Chapter

Implications of Radiosensitizer and Radioprotector Factors in Refining the Dose-Volume Constraints and Radiobiological Models

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Abstract

Radiotherapy is a cornerstone of the modern treatment of many types of cancer, having both curative and palliative roles. It is estimated that more than half of cancer patients will need radiation therapy in the course of evolution. The goal of radiotherapy is to maximize tumor control, reducing adverse effects on normal tissues in close proximity at the same time. Improving the therapeutic ratio is the main goal of the efforts made to improve the technique and accuracy of the radiotherapy by using the targeting of the tumor volume with the help of the imaging guide and the dose conformation around the target volume. The use of the multi-leaf collimator (MLC) allowed a better coverage of the target volume in the irradiation field, thus reducing the unnecessary irradiation of healthy tissues. The use of radioprotective agents and radiosensitizers is another strategy to maximize the effect of radiotherapy. Recently, interest has focused on the design of irradiation protocols that exploit the differences in biology in terms of the response to irradiation between tumor cells and normal tissues.

Keywords: radiotherapy, IMRT, VMAT, SIB, dosimetry

1. Introduction

The transition in the 1990s from conformal 3D radiotherapy to intensity-modulated intensity radiotherapy (IMRT) allowed the high-dose irradiation of volumes with irregular shapes [1, 2]. The use of radioprotective agents and radiosensitizers is another strategy to maximize the effect of radiotherapy. Recently, interest has focused on the design of irradiation protocols that exploit the differences in biology in terms of the response to irradiation between tumor cells and normal tissues [2, 3].

From the clinical point of view, tissue radiosensitivity is reported as the difference in the degree of response at the same dose of irradiation or at different doses required to produce the same response to different subjects. The radiosensitivity and radioresistance of the different types of tissues is determined by the mitotic rate and the cellular repopulation, being proven that the cells with low rates of

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repopulation are more radioresistant. Especially for cells with long post-mitotic life, for which the main mechanism of radiation induced hypoplasia and atrophy, is death in interphase, the response is obtained only at high doses of radiation [1, 2, 4].

2. Dose-volume-toxicity correlations - from radiobiology to guidelines and clinical practice

With all the technical and ballistic advances in the planning and delivery of radiation therapy that has occurred in over 100 years since the use of radiation in anticancer treatments, it has not been possible to obtain a perfect therapeutic ratio for which the irradiation of healthy tissues tends to zero. Historically, the first initiative to guide doctor radiation oncologists was the publication of Rubin and Cassarett, a collection of reports on toxicities and doses to which they were reported. The 1980s were a significant evolution in the field of radiation oncology, the radiotherapy being transformed from a two-dimensional (2D), based on the approximate evaluation of the position of the radiosensitive organs based on the anatomical landmarks and subsequently of the 2D simulator with conventional radiographs, to a three-dimensional (3D/volumetric) process. This evolution has shown that previous knowledge about tumoricidal doses and tolerance of radiosensitive organs to irradiation does not present accuracy and new information is needed regarding partial organ volumes and toxicities [2, 5].

In this context, a scientific committee has carried out an extensive review on the dose data received from different organs and toxicities, reaching the consensus to evaluate the data using a volumetric division of organs in one-third, two-thirds, and the whole organ. The consensus of eight experts from reference centers in the United States was published under the name "Emami Paper." The paper was a reference for assessing the risk of toxicity associated with doses, but being a literature review until 1991, it contained data from the previous 3D-CRT technology. Another limitation of the study was the evaluation of toxicities after conventional irradiation (2 Gy/fraction), and at that time neither the dose-volume histograms were routinely used in dosimetry. From the clinical point of view, only the most severe toxicity was evaluated, without any grading system for these adverse effects [1, 2, 6, 7].

The next decades have brought a revolution in terms of oncological treatments. A multidisciplinary approach has become a standard in oncology, and sequential and increasingly concomitant therapeutic associations are increasingly used. In terms of technology, most cobalt units have been replaced with linear accelerators, and radiotherapy planning based on CT simulation has become standard. 3D-CRT and IMRT techniques based on IGRT have been widely implemented, and delineation of tumor target volumes using CT, MRI, and PET-CT imaging has become a standard. The complexity and the large number of factors that influence the response to the irradiation of the tumors and the probability of the complications of the normal tissues have made it necessary to develop predictive models for the clinical complications associated with the radiation therapy. The large number of data reported in relation to the different toxicities and conditions of registration make analysis difficult to identify value parameters. A group of clinicians and researchers performed a retrospective analysis called "Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC)." The aim of this approach was to review the available literature on the correlation of dose-volume parameters with the complications of normal tissues, the study being the analysis of the literature of the last 18 years. The paper QUANTEC, resulting from the collective effort of 57 experts, appears with the support of the American Association of Radiation Therapy (ASTRO) and American Association of Medical Physics (AAPM) and is published in the supplement of the journal "International Journal of Radiation Oncology, Biology, Physics" (the Red Journal) [2, 5–8].

The QUANTEC group aimed to provide a reliable prediction at the time of radiotherapy planning of the risk of occurrence of toxicity depending on the volume parameters extracted from the dose-volume histograms.

Although these publications contain a comprehensive review of scientific papers of the information published in order to be a guide for clinicians, the use of this guide cannot substitute for the judgment of the radiation oncologist clinician, considering the large number of intrinsic and extrinsic factors on which the radiosensitivity of each organ depends [7, 8].

There is no model that accurately predicts normal tissue responses to irradiation for routine clinical use, most models being more descriptive than predictive. The use of the multi-leaf collimator (MLC) allowed a better dosimetric coverage of the target volumes also offering a significant reduction in the irradiation of the healthy tissue from the proximity of tumors.

$$(BED) = n \cdot d\left(1 + \frac{d}{\alpha/\beta}\right) \tag{1}$$

The isoeffect formula for conversion to standard fractionation is commonly used in cases where another fractionation scheme (hypofractionation or hyperfractionation) is used to assess the toxicity risk according to the "QUANTEC" data:

$$(\mathrm{EQD2}) = \mathrm{D}\frac{\mathrm{d} + (\alpha/\beta)}{2 + (\alpha/\beta)} \tag{2}$$

The α/β index is calculated based on information from cell survival curves on in vitro cell cultures, assigning values for the α/β ratio, and using these values to calculate a normal dose of tissue tolerance may be risky in estimating clinical complications [2, 7, 9].

Organs at risk (OAR) are those organs that if irradiated can be structurally and functionally affected. The structures that are in the proximity of the irradiated volume or by their anatomical function are defined as OAR, receive a certain dose during the treatment. These OAR's have been divided from the radiobiological/functional point of view into serial organs and parallel organs. The spinal cord is the most relevant example of OAR with serial architecture. Each subunit of the spinal cord is vital to the functioning of the entire organ. The parallel structural organization is based on the functional independence of the subunits. The impairment of a limited number of structures does not compromise the function of the whole organ; the dysfunction occurs if a large number of subunits have been affected, because the remaining functional ones do not have sufficient compensatory capacity. An example of an organ with parallel architecture would be that of the parotid glands. In these cases the average dose absorbed throughout the organ is the most significant predictor of toxicity [5, 7, 8].

Using a Lyman mathematical model and the algorithm proposed by Kutcher and collaborators, a radiobiological model was proposed based on extrapolation of Emami guides to any dosimetric distribution, using dose-volume histograms (DVH). The Lyman-Kutcher-Burman (LKB) model was and is one of the most used radiobiological mathematical models, but the multitude of factors involved in producing toxicities made this model an ideal one, without being implemented in clinical practice as a standard. The QUANTEC is one of the most valuable analyzes on dose-volume parameters based on numerous retrospective studies. However, the therapeutic and technical diagnostic advances in the multimodal treatment of the pathological pathology make it necessary to update and validate new recommendations regarding the dose-volume parameters correlated with toxicities [7–10].

With the implementation of inverse planning techniques (IMRT and volumetric intensity-modulated volumetric arc therapy (VMAT)), it became necessary to define a risk-exposed volume (RVR) in order to obtain an optimal dose distribution using the planning software, trying to limit the risk of developing high-dose regions outside the target volume. ICRU83 defines RVR as the difference between the volume included in the external contour and the volumes CTV and OAR. With the implementation of IMRT, the dose received by RVR can be a predictor of the risk of radioinduced carcinogenesis, and a reduction of large volumes receiving low doses is necessary. In fact, there are numerous intrinsic and extrinsic factors that influence the radiosensitivity of each tissue/organ, related to the patient (age, comorbidities, Karnofsky score/ECOG performance status) and dependent on the radiosensitivity of each organ (serial dose-effect organization, the most eloquent case being of the spinal cord, parallel radiobiological organization volume-effect structure as in the case of liver and lungs, mixed serial and parallel organization described in the literature in the case of kidneys), but it is also influenced by the previous treatments applied. Radiotherapy treatment influences the response of radiosensitive organs by parameters as the maximum dose, average, minimum, dose rate, general treatment time, irradiation beam energy, and irradiated volume. Systemic treatments (radiosensitizing and radioprotective agents, chemotherapy, biological and immunotherapy) influence the tissue radiosensitivity and determine the variability of the different responses at the same irradiation dose. The most recent studies show the involvement of molecular and genetic profiles in radiosensitivity. According to Emami and QUANTEC studies, cerebral radionecrosis usually occurs late from 3 months up to a few years after radiotherapy with initially a 5% risk at 5 years after treatment at a dose of 60 Gy received by one-third of the brain by standard fractionation. Using the ratio $\alpha/\beta = 3$ in formulas derived from the quadratic linear model, radiation necrosis was estimated at <3% for a dose <60 Gy, increasing to 5% if the brain tissue received dose is 72 Gy. The toxicity caused by the irradiation of the brainstem can be potentially lethal. The Emami study considered TD 5/5 of 50 Gy for the entire brainstem and 60 Gy in one-third of the brainstem as the tolerance limit, but reviewing the study literature evaluates a brain stem tolerance up to 54 Gy with <5% risk of brainstem necrosis or neurological toxicity. It is also recommended to limit doses up to 59 Gy per volume (1–10 cc). In exceptional situations the brainstem can tolerate up to 59 Gy (<< 1 cc) and can receive up to 64 Gy [2, 8, 11].

Toxicity by spinal cord irradiation is also severe, and myelopathy is often disabling. For a ratio $\alpha/\beta = 0.87$, the risk of myelopathy is 0.2% at 50 Gy and 5% at 59.3 Gy, using the quadratic linear model. The values used in the literature for the α/β ratio are usually higher and make necessary to convert the dose of treatment per fractions to 2 Gy [8, 9, 12].

Radiation-induced optic neuropathy (RION) is severe toxicity leading to a rapid assessed blindness. Emami's recommendations are TD 5/5 of 50 Gy for the entire organ.

Based on the QUANTEC review, a dose of 50 Gy received by the whole organ is associated with <1% risk of toxicity, and the risk increases from 3–7% for doses between 55 and 60 Gy, the increase in toxicity rate being significant for doses greater than 60 Gy [2, 7, 8].

For the radiotherapy of thoracic tumors, radiation-induced pneumonitis is one of the most common toxicities in patients treated with radiation for cancers of the lung, breast, and other mediastinal tumors, often being the dose-limiting toxicity. Parameter V20 was identified as the most significant predictor of pneumonitis.

Radiation-induced pericarditis is associated with increased levels of mortality, the most relevant cardiac toxicity of irradiation. It was considered that the pericarditis risk is less than 15% when the mean pericardial dose was <26Gy, another dosimetric constraint considered predictive for pericarditis being V30 (pericardium) <46% in the case of breast cancers irradiation [2, 7].

Radiation-induced liver disease (RILD) usually occurs between 2 weeks and 3 months after radiation therapy. Emami guideline estimates an associated risk of <5% toxicity for an average dose of ≤30 Gy received by the liver, with a reduction to a maximum of 28 Gy required in patients with pre-existing liver disease.

Radiation-induced renal dysfunction is manifested in a variety of ways, from clinical symptoms to biochemical or imaging changes, most commonly with decreased creatinine clearance or even renal failure. An average dose of 18 Gy is considered to be associated with a 5% risk of toxicity at 5 years, with limitation to an average dose of 20 Gy being considered a feasible option in clinical practice [2, 5, 7].

Treatment toxicity for pelvine tumors includes femoral neck and head necrosis, associated with possible fracture. Factors such as osteoporosis and androgen treatment in the background increase the risk of irradiation toxicity. A 52 Gy dose for the entire femoral head was considered the recommended limit according to Emami publication, limiting the dose below 50 Gy and reducing the risk of neck/femoral neck necrosis to <5%. However, there are studies that report toxicities for large doses delivered on smaller volumes [7, 9, 13].

Without proposing to present all the recommendations of these guides, we have exemplified some recommendations and their predictive value on the toxicities for radiotherapy of tumors of the cervical, thoracic, abdominal, and pelvic regions.

The development of mathematical models in cancer biology and radiotherapy treatment is a step motivated by the desire to evaluate the probability of tumor control and the probability of healthy tissue complications. The technical evolution of radiotherapy and the complexity of the treatment plans have led to the emergence of increasingly complex treatment plans, with unpredictable difficulty to evaluate dose distributions. The desire to obtain an optimal plan and to increase the tumor control, limiting the risk of complications at the lowest possible level, has oriented the research toward the development of radiobiological models with a predictive value of the tumor response and the toxicity rate. The development of radiobiological models originated three decades ago, but in recent years efforts have been intensified to introduce these models into clinical practice. The inability to consider variables as clinical data and histological type of tumor made it difficult to introduce these models as standard in the process of evaluating treatment plans. However, some producers have included radiobiological models in commercial TPS that use DVH curves in the treatment plan and biological parameters such as histologic type and characteristics of nearby healthy tissues to calculate tumor control probability (TCP) and normal tissue complication probability (NTCP). The radiobiological models included in the TPS software are based on the Poisson TCP model and the LKB model for the calculation of NTCP [9, 14].

Although not yet implemented as a standard of assessment in clinical routine, TCP and NTCP models offered the radiation oncologist and medical physicist a useful tool in evaluating treatment plans and selecting the best treatment plan but also in evaluating geometrical errors and in comparison of the most modern radiotherapy techniques.

Dosimetric comparisons between treatment plans have been used extensively in validating treatment plans generated by the inverse planning techniques IMRT and VMAT, determining according to EMAMI/QUANTEC recommendations and the latest RTOG recommendations the possibility of reducing the risk of toxicities associated with irradiation. The use of radiobiological models has shown a small benefit in TCP and a significant reduction of NTCP when using the IMRT technique in prostate cancer radiotherapy. TCP/NTCP models were also used to compare sequential IMRT plans with SIB-IMRT plans. The use of the boost integrated in the

VMAT technique demonstrated the ability to reduce the average dose received by the rectum and bladder by 13 and 17% [2, 7, 15].

Also the use of radiobiological models can highlight the percentage with which the TCP value increases by increasing the dose to a certain value. In the case of comparative VMAT single-arc vs. VMAT double-arc treatment plans, the use of NTCP radiobiological models revealed similar values regarding the risk of radionecrosis of the femoral heads, on irradiation plans for prostate cancer although the dosimetric distribution is significantly different between the two plans. However, some authors report lower mean NTCP values for VMAT double-arc plans.

Biological optimization based on NTCP of treatment plans has become a feasible alternative, based on dose-volume optimization, demonstrating the possibility to reduce up to 3 times the doses received by the parotid glands in the case of locally advanced nasopharynx cancers treated by IMRT technique [16, 17].

Patient repositioning based on imaging guidance is routinely performed in most radiotherapy centers using modern radiotherapy techniques using daily setup and four-dimensional computer tomography (CBCT) images performed with onboard imaging (OBI) systems which are increasingly used to compare planned and treated target volumes. TCP and NTCP radiobiological models can be used to evaluate the effect of systematic and random errors on the probability of tumor control and on the risk of toxicity, using information from the DVH curves. Some authors have used EPID portal dosimetry to check the dose received by critical organs as heart for the purpose of evaluating NTCP [2, 16–18].

Another direction of interest was the evaluation with the help of the NTCP of the advantage of the new four-dimensional computer tomography (4D-CT) technology in radiotherapy planning. The radiobiology studies proved a minor benefit in TCP in many situations. This evaluation has the role to give a suggestive image of the situations in which the 4D-CT technique offers a clear advantage over 3D image-based planning. Reposition during treatment is made according to the geometric variations of the target volumes and to the changes in the anatomical conformation of the body. The adjustments in treatment position using CBCT imaging is often used without being able to accurately estimate the consequences from the point of view of toxicities and tumor control [2, 18–20].

Currently, replanning of treatment using weekly CBCT imaging for radiotherapy patients can be done during the course of treatment, to provide a more accurate dose and to avoid erroneous treatment due to daily movement of organs. Adaptive radiation therapy is defined as changing the radiological treatment plan delivered to a patient during a course of radiation therapy to take into account temporal changes in anatomy, such as tumor contraction, weight loss, or internal movement, etc. However, the biological consequences of this intervention during the course of treatment may remain unclear to some practitioners. The clinical impact of adaptive radiotherapy has been evaluated using biological modeling of bladder cancer. In the Wright et al. study, various adaptive planning target volumes (PTV) were generated from the inter-fractional variation of the bladder observed in the first four CBCT sessions. In addition to IMRT plans that deliver 60 Gy to a given PTV, simultaneous integrated impulse (SIB) plans have been generated. For uniform clonogenic cell density throughout the bladder, TCP ranged from 53–58% for 60 Gy planes, while it was between 51 and 64% for SIB planes. They showed that dose tracking and TCP calculation can provide additional information on standard criteria, such as geometric coverage for selected cases [20–23].

It is assumed that the use of IGRT can lead to an improvement in TCP by increasing the PTV dose coverage in daily treatment while decreasing NTCP by using low uncertainty CTV-PTV margins in the case of prostate cancer radiotherapy, demonstrating the ability to improve therapeutic for both IMRT and 3D-CRT plans.

With all the efforts made to develop radiobiological models, they remain ideal models. Including the individual biological parameters of the patients in the treatment decision will contribute to the understanding of differentiated response of tumors to radiotherapy and will be able to transform these models into feasible models applicable in clinical practice. The number of malignant stem cells and their intrinsic cell radiosensitivity, cell repopulation, tumor and tissue hypoxia, and the ability of tumor cells to reoxygenate and repair DNA damage are factors whose introduction into the radiobiological mathematical models will increase the accuracy of each case of tumor control and toxicity predictions. Thus, a step forward will be taken in the use of these models in clinical practice within the concept of personalized medicine, modulating the treatment for each patient in order to obtain the best therapeutic ratio.

Identifying new biomarkers to guide radiotherapy tailored to each case depending on the radiosensitivity of tumor cells and healthy tissue requires the identification of a large number of pre-therapeutic factors with predictive value on tumor toxicity and control. If the data obtained from the tumor histology and the patient performance status and comorbidities are taken into account in the evaluation and pre-therapeutic optimization of the plans, the biological parameters of the tumor are rarely considered in the modulation of the treatment. Also, early response to imaging-evaluated therapy may be a predictive factor of tumor control [2, 23–25].

The development, validation, and integration of imaging biomarkers using CT, PET-CT, and MRI to improve the response to radiotherapy are part of the areas of interest of clinical and preclinical studies, this research directive being integrated under the name of "radiomics." There are two directions for using predictive biomarkers for individualized treatment, to choose the treatment offered to a patient (e.g., intensifying and choosing a multimodal therapy for a hypoxic tumor with radiation and chemotherapy resistance factors or de-escalating treatment for tumors with radiosensitivity-associated factors such as HPV viral etiology for head and neck cancers). The modulation of the treatment by altered therapeutic and fractional associations (hypo- and hyperfractionation) aims to obtain a higher TCP with the limitation of NTCP of the tissues from the vicinity of target volumes, avoiding the risk of toxicity [2, 24, 26, 27].

Biomarkers can also be used for early evaluation of therapeutic outcomes to decide whether to discontinue or continue a therapeutic procedure or modify the initial treatment, but validating some biomarkers and including them in radiobiological models that are part of the clinical decision algorithm is still a strategy used only in preclinical and clinical studies. Regarding systemic therapy significant progress has been made, by discovering new therapeutic targets that have changed the clinical oncological practice, making it necessary to identify biomarkers to guide the therapeutic decision. HER-2 and hormone receptor status evaluated at breast cancer patient biopsy is currently used for therapeutic protocol decision, EGFR mutation targets treatment for targeted molecular therapy in lung cancer, KRAS mutational status is integrated into colorectal cancer treatment to allocate patients for anti-EGFR therapies for KRAS wild-type tumors, PD-L1 expression becomes a marker of response to immunotherapy in more and more nonplastic locations, and even though we have presented only a few suggestive examples, there is an increasing number of biomarkers with potential predictive for response to radiotherapy [2, 5, 27, 28].

Radiation oncology has a long history of research into understanding the implications of genetics in the variation of the response to treatment for each patient in order to personalize the therapy. The identification of new biological signaling pathways will explain the variation in the individual response of some tumors to irradiation. The use of elements from the genetic signature of each patient could constitute biomarkers of the clinical response to irradiation by modifying radiosensitivity of the tumor and healthy tissue. Since 1936 the different effects for subjects of irradiation with an identical radiation dose have been demonstrated by the occurrence of early skin toxicity, the near-Gaussian frequency distribution of individual sensitivity being highlighted. Subsequent research has shown the involvement of genetic syndromes in the early onset of toxicities, with the subtraction of cell hypersensitivity to irradiation, caused by affecting the DNA chain repair mechanisms. In addition to the ATM gene associated with ataxia-telangiectasia syndrome, other genes such as NBS1, LIG4, and MRE11 have been linked with syndromes associated with high radiosensitivity, caused by impaired DNA chain repair mechanisms [29, 30].

Modern radiobiology research has highlighted the applicability of genomics in predicting the adverse effects of radiotherapy, based on the application of genomics in radio-oncology. Advances in high-throughput approaches will support increased understanding of radiosensitivity and the development of future predictive analyses for clinical application. There is an established contribution of genetic risk factor to adverse radiotherapy reactions. The radiosensitivity of an individual is an inherited polygenic feature, and in order to elucidate the genomic involvement in radiosensitivity, the Radiogenomics Consortium was set up to allow large data cohorts for research development, and the REQUITE project would collect standardized and genotyped data for~5000 patients [31]. Linking their information with the dosimetric data will lead to the generation of multivariable models that can be used in the clinic, identifying new genes that have an impact on the radiosensitivity of the toxicity pathogenesis and the tests that will be incorporated into the clinical decision-making process [30, 32].

The development in the last decades of imagistic techniques and their non-invasive or minimally invasive character allowed the dynamic evaluation of the changes of the biological characteristics of the tumor. Molecular imaging brings pre-treatment information but also has the ability to evaluate the changes produced by the treatment since the first irradiation fractions. CT and MRI imaging already has a significant role in radiotherapy planning, CT simulation becoming a standard, and MRI imaging contributes to a more precise delineation of tumor invasion into adjacent organelles. The increasing use and availability of PET-CT imaging and its inclusion in treatment planning make it possible to use different tracers as a biomarker of tumor radiosensitivity in click practice [33]. *18F*-Fluorodeoxyglucose (18F-FDG) is one of the most used biomarkers in experimental and clinical investigations, the SUV values before and during the treatment being investigated as possible biomarkers of the treatment by chemotherapy and radiotherapy. The concept of "biological dose painting" is based on the delimitation of target volumes on functional criteria; the irradiation of a tumor with different doses and the escalation of the doses in areas with high uptake of 18F-FDG were discussed with the introduction of IMRT and VMAT techniques that allow the irradiation with different doses of some subvolumes from the target volume. 18F-FDG can identify tumor regions with high cell density and radioresistant regions due to hypoxia. Identifying the most common relapses after radiotherapy in the areas with higher uptake of 18F-FDG is a new argument for dose escalation in these regions.

The observation that in several cases of locally advanced cancers the tumor control after irradiation was not satisfactory made necessary a careful analysis of the areas where recurrence occurs. The analysis of the characteristics of the tumors with recurrence risk revealed an increased risk for the hypoxic regions or with an increased number of clonogens with proliferation capacity. One of the strategies used to control the tumor response is to use the boost on subvolumes with radioresistance pattern, considering the results of the studies that prove the survival rates associated with better locoregional control [34, 35].

The use of routine boost for all patients is a controversial topic. For head and neck cancers and for prostate cancer, there was a benefit in escalating doses by 10–20% in the topographic regions of the tumor with an increased risk of recurrence. An EORTC trial shows a minor benefit of breast boost but with a significant increase in toxicity rate.

Using radiobiological models, an increase of up to 20% of the TCP was observed in the case of a 10–30% dose escalation on a sub-volume of 60–80% of the primary tumor target volume. The introduction of IGRT and PET-CT hybrid imaging opens the horizons of a new challenge, the topographic identification of the region where the boost will be made, based on the clinical rationale balancing the benefit and the toxicities.

Adaptive risk optimization uses a biological objective function instead of an objective function based on dose-volume constraints, maximizing TCP for different regions of the tumor with recurrent risk while also minimizing NTCP for risk organs [2, 26, 36].

The tendency to include biological information in radiotherapy will lead to the use of cellular, molecular, and physiological characteristics in the treatment planning. PET-CT radiotracers 18F-FMISO-PET,^{60}Cu-ATSM-PET, and blood oxygen diffusion (BOLD)-MRI are frequently investigated in translational research related to tumor hypoxia. Investigation of tumor proliferation proved benefits from 18F-labeled fluorotime (FLT) as a biomarker.

The development of multivariable radiobiological models and dose prescription protocol based on functional data obtained from hybrid imaging is part of the tendency to include modern radiotherapy in the precision medicine trend, exploiting variations in tumor radiosensitivity and healthy tissues in clinical practice [2, 21, 37, 38].

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