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Original Article

ESMO-ESTRO framework for assessing the interactions and safety of combining radiotherapy with targeted cancer therapies or immunotherapy

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ABSTRACT

With the emergence of targeted therapies and immunotherapy, various cellular pathways are utilized to improve tumor control and patient survival. In patients receiving these new agents, radiotherapy is commonly applied with both radical and palliative intent. Combining radiotherapy with targeted therapies or immunotherapy may improve treatment outcomes, but may also lead to increased toxicity. High-quality toxicity data and evidence-based guidelines regarding combined therapy are very limited. The present framework, developed by ESMO and ESTRO, explores the main biological effects and interaction mechanisms of radiotherapy combined with targeted agents or immunotherapy. It addresses general clinical factors to take into consideration when deciding

Abbreviations: ALK, anaplastic lymphoma kinase; ATM, ataxia-telangiectasia mutated; ATR, Rad3-related; BRAF, B-rapidly accelerated fibrosarcoma; CDK, cyclin-dependent kinase; CTLA-4, cytotoxic T lymphocyte antigen 4; DAMPs, damage-associated molecular patterns; DDR, DNA damage response; DNA-PK, DNA-dependent protein kinase; DNA-PKcs, DNA-PK catalytic subunit; DSB, double-strand DNA break; EDIC, Effective radiation Dose to the Immune Cells; EGFR, epidermal growth factor receptor; EORTC, European Organisation for Research and Treatment of Cancer; ESMO, European Society for Medical Oncology; ESTRO, European SocieTy for Radiotherapy and Oncology; HER2, human epidermal growth factor receptor 2; HR, homologous recombination; ICI, immune checkpoint inhibitor; KRAS, Kirsten rat sarcoma viral oncogene homolog; mAb, monoclonal antibody; MHC-I, major histocompatibility complex I; MTOR, mammalian target of rapamycine; NHEJ, non-homologous end joining; PARP, poly (ADP-ribose) polymerase; PD-1, Programmed Cell Death 1; PD-L1, Programmed Death-Ligand 1; SSB, single-strand DNA break; TKI, tyrosine kinase inhibitor; VEGF(R), vascular endothelial growth factor (receptor); XRCC4, X-ray repair cross complementing 4.

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on whether and/or how to combine radiotherapy with these agents. Furthermore, it provides pragmatic, biological mechanism-based, clinical considerations for combining radiotherapy with various targeted agents or immunotherapy.

Introduction

Systemic therapy plays a central role in the treatment of cancer, together with surgery and radiotherapy. Cytotoxic chemotherapy has been and still is the mainstay of systemic therapy for many cancer types [1]. Chemotherapy primarily acts through interference with DNA and RNA synthesis, production of chemical DNA damage, inhibition of mitosis or induction of cell cycle arrest and apoptosis [2]. Additionally, endocrine therapy has a well-established role in the treatment of hormone-sensitive cancers, such as breast and prostate cancer [3,4].

Over the past decade, the range of systemic treatment options for cancer patients has expanded considerably [5–7]. With the emergence of targeted therapies, including monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs), a new array of cellular pathways is utilized to improve tumor control and patient survival [8]. Well-known targeted therapies inhibit membrane receptor-dependent pathways including epidermal growth factor receptor (EGFR), vascular endothelial growth factor (receptor) (VEGF(R)), or B-rapidly accelerated fibrosarcoma (BRAF) [7]. Using the immune system to control cancer has been widely explored in research, and recently immune checkpoint inhibitors (ICIs), primarily including mAbs targeted against Programmed Cell Death 1 (PD-1), Programmed Death-Ligand 1 (PD-L1), and cytotoxic T lymphocyte antigen 4 (CTLA-4), have been approved in various tumor settings [7]. Targeted agents and ICIs have made a clinical impact by improving outcomes for many cancer types and have reshaped the treatment landscape. Meanwhile, an increasing number of new agents continues to be added to the oncological armamentarium.

Approximately 50 % of cancer patients receive radiotherapy at some point during their treatment course, with either curative, radical or palliative intent [9–11]. In patients receiving targeted therapies or immunotherapy, local radiotherapy is commonly added for palliative treatment (e.g., pain control), for ablation of oligometastases or to stop oligoprogression [12–16]. Although new combined-modality treatments of radiotherapy with targeted therapies or immunotherapy might have the potential to improve treatment outcomes, they also pose a risk to patients due to potentially increased toxicity. Therefore, this increasingly raises the question of whether radiotherapy can be used safely in patients receiving these new systemic agents [15].

Toxicity data of these combined-modality treatments are often scarce and based on retrospective studies, carrying the risk of bias and underreporting [15,17,18]. There is only a limited number of combined-modality trials. The required registration clinical trials for approval of new systemic anti-cancer agents often do not allow the use of concurrent radiotherapy. If radiotherapy is permitted, specific radiotherapy-related toxicity is often not evaluated or reported. Moreover, many randomized phase III trials lack statistical power for adequate analysis of (uncommon) toxicities, as toxicity is usually not the primary endpoint [19–21]. Because of this, many of these new systemic anti-cancer agents are introduced in clinical practice without solid toxicity data when combined with radiotherapy. After clinical introduction, several drugs appeared to be safe in combination with radiotherapy, but unexpected toxicity has been reported for several treatment combinations, giving rise to safety concerns [18,22–29]. This variable outcome may be due to different radiation responses in non-neoplastic tissues according to the type of systemic therapy, its dose, the irradiated organ and its disease state (e.g., vascular disease), the radiotherapy dose, the fractionation scheme, and the irradiated volume. Moreover, case series may only report on a selected group of patients with severe toxicity, which may represent a minority of all treated patients in prospective series [30].

The limited amount of toxicity data poses a challenge to physicians. On the one hand, serious toxicity of combined-modality treatment should be avoided. On the other hand, temporary drug discontinuation or drug dose reduction may lead to lower clinical efficacy or tumor flare [31–33], while radiotherapy de-escalation may lead to reduced tumor or symptom control. Due to the complexity of these treatment decisions, adequate interdisciplinary communication is imperative. Some new projects have been initiated in this field [34,35], including a collaboration between the European SocieTy for Radiotherapy and Oncology (ESTRO) and the European Organisation for Research and Treatment of Cancer (EORTC) [35]. However, a clear knowledge gap and a lack of consensus on this topic still exist, and in addition to the lack of solid data, multidisciplinary consensus protocols are often not available [15,36,37]. This demonstrates the urgent, unmet need for multidisciplinary, evidence-based recommendations regarding the combination of these systemic therapies with radiotherapy.

These multidisciplinary recommendations should be based on the available clinical evidence and the general biological interaction mechanisms. A thorough analysis of the possible biological interaction mechanisms of specific drug classes with radiotherapy will assist the generation of consensus recommendations for clinical decision making, particularly when the amount of high-quality toxicity data is small, which is the case for a vast number of recently introduced and upcoming targeted therapies and ICIs.

Therefore, the European Society for Medical Oncology (ESMO) and the ESTRO decided to provide a series of joint clinical safety statements regarding the combination of radiotherapy with targeted cancer therapies (excluding antibody-drug conjugates) or immunotherapy (focusing on ICIs), covering the clinical toxicity data and the biological interaction mechanisms. This series of four papers will contain three papers with systematic reviews and detailed, drug-specific and radiotherapy scenario-specific consensus statements regarding the safety of combined treatment for 10 common drug classes. To complement these statements, this first publication provides clinicians with a framework of the most important (radio)biological and pharmacological factors, as well as with general considerations for clinical practice. This paper offers guidance for the numerous new targeted or immunotherapy agents that are not included in the three papers, as well as those that are yet to be developed.

Biology of radiotherapy and drug-radiotherapy interactions

Radiotherapy causes a plethora of cascades in human cells, from the start of radiotherapy until years after radiotherapy (**Fig. 1**). In order to predict the potential interactions between radiotherapy and targeted therapies or immunotherapy, it is crucial to understand the most important effects of ionizing radiation on cells and tissues and the involved biological pathways. Additionally, it is relevant to differentiate between early and late effects. In the next sections we discuss the most important interactions between the biological effects of radiotherapy and targeted agents or immunotherapy.

DNA damage and DNA damage response

While ionizing radiation exerts harmful effects on all cell components, the main cause of cell death is the formation of double-strand DNA breaks (DSBs) [38–40]. On a molecular level, ionizing radiation-induced DNA damage is generated directly and indirectly: direct damage results from direct interactions between radiation or its secondary electrons and DNA, while indirect damage is primarily caused by radiation-generated ionizations and free radical formations from water

molecules [11,40,41]. Although influenced by various factors, 1 Gray is estimated to cause 20–40 DSBs per cell in normoxic conditions [42–46]. Other types of radiation-induced DNA damage also contribute to cell death, including single-strand DNA breaks (SSBs), base damage and DNA backbone sugar damage. Clustering of these types of DNA damage around DSBs impairs DSB repair [38,39]. Moreover, SSBs can be converted to DSBs when they are still present during DNA replication [47,48]. Accumulation of unrepaired SSBs can therefore become detrimental for cells.

Once DNA damage is recognized, DNA damage repair is initiated, while cell cycle checkpoints prevent premature continuation of cell growth and division, until these lesions are repaired [49]. DNA-dependent protein kinase (DNA-PK), ataxia-telangiectasia mutated (ATM), and ATM- and Rad3-related (ATR) are important proteins that detect DNA damage and initiate repair and cell cycle pause [50,51]. To prevent premature continuation of cell division, CHK1 and CHK2 kinases regulate CDC25, WEE1, and p53. These proteins inactivate cyclin-dependent kinases (CDKs), thereby inhibiting cell-cycle progression until DNA is repaired [52]. Most DSB repair occurs within the first hours after irradiation [53–56], via two main DNA damage response (DDR) pathways: homologous recombination (HR) and non-homologous end joining (NHEJ). The most reliable pathway is HR. It uses the sequence of the sister chromatid as template, to correctly repair the DSB, but is only active during the S and G2 phase of the cell cycle [11,49,57]. Important proteins for HR are for example RAD51, BRCA1 and BRCA2 [57]. Conversely, NHEJ is a more error-prone repair method, as DSBs are ligated after very limited end processing, which can cause nucleotide insertions or deletions [39,57]. NHEJ is available during the whole cell cycle [39,57]. Pivotal NHEJ proteins are KU70, KU80, DNA-PK catalytic subunit (DNA-PKcs), X-ray repair cross complementing 4 (XRCC4) and ligase 4 [57]. In many cancer cells, these cell cycle checkpoints and DNA repair pathways are dysregulated [57,58].

As the generation of DNA damage plays a pivotal role in radiation-induced cell death, systemic treatments that interact with DDR pathways can increase the effect of radiotherapy. Inhibitors of DDR proteins are capable of enhancing the DNA-damaging effects of radiotherapy and several have been tested clinically [51,59,60]. To illustrate, poly (ADP-ribose) polymerase (PARP) inhibitors act by inhibiting PARP molecules that play an important role in the repair of SSBs and DSBs. This leads to inhibition of the PARP-associated repair processes and to trapping of PARP on the DNA [47,61]. DNA replication with unrepaired SSBs due to PARP trapping can cause DSBs. Particularly cells with HR deficiencies are affected by this [47,61]. BRCA1 and BRCA2 gene mutations are striking examples. As these proteins play an essential role in DNA damage recognition and HR, BRCA mutation carriers have a higher risk of particularly breast and ovarian cancer [49]. On the other hand, the reduced number of DSB repair options in BRCA-mutated cancers makes these cells particularly vulnerable for PARP inhibitors. The lethality of these combined factors, while one factor is not sufficient to cause cell death, is called synthetic lethality [47,57,61]. The radiosensitizing properties of PARP inhibitors have gained traction with several clinical studies that concurrently combine PARP inhibitors with radiotherapy [23,24,62–64]. PARP-induced radiosensitization can increase radiotherapy toxicity, even at PARP inhibitor dosages that are considerably lower than common monotherapy dosages [23,65,66]. This illustrates that common drug monotherapy dosages are not always optimal for combined treatment with radiotherapy.

Cell death and cell cycle arrest

If not correctly repaired, the presence of DSBs leads to genomic instability and can lead to cell death, either directly (e.g., apoptosis) or upon mitosis, with a variable time lag after radiotherapy [11,67,68]. Alternatively, cells can undergo senescence, resulting in a permanent cell cycle arrest and a senescence-associated secretory phenotype, causing the production of cytokines, chemokines, growth factors and proteases that regulate endothelial cell activation, propagation of senescence and immune cell recruitment to balance tissue repair and chronic inflammation [11,58,69–72].

When radiotherapy causes cell death in normal tissues, the loss of viable cells can lead to loss of tissue integrity and hence to tissue dysfunction. Additionally, irradiated cells release factors that not only influence the surrounding tissue or organ, but also the rest of the body, leading to bystander effects, including genomic instability [11,73–75]. Rapid radiation-induced cell death particularly occurs in fast-dividing tissues [11]. For example, radiation-induced denuding of epithelial tissues, such as the skin and gastro-intestinal epithelium, can become symptomatic within weeks after the start of radiotherapy. The release of growth factors causes the remaining stem cells to divide more rapidly to compensate for the increased cell loss [76]. However, a high amount of

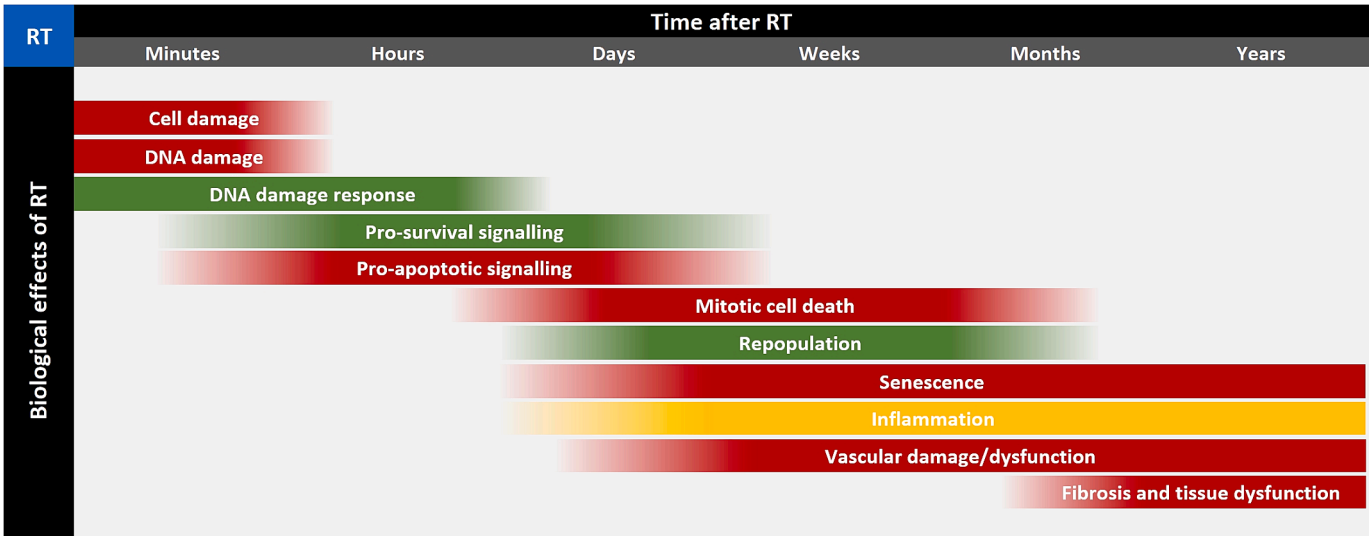

Fig. 1. Biological effects of radiotherapy over time. Minutes after radiotherapy, DNA damage leads to DNA damage response and repair signaling. Shortly thereafter, cells with too much damage will die and the surrounding tissue starts to repopulate in order to restore tissue integrity. The irradiated area can remain in a heightened inflammatory state up to years after radiotherapy. In the later stages following radiotherapy, tissues may become more fibrotic, and vascular damage or dysfunction may persist. Green bars: beneficial for normal tissues. Red bars: harmful for normal tissues. Yellow bar: various effects on normal tissues. *Abbreviations:* RT, radiotherapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(stem) cell loss can cause insufficient tissue repair, leading to acute and (consequential) late tissue defects and/or dysfunction [11,77]. Depending on the irradiated tissue, radiation dose, irradiated volume, fractionation scheme, radiotherapy technique, and patient factors, acute adverse events can occur during and after radiotherapy. These may include general (fatigue, pain), dermatological (dermatitis), neurological (headache, seizure), pulmonary (cough), gastro-intestinal (dysphagia, nausea, diarrhea), and hematological symptoms (reduced blood cell counts) [11,78,79].

In slowly regenerating tissues or structurally important cells, relatively more cells undergo permanent cell cycle arrest, instead of cell death. Together with insufficient cell renewal or repair and a chronic, amplified inflammatory state and wound healing process, this can cause long-term, often irreversible fibrosis, vascular damage and tissue dysfunction [11]. Fibrosis-related symptoms can vary from mild pulmonary symptoms to severe bowel obstruction [80,81]. Radiation-induced vascular damage can induce bleeding, but also ischemic events in various organs, as described in the section on vascular effects [82–84]. Other examples of late adverse events after radiotherapy are neurocognitive impairment, neural damage, and gland dysfunction in secretory organs like the salivary glands or the pancreas [11].

Tumor cell proliferation often depends on the evasion of cell cycle checkpoints and the upregulation of distinct oncogenic pathways [8,85]. Upregulated oncogenic pathways may vary across tumor types, individual tumors and even within a single tumor or between the tumor and its metastases [8,86,87]. This upregulation can be caused by alterations in genes such as anaplastic lymphoma kinase (ALK), BRAF, EGFR, human epidermal growth factor receptor 2 (HER2), Kirsten rat sarcoma viral oncogene homolog (KRAS), mammalian target of rapamycine (MTOR), and others that play a pivotal role in regulating cell growth and division [86,88,89].

Over the last decades, numerous kinase inhibitors and monoclonal antibodies have been developed to block these specific oncogenic pathways, thereby inhibiting tumor cell proliferation and sometimes inducing cell death [8,86,90]. One of the advantages of kinase inhibitors is the specific 'targeting' of tumor cells carrying these gene alterations, while having less impact on normal tissue cells [8]. However, many of these pathways have physiological functions in normal tissues [91]. Crosstalk between different pathways may also occur [92]. Moreover, the molecular specificity of kinase inhibitors is often limited, resulting in off-target effects [86,92,93]. Targeted agents can therefore also induce tissue dysfunction and damage in normal tissues, leading to various side effects [86]. It is apparent that the combination of these agents with radiation can lead to increased acute and late normal tissue toxicity. Also, cell cycle checkpoint blockade by CDK4/6 inhibitors can possibly enhance radiotherapy efficacy and toxicity by preventing cell cycle progression and division after radiotherapy [18].

Inflammatory and immunological effects

The immune system plays a crucial role in the observed acute and late effects after radiotherapy. Radiotherapy increases the presentation of existing cancer cell neoantigens, but it also creates neoantigens by generating DNA mutations [94]. Furthermore, radiation-induced cell damage and cell death leads to increased major histocompatibility complex I (MHC-I) expression on tumor cells and release of damage-associated molecular patterns (DAMPs), type I interferons, chemokines and pro-inflammatory cytokines [94]. These factors cause inflammation, increased T cell infiltration, and immune-mediated cell death. As a result, radiotherapy can theoretically convert poorly immunogenic, 'cold' tumors into immunogenic, 'hot' tumors, which may increase the chance of an effective antitumor immune response [11,94]. There are data suggesting that hypofractionated radiotherapy better induces an immunogenic tumor environment than conventionally fractionated radiotherapy or high-dose single-fraction stereotactic radiotherapy [11,94–100].

However, negative inflammatory and immunological effects associated with radiotherapy have been described as well. Radiotherapy can cause unfavorable inflammation of normal tissues in the irradiated field, including dermatitis, mucositis, and pneumonitis. Inflammation contributes to the development of brain radionecrosis as well [101–103]. Radiotherapy can also activate various counterbalancing *immunosuppressive* signaling pathways, undermining antitumor immunosurveillance [94,104]. Furthermore, due to the high radiosensitivity of lymphocytes (particularly B cells and naïve T cells), irradiation of circulating lymphocytes and lymphoid organs can potentially impair antitumor immunity by the induction of lymphopenia [11,105]. The incidence and severity of lymphopenia are affected by the in-field volume of blood(-containing organs), the radiotherapy dose and fractionation. Different models to predict lymphopenia have been proposed, including the Effective radiation Dose to the Immune Cells (EDIC) model [106,107]. A lower EDIC is correlated with a better overall survival in non-small cell lung cancer [108]. There is a potentially lower risk of lymphopenia from hypofractionation, compared to conventional fractionation schemes, as there is a lower number of radiation doses affecting the major blood pool and circulating lymphocytes [107,108]. Also, the often smaller irradiated volumes with stereotactic radiotherapy may reduce this risk.

Immunotherapy has the potential to counteract immunosuppressive signaling pathways after radiotherapy [95,104]. The most commonly used ICIs inhibit the binding of CTLA-4 to B7, or the binding of PD-1 to PD-L1. In the lymph nodes, CTLA-4 plays an important role. Upon T cell activation by recognition of an antigen-presenting cell in a lymph node, CTLA-4 is expressed on the cell surface of the T cell. Binding of CTLA-4 to B7 ligands on the antigen-presenting cell inhibits T cell activation. CTLA-4 inhibitors (e.g., ipilimumab and tremelimumab) prevent this CTLA-4-mediated suppression of T cell activation, thereby enhancing the priming of T cells and ultimately the cellular immune response [109,110]. In the tumor microenvironment, the interaction between PD-1 and PD-L1 suppresses immune cell activation. PD-1 is expressed on the cell membrane of activated T cells, B cells and natural killer cells [109–111]. After engaging with tumor cells expressing PD-L1 or PD-L2, PD-1 binding to these ligands leads to inhibition of T cell activation. PD-1 (e.g., nivolumab and pembrolizumab) and PD-L1 inhibitors (e.g., avelumab and durvalumab) enhance the immune response by preventing this interaction [109,110]. These effects can theoretically increase the efficacy of radiotherapy, particularly when combined with hypofractionated radiotherapy schedules and small irradiated volumes [11,94,95,97–99,112]. However, there is also a possible risk of increased inflammatory toxicity.

Vascular effects

Ionizing radiation influences the microvasculature of tumors and normal tissues. Particularly microvascular endothelial cells are radiosensitive [113]. Although there are many unanswered questions, it generally appears that radiotherapy can inhibit the formation of new blood vessels, while having limited impact on mature vessels. This inhibiting effect might be particularly the case for high doses, while low (fraction) doses may promote angiogenesis, also by causing increased expression of pro-angiogenic growth factors like VEGF [114]. Furthermore, radiotherapy can induce recruitment of bone marrow-derived circulating cells that are involved in neovascularization [114,115]. Telangiectasia are a visible example of radiation-induced vascular endothelial cell injury [116].

The goal of angiogenesis inhibitors is to decrease blood flow and tumor oxygenation in order to reduce tumor growth. However, there is evidence that a couple of days after introduction of an angiogenesis inhibitor, there is a transient blood vessel normalization, temporarily leading to *increased* oxygenation of the tissue [114,117]. When radiotherapy is administered during this time window, the increased tissue oxygenation can possibly increase radiosensitivity [117–121].

Furthermore, VEGF(R) inhibition can lead to more endothelial cell apoptosis after radiotherapy [122].

Ionizing radiation also causes macrovascular injuries. As shown in atomic bomb survivors, even a low radiation dose (above 0.5 Gy) increases the risk of cardiovascular diseases [123]. In Hodgkin lymphoma and breast cancer patients, the risk of myocardial infarction and acute coronary events increases dose-dependently with the radiation dose to the heart [124–127]. In head and neck cancer patients, radiotherapy increases the risk of ischemic cerebrovascular events and this risk is also associated with the radiation dose (10 Gy and higher) to the carotid arteries [83]. Before these events occur, early radiation-induced vascular changes are observed as well, including a dose-dependent increase of the arterial wall intima-media thickness, which is an ultrasound-assisted early marker of atherosclerosis [128–133]. Some studies indicate that atherosclerotic plaques induced by radiotherapy have a lower density and less calcification compared to 'conventional' atherosclerosis, possibly leading to a higher risk of ischemic vascular events [83,128,131,134,135].

Angiogenesis inhibitors can cause hemorrhagic events, probably by attenuating the microvasculature of tissues, making them more prone to both thrombotic events and bleeding [136,137]. Radiotherapy-induced vascular damage could also cause hemorrhagic events, for example rectal bleeding in prostate cancer patients or bleeding after stereotactic radiotherapy to (ultra)central lung lesions [82,138]. This can occur even years after radiotherapy.

Several studies indicate that combining radiotherapy with angiogenesis inhibitors increases the hemorrhage risk [139–142]. In addition to an increased bleeding risk, several (mainly small) reports show that the combination of radiotherapy and angiogenesis inhibitors may also lead to ulcers, fistulae and perforations [143–150]. Also, non-concurrent treatment of radiotherapy and angiogenesis inhibitors can increase this risk, as shown in patients receiving angiogenesis inhibitors with a history of radiotherapy, but without concurrent treatment [143,151–153]. This risk appears to be particularly elevated when mucosa is irradiated with a high radiotherapy dose. One of the most common angiogenesis inhibitors is bevacizumab, a mAb against VEGF, but several other VEGF(R) inhibitors are on the market, including the TKIs sunitinib, pazopanib and sorafenib [154,155]. These TKIs not only inhibit the VEGFR, but they inhibit other receptor tyrosine kinases as well [154].

Biology of hypofractionated radiotherapy

Hypofractionated radiotherapy (officially > 2 Gy per fraction) is commonly used for palliative treatments of larger target volumes (e.g., 1 x 8 Gy) and for high-precision radical (stereotactic) radiotherapy of small target volumes [12,14,156]. Hypofractionated radiotherapy is also increasingly used as local standard treatment for non-metastatic breast and prostate cancer [156]. The use of higher fraction doses is less favorable for slowly regenerating tissues, leading to a higher risk of late normal tissue toxicities compared to normofractionated radiotherapy [156,157]. Although hypofractionation has less impact on acute toxicity, the reduced number of fractions often leads to a reduced overall treatment time, allowing for less repair of fast-dividing tissues during treatment [156].

Current stereotactic radiotherapy techniques can precisely deliver high radiation doses to small target volumes, while minimizing the volume of irradiated normal tissues, which radically reduces normal tissue toxicity [11,100,156]. This is a major advantage of stereotactic radiotherapy, when compared to conventional high-dose radiotherapy. However, with high-dose stereotactic radiotherapy close to critical normal tissues, the normal tissue tolerance thresholds can be reached. Because of these factors, concomitant use of radiosensitizing agents may theoretically lead to exponentially increased toxicity, particularly in serially organized organs (e.g., spinal cord) [158].

Clinical approach: Considerations for decision making

When patients on targeted therapies or immunotherapy have an indication for radiotherapy, there are several aspects to consider before deciding whether the two treatments can be combined and if any treatment adaptations are required. The aim of this section is to assist clinicians by providing a decision-making roadmap that takes account of the key factors that may predict the toxicity and feasibility of a particular drug-radiotherapy combination. These considerations are summarized in Fig. 2.

As a first step, we suggest searching for available clinical toxicity data regarding the combination of this targeted drug or ICI with radiotherapy, preferably arising in the irradiated region. Additionally, it is relevant to retrieve the available clinical toxicity data on the combination of the drug *class* with radiotherapy. As the radiosensitizing mechanism of other drugs with the same target is probably similar, this approach often offers additional relevant toxicity data. The toxicity of combining this drug class with radiotherapy to *other tissues* can also offer relevant information. Furthermore, it can be relevant to look for evidence-based clinical protocols on how to combine radiotherapy with targeted agents or immunotherapy. Unfortunately, these are often lacking, but some initiatives have started [34,35], including this joint ESMO-ESTRO initiative which will provide clinical consensus statements on the safety of combining ten common cancer drug classes with radiotherapy.

If the amount of clinical toxicity data is insufficient, estimating the expected toxicity can be performed by searching for preclinical data on the drug mechanism, possible off-target effects and the potential to enhance radiosensitivity, radiation-induced toxicity, and/or drug sensitivity. Additionally, if drug monotherapy toxicities have overlap with the expected toxicity of the intended radiotherapy treatment, at least additive toxicity can be expected. It is also relevant to analyze the drug distribution through the body. Particularly, the blood–brain barrier penetration can vary considerably among different targeted agents [159]. The blood–brain barrier penetration might also be higher at the location of a tumor and after radiotherapy [160,161]. Additionally, the expression of the drug target in the irradiated normal tissues should be considered, as a low target expression might lead to weaker drug effects in that tissue. Drug target expressions can be found via the online Human Protein Atlas portal (https://www.proteinatlas.org) [162,163]. Unfortunately, there are often no data available on target upregulation in irradiated tissues.

The drug elimination time is a key factor to consider, as short drug half-lives allow for relatively short drug interruptions before radiotherapy in order to reduce the risk of synergistic toxicity. To prevent a drug-radiotherapy interaction in case of a high expected risk of synergistic toxicity, interrupting the drug approximately 5 elimination half-lives before radiotherapy could be considered, as it takes approximately 5 drug elimination half-lives to reach steady-state drug plasma concentrations or to eliminate 97 % of the drug after interruption [34,164–167]. Drug plasma concentrations are frequently used as surrogate for the drug concentrations in tissues [168]. However, it is important to exercise caution when using this arbitrary threshold of 5 elimination half-lives to determine the time interval between drug interruption and radiotherapy. This recommendation is intended primarily as a directional aid rather than a strict rule, and only in cases where any drug-radiotherapy interaction should be avoided for safety reasons. In case of long drug elimination half-lives (particularly for monoclonal antibodies [169]), interrupting the drug long enough before radiotherapy is often not feasible. In some cases, the drug treatment schedules contain drug pauses [170]. These time windows could be used for radiotherapy, although still an extended drug pause can be necessary. The expected decrease of synergistic toxicity by a drug interruption should always be balanced against the risk of tumor progression or tumor flare [31–33].

In all patients, the radiotherapy indication and available alternative

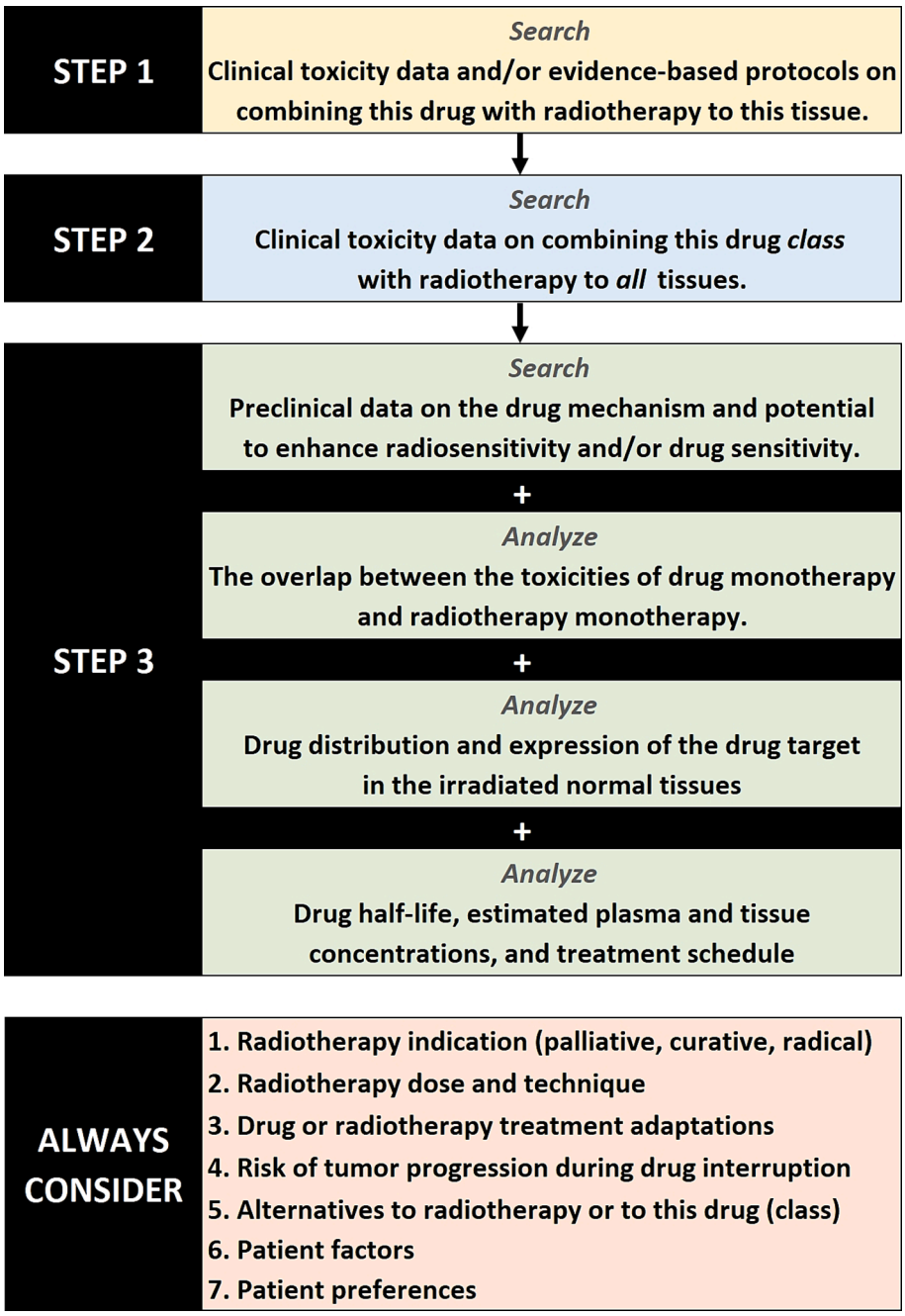

Fig. 2. Considerations for clinical decision making regarding the combination of radiotherapy with various types of targeted therapy or immunotherapy agents.

treatment options should be considered. It is also important to consider more subtle treatment adaptations, such as drug dosage reduction, a reduced radiotherapy dose (per fraction), or the use of more conformal radiotherapy techniques [15]. However, drug dosage or radiotherapy dose reductions may result in decreased treatment efficacy. It is furthermore relevant to account for patient factors, including their estimated survival, comorbidities and previous radiotherapy. Even though the available clinical toxicity data may be limited, it is important to discuss the potentially increased toxicity of combining radiotherapy with targeted agents or immunotherapy and to consider the preferences of the patient [171].

Clinical approach: Drug class-specific considerations

Most targeted or immunotherapy agents can interfere with at least one of the four previously described biological effects after radiotherapy. Even in case of insufficient clinical toxicity data on combining these agents with radiotherapy, defining the drug mechanism and understanding the radiobiological effects it interacts with, can help estimate the expected toxicity. In this section, the expected toxicities are described for combining various drug classes with radiotherapy. These are summarized in Fig. 3. A list with drug examples for common drug classes is provided in the Supplementary Data.

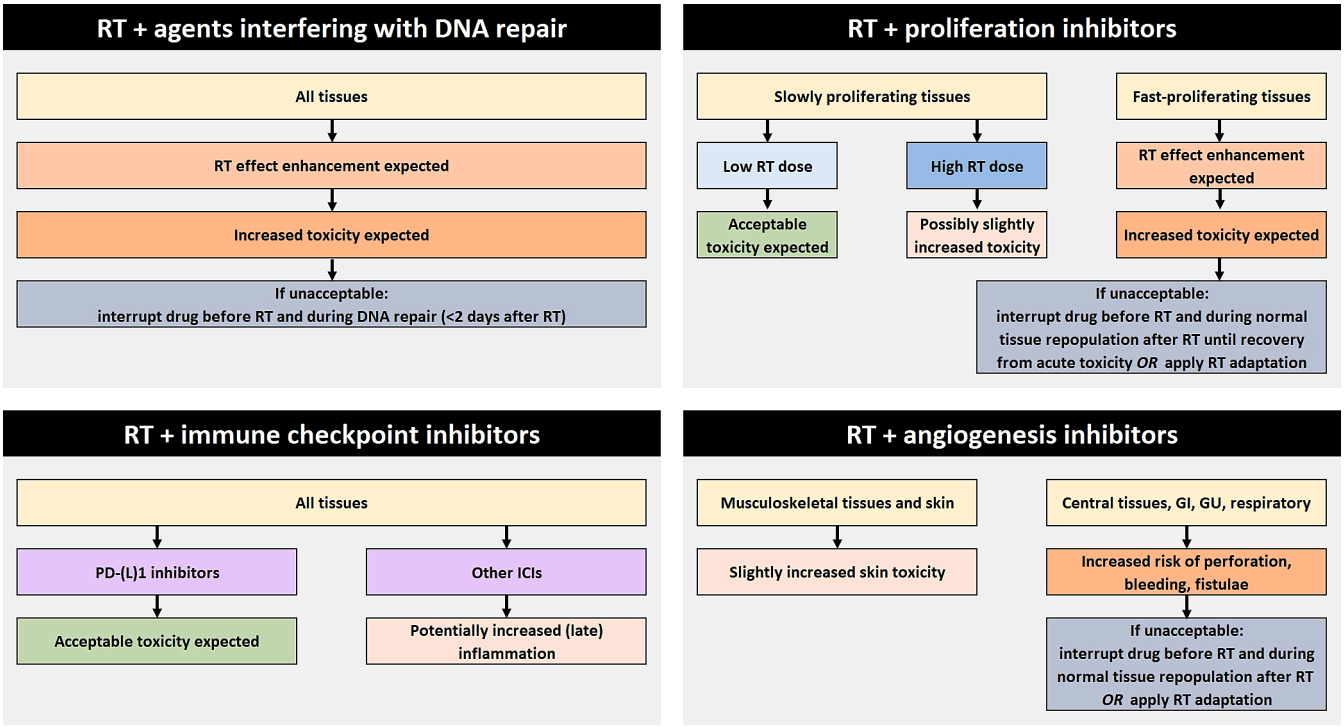

Fig. 3. Expected toxicity and general considerations regarding the combination of radiotherapy with various classes of targeted or immunotherapy agents. *Abbreviations:* GI, gastrointestinal; GU, genitourinary; ICIs, immune checkpoint inhibitors; PD-(L)1, Programmed (Cell) Death(-Ligand) 1; RT, radiotherapy.

Agents interfering with DNA repair

The main mechanism of action of radiotherapy is inducing DNA damage, which is counteracted by several DNA repair pathways. As previously described, agents that interfere with DNA damage repair can enhance the DNA-damaging effects of radiotherapy. As most DNA damage repair occurs within the first hours after radiation [53–56], the strongest drug-radiotherapy interaction is expected during this period. If these drugs are interrupted before radiotherapy, they can possibly be restarted within two days after radiotherapy to limit the risk of synergistic toxicity, thereby allowing for most DNA damage repair (at least 5 DNA damage repair half-lives) before reintroducing the drug [156,172]. Alternatively, a radiotherapy dose reduction or normal tissue sparing by a different radiotherapy technique can be considered.

Proliferation inhibitors

Proliferation inhibitors, including ALK, BRAF, CDK4/6, EGFR, HER2, KRAS and mTOR inhibitors, can cause cell cycle arrest and/or cell death. Particularly in fast-dividing tissues, combining these drugs with radiotherapy can inhibit the normal tissue repair and stem cell division, leading to increased acute toxicity and/or a longer duration of acute toxicity. Recovery of fast-dividing normal tissues after radiotherapy usually takes days to weeks. If proliferation inhibitors are interrupted during radiotherapy, they should ideally be withheld for more than one week after radiotherapy, as fast-dividing tissues need several weeks to repopulate and to recover [11]. However, this is often not clinically feasible or necessary. When the expected cell damage or toxicity is low, and the need to restart the drug high, it can pragmatically be restarted within a week after radiotherapy. In case of high radiotherapy doses to normal tissues and in case of ongoing symptomatic radiotherapy toxicity, interrupting the drug until recovery from this toxicity can be considered. Alternatively, a radiotherapy dose reduction or normal tissue sparing by a different radiotherapy technique can be considered. Based on the mechanism of proliferation inhibitors, the effect on slowly regenerating tissues may be less pronounced.

Immune checkpoint inhibitors

The inflammatory toxicity of combining immune checkpoint inhibitors with radiotherapy appears mild, particularly for PD-(L)1 inhibitors. For CTLA-4 inhibitors (+/- PD-(L)1 inhibitors), the level of evidence is lower and the toxicity might be slightly higher. This can potentially lead to increased early or late inflammation after radiotherapy that may vary in different tissues (e.g., lung). Given that most ICIs are monoclonal antibodies with long drug half-lives and prolonged immunologic effects after drug discontinuation [169,173], it is questionable whether a short drug interruption or treatment delay is effective as a strategy for reducing the risk of inflammatory toxicity. Alternatively, a radiotherapy dose reduction or normal tissue sparing by a different radiotherapy technique can be considered.

Angiogenesis inhibitors

As shown previously, combining angiogenesis inhibitors (including VEGFR-targeting multitargeted TKIs) with radiotherapy can increase the risk of tissue damage with bleeding, ulcers, fistulae and perforations. Increased toxicity has also been reported for non-concurrent combinations of radiotherapy with VEGF(R) inhibitors. For tissues less prone to these toxicities, such as musculoskeletal tissues and the skin, the increase in toxicity is probably limited, although there may be a higher chance of skin toxicity [174–176].

Conclusions

The rapid, continuing introduction of targeted cancer therapies and immunotherapy across various cancer types presents a dilemma for medical and radiation oncologists, compelling them to assess the safety of combining these new drugs with radiotherapy. Due to the very limited high-quality clinical toxicity data of combining these treatments with radiotherapy, the aim of this paper is to elucidate the general biological mechanisms behind various possible drug-radiotherapy interactions and to assist with the decision-making process in these patients. These

pragmatic considerations are intended for real-world drug-radiotherapy combinations and they are not designed as guidance or substitute for clinical trials or high-quality registries evaluating the synergy of targeted agents or immunotherapy with radiotherapy.

This publication is part of a series of joint ESMO-ESTRO consensus statements. Further papers contain drug class-specific and irradiated tissue-specific systematic reviews and Delphi consensus statements on the safety of combining radiotherapy with various common targeted cancer agents (excluding antibody-drug conjugates, due to their different mechanism of action) and immunotherapy (focusing on ICIs). These evidence-based, multidisciplinary consensus statements, developed by ESMO and ESTRO, have been developed to provide clinically applicable suggestions for a large variety of drug-radiotherapy scenarios.

For (new) drug-radiotherapy combinations that are not covered in the other papers, the current publication aims to provide generic guidance. The statements in this publication should be used with clinical interpretation of individual treatment contexts. The intention of this paper is not to offer strict guidelines, but rather to provide a biological mechanism-based framework for decision making.

The clinical dilemmas that arise from the rapid introduction of targeted and immunotherapy agents without first acquiring toxicity data regarding their interactions with radiotherapy, highlight the urgency of developing clinical trials, high-quality registries, prospective cohort studies and real-world studies that combine these agents with radiotherapy [15]. These studies should be properly designed to measure synergistic acute and late toxicities. Several roadmaps and solutions have been proposed to accelerate the development of these drug-radiotherapy combinations [19,20], but their application, and hence their impact, is currently insufficient. Intensive collaborative and interdisciplinary efforts, as for example the ESTRO Focus Group on combining radiotherapy with systemic therapies, are therefore continuously needed to expand the amount of essential clinical toxicity data of combined therapy.

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT (OpenAI) and DeepL (DeepL SE) in order to improve language and readability. After using these tools/services, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

CRediT authorship contribution statement

Evert S.M. van Aken: Conceptualization, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Bharti Devnani:** Writing – review & editing. **Luis Castelo-Branco:** Conceptualization, Methodology, Writing – review & editing. **Dirk De Ruysscher:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Diogo Martins-Branco:** Writing – review & editing. **Corrie A.M. Marijnen:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing. **Barbara Muoio:** Writing – review & editing. **Claus Belka:** Conceptualization, Methodology, Writing – review & editing. **Florian Lordick:** Conceptualization, Methodology, Writing – review & editing. **Stephanie Kroeze:** Writing – review & editing. **George Pentheroudakis:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Dario Trapani:** Writing – review & editing. **Umberto Ricardi:** Conceptualization, Methodology, Writing – review & editing. **Ajeet Kumar Gandhi:** Writing – review & editing. **Arsela Prelaj:** Writing – review & editing. **Sean M. O'Cathail:** Writing – review & editing. **Monique C. de Jong:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Bharti Devnani has declared non-financial interests as a member of ASTRO, Indian Society of Neuro-Oncology, Indian Society of Oncology, Association of Radiation Oncologists; Leadership role for Oncoalert. Luis Castelo-Branco has declared speaker engagements from AiCME, Eversana, and Novacure; employment from ESMO (2021-2023); Advisory role with the World Health Organization. Dirk De Ruysscher has declared institutional financial interests (no personal financial interests) for AstraZeneca, BMS, Beigene, Philips, Olink, Eli-Lilly. Diogo Martins-Branco has declared full-time employment from the European Society for Medical Oncology since September 1, 2023; participation as medical research fellow in research studies institutionally funded by Eli Lilly, F. Hoffmann-La Roche Ltd, and Novartis to Institut Jules Bordet (2021-2023); and non-financial interests as a board member of Associação de Investigação e Cuidados de Suporte em Oncologia (2022-2024) and member of American Society of Clinical Oncology, Associação Portuguesa de Cuidados Paliativos, Multinational Association of Supportive Care in Cancer, and Sociedade Portuguesa de Oncologia. Barbara Muoio has declared advisory board role for Immedica Pharma, Pharmamar, Servier; and Invitation to ESMO 2024 congress from Roche. Florian Lordick has declared speaker engagement for Art Tempi, Astellas, AstraZeneca, BMS, Daiichi Sankyo, Eli Lilly, Imedex, Incyte, Medscape, MedUpdate, Merck Serono, MSD, Servier, and StreamedUp!; advisory board role for Astellas, Beigene, BMS, Daiichi Sankyo, MSD and PAGE; institutional research grants from AstraZeneca, BMS, and Gilead;

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Appendix A. Supplementary data

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