European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus on re-irradiation: definition, reporting, and clinical decision making

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Abstract

Re-irradiation can be considered for local recurrence or new tumours adjacent to a previously irradiated site to achieve durable local control for patients with cancer who have otherwise few therapeutic options. With the use of new radiotherapy techniques, which allow for conformal treatment plans, image guidance, and short fractionation schemes, the use of re-irradiation for different sites is increasing in clinical settings. Yet, prospective evidence on re-irradiation is scarce and our understanding of the underlying radiobiology is poor. Our consensus on re-irradiation aims to assist in re-irradiation decision making, and to standardise the classification of different forms of re-irradiation and reporting. The consensus has been endorsed by the European Society for Radiotherapy and Oncology and the European Organisation for Research and Treatment of Cancer. The use of this classification in daily clinical practice and research will facilitate accurate understanding of the clinical implications of re-irradiation and allow for cross-study comparisons. Data gathered in a uniform manner could be used in the future to make recommendations for re-irradiation on the basis of clinical evidence. The consensus document is based on an adapted Delphi process and a systematic review of the literature was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Introduction

An increasing number of patients with cancer are treated with high-dose radiotherapy to a previously irradiated area of the body, commonly referred to as re-irradiation.[1] This increase is probably a result of new radiotherapy techniques that have improved the precision of planning and delivery by avoiding excessive dose to organs at risk without compromising the target coverage, and new radiotherapy regimens that use high doses, offer the possibility of ablative doses, have recurred after radiotherapy, or are adjacent to a previously irradiated site. Additionally, the availability of more reliable information on previously delivered doses from CT-based treatment planning and better dose calculation algorithms facilitates a more accurate assessment of cumulative doses and overlap with old radiation fields. Therefore, indications to perform re-irradiation might include local recurrence, adjacent new primary tumours, or local ablative treatment for metastatic disease.[2–8] To meet treatment goals, ranging from alleviating or preventing symptoms to local ablation, and potentially a cure, the entire spectrum of radiotherapy techniques could be applied for reirradiation, including external beam photon radiotherapy and particle therapy (including protons), with the use of intensity-modulated radiotherapy, volumetric-modulated arc therapy, or brachytherapy.[9,10] External beam radiotherapy techniques can be applied to deliver radio surgery and stereotactic ablative radiotherapy. [11,12] High-level prospective evidence on re-irradiation is scarce, especially with regards to optimal patient selection and the safety of high cumulative doses.

In this Delphi consensus among international experts, endorsed by the European Society for Radiotherapy and Oncology (ESTRO) and the European Organisation for Research and Treatment of Cancer (EORTC), we propose a universally applicable definition of re-irradiation and standardised nomenclature to describe clinical scenarios that do (and do not) fulfil the criteria for re-irradiation. Additionally, we offer recommendations for reporting in clinical studies, and decision making in clinical practice.

Methods

We developed this consensus during the implementation of the prospective observational ReCare cohort (EORTC RP-2011) within the ESTRO-EORTC RADiation

InfrAstrucTure for Europe (E^2-RADIatE) project (NCT03818503), which aims to gather real-world data on the safety and effictiveness of high-dose re-irradiation and to derive evidence-based dose constraints for safe reirradiation. This consensus document is based on an adapted Delphi process, as outlined, and was endorsed by the EORTC Board and the ESTRO Scientific Council. The 17 panellists of the Delphi process (which included all authors, except JW and NAl) were selected to represent different professions involved in radiotherapy, so that both the clinical and technical aspects of re-irradiation could be covered. Panellists should have a clinical background and established scientific knowledge regarding different tumour entities, radiotherapy techniques, and reirradiation. Women and men from different European countries were chosen to ensure diversity of the panel and represent a broad range of opinions and clinical practices. Panellists were selected from both the ESTRO and EORTC networks (appendix p 2).

Systematic review

We did a systematic review on the quality of reporting of re-irradiation publications from Jan 1 to Dec 31, 2020 to support a hypothesised absence of standardised reporting in clinical studies on re-irradiation. We did the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (appendix p 3).24 The articles were reviewed,

selected, and analysed for data extraction by one author (NAl). Two authors (NAn and JW) reviewed the results.

Delphi consensus process

An adapted Delphi process was used for consensus formation on three different topics: (1) a definition of reirradiation and additional nomenclature for scenarios of retreatment with radiotherapy that do not fulfil the proposed criteria for re-irradiation; (2) reporting guidelines for research studies on re-irradiation; and (3) recommendations for decision making on re-irradiation in clinical practice (appendix p 34).25

The three topics were developed independently, starting with a baseline assessment among the panellists and then three rounds for consensus formation (topics 1–3) and establishing prioritisation for reporting (topic 3 only). Each round consisted of an online survey with Google Forms and then a virtual meeting and discussion via video conference. The panellists could vote on different items on a 5-point Likert scale (1: strongly agree, 2: agree, 3: not sure, 4: disagree, and 5: strongly disagree). The level of agreement among the panellists was defined as the combined proportion of votes for strongly agree and agree. Statements that did not reach a consensus after the third voting round were excluded. Sub-rounds were necessary so that statements could be reworded for clarity without the need for additional voting. To reach a consensus, agreement of at least 75% of the panellists was necessary. The panellists could add free-text comments to indicate whether any adjustments or additions were needed in their opinion. After the online voting rounds, panellists discussed the results in virtual meetings. When no consensus was reached, panellists voted again after discussion and adaptation of the items in the next round. Once a consensus was reached, only minor changes to the wording were allowed. For the reporting guideline, the panellists prioritised different items as required, recommended, optional, or not relevant in research studies on re-irradiation (appendix).

Findings

Level of reporting in studies on re-irradiation

493 studies were included in the systematic review (appendix pp 5–33), which showed a marked increase in clinical research on re-irradiation from 2000 to 2020 (appendix p 4). Most publications were retrospective cohort studies (390 [79%] of 493 studies), 72 (15%) were prospective clinical studies, and 31 (6%) were systematic reviews. Most studies included only patients treated with re-irradiation in a single anatomical site (475 [96%]; of which 156 [32%] were for the head and neck and 117 [24%] were for brain). Of note, sample sizes were typically small, with 300 (61%) of the 493 studies including 50 patients or less.

Median follow-up was consistently reported (431 [87%]) and revealed a median follow-up of more than 12 months in 327 (66%) of the 493 studies for reliable evaluation of long-term sequelae. Of the two key endpoints, overall survival was reported in 460 (93%) of the studies and toxicity was reported in 485 (98%) of the studies. Quality of life after re-irradiation was reported in only 40 (8%) of the included studies.

The entire spectrum of radiotherapy modalities was applied to deliver re-irradiation. Re-irradiation was delivered with external beam photon radiotherapy in 265 (54%) of the studies, in which 3D conformal radiotherapy (n=75), intensity modulated radiotherapy or volumetric modulated arc therapy (n=64), or stereotactic re-irradiation to cranial (n=46) or extracranial targets (n=80) were used. By contrast, particle therapy reirradiation was reported in 39 (8%) of the studies, irrespective of the target location. Brachytherapy was

addressed in 46 (9%) of the included studies, but only 6 (1%) studies used intraoperative radiotherapy techniques. 129 (26%) of the remaining studies included different techniques (mostly external beam photon radiotherapy) or combined modalities (eg, external beam radiotherapy with photons or electrons plus hyperthermia), whereas few studies applied experimental treatments (n=2; semicontinuous low-dose-rate teletherapy and pulsed reduced dose-rate radiotherapy) or had clear information on the techniques used (n=6).

All studies reported at least the prescription dose of the re-irradiation, and most (464 [94%]) also reported the dose for the previous courses of radiotherapy. Only 71 (14%) of the studies reported the constraints of the dose for organs at risk that were applied during treatment planning for re-irradiation, and only 83 (17%) reported cumulative dose volume parameters for organs at risk and only 38 (8%) reported target volumes, such as minimum, maximum, mean, or median doses and doses based on absolute or relative volumes. 30 (6%) of the studies reported cumulative doses derived from summation of threedimensional (3D) dose distributions without recalculation to account for fractionation schedules, whereas 124 (25%) reported a numerical sum of prescription doses without the use of treatment plans. Generally, cumulative dose parameters were infrequently and inconsistently reported. Equivalent dose in 2 Gy fractions (EQD2) was reported in 103 (21%) studies, biologically effective dose was reported in 120 (24%), and equivalent uniform dose was only reported in two (1%).

Reporting on important cumulative dose volume parameters for target volumes and organs at risk was poor, and the same was true for reporting of quality-of-life parameters, rendering the assessment of safety and efficacy for clinical translation of most of these published results challenging, if not impossible.

Definition of re-irradiation

After baseline assessment by the Delphi consensus panellists, 14 potential defining characteristics of reirradiation were collated and grouped into four categories (irradiated region, prescription dose, time interval between treatments, and degree of overlap of radiotherapy between treatments; appendix p 35). Three of the categories eventually reached consensus to be included into the final definition of re-irradiation: (1) a new course of radiotherapy, (2) overlap of irradiated volumes, or (3) having a concern for toxicity from cumulative doses.

The panellists agreed on a definition of re-irradiation: “re-irradiation is a new course of radiotherapy, either to a previously irradiated volume (irrespective of concerns of toxicity) or where the cumulative dose raises concerns of toxicity”.

Therefore, re-irradiation is a general term for two scenarios that we will distinguish in this consensus by referring to type 1 or type 2 re-irradiation: re-irradiation type 1 is a new course of radiotherapy that has geometrical overlap with the irradiated volume of previous courses, and re-irradiation type 2 is a new course with concerns of toxicity from the cumulative doses but in which there is no overlap with the irradiated volume of previous courses. Irradiated volume, as agreed by the panellists, was defined as the volume of tissue receiving a dose that is considered clinically significant in comparison with normal tissue tolerance, according to International Commission on Radiation Units & Measurements

Report 50.[26] Overlap of irradiated volumes, rather than overlap of specific target volumes or isodose lines, takes into account the dose to organs at risk; therefore, overlap of irradiated volumes should

be applied to different clinical scenarios, as was desired for our general definition of re-irradiation. The panellists noted that there should be a concern of toxicity from cumulative doses if dose constraints for an acceptable treatment plan for a primary course of radiotherapy are exceeded. Several specifications for re-irradiation that were initially proposed were eventually not included in our proposed definition of reirradiation. The panellists agreed on using radiotherapy to a previously irradiated volume, as defined by the International Commission on Radiation Units &

Measurements, for the spatial definition of re-irradiation because it accounts for the delivered dose in relation to organ-at-risk tolerance. We opposed using any target volume (eg, the planning target volume) because these volumes are based on treatment planning and delivery concepts and might not necessarily coincide with the relevant dose distribution. Additionally, target volumes would not account for the dose to normal tissues, which was regarded as a crucial specification. The use of an overlap of area or region was also rejected, since these were regarded by the panellists as ill-defined, anatomical concepts and unrelated to the delivered doses. Regarding a specification of dose in the definition, individual panellists proposed a radical dose of 60 Gy EQD2 or more, a therapeutic dose (radical or palliative), or stated that the definition should be independent of dose; none of these suggestions received agreement. Instead, the panellists agreed on the risk-based specification of dose (ie, cumulative doses causing a concern for toxicity), which was deemed inclusive of different scenarios. We opposed defining re-irradiation by an overlap of specific isodose lines. The overlap of isodose lines ranging from 30% to 80% of the prescription dose was proposed by panellists, but not included into the definition, since any specific cutoff was deemed arbitrary and thus inappropriate for a universally applicable definition of reirradiation. Because there was no consensus among the panellists to include a specific time interval between radiotherapy courses, there is no minimum time between two courses to classify a new course of radiotherapy as reirradiation. However, the time interval between two radiotherapy courses should be taken into account when assessing feasibility and safety because recovery might be assumed with increasing time from previous irradiation (eg, as is known for the brain and spinal cord).[16,27] Scenarios in which the decision for multiple consecutive treatment courses have been taken at a single time, such as consecutive rather than simultaneous treatment of multiple metastases, should not be considered as re- irradiation.

The panellists also developed a nomenclature to differentiate re-irradiation from other clinical scenarios of repetitive radiotherapy (panel 1). A decision tree, based on three binary questions, was derived to help classify reirradiation type 1 and 2; repeat organ irradiation; and repeat irradiation in clinical practice (figure 1). Three questions could be answered in hierarchical order until a re-irradiation type is established. Figure 2 shows schematic clinical scenarios of re-irradiation and retreatment with radiotherapy (appendix p 35).

Reporting guidelines for clinical studies on re-irradiation

In the first round of the Delphi process, the panellists identified a set of 41 items to be included in the reporting guidelines. In the second round, the priority for reporting of each item was scored as required, recommended, optional, or not relevant. Two items that received a draw were voted on again in the third round, together with six new items and one new category that was derived from and proposed in the second round. A definitive priority was reached for all items; no item was voted as not relevant (panel 2; appendix pp 36–40).

Recommendations for decision making on re-irradiation in clinical practice

For requirements and best practices for re-irradiation, we identified 41 areas of interest that were evaluated and rated in the first round. On the basis of the rating, comments, and discussion among the panellists in the second round, 17 items were consolidated and grouped into four categories:

interdisciplinary management and shared decision making, factors specific to patients and tumours, radiobiological aspects, and factors specific to reirradiation. In the second round, the panellists agreed with all categories and considerations; no additions were made. 22 considerations and recommendations for re-irradiation were agreed for clinical practice (voting results and version history of each statement in appendix pp 41–48).

Discussion

In this ESTRO-EORTC consensus, we propose a general definition of re-irradiation and a standardised nomenclature for scenarios of repetitive radiotherapy that do not fulfil the criteria for re-irradiation.

To further guide the generation of high-quality evidence related to the safety and efficacy of re-irradiation in the future, we propose reporting guidelines for clinical studies on re-irradiation. Although evidence-based recommendations are scarce or related to very specific re-irradiation conditions, we developed expert recommendations that could serve as a general decision-making aid when considering re-irradiation in clinical practice.

Defining re-irradiation

A perceived challenge of defining re-irradiation was the development of recommendations with a general applicability for re-irradiation rather than being specific for a primary tumour entity, anatomical region, or radiotherapy technique, while being profound enough to inform clinical practice.

Any scenario with overlap of irradiated volumes, irrespective of concerns for toxicity from cumulative doses, is considered as re-irradiation (panel 1). Additionally, scenarios without any immediate geometric overlap, but with relevant dose spillage that might raise concerns of toxicity from cumulative doses, are also included in this definition.

Previous consensus guidelines have aimed to define reirradiation for specific radiotherapy techniques, diseases, or anatomical locations.[19,20] Slevin and colleagues[19] defined stereotactic ablative radiotherapy (SABR) re-irradiation in the pelvis as "Delivery of SABR, after initial radiotherapy to the pelvis, and where there is overlap of previously delivered dose with the new treatment that could result in excess dose to an OAR [organs at risk] and/or significant toxicity." Besides being specific for a radiotherapy technique and an anatomical region, this definition focused on dose overlap and the resulting risk of toxicities. Rulach and colleagues[20] did not reach consensus on a single definition of thoracic re-irradiation for non-small cell lung cancer; the authors concluded that the scarcity of evidence on the effects of overlapping doses in serial organs and large-volume low-dose areas in parallel organs, such as the lungs, caused this disagreement. Rulach and colleagues[20] proposed to differentiate re-irradiation for local relapse and for new primaries; however, this proposal was not agreed upon by the majority of panellists. We believe that the definition of re-irradiation we propose in this consensus will complement the previous attempts to define re-irradiation because of its broad and inclusive nature; any case that would be termed as re-irradiation according to the definition proposed by Slevin and colleagues[19] would also classify as re-irradiation with our definition. Our definition also covers all scenarios that were considered by Rulach and colleagues[20] (ie, scenarios of concern because of overlap in serial organs, and those with large non-overlapping low-dose volumes from different courses in case they cause concern of toxicity), who did not reach a consensus on any definition. Additionally, the definition is independent of the tumour stage and clinical history, and thus applicable for a new primary tumour, local recurrence, and metastases.

Reporting guidelines for clinical studies on re-irradiation

More than half of the available studies included patients treated with re-irradiation in the brain or head and neck region. Only a few papers report on re-irradiation in other anatomical sites. Whether this scarcity is because of a publication bias or the frequency of re-irradiation in these sites is unclear, which is also true for the range of different radiotherapy methods that are reported on. The frequently small sample size per study highlights the need for pooled analyses to make firm conclusions about safe and effective re-irradiation. Fortunately, overall survival and toxicity are reported consistently in most papers, although with the inherent bias of under-reporting in retrospective studies. However, one of the most important parameters for the indication for re-irradiation and shared decision making, namely quality of life, is absent in most of these studies. Additionally, radiotherapy parameters of particular importance in the setting of re-irradiation are infrequently reported. Most studies only report the prescription dose from previous radiotherapy and reirradiation; cumulative dose parameters for targets and organs at risk are rarely reported. Knowledge of dosimetric parameters is crucial to allow for cross-study comparison and the safe implementation of these parameters into clinical practice.

The reporting guidelines we propose aim to offer guidance for researchers who do studies on re-irradiation, to ensure standardised, high-quality reporting, and to facilitate cross-study comparison or meta-analysis-based systematic reviews. Reporting recommendations for research studies are increasingly endorsed by scientific journals to improve the quality of reporting and to improve the reproducibility of published results. General frameworks, such as PRISMA (for systematic reviews and meta-analyses) and Strengthening the Reporting of Observational studies in Epidemiology (guidelines for observational studies) exist and are complemented by radiotherapy oncology guidelines, such as the Radiotherapy Treatment PlannING Study guidelines**.**[28–30] Our guideline is meant to complement such reporting guidelines by outlining items of particular relevance for clinical research on re-irradiation.

Interdisciplinary management and shared decision making

For patients with a short life expectancy, re-irradiation for symptom control might be considered without concerns for irreversible toxicity, despite excessive cumulative doses (ie, exceeding established dose constraints for primary irradiation; statement 2; table). The differentiation between reversible and irreversible toxicities, rather than between early and late toxicities, presents clinical relevance for patients and should be considered. Additionally, latencies of toxicities might be altered after previous radiotherapy, further hampering the distinction.[32] Ultimately, provided that all information on the possible risk for irreversible toxicity is available and shared during conversations between the patient and their physician, whether any possible risk outweighs the benefits of re-irradiation remains a patient's individual decision. Consecutive conversations might be needed to cover all aspects of shared decision making.

Factors specific to patients and tumours

Although we do not recommend high-dose re-irradiation in curative intent if the estimated survival is less than 6 months (statement 5; table), we acknowledge that predicting the survival of patients is notoriously challenging and physicians tend to overestimate survival. However, physicians' predictions are correlated with actual survival, and the accuracy of survival predictions might improve when performance status and symptoms are considered.[33] Thus, we recommend stable Eastern Cooperative Oncology Group performance status of 2 or less for patients who are considered for high-dose reirradiation (statement 4; table).

Interdisciplinary decision making, taking the patients risk acceptance into account, is essential.

Radiobiological aspects

Rather than general radiobiological assumptions, the response to and benefit from initial radiotherapy should guide the decision for or against re-irradiation and might help to estimate the most appropriate dose in case of recurrence within the previously irradiated volume (statement 9; table). Probability models for dosedependent control of tumours for re-irradiation might guide individualised treatment schedules in the future, but research is ongoing.

When considering concomitant radiosensitising systemic therapy with re-irradiation, the potential of excess radiatiotherapy-induced toxicities should be discussed critically. Generally, knowledge about the safety and efficacy of concomitant treatment for primary radiotherapy scenarios should be obtained in a primarytumour-specific and anatomical-site-specific manner. Combination therapies should be viewed critically, especially in palliative re-irradiation situations, to avoid unnecessary impairment of quality of life.

The linear-quadratic model is the most widely used and validated radiobiological model for explaining both the effect of fractionation and the specific differences in response to irradiation between different primary tumours or normal tissues (statement 10; table). Bentzen and colleagues[34] have reviewed the usage, interpretation, and challenges of the linear-quadratic model. In the setting of re-irradiation, the linear-quadratic model might be applied for calculating radiobiological equieffective doses (eg, EQD2) for different dose and fractionation schemes, which is crucial for assessing cumulative doses. In the absence of clinical radiobiological data specific for re-irradiation, published established α/β values for primary irradiation of tumour and organs at risk should be used (appendix p 48). These values could be used as guidance when assessing cumulative doses and estimating the responses to re-irradiation, acknowledging the uncertainties about estimated α/β for primary irradiation.

Factors specific to re-irradiation

If high-dose re-irradiation is considered, the panellists agreed that access to full information on previous treatments, including imaging, treatment plans, and dose distributions is strongly recommended for assessing cumulative dose summation, but not mandatory (statement 12; table). For patients who received their previous radiotherapy decades ago or in a different country than they are currently seeking treatment, information on previous treatments might not be readily available anymore. However, high-dose re-irradiation can be considered with the caveat that the uncertainty for assessing cumulative doses increases without full access to information from previous treatment. In this situation (ie, in which the previous dose distribution is not available in any reasonable format for dose reconstruction), the prescription dose might be assumed to be given homogeneously to an area or organ at risk for a conservative approximation of cumulative doses (statement 13; table).

In general, when the previous dose distribution is available in electronic format, the panellists noted that specific knowledge of treatment technique and dose prescription is irrelevant; only the dose distribution matters for assessing overlap, irrespective of how the dose was delivered. However, if information on the full 3D dose distribution is not directly available, and dose reconstruction is necessary, then information about treatment technique and field placement should be taken into account for dose reconstruction (statement 14; table), as some older treatment techniques might have resulted in clinically significant hotspots (ie, doses higher than 107% of the prescription dose outside the target volume) in normal tissue.

If the previous dose distribution is available electronically, at least an overlay of dose distributions in 3D is mandatory, rather than a numerical summation of the prescribed physical dose (statement 15; table). We emphasise that a physical dose summation across multiple treatment courses will almost never make radiobiological sense, except for the few random voxels in which the dose per fraction happens to be the same for the different treatments.

Biologically equieffective doses should be calculated when performing dose summations of treatment plans, especially when different doses are used per fraction (statement 16; table). Generally, dose per fraction to normal tissue will never be the same across treatments, even when prescription dose per fraction is the same, and this effect will be even more pronounced when different prescription doses are used per fraction. Optimally, the full 3D dose distributions should be converted to equieffective doses before dose summation to allow any volume effects to be considered. Alternatively, cumulative point dose estimates (after conversion to equieffective dose) can be used. The panellists further suggested using the term biologically equieffective doses, as proposed by Bentzen and colleagues[34], instead of referring to equivalent doses.

Potentially shorter latencies of irreversible toxicities after previous irradiation should be considered when organs-at-risk doses are evaluated during treatment planning (statement 18; table).[27] The differentiation between early and late toxicities is not recommended because of lack of clinical relevance.

Although tissue-dependent recovery after radiotherapy or dose discount is still subject to ongoing research and, therefore, a reliable recommendation on their use is not possible, we emphasise the evidence for the recovery specifically of the brain and the spinal cord based on preclinical animal models, but also on retrospective series in humans (statement 20; table).[16,17,27]

After high-dose re-irradiation, a follow-up every 3–4 months during the first year, and yearly thereafter, is advised, unless the anticipated risk of clinically significant irreversible toxicity is low (statement 22; table). These recommended intervals should serve as guidance and were derived from the consensus process, as evidencebased data are scarce. But follow-up schedules in clinical practice should always be individualised. In fact, some follow-up might be unnecessary and pose an additional burden to the patient without any meaningful benefit, particularly when the risk of irreversible toxicity is low. In the setting of clinical trials, more intensive follow-up schedules are warranted as they enable rigorous data collection and thus inform clinical practice.

Conclusions

In this ESTRO-EORTC consensus, we propose a universally applicable definition for re-irradiation and nomenclature for scenarios of retreatment with radiotherapy that do not fulfil the criteria for re-irradiation. The definition of re-irradiation covers scenarios with overlap of irradiated volumes, but also scenarios without overlap that raise concerns for toxicity from cumulative doses. It will be applicable to define re-irradiation, irrespective of disease type (new primary tumour, local recurrence, or metastases), irradiated area or organ at risk, and the radiotherapy technique used to deliver the dose. In addition, recommendations for minimal reporting in clinical studies and for decision making in clinical practice have been developed. The definition of re-irradiation and reporting guidelines will be applied to the prospective observational ReCare study (NCT03818503), which also seeks to validate the recommendations for decision making and derive safe dose constraints for re-irradiation. We hope our guidelines will help the development and standardised reporting of prospective and randomised trials, to better define how to optimally select and treat patients with re-irradiation. Uniform reporting will facilitate pooled data analyses of trials and on an

individual patient level, and could thus help to obtain high-quality evidence to guide decision making for re-irradiation.

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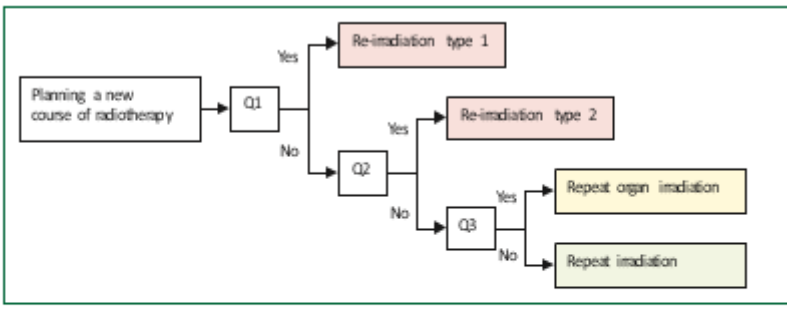

Figure 1: **Decision tree for the definition of re-irradiation and classification for scenarios with radiotherapy retreatment**

When a new course of radiotherapy is planned after previous courses, questions 1, 2, and 3 should be answered in a chronological order until reaching the first of the three categories: re-irradiation (red), repeat organ irradiation (yellow), or repeat irradiation (green). Q1=is there a geometrical overlap of the irradiated volumes? Q2=is there a concern for toxicity from the cumulative doses? Q3=are the target volumes of current and previous radiotherapy located in the same organ?

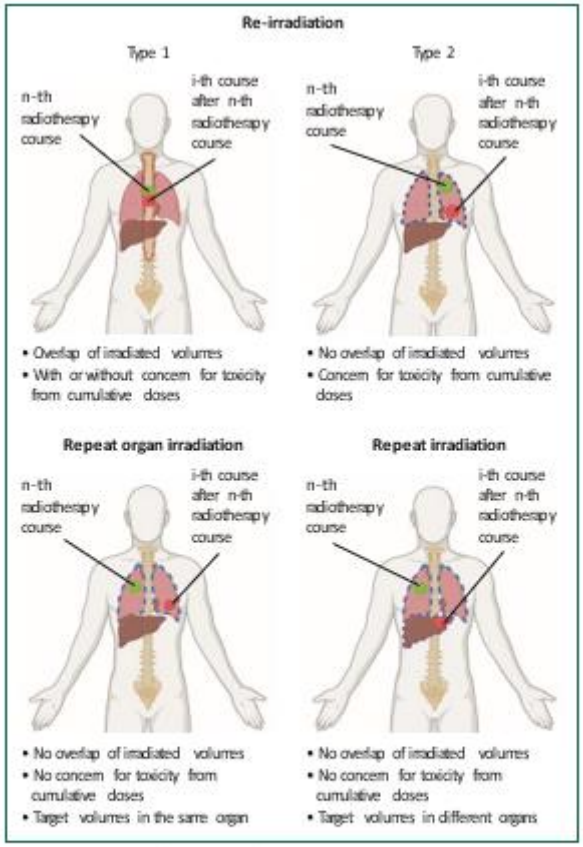

Figure 2: **Examples of scenarios of re-irradiation and retreatments with radiotherapy**

The letters n and j are natural numbers and refer to the number of consecutive radiotherapy courses; eg, the first and second course of radiotherapy, or later courses, such as the fourth and fifth course.