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Re-irradiation: Definition, reporting, and clinical decision making. A European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus document.

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Summary

Re-irradiation may be considered for local recurrence or new tumours adjacent to a previously irradiated site to achieve durable local control for cancer patients with otherwise limited therapeutic options. With the use of new radiation techniques, allowing for conformal treatment plans, image guidance and short fractionation schemes, the use of re-irradiation for different sites is increasing. Yet, prospective evidence on re-irradiation is scarce and our understanding of the underlying radiobiology is limited.

This consensus on re-irradiation aims to assist in re-irradiation decision making, and to assure standardisation of classifying different forms of re-irradiation and reporting, and has been endorsed by the European Society for Radiotherapy and Oncology (ESTRO) and European Organisation for Research and Treatment of Cancer (EORTC). Using 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 may be used in the future to make recommendations for re-irradiation based on clinical evidence. The consensus document is based on an adapted Delphi process. A systematic review of the literature was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to confirm a hypothesized lack of standardized reporting in clinical studies on re-irradiation.

Introduction

An increasing number of cancer patients are treated with high-dose radiotherapy to a previously irradiated area of the body, commonly referred to as re-irradiation.[1] This is likely a result of new radiation techniques for planning and delivery allowing avoidance of organs at risk without compromising the target coverage, along with new radiation regimens using high dose per fraction, offering ablative doses with high precision to various tumour sites that are resistant/recurred after radiation or are adjacent to previously irradiated site. Additionally, the availability of more reliable information on previously delivered doses due to CT-based treatment planning and better dose calculation algorithms facilitate a more accurate assessment of cumulative doses and overlap with old fields. Therefore, indications to perform re-irradiation may include local recurrence, adjacent new primary tumours, or local ablative treatment for metastatic disease.[2–8] In order to achieve treatment goals ranging from alleviating or preventing symptoms to local ablation and potentially cure, the entire spectrum of radiotherapy techniques may be applied for re-irradiation, including external beam photon radiotherapy and particle therapy (including protons) - using intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) - or brachytherapy.[9,10] The former techniques may be applied to delivery radiosurgery and stereotactic ablative radiotherapy (SABR).[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. On a basic level, no commonly agreed definition of re-irradiation exists. Current clinical approaches to re-irradiation are mostly based on expert opinions and retrospective research with varying quality of reporting – and different definitions of re-irradiation. Additionally, our understanding of the underlying radiobiology is limited, stemming mostly from pre-clinical research and retrospective clinical modelling studies.[13–16] Reliable dose constraints for re-irradiation are

therefore practically non-existent, with few exceptions. The need for standardisation and lack of high-level evidence is reflected in various recently published re-irradiation expert consensus guidelines for specific anatomical locations or radiotherapy techniques which intend to offer guidance for decision making: we refer the reader to Panel 1 for an overview of these guidelines, which include anatomical site- and radiotherapy technique-specific recommendations for re-irradiation in clinical practice. Recommendations for reporting in research studies specific for re-irradiation are completely lacking, while needed to allow for the comparison of results and facilitate their safe implementation into clinical practice. In the absence of high-level evidence, consensus-based recommendations as a guidance for re-irradiation are needed to ensure common standards.

In this Delphi consensus among international experts, endorsed by the European Society for Radiotherapy and Oncology (ESTRO) and 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 which 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

This consensus document was developed 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 efficacy of high-dose re-irradiation and derive evidence-based dose constraints for safe re-irradiation.

The consensus document is based on an adapted Delphi process, as outlined below. The 17 panellists of the Delphi process (all authors except JW and NaAl) have been selected to represent different professions involved in radiotherapy, so that both clinical and technical aspects of re-irradiation could be covered. Panellists should have a strong expertise and scientific track record regarding different tumour entities, radiotherapy techniques and re-irradiation. Women and men from different European countries were chosen to ensure diversity of the panel and to represent a broad range of opinions and clinical practices. Panellists were selected from both the ESTRO and the EORTC network. The profession, years of experience since specialization and country of practice of each panellist are outlined in Appendix page 2.

Additionally, a systematic review of the literature was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to confirm a hypothesized lack of standardized reporting the in clinical studies on re-irradiation.

Systematic review

We conducted a systematic review on the quality of reporting of re-irradiation publications in the last two decades to confirm a hypothesized lack of standardized reporting in clinical studies on re-irradiation. The systematic review followed the PRISMA guidelines [17]. PubMed was searched for prospective clinical trials and retrospective studies, systematic reviews and meta-analyses on re-irradiation for any solid malignancies, published between 2000 and 2020. The search terms were: ("re-irradiation" OR "re irradiation" OR "reirradiation" OR (("retreatment" OR "repeat") AND ("radiotherapy" OR "irradiation")). Non-English language studies or studies on benign diseases were excluded. Modelling studies, in silico studies, and technical reports were also excluded. The articles were reviewed, selected and analysed for data extraction by

one author (NaAl). Two authors (NA and JW) reviewed the results. The PRISMA flow chart is provided in the Appendix page 3.

Delphi consensus process

An adapted Delphi process was used for consensus formation on three different subjects: I) a definition of re-irradiation and additional nomenclature for scenarios of re-treatment with radiotherapy which do not fulfil the proposed criteria for re-irradiation, II) reporting guidelines for research studies on re-irradiation, and III) recommendations for decision making on re-irradiation in clinical practice.[18] A schematic overview of the Delphi process is depicted in Figure 1.

The three topics were developed independently: starting with a baseline assessment among the panellists, three rounds followed for consensus formation (subject I-III) and determining prioritisation for reporting (subject III only). Each round consisted of an online survey using Google Forms followed by 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; 5: strongly disagree). The level of agreement among the panellists was defined as the combined proportion of votes for “strongly agree” and “agree”. In order to reach consensus, agreement of at least 75% of the panellists was necessary. The panellists could add free text comments to indicate if any adjustments or additions were needed in their opinion. The online voting rounds were followed by virtual meetings in which the panellists discussed the results. In case no consensus was reached, the panellists could vote again after discussion and adaptation of the items in the next round. Once consensus was reached, only minor changes to the wording were allowed. For the reporting guideline, the panellists prioritised different items as “required”; “recommended”, “optional”, “not relevant” in research

studies on re-irradiation. The consensus finding for the three subjects is described in detail in the Appendix page 35.

Findings

Level of reporting in studies on re-irradiation

A total of 493 studies were included in the systematic review, which showed a marked increase in clinical research on re-irradiation from 2000 to 2020 (Appendix page 4). A list of all included articles is included in the Appendix page 5-33. By far, most publications are retrospective cohort studies (n=390, 79%), 15% (n=72) were prospective clinical studies and 6% (n=31) consisted of systematic reviews. Most studies included only patients treated with re-irradiation in a single anatomical site (n=475, 96%; head and neck: n=156, 32%; brain: n=117, 24%). Noteworthy, sample sizes are typically small, with 61% (n=300) of the studies including 50 or less patients.

Median follow-up was consistently reported (n=431, 87%) and revealed a median follow-up of more than 12 months in 66% of the studies (n=327) for reliable evaluation of long-term sequelae. The key endpoints overall survival and toxicity were reported in 93% (n=460), and 98% (n=485) of studies, respectively. Quality of life after re-irradiation was reported in only 8% (n=40) 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 54% (n=265) of the studies; using 3D conformal radiotherapy (n=75), IMRT or VMAT (n=64), or stereotactic re-irradiation to cranial (n=46) or extracranial targets (n=80). Compared to that, particle therapy re-irradiation was reported in 8% of the studies (n=39), irrespective of the target location. Brachytherapy was addressed in 9% (n=46) of the included studies, while only 1% (n=6) used

intraoperative radiotherapy techniques. Most of the remaining studies (n=129) included different techniques (mostly external beam photon radiotherapy) or combined modalities (e.g. external beam radiotherapy with photons or electrons plus hyperthermia), while few applied experimental treatments (n=2; semicontinuous low-dose-rate teletherapy and pulsed reduced-dose-rate radiotherapy) or lacked clear information (n=6).

All studies reported at least the prescription dose of the re-irradiation, and most (n=464) also did for the previous courses of radiotherapy. Only 14% of the studies (n=71) reported the organ at risk dose constraints that were applied during treatment planning for re-irradiation, and only 17% (n=83) and 8% (n=38) reported cumulative dose volume parameters for organs at risk and target volumes, such as minimum, maximum, mean/median doses and doses based on absolute or relative volume. Six percent of the studies (n=30) reported cumulative doses derived from summation of 3D dose distributions without recalculation to account for fractionation schedules, while 25% (n=124) reported a numerical sum of prescription doses without using treatment plans. Generally, cumulative dose parameters were infrequently and inconsistently reported: equivalent dose in 2 Gy fractions (EQD2) were reported in 21% (n=103), in biologically effective dose (BED) in 24% (n=120) and in equivalent uniform dose (EUD) in less than 1% (n=2).

Taken together, 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 amongst the Delphi consensus panellists, 14 potential defining characteristics of re-irradiation were collated and grouped into four categories (irradiated

region, prescription dose, time interval between treatments and degree of overlap) (Appendix page 34). Three of these eventually reached consensus to be included into the final definition: 1) a new course of radiotherapy, 2) overlap of irradiated volumes or 3) a concern for toxicity from cumulative doses.

The panellists therefore agreed on the following 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”.

Re-irradiation is therefore an umbrella term for two scenarios and thus will be distinguished by referring to as “type I” or “type II” re-irradiation: re-irradiation *type I* is a new course of radiotherapy that has geometrical overlap with the irradiated volume of previous courses, re-irradiation *type II* is a new course with concerns of toxicity from the cumulative doses but where there is no overlap. *Irradiated volume* as consented by the panellists was defined as the tissue volume which receives a dose that is considered significant in relation to normal tissue tolerance, according to International Commission on Radiation Units & Measurements (ICRU) Report 29.[19]. Overlap of irradiated volumes - rather than overlap of specific target volumes or isodose lines - takes doses to organs at risk into account and can therefore be applied to different clinical scenarios, as was desired for our general definition of re-irradiation. The panellists perceived 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 initially proposed specifications for re-irradiation were eventually not included in our proposed definition of re-irradiation. The panellists agreed on using radiotherapy to a previously *irradiated volume* - as defined by the ICRU - for the *spatial definition* of re-irradiation as it accounts for the delivered dose in relation to organ at risk tolerance. We opposed using any *target volume*, e.g. the planning target volume (PTV), as these are based on treatment planning and delivery concepts and may not necessarily

coincide with the actually relevant dose distribution. Additionally, target volumes would not account for the dose to normal tissues, which was regarded as a critical specification. Using overlap of *area* or *region* was also rejected, since these were regarded by the panellists as ill-defined anatomic 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 received agreement. Instead, the panellists agreed on the risk-based specification of dose: i.e. *cumulative doses causing a concern for toxicity*, which was deemed inclusive for different scenarios. We opposed defining re-irradiation by an *overlap of specific isodose lines*. The overlap of isodoses 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 re-irradiation. As there was no consensus among the panellists to include a specific time interval between radiotherapy courses, there is no minimal time between two courses to classify a new course of radiotherapy as re-irradiation. Still, the time interval between two radiotherapy courses should be taken into account, when assessing feasibility and safety, as with increasing time from previous irradiation recovery might be assumed, e.g. as known for brain and spinal cord.[16,20] Scenarios where the decision for multiple consecutive treatment courses has been taken at a single time - e.g. consecutive rather than simultaneous treatment of multiple metastases - should not be considered as re-irradiation.

The panellists further developed a nomenclature to differentiate re-irradiation from other clinical scenarios of repetitive radiotherapy (Panel 2). A decision tree, based on three binary questions, was derived to help classify re-irradiation type I and II, repeat organ irradiation and repeat irradiation in clinical practice (Figure 2). The questions could be answered in hierarchical order until reaching one of the categories: 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 3 depicts schematic clinical scenarios of re-irradiation and re-treatment with radiotherapy.

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 ("required"; "recommended", "optional", "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 were derived from and proposed in the second round. A definitive priority was reached for all items, no item was voted as "not relevant". The final reporting guidelines are presented in Table 1, a detailed outline including voting results in the Appendix page 35-39.

Recommendations for decision making on re-irradiation in clinical practice

For requirements and best practices for re-irradiation, we identified 41 areas of interest which were evaluated and rated in the first round. Based on 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, patient and tumour specific factors, radiobiological aspects and re-irradiation specific factors. In the second round, the panellists agreed with all categories and considerations, no additional ones were added. Table 2 depicts the final 22 considerations and recommendations for re-irradiation in clinical practice, while all voting results and version history of each statement are listed in the Appendix page 40-46.

Discussion

In this ESTRO EORTC consensus document, we propose a general definition of re-irradiation and in addition 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 proffer reporting guidelines for clinical studies on re-irradiation. While evidence-based recommendations are still scarce or related to very specific re-irradiation conditions, we developed expert recommendations which may serve as a general decision making aid when considering re-irradiation in clinical practice.

Defining re-irradiation

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

With the definition depicted in Panel 2, any scenario with overlap of irradiated volumes irrespective of concerns for toxicity from cumulative doses is considered as re-irradiation. Additionally, scenarios without any immediate geometric overlap, but with relevant dose spillage which might give rise to concerns for toxicity from cumulative doses are therefore also as well embraced by this definition.

Previous consensus guidelines have aimed to define re-irradiation for specific radiation techniques, diseases or anatomical locations: Slevin et al. defined 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 and/or significant toxicity”.[21] Besides being specific for a radiotherapy technique and an

anatomic region, this definition focussed on dose overlap and the resulting risk of toxicities. Rulach et al. did not reach consensus on a single definition of thoracic re-irradiation for non-small cell lung cancer (NSCLC).[22] The authors concluded that the lack of evidence on the effects of overlapping doses in serial organs and large-volume low-dose areas in parallel organs such as the lung caused this discern. Besides, the authors proposed to differentiate re-irradiation for local relapse and for new primaries; however, this was not consented. We believe that the definition of re-irradiation we propose in this consensus documents will complement the previous attempts to define re-irradiation, due to its broad and inclusive nature: any case that would be termed as re-irradiation according to the definition proposed by Slevin et al. would also classify as re-irradiation using our definition. Our definition also covers all scenarios that were considered by Rulach et al., who did not reach consensus on any definition: 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. Additionally, the definition is independent of the tumour stage and clinical history, and thus applicable for new primaries, 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 limited number of papers report on re-irradiation in other anatomical sites. It is unclear if this is due to a publication bias or actually reflecting the frequency of re-irradiation in these sites. The same holds true for the range of different radiotherapy modalities that are reported on. The often 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 underreporting 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 the vast majority 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 re-irradiation – 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 into clinical practice.

The reporting guidelines we propose aim to offer guidance for researchers who conduct studies on re-irradiation; ensuring standardised, high-quality reporting and facilitating 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 like PRISMA for systematic reviews and meta-analyses, and STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines exist and are complemented by radiation oncology guidelines such as the RATING (Radiotherapy Treatment plannINg study) guidelines.[23,24] Our guideline is meant to complement such reporting guidelines by outlining items of particular relevance for clinical research on re-irradiation.

Recommendations for decision making on re-irradiation in clinical practice

A list of statements has been developed to guide decision making in re-irradiation, while high level evidence is still lacking for many scenarios. The primary intent of these statements was to give general guidance on decision making aspects for re-irradiation irrespective of tumour entity or treatment planning; we did not intend e.g. to give specific recommendations for organs at risk constraints. The latter are left to efforts on specific clinical re-irradiation scenarios, as outlined in Panel 1.

Interdisciplinary management and shared decision making

For patients with limited life expectancy, re-irradiation for symptom control may be considered without concerns for *irreversible* toxicity despite excessive cumulative doses, i.e. exceeding established dose constraints for primary irradiation (statement S2). The differentiation between *reversible* and *irreversible* toxicities - rather than between *early* and *late* - confers clinical relevance for patients and should thus be considered. Additionally, latencies of toxicities may be altered after previous irradiation, further hampering the distinction.[25] Ultimately, provided that all information on the possible risk for irreversible toxicity is available and shared during conversations, it remains a patient individual decision whether any possible risk outweighs the benefits of re-irradiation. Consecutive conversations may be needed to cover all aspects of shared decision making.

Patient and tumour specific factors

While we do not recommend high-dose re-irradiation in curative intent if estimated survival is less than 6 months (statement S5), we acknowledge predicting survival of patients is notoriously challenging and physicians tend to overestimate survival. Yet physicians' predictions are correlated with actual survival, and the accuracy of survival predictions may improve when performance status and symptoms are considered.[26] Thus, we recommend stable Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 for patients who are considered for high-dose re-irradiation (statement S4).

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 radiation therapy should guide the decision for or against re-irradiation and might help estimating the most appropriate dose in case of recurrence within the previously irradiated volume (statement S9). Dose-dependent tumour control probability models for re-irradiation

might guide individualised treatment schedules in the future but are currently subject to ongoing research.

When considering concomitant radiosensitizing systemic therapy with re-irradiation, the potential of excess radiation-induced toxicities should be critically discussed. Generally, knowledge about the safety and efficacy of concomitant treatment for primary radiotherapy scenarios should be obtained in a primary tumour- 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 (LQ) model is the most widely used and validated radiobiological model for explaining both the impact of fractionation, and the specific differences in response to irradiation between different primary tumours or normal tissues (statement S10). For an in-depth review of usage, interpretation and challenges of the LQ model, we refer the reader to the review by Bentzen et al..[27] In the setting of re-irradiation, the LQ model may be applied for calculating radiobiological equieffective doses (e.g. 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. An overview of α/β values for different organs at risk can be found in the Appendix page 47. These values may be used as a guidance when assessing cumulative doses and estimating the responses to re-irradiation, acknowledging the uncertainties even with regard to estimated α/β for primary irradiation.

Re-irradiation specific factors

If high-dose re-irradiation is considered, the panellists agree 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

S12). For patients who received their previous radiotherapy decades ago or in a different country, this information may not be readily available anymore. Yet, high-dose re-irradiation can be considered with the caveat that uncertainty for assessing cumulative doses increases without full access to this information. In this situation (i.e. where the previous dose distribution is not available in any reasonable format for dose reconstruction), the prescription dose may be assumed to be "given homogeneously to an area or organ at risk" for a conservative approximation of cumulative doses (statement S13).

In general, when the previous dose distribution is available in electronic format, the panellists perceived that specific *knowledge of treatment technique and dose prescription* is irrelevant; only the dose distribution matters for assessing overlap, irrespective of how it 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 S14), as e.g. some older treatment techniques may have resulted in significant hotspots 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 S15). We emphasise that a physical dose summation across multiple treatment courses will almost never make radiobiological sense - except for the few random voxels where 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 using different doses per fraction* (statement S16). 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 using different prescription doses per fraction. Optimally, the full 3D dose distributions should be converted to equieffective doses prior to dose summation, to allow any volume effects to

be considered. Alternatively, cumulative point dose estimates (following conversion to equieffective dose) can be used. The panellists further suggest using the term biologically *equieffective* doses, as proposed by Bentzen et al., instead of referring to *equivalent* doses.[27] Potentially shorter latencies of *irreversible* toxicities after previous irradiation should be considered when organs at risk doses are evaluated during treatment planning (statement S18).[20] The differentiation between *early* and *late* toxicities is not recommended, due to lack of clinical relevance.

While tissue-dependent recovery after irradiation 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 S20).[16,20,28]

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 significant irreversible toxicity is low* (statement S22). These recommended intervals should serve as guidance and were derived from the consensus process, as evidence-based data is lacking. But follow-up schedules in clinical practice should always be individualised. In fact, some follow-up may be unnecessary and pose an additional burden to the patient without any meaningful benefit - particularly when the risk for 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 document 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, 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, which also seeks to validate the recommendations for decision making and derive safe dose constraints for re-irradiation.

We hope our guidelines will foster 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 may thus help obtaining high level evidence to guide decision making for re-irradiation.

Abbreviations

BED - biologically effective dose

CT – computed tomography

E2-RADIatE - ESTRO-EORTC RADiation InfrAstrucTure for Europe

ECOG - Eastern Cooperative Oncology Group

EORTC – European Organisation for Research and Treatment of Cancer

EQD2 - equivalent dose in 2 Gy fractions

ESTRO - European Society for Radiotherapy and Oncology

EUD - equivalent uniform dose

ICRU - International Commission on Radiation Units & Measurements

IMRT - intensity modulated radiotherapy

LQ-model - linear-quadratic model

NSCLC - non-small cell lung cancer

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PTV - planning target volume

RATING - Radiotherapy Treatment plannINg study

SABR - stereotactic ablative radiotherapy

STROBE - STrengthening the Reporting of OBservational studies in Epidemiology

VMAT - volumetric modulated arc therapy

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Figures

Figure 1

Schematic overview of the Delphi process. Dates indicate the time of virtual meeting to discuss the rounds' online voting results. Dates indicate the start of the respective round.

Figure 2

Decision tree for the definition of re-irradiation and classification for scenarios with radiotherapy re-treatment. When a new course of radiotherapy is planned after previous courses, the questions 1, 2 and 3 should be answered in a hierarchical order until reaching the first of the three categories re-irradiation (red), repeat irradiation (yellow) or a new course of radiotherapy (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 3

Examples for scenarios of re-irradiation and re-treatments with radiotherapy. Abbreviations: n-*th* RT: the n-*th* course of radiotherapy; n+i-*th* RT: the i-*th* course after the n-*th* course of radiotherapy.

Panels

Panel 1: Available guidelines on re-irradiation

We searched PubMed on November 1st 2021 for publications with the terms ((“reirradiation” OR “re-irradiation”) AND (“guideline”)) to identify existing guidelines on re-irradiation. The search was limited to the title and abstract search fields. Systematic reviews, surveys and guidelines that were not specific to re-irradiation, i.e. also including other treatments for recurrent disease, were excluded. This search found six guidelines of re-irradiation, for which the full texts were assessed. Screening the references of these guidelines identified another guideline of re-irradiation. The guidelines focus on brachytherapy and SBRT for intraprostatic relapse after prostate cancer radiotherapy, SBRT for pelvic re-irradiation, radical thoracic re-irradiation for non-small cell lung cancer, IMRT for locally recurrent nasopharyngeal carcinoma, recurrent glioblastoma and breast cancer.[21,22,29–33]

Panel 2: Consensus definition and classification of re-irradiation.

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. Thus, re-irradiation is an umbrella term for two different scenarios: re-irradiation *type I* is any new course of radiotherapy that has geometrical overlap with the irradiated volume of previous courses, re-irradiation *type II* is a new course with concerns of toxicity from the cumulative doses without overlap of irradiated volumes.

Repeat organ irradiation

Repeat organ irradiation is a new course of radiotherapy to a previously irradiated organ but without overlap of the irradiated volumes and without concerns for toxicity from cumulative doses.

Repeat irradiation

Repeat irradiation is a new course of radiotherapy to an organ that has not been irradiated, without overlap of irradiated volumes, and without concerns for toxicity from cumulative doses.

Search strategy and selection criteria

The references in this Policy review were chosen on the basis of originality and relevance to the broad scope of this Policy Review. Articles were identified through searches of the authors' own files and out of the systematic review based on a PubMed search with the search terms ("re-irradiation" OR "re irradiation" OR "reirradiation" OR (("retreatment" OR "repeat") AND ("radiotherapy" OR "irradiation")), from January 1, 2000, until December 31, 2020. Prospective clinical trials and retrospective studies, systematic reviews and meta-analyses on re-irradiation for any solid malignancies were included. Non-English language studies or studies on benign disease were excluded. Studies with less than 10 patients, abstracts, modelling studies, in silico studies and technical reports were also excluded.

Contributors

NA, JW and CL contributed to study conceptualisation, data curation, formal data analysis, investigation, consensus methods, project administration, consensus supervision, validation. JW contributed to visualisation. NA, JW, CL, ALA, PH and PP contributed to writing of the original manuscript draft, and its revision and editing. NaAl contributed to the systematic review. All authors contributed to the interpretation of data, and the revision, editing and approval of the manuscript.

Declaration of interests

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monitoring board or advisory board for Multicentre BRIOCHE Trial UK (BRIOChe study: Brain Re-Irradiation Or Chemotherapy: a phase II trial of re-irradiation or chemotherapy for recurrent glioblastoma) from University of Leeds, and is general secretary in SASRO board and member of scientific board of SAKK. MH declares a honorarium for giving a lecture at a symposium arranged by Varian in Copenhagen, 6 May 2022. JL declares several research grants by the European Union and the Dutch Cancer Society, Consulting fees paid to UMCG Research BV by IBA, honorarium for presentations paid to UMCG Research BV by IBA. JL is Chair of the Safety Monitoring Committee of the UPGRADE-trial from the University Medical Center Nijmegen, Member of the Global Advisory Committee at IBA, and Member of the RayCare Clinical Advisory Board at RaySearch, and serves as Chair (unpaid) of the Netherlands Society for Radiation Oncology (NVRO). PP is a medical advisor of Sordina IORT Technologies, S.p.A.. STL declared that her husband is an employee at Varian. IM declares occasional small fees (consulting fees) from Novartis, Pfizer, Eli Lilly, Seagen, Accuray, and occasional small fees (payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events) from Novartis, Pfizer, Eli Lilly, Seagen. MN declares honoraria and speaker fees from Brainlab, and is a member of the advisory board at Novocure. All other authors declare no competing interests.

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