did not reduce the incidence of local recurrence, with toxicities [18]. For this reason, this indication has disappeared from many radiotherapy departments.

Some indications for irradiation of benign pathologies have (almost) disappeared in France, due to the benefit/risk ratio with the risk of radiation-induced cancers: infantile tinea, calcaneal spines [19].

2.3. *Residual indication: skin irradiation*

Electrons are useful for thin skin cancers with a regular, plane surface. EBRT and brachytherapy (BT) provide excellent local control for non-melanoma carcinoma, with comparable published results [20]. However, BT allows more limited irradiation over a shorter period of time. It is particularly appropriate in the proximity of organs at risk (OARs). BT can be interstitial, the most precise form of irradiation with a maximum dose under the skin rather than on it, but requires an invasive procedure and often hospitalization. Surface BT has the advantage of not being invasive and of being performed on an ambulatory patient. It can treat lesions less than 5 mm thick, but delivers higher doses to the surface of the skin. The aim is to obtain vectors that respect the Paris system, on a bolus of around 5 mm, that adhere well to the skin and have no air in between [21,22]. Techniques are progressing with the emergence of personalized applicators created by 3D printers, allowing applications to complex sites, particularly on the face [23]. It requires less training than interstitial BT. A third option is contact therapy for limited, flat areas, delivered by kV applicators that do not require a bunker in terms of radiation protection [24], or by Valencia®-type applicators on an high dose rate (HDR) projector [25]. The limits of BT are areas which are not very or poorly accessible (external auditory canal for example) but which are even less accessible to electrons.

Adjuvant irradiation of keloids is the most effective treatment for lesions resistant to medical treatment [26]. Electrons are superior to photons for this very superficial irradiation. The results of electrons and BT are similar [27]. However, BT enables irradiation to be carried out directly in the operating bed, so there is less irradiation of the skin and a smaller irradiation volume, with no planning target volume (PTV). Electrons need a PTV and a minimum field width of 4 cm. Optimal BT is interstitial with intraoperative placement of the vector, but surface BT, delivering a higher dose to the skin, may be an alternative (Fig. 2). Irradiation of keloid needs cooperation with the surgical team to deliver the irradiation in the hours after the operation, in order to limit recurrence.

In sum, with technical progress and the disappearance of some indications, few indications for irradiation with electrons are still relevant today. The indications that remain of interest are limited and can be replaced by EBRT, especially IMRT or BT.

3. Clinical need of electrons: the clinical point of view

The feature that makes electron beams very useful for numerous clinical applications is the shape of the depth dose curves. This allows for relatively uniform dose delivery to well-defined regions

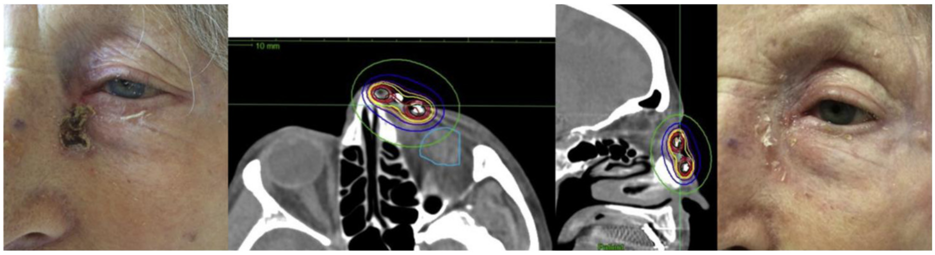

Fig. 2. Interstitial brachytherapy: beforehand (left), dosimetry (middle) and results (right).

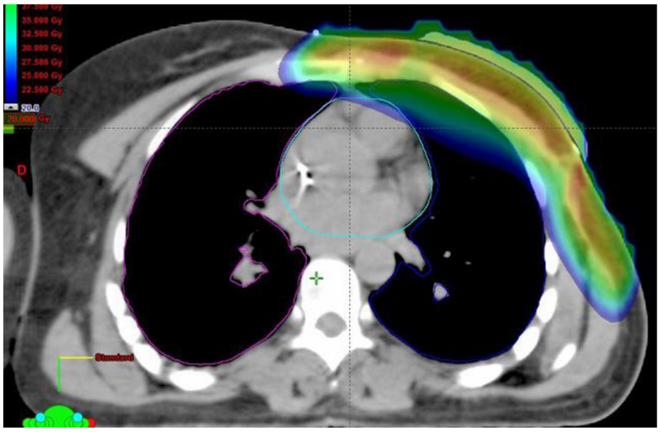

Fig. 3. Dose distribution of chest wall and internal mammary nodes electron irradiation using bolus.

from the surface to the therapeutic range with sparing of underlying tissues and OARs due to the rapid reduction of the dose towards the practical range [28]. Common applications include skin cancers and lymphomas, non-reconstructed chest wall irradiation after mastectomy for breast cancer, paediatric tumours, some ophthalmic lesions when the protons are not available. This treatment becomes very "select" and it is developed only in specialized centres.

Total skin irradiation has already shown efficacy in the radical treatment of mycosis fungoides and Sezary syndrome with high response rates, as well as complete remission as clinical result with acceptable toxicity [29]. For the moment, no alternative technique has been found. An international panel of experts is working on total skin electron beam technique and quality assurance recommendations (ESTRO consensus guidelines).

Another very useful electron treatment with excellent long-term results is the irradiation of the chest wall after mastectomy with bolus [30–32]. Because of the adequate skin dose of chest wall electron irradiation using bolus, it has been shown that there is better local control and increased disease-free survival (DFS) compared with photon chest wall irradiation [33]. In some cases, the dose to lungs could be lower with electrons than with photons or protons. An example of chest wall electron irradiation is given in Fig. 3.

In numerous countries, there is no protons facility and electrons could be very useful for the treatment of paediatric tumours and decrease the risk of long-term toxicity (Fig. 4). There is strong evidence-based data that in patients treated with photons, there are long-term complications, especially in young patients treated during childhood.

In sum, the use of electrons can still be beneficial for numerous oncological indications. Therefore, a good knowledge of dose calculation and dosimetry is needed in the modern radiation oncology department, especially in academic centres.

4. Flash therapy: the gracious return of electrons?

A seminal development in the field of radiation oncology occurred, in the last 10 years, using electrons: flash radiation therapy (RT). It consists of the delivery of radiations at ultra-high dose rates (UHDR), with specific beam parameters, permitting a treatment that traditionally lasts several minutes to be delivered within milliseconds [4]. Beyond the obvious ballistic advantage of flash RT, by freezing motion, an unsuspected radiobiological advantage, the flash effect, permitting the same tumour kill with reduced normal tissue toxicity, has been shown [34]. In the setting of electron beams, conventional RT is delivered at a dose rate of 1 Gy/min (0.017 Gy/s), with a dose per pulse in the milligray range, whereas flash RT is delivered at a dose rate of over 40 Gy/s, and a dose per pulse in the gray range or more. The flash effect, initially shown with electrons, was subsequently validated with protons, photons, carbon ions [35–39]. It seems that the lower threshold to obtain the flash effect is at around a dose rate of 100 Gy/s while additional parameters need to be considered, such as the irradiation time [40].

Since the seminal publication of Favaudon et al. in 2014, flash RT has been the object of enthusiasm in the radiation oncology community [4,41]. Indeed, over 45 publications from different groups around the world in the last 10 years have confirmed the normal-tissue-sparing flash effect (in early and late-responding tissues) in experimental models ranging from zebrafish and mice to big animals [42]. Tissue preservation by flash technique has for example been confirmed in numerous organs in small animals, including lung, intestine, skin, brain, cat face and pig skin [4,42–45]. The molecular and chemical mechanisms underlying this differential effect are still poorly understood and constitute one of the main challenges for future biological studies of the flash effect. The role of the various irradiation parameters in triggering the effect also remains to be elucidated too. In addition to the average dose rate, the total dose and the total duration of irradiation, the pulsatile nature of irradiation (dose per pulse, pulse duration, instantaneous dose rate and pulse repetition frequency) also seem to be able to influence the flash effect. A dose-modifying factor (DMF) higher than 1.4 has been shown for late-responding tissue and higher than 1.1 for early responding tissue. This normal tissue-sparing flash effect has been shown for high-dose extreme hypofractionation, moderate hypofractionation and more recently standard fractionation [46].

Over 18 publications, through 23 tumour types, in the last 10 years confirm the iso-antitumoral efficacy to conventional RT with single-dose extreme hypofractionation and moderate hypofractionation [42].

Biological mechanisms explaining the normal tissue-sparing flash effect are still under study. DNA damage and repair do not convincingly seem to be the underlying main mechanism [47]. Oxygen depletion has been recently dismissed as a hypothesis [48]. The most plausible explanation to date seems to be lipid and protein

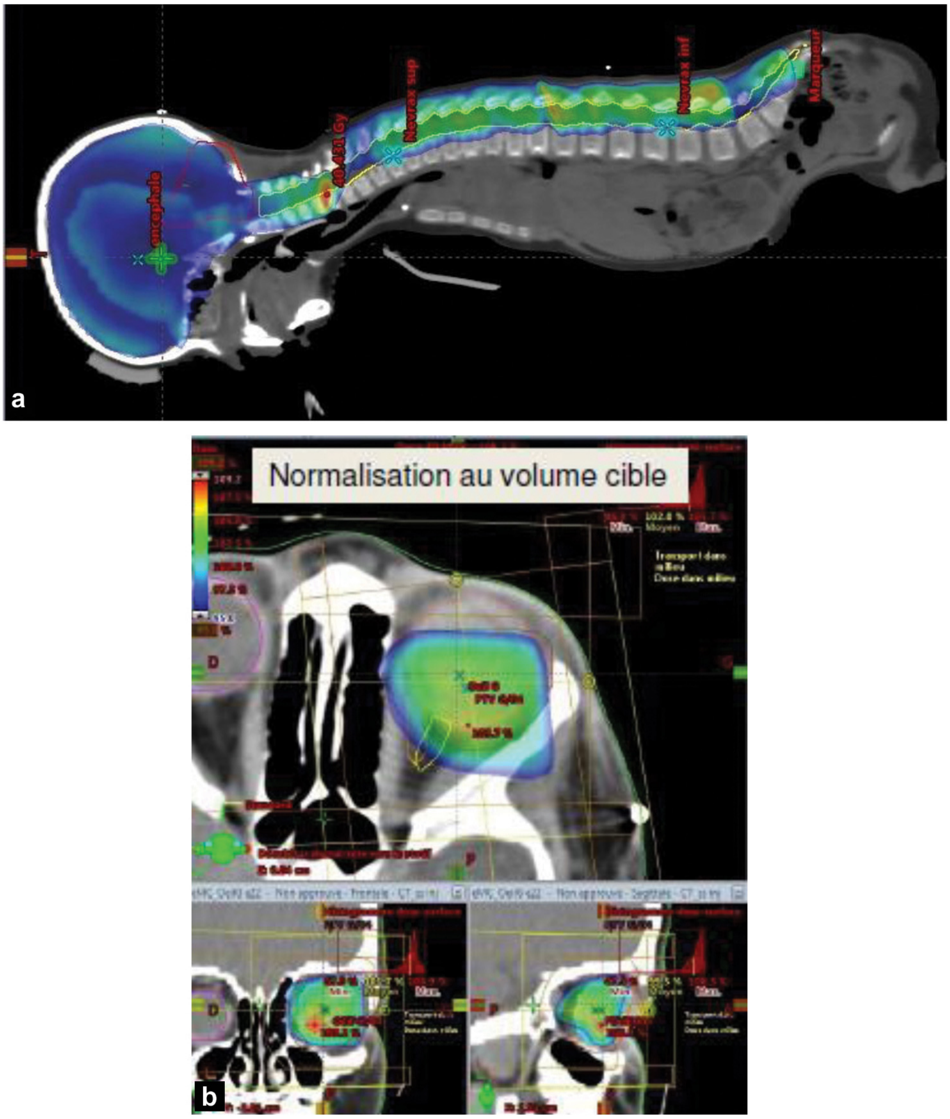

Fig. 4. Paediatric radiotherapy. a: craniospinal irradiation using photons and protons; b: dose distribution of electron irradiation of ophthalmic tumours.

peroxidation [49,50]. Less apoptosis and enhanced preservation of progenitors and stem cells seem to be involved, as well [51,52]. Less inflammation and organ function preservation have also been described, associated to less vascular damage [53,54].

Clinical evidence supporting the translation of flash is still scarce. Studies in large patients-animals, such as cats, dogs and mini-pigs are ongoing [55], while the first patient in the world to receive flash RT was treated in the Centre hospitalier universitaire vaudois (CHUV) in Lausanne, Switzerland [56]. The first clinical study in humans has been performed with proton flash irradiation in Cincinnati, where ten patients with bone metastases of the extremities, were treated in the context of a phase I, nonrandomized trial, with conventional palliative dose of 8 Gy in a single fraction to show feasibility, which was shown [57].

Combined, these data promise a vastly enhanced therapeutic window, allowing a better cure of cancer with fewer side effects that all clinicians and patients hope for, justifying the fact that flash RT quickly became one of the most vivid areas of interest in modern radiation oncology in the last 5 to 10 years and that a flash RT community was born [40].

However, and even more so in flash, there are few means available for treating deep-seated tumours with electrons. As an example, the use of electrons to treat deep-seated tumours was initially tested using medium to high energy beams (15–50 MeV), but these proved to be of little benefit in the clinical cases studied [58]. It should also be noted that cohorts of patients were treated in the 1960s at the University of Chicago with electron beams scanned at between 3 and 50 MeV [59]. Long-term follow-up of these patients revealed much lower complication and skin toxicity rates than with conventional irradiation. These healthy tissue preservation effects were attributed to a possible effect of the dose rate, which was very high at the time for these hypofractionated treatments (between 7 and 10 Gy). Very high energy electron radiotherapy, in the 100 to 250 MeV energy range, was then proposed in the 2000s. It is a particularly precise mode of irradiation with little sensitivity to tissue heterogeneity (unlike low-energy electrons or protons), which could be applicable in a large number of deep anatomical locations [5]. Its development is also potentially less costly than for heavy ion or proton radiotherapy techniques, and would enable accelerated treatment, for example thanks to electromagnetic scanning of the beams, delivering high doses per fraction and thus improving antitumour efficacy. It would then be possible to take advantage of recent work on flash RT to simultaneously reduce the occurrence and severity of early and late complications affecting healthy tissues.

The accelerator community has therefore recently focused on the development of new machines adapted to delivering flash irradiation, such as accelerators for very high energy electrons exceeding 100 MeV (PHASER programme), accelerators using plasma-laser interactions, considered very promising for radiotherapy applications [60–62]. Although photons (X-rays or gamma rays), protons or electrons can be used to generate the flash effect, the majority of preclinical studies have been carried out with electrons from linear accelerators. Provided their energy is sufficient to ensure good penetration of the tissues, electrons could still offer many advantages over other types of radiation.

5. Conclusion

Although it has been replaced in most indications by more modern techniques, in the last years a renewed interest for electrons has been observed, accompanied by very challenging developments. All the elements for the clinical implementation of complex electron therapy, for example with intensity modulation, dynamic or arc therapy, seemed to be in place in the early 2010s (at least for superficial tumours), but in the end these did not happen, probably due to the advent of modern IMRT techniques such as tomotherapy or VMAT. Still widely in use today for intraoperative applications or the treatment of mycosis fongoides, electrons are being developed at very high energies, which could allow them to be used in flash radiotherapy and regain their position in radiotherapy.

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