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Review Article

Radiobiology and modelling in Brachytherapy: A review inspired by the ESTRO Brachytherapy pre-meeting course

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A B S T R A C T

Brachytherapy (BT) plays a key role in cancer treatment by delivering a high dose to a small volume over a short time. The use of BT is currently validated in a wide range of cancers such as cervical, prostate and breast cancers while being a favourable choice for organ preservation, such as in penile or rectal cancer, or in the setting of reirradiation. Consideration of the radiobiology of BT is integral to the choices made around dose and fractionation and combination with other techniques such as external beam radiotherapy (EBRT). Much of the radiobiology of brachytherapy is based on historic data, but fortunately there is a drive to integrate translational research including radiobiologic parameters into modern BT research. In a changing therapeutic landscape moving to a high dose rate (HDR) based on high dose per fraction, it is important to ensure that the incorporation of new radiobiology knowledge helps to drive clinical practice.

This manuscript takes the ESTRO Brachytherapy pre-meeting course (May 3, 2024 - Glasgow ESTRO meeting) as a base and develops the concepts to present an overview of radiobiology in brachytherapy. Presented are 3 different considerations: the fundamentals of BT radiobiology (BT radiobiology history, biology and BT, α/β and re-irradiation), the pre-clinical radiobiology approach (pulsed dose radiotherapy (PDR) vs HDR, BT vs best EBRT techniques, high dose regions and integrated boost) and clinical radiobiology approaches (optimal number of BT fractions, radiobiology in BR for cervical, prostate, breast, skin/H&N and gastro-intestinal cancers). Presented is an analysis of radiobiology and modelling in BT aiding the integration of scientific pre-clinical and clinical data to allow a better understanding of the use of radioactive sources for cancer treatment.

Introduction

In the landscape of cancer treatment, brachytherapy (BT) plays a key role. Whilst it is predominantly used for cervical and prostate cancer, in other clinical situations it represents an optimal treatment choice such as shortening adjuvant radiation or treating local recurrence in a previously irradiated area [1]. The powerful tryptic of BT is 'high dose, small volume, short time' both for primary treatment as well for re-irradiation. High dose; as prescribed on the reference isodose, small volume; with internal dose gradient volumes inside the clinical target

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volume (CTV) and short time; over a few days, hours or even minutes.

Consideration of the radiobiologic principles underpinning BT is essential, perhaps even more so than for other forms of radiotherapy (RT), with increased complexity. In comparison to external beam radiotherapy (EBRT) BT uses a variety of methods of dose delivery with a much greater variation in dose per fraction. In order to assess different BT dose schemes, it is useful to consider the equivalent dose in 2 Gray per fraction (EQD2) either combined with or compared to EBRT. For this, the linear quadratic (LQ) model is used and doses are calculated as EQD2. This model describes a relationship between the total isoeffective dose and the dose per fraction and dose rate. Within this model, there are two components of radiation damage; the alpha (α) component which represents a single ionising radiation event which simultaneously damages two individual targets. This damage is not repairable and increases in a linear pattern with dose, thus it is influenced by overall dose rather than fractionation. The beta component (β) represents damage caused by two ionising events. The two sub-lethal events combine to form a lethal event. This damage is potentially repairable and increases in a quadratic pattern. It is influenced by fractionation and dose rate rather than overall dose. The α/β ratio is a measure of how a tissue will respond to a change in total dose, fractionation or dose rate. The LQ model is fundamental but, as with all mathematical models, it is not perfect [2]. Indeed, in its standard formula, it doesn't take into account key aspects of BT such as the time factor (short treatment time) or the impact of the internal dose gradient and it is limited for high doses per fraction [3,4]. As a very high dose per fraction is utilized increasingly frequently, it is recognized that the LQ model may fail to provide accurate results for a high dose per fraction, such as doses higher than 9 Gy [5].

Last but not least, BT radiobiology is also linked with technical factors. Indeed, in April 2018, production of low dose rate (LDR) Iridium wires ceased but, thanks to pulsed dose radiotherapy (PDR) afterloader machines, it was possible to continue to use a LDR BT concept in regard to its radiobiological properties but with the advantage of a stepping source [6]. However, the future of PDR afterloader devices is uncertain, and it is likely that the future of BT lies mainly in high dose rate (HDR) technologies. Currently, increasing levels of convincing clinical data provide evidence for BT use while the radiobiological rationale and demonstration for new BT approaches still remain under debate. We present a review based on the proceedings of the 2024 ESTRO Brachytherapy pre-meeting course analysing radiobiology and modelling in BT in order to bring more scientific pre-clinical and clinical data to better understand the use of radioactive sources for cancer treatment.

2. Fundamentals of BT radiobiology

2.1. Brachytherapy radiobiology history

From the moment Pierre Curie affixed a tube of radium to his arm and assessed the resultant ulcer and its healing, the radiobiologic effects of BT have been investigated. Fortunately, the research moved to the laboratory for the further ground-breaking early experiments. Most of the available knowledge of BT radiobiology derives from historical in-vitro preclinical models testing the effect of dose rate and dose per fraction on clonogenic survival in cultured cell lines [7]. This historic approach has accompanied the clinical developments of BT and a range of clinical studies have validated the impact of treatment modalities on tumour control probability (TCP) or normal tissue complication probability (NTCP). Even in the precursor era of radiotherapy (RT) developments, the notion of differential effect (following Bergonié's and Tribondeau's law in 1906) and the empiric concepts of fractionation exploiting the higher sensitivity of proliferating cells (proposed by Coutard and Regaud in 1922 [8]) emerged as important tools to understand the effects of radiation exposure, including for BT treatments.

With the increasing developments within modern radiobiology, mainly derived from EBRT models testing the impact of microenvironment on radiation response, there is a need to refine the classical radiobiological modelling of BT effect [9]. Indeed, this outdated model only partially considers the impact of tumour heterogeneity and patient sensitivity and thus neglects the huge potential of BT in the context of modern radiobiology, including radio-immune modulation [10,11]. Future radiobiology research can build on the important historic perspectives but must not dwell there.

2.2. Biology and brachytherapy

Biology is a broad natural science. It assumes that all organisms are made of cells that process hereditary information encoded in genes, which can be passed on to future generations. BT, as a form of RT, interacts with living organisms at the systemic, cellular, and intranuclear levels. The 7 'R's concept and the LQ model attempt to describe this concept [10,12–14]. However, in relation to the currently used types of BT, both theories do not always provide complete and detailed answers for the crucial question – how does it work? There is a small amount of scientific research detailing the biological mechanisms of modern ultra-low-dose-rate (uLDR) and HDR BT in the context of different levels of interactions and particular R's: Repair, Repopulation, Redistribution [15–18], Reoxygenation, immune Reactivation, and tumour Reinforcement [19–23]. Despite the clinical relevance, there remains a notable gap in direct biological studies specifically addressing Radiosensitivity at the cellular level for BT.

Recent studies highlight the complexity of biological mechanisms critical to understanding the effects of BT. Chargari et al. [10] and Boustani et al. [12] discuss the use of the LQ model in analysing the effects of BT, highlighting its limitations with uLDR BT [8]. Research like that of Wideł et al.[14], Zhuang et al. [18], Omura et al. [15], Collis et al. [16], and Geraldo et al. [17] indicates the significance of the bystander effect and continuous LDR irradiation in inducing molecular and cellular changes that may affect treatment efficacy. Meanwhile, studies by Cron et al. [19], van den Berg et al. [20] and Chen et al. [21] explore changes in the tumour microenvironment during LDR seed implantation and the effects of tissue trauma in experimental models, which may provide insights into exploiting tumour hypoxia or mitigating it in interstitial BT. Works by Jarosz-Biej et al. [22] and Li et al. [23] further explore the potential benefits of using BT as an 'in situ' vaccine, emphasizing the role of the tumour microenvironment and the involvement of cytokines and lymphocytes in response to therapy. These studies shed light on the comprehensive biological response to BT, emphasizing the need for further research to fully understand and optimize this therapeutic approach.

2.3. α/β

α/β values describe the biological properties of the radiation response of cells or tissues. In cell culture, clonogenic survival curves are fitted with the LQ equation. Clonogenic survival is defined as cell survival with the capacity to initiate a recurrence and form "colonies" with > 50 cells in vitro. The α/β ratio describes the "curve" of the cell survival model [24]. α/β ratios describe the sensitivity of cells and tissues to fractionation of radiation [25]. Fast proliferating tumour cells and early responding normal tissue cells have a high α/β ratio whereas late responding and slowly proliferating cells have low α/β ratios. In the clinical setting, α/β ratios of tumours and normal tissues (predictive of specific side effects) can only be determined from outcome data of randomized trials testing different fractionation schedules. As these data are scarce, clinically estimated α/β ratios usually have broad confidence intervals [26].

Comparing different fractionation schedules always requires several calculations of equivalent doses for tumour tissue and different side effects in different normal tissues. For radiotherapy of prostate cancer, these facts imply that slow growing prostate cancer (e.g. Gleason $3 + 3$) probably has a different α/β value than highly aggressive subtypes (e.g.

Gleason 4 + 5). Concerning rectal toxicity, there is not one α/β value for the rectum, instead the α/β value for acute toxicity is much higher than for late toxicity. In BT, a specific challenge in dose comparisons is the inhomogeneous dose distribution, requiring additional steps to compare tumour control rate and predicted side effects between treatment regimens and individual patients [27]. This can either be achieved with equivalent uniform dose (EUD) concepts, which might be limited for the large dose differences in BT or a comparison of several dose parameters in different subvolumes [4,28]. In addition, the half time of repair needs to be taken into account. De Leeuw et al. provided an idea of how different modelling parameters will affect calculated EQD2 values in BT for cervical cancer, creating an awareness of the difficulties in comparing different treatment approaches [29]. The START trials have added significant data regarding the α/β values for breast cancer [30] which has been invaluable in the development of BT fractionation schemes and in trial development for partial breast irradiation [31].

2.4. Re-irradiation

Re-irradiation is a critical and evolving aspect of oncology, particularly for managing recurrent cancers in previously treated areas [32]. Historically, re-irradiation dates back to the early 20th century, when individualized treatments were employed to address recurrent cancer cases with significant success. Even then, practitioners recognized that while prior radiation altered tissue response, it did not always contraindicate re-irradiation if curative or palliative outcomes were achievable.

Today, re-irradiation remains a challenge due to insufficient evidence on optimal dose fractionation and dose constraints for organs at risk (OAR). The complexity arises from balancing therapeutic dose delivery with the risk of damage to tissues that may have already reached their tolerance limits. This is where BT stands out. BT's ability to deliver highly localized radiation, with rapid dose fall-off, allows for superior sparing of surrounding healthy tissues compared to EBRT [33]. This makes it an attractive option for re-irradiation, particularly in complex anatomical regions or cases where previous treatments have limited the ability to safely deliver more radiation which is reflected in reirradiation recommendations [34]. In prostate cancer, for example, re-irradiation is increasingly explored for biochemical failure, where BT offers precise targeting [35]. Similarly, in gynaecological cancers, where pelvic recurrence is a significant issue, BT has demonstrated better outcomes with lower toxicity compared to EBRT [36]. By carefully selecting patients and utilizing modern imaging technologies like PSMA-PET or multiparametric MRI, clinicians can improve the precision of re-irradiation strategies, ensuring that high doses are delivered to the tumour while minimizing damage to critical structures.

Looking forward, advanced imaging and molecular biomarkers are likely to play a pivotal role in guiding re-irradiation [37]. Functional imaging and markers of radiation-induced tissue toxicity (such as TGF-β and IL-1) hold the potential to predict tissue response and optimize treatment plans. Additionally, emerging concepts like spatial fractionation (GRID or lattice therapy) and harnessing immune-mediated abscopal effects offer new avenues for enhancing the efficacy of re-irradiation while reducing long-term toxicities [38]. In summary, while re-irradiation presents numerous challenges, BT remains a powerful tool in addressing recurrent cancers. Coupled with advancements in imaging and biological understanding, it holds promise for more precise and effective future treatments.

3. Pre-clinical radiobiology approach

3.1. PDR vs HDR

Radiobiological effects after tissue radiation are influenced by various processes, with repair during BT being crucial, particularly affecting the outcomes of PDR and HDR treatments [39]. Normal tissues, having different repair capacities compared to tumour tissues, are more sensitive to fractionation, making PDR schedules more sparing than HDR for the same tumour effect, thus widening the therapeutic window [39]. An essential aspect of PDR treatments is the half time of tissue repair, where rapid sequences of PDR pulses within 1–2 h, limit repair of sublethal damage, increasing risk for tissues with short repair half times, especially at pulse sizes over 1.5 Gy. If PDR is given at a pulse width of 10 min and a 1 h pulse interval the dose is equivalent to LDR 0.6 Gy/hr [40,41]. If the dose per pulse is small (≤0.5 Gy) and the normal tissue repair half time is over 30 min, the differential effect to LDR is < 10 %. If the dose per pulse is over 2 Gy or the tissue repair half-time is under half an hour this is not the case and the PDR effect becomes biologically closer to a highly fractionated HDR treatment, especially in close proximity to the source [39]. Therefore, a lower total dose than LDR can be given with PDR in the same overall time to achieve equivalent clinical effect.

Clinical comparisons between PDR and HDR are limited, with scarce data available [42–45]. However, some LDR studies, such as those on locally advanced cervical cancer, show minimal differences in toxicity, suggesting that, in some cases, differences between PDR and HDR might be small or undetectable, although variations in tumour size and dose adjustments in HDR treatments could influence outcomes [46]. In a comparative analysis of HDR cervical cancer patients replanned using PDR a small subset of patients was defined who may benefit more from PDR specifically those with a larger target volume (>67.5 cm^3) [47].

3.2. BT vs best 'high-tech' external beam techniques

In the early 2000 s, several published papers compared dose distributions of simple BT applicators with those of advanced EBRT techniques. In addition to the unbalanced use of different technology levels, the analysed dose distributions were simply presented by single number dose metrics causing misleading results and conclusions [48]. Although important BT guidelines such as those from GEC-ESTRO [49] or the ICRU report 89 [50] promote the use of a limited set of dose volume histogram (DVH) parameters in daily clinical practice, the recommendations also emphasize a deep understanding of the entire dose-volume situation, including spatial dose distribution, tumour cell density, risk level and tumour response patterns. Sound comparisons of single modality techniques and combining EBRT and BT, have to take into account those heterogeneous field quantities [51–53]. A simple application of the EQD2 concept is not always valid in general, especially when simulating and applying changes in treatment fractionations using BT and EBRT methods.

When 'high tech' EBRT was compared to 'high tech' BT delivering a boost for cervix cancer, Georg et al. demonstrated that EBRT delivered inferior dosimetry to BT and the volumes receiving lower, but still clinically very significant doses, were increased with EBRT [51]. More recently Benkhaled et al. also demonstrated superiority of BT over EBRT delivering stereotactic body radiotherapy (SBRT), with BT delivering a significantly better dose to the target with lower doses to OAR [54]. Although investigators have described techniques of delivering EBRT when patients cannot have BT [55], it should be carefully examined why BT cannot be offered and, if it is for any reason other than patient fitness to undergo an implant, they should be referred on to a centre that specialised in complex BT implants or high risk anaesthesia.

3.3. High dose regions (focal/integrated boost)

The intricate nature of the highly heterogeneous BT dose distributions prompts dose characterization through various DVH, aiming to encapsulate the diverse dose levels irradiating different sections of the target and OAR. In cervix, prostate, breast and head & neck cancer, it is recommended to prioritize reporting of target DVH parameters that reflect near minimum doses or doses to "cold regions" within the target (e.g. D98% or D90%) assuming that these regions bear a higher risk of

local recurrence, which is also supported by clinical evidence [56].

While near-minimum doses hold precedence, it's crucial to acknowledge that high dose volumes may independently impact local control likelihood. Thus, alongside reporting near-minimum target doses, it is possible to supplement with characteristics of high dose volumes, such as D50% of target volumes [50]. Parameters like volumes receiving 150 % and 200 % of the prescribed dose have also been proposed [57,58]. Yet evidence correlating these "high dose" parameters with risk of local recurrence or morbidity remains limited. This limitation can probably be related to significant uncertainties in calculating EQD2 for these high physical fractional doses (e.g. exceeding 15 Gy).

A phase II study using HDR BT in prostate cancer investigating the toxicity and efficacy of focal dose escalation demonstrated a five year local recurrence rate of only 1 % with only 4 % grade 3 toxicity, all urinary [59]. High dose volumes may also serve as an "integrated boost". For indications such as intact cervix cancer and prostate cancer, patients often present at the time of BT with both GTV and CTV volumes. BT has the inherent advantage that the heterogeneous dose distribution often helps to escalate dose in the GTV.

4. Clinical radiobiology approach

4.1. Optimal number of brachytherapy fractions: Is less always better?

Delivering treatment in a number of fractions (fractionation) is a fundamental principle of RT. The National Cancer Institute dictionary defines it as: "A way of dividing a total dose of radiation … into separate doses that are larger or smaller than usual". The question is what "usual" means, and it resonates even more in HDR BT [60]. A long-established practice in HDR BT is to use hypofractionated schedules [61]. It is efficient and safe because the applicators are close to or inside the tumour. High doses in a small volume (a paradigm of SBRT) with a very short overall treatment time are the ingredients of HDR BT success. Modern imaging and planning systems allow us to shorten schedules even more.

One of the challenges on moving from LDR to HDR BT was how to divide the doses-what fraction size and how many fractions. At this stage one of the Rs of radiobiology, repair, came into consideration. The repair half-time ($T_{1/2}$) is the time taken for half the maximum repair to occur. This is important for normal tissue repair following individual HDR BT fractions. It was initially suggested that late responding normal tissue $T_{1/2}$ was 1–1.5 h [6,62] however there are indications that it is longer [63], if the repair half-life were 1.5 h, an HDR dose of 2–3 Gy per fraction would be equivalent to LDR at 0.5 Gy/hr. In contrast, if it were 4 h, HDR doses of 5–12 Gy per fraction would be equivalent; the latter matches current practice more closely. Of course, repair may not simply be a function of time and may have fast and slow components [64].

A high dose per fraction with a low fraction number is established in skin HDR BT with single fractions being commonly used [65]. There is growing data on using single fractions in other clinical scenarios, particularly partial breast BT [66,67]. Single-dose HDR BT alone has not established its position in the sole treatment of prostate cancer [68], but it is standard as a boost [58,69]. We still do not know where the limitations are and where the highest advantage lies. Radiotherapy causes cell kill not only by direct effects on the DNA but also by alteration of the immune microenvironment. There is data from melanoma mice model research showing that for optimal clinical effect there should be a robust CD8 lymphocyte response [22]. Using contact BT a dose of 5 Gy caused tumour shrinkage but a dose of 10 Gy caused not only tumour shrinkage but also CD8 lymphocyte activation. As the dose rose to 15 Gy natural killer lymphocytes numbers rose within the tumour which may be beneficial but equally has been postulated to decrease T-cell function which is an immunologic disadvantage [70]. Therefore, while the clinical trend is to shorten overall treatment time using higher doses per fraction, we should be cautious of not going too ultra in our hypofractionated regimens.

4.2. Radiobiology in Brachytherapy; cervical cancer

LDR BT has been used for decades for cervical cancer. The development of the afterloading technique facilitated BT with HDR. PDR was introduced to radiobiologically emulate LDR treatment, but utilize the advantage of an afterloading technique. Today, both PDR and HDR cervical cancer BT is used worldwide and in the EMBRACE-I study 57 % of the patients were treated with HDR BT [71]. In addition to the different dose rates, a large variation in fractionation schedules was seen.

In 2006, the GEC-ESTRO committee recommended to use the LQ model (EQD2) for prescription and reporting [49].This facilitated comparison across dose rate and fractionation schedules for large volumes of patients [50] and today we have high level clinical evidence for dose–effect relations for both disease and morbidity endpoints [72]. However, the LQ model does not take tumour re-oxygenation and repopulation into account. When comparing clinical outcomes between different cohorts, re-oxygenation should be considered. It is likely that factors related to hypoxia should be balanced in the different groups but hypoxia and re-oxygenation are challenging to model. Functional magnetic resonance imaging (MRI) has been shown to assess these effects [73] with pre-treatment hypoxia being predictive of outcome, particularly when combined with functional and volume regression at the time of BT. Repopulation plays a role when overall treatment time is exceeding 50 days [74]. Thus, the total treatment time needs to be reported in order to develop models that takes this effect into account.

4.3. Radiobiology in Brachytherapy; prostate cancer

The use of HDR BT for prostate cancer is based on exploiting the ability to deliver large doses per fraction which, if the predicted α/β ratio is as low as reported at around 1.5–3 Gy, will enable very high biological doses to be delivered [75]. Single fraction HDR BT for sole therapy of prostate cancer has not shown the promise that was expected [76]. This may be due to the failure of current dose models to take other radiobiologic factors into account. Tien and Chen modelled doses taking into account intrafraction sublethal damage repair and demonstrated that the biological dose may be decreased by as much as 37 % [77].

Data on other aspects of the cell kinetics and radiation response are also less robust [78]. A long potential doubling time (Tpot) has been reported, ranging from 23-61 days [79] although this has been disputed based on modelling clinical data [80]. A delayed accelerated repopulation also is proposed. Both of these properties may impact on the efficacy of LDR BT with radiation release over several months. Finally prostate cancer has been shown to have hypoxic elements and these will also impact on radiosensitivity [81].

4.4. Radiobiology in Brachytherapy; breast cancer

The breast hypofractionation START Pilot-B and the Canadian OCOG trials allowed an estimation of α/β ratio for local–regional relapse of 4 Gy, 2.9 Gy for marked changes on normal tissues and 3.1 Gy for breast induration [31,82]. This is the basis for accelerated partial breast irradiation (APBI) with BT in 8 fractions of 4 Gy or 7 fractions of 4.3 Gy, and for very accelerated partial irradiation (VAPBI) in 4 fractions of 6.2 Gy or 3 of 7.45 Gy. As discussed due to the limitations of higher doses per fraction, the single fraction schedule of 16 or 18 Gy cannot be calculated with the LQ model and its results are empirical. The effect on the tumour microenvironment is also very important for breast BT. When given intraoperatively breast BT has been shown to change the microenvironment such that it changed the surgical wound fluid from an environment that promoted cell growth and invasion to one that did not [83].

The inevitable dose gradient in BT ensures non-uniform dosage within the target volume and this extra dose has its own biological effect [3,84]. The therapeutic window between tumour control and late effect

is narrow for breast. If the selected schedule is overtreating, the complication rate will be unacceptable. If it is undertreating, a long follow-up is required to discover it [85].

4.5. Radiobiology in Brachytherapy; skin and head and neck cancers

Head and neck (H&N) and non-melanoma skin cancers (NMSC) are common neoplasms with increasing incidence. RT is a valid treatment option for both localized and advanced cases, with multiple fractionation options available [86]. BT can be considered as exclusive treatment or as boost integrated with EBRT [87]. Moreover, in this scenario, a combined approach using several therapies such as chemotherapy, immunotherapy and/or surgery could be a mechanism to improve outcomes [88].

Skin neoplasms and H&N neoplasms have many similarities but different histologies require different fractionation schedules based on radiobiology. Hypofractionated regimens have been shown to be non-inferior to conventional fractionation in terms of overall survival [89,90]. In this context, the tumour microenvironment plays a crucial role in tumour immune suppression and can be modified by radiation therapy and other factors [91,92].

A high dose per fraction and reduction of the overall treatment time can have greater anti-tumour effects and can also modulate the immune response [93]. Moreover, stressful events can also induce immune system downregulation, but psychological intervention has been shown to increase wellbeing and can modulate the immune microenvironment modifying the radiobiological effects. This is important as BT can be perceived as a stressful event by patients.

4.6. Radiobiology in Brachytherapy; GI cancers

Oesophageal BT is generally delivered using a single lumen catheter, with catheter diameter varying. The heterogeneity of BT dose across a volume gives rise to a 'hyperdose sleeve' the volume of which varies greatly at the same prescription depth, according to catheter diameter, which greatly affects dose delivered [94]. This is a factor which a clinician may not be considering when prescribing dose. Thus use of the radiobiologic principle of EUD can aid understanding of dose and effect [4]. The radiobiology of dose delivery may explain the difference in outcomes between two randomised trials of BT versus stenting, possibly explaining why a significant benefit was seen when using a higher dose single fraction but not when using multiple fractions of a lower dose [95,96].

Consideration of basic radiobiologic principles is very important when choosing rectal RT techniques to deliver dose. Individual tumours display differing radiosensitivity but in general rectal adenocarcinoma is relatively radioresistant therefore dose escalation is important when attempting to achieve organ preservation in rectal cancer [97]. The delivery of RT using contact X-ray BT (CXB) takes advantage not only of the physical properties of treatment delivery but also of a number of radiobiologic effects to achieve this dose escalation: fractionation effect, dose rate effect, volume effect and relative biological effectiveness [98]. The OPERA trial demonstrated that dose escalation using CXB delivers a greater rate of organ preservation than EBRT alone [99]. However, examining dose delivery and tissue response more closely shows that there is likely to be a range of dose delivered as compared to the standard dose prescribed [100], understanding this difference could prompt a move away from a single 'one prescribed dose fits all' approach to a 'customised delivered dose' approach. Unexpectedly when CXB was used as a boost after local excision, improved outcomes were seen for disease free and overall survival if the CXB was given prior to EBRT compared to after EBRT, giving rise to the question does CXB induce an abscopal effect? [101] Therefore trials are planned that endeavour to enhance radiobiologic features such as radiosensitivity using immune checkpoint inhibitors and other agents [102].

High dose rate rectal BT using Iridium-192 also takes advantage of radiobiologic effects when used to deliver conformal radiation boosts. Outcomes vary between series, with the HERBERT trial showing marked toxicity using doses $>$ 7 Gy per fraction [103] but Vuong et al. delivering 10 Gy per fraction routinely with similar or lower toxicity [104]. Radiobiologic principles can be used to compare the dose delivery between these series, demonstrating for example that the 10 Gy per fraction group delivered a lower dose to rectal mucosa than the 7 Gy per fraction group. Utilising radiobiology in the selection of doses and fractions will deliver a better prediction not only of outcomes but also treatment toxicity. Future standardisation of dose reporting should also improve inter-series comparison.

5. Conclusion

Modern technical developments in BT have combined with new fractionation schemes and treatment indications to rethink the radiobiology of BT. We have reviewed important aspects of basic science and highlighted clinical considerations in the most frequent indications. BT remains an essential weapon against cancer. A better understanding of its principles of biological action will allow BT to continue and promote its research and development.

Declaration of competing interest

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