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Original Article

Re-irradiation in clinical practice: Results of an international patterns of care survey within the framework of the ESTRO-EORTC E^2-RADIatE platform

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ABSTRACT

Background: Re-irradiation is an increasingly utilized treatment for recurrent, metastatic or new malignancies after previous radiotherapy. It is unclear how re-irradiation is applied in clinical practice. We aimed to investigate the patterns of care of re-irradiation internationally.
Material/Methods: A cross-sectional survey conducted between March and September 2022. The survey was structured into six sections, each corresponding to a specific anatomical region. Participants were instructed to complete the sections of their clinical expertise. A total of 15 multiple-choice questions were included in each section, addressing various aspects of the re-irradiation process. The online survey targeted radiation and clinical oncologists and was endorsed by the European Society for Radiotherapy and Oncology (ESTRO) and the European Organisation for Research and Treatment of Cancer (EORTC).
Results: 371 physicians from 55 countries across six continents participated. Participants had a median professional experience of 16 years, and the majority (60%) were affiliated with an academic hospital. The brain region was the most common site for re-irradiation (77%), followed by the pelvis (65%) and head and neck (63%). Prolonging local control was the most common goal (90–96% across anatomical regions). The most common minimum interval between previous radiotherapy and re-irradiation was 6–12 months (45–55%). Persistent grade 3 or greater radiation-induced toxicity (77–80%) was the leading contraindication. Variability in organs at risk dose constraints for re-irradiation was observed. Advanced imaging modalities and conformal radiotherapy techniques were predominantly used. A scarcity of institutional guidelines for re-irradiation was reported

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(16–19%). Participants from European centers more frequently applied thoracic and abdominal re-irradiation. Indications did not differ between academic and non-academic hospitals.
Conclusion: This study highlights the heterogeneity in re-irradiation practices across anatomical regions and emphasizes the need for high-quality evidence from prospective studies to guide treatment decisions and derive safe cumulative dose constraints.

Re-irradiation refers to a new course of radiotherapy either to a previously irradiated volume (irrespective of concerns of toxicity) or where the cumulative dose raises toxicity concerns [1]. This approach is now a viable treatment option for an increasing number of patients, as advances in systemic therapies have improved patient outcomes, and modern precision radiotherapy techniques have become widely available. Re-irradiation may be offered to patients with recurrent, metastatic, or new malignancies following initial radiotherapy in different anatomical regions [2–6]. The need to balance tumor control with the risk of severe toxicity from cumulative radiation doses to previously irradiated organs is the crucial challenge in re-irradiation.

Given the relative scarcity of high-quality evidence from prospective trials, guidelines and expert recommendations are crucial to ensure common standards and best practices are met when re-irradiation is considered. Notable published guidelines and/or expert consensus documents cover re-irradiation with IMRT for nasopharyngeal cancer [7], radical thoracic re-irradiation for non-small cell lung cancer (NSCLC) [8], stereotactic body radiotherapy (SBRT) for pelvic tumor recurrences [9], and SBRT [10] or brachytherapy [11,12] for recurrent prostate cancer after previous RT. The recent consensus by the European Society for Radiotherapy and Oncology (ESTRO) and the European Organisation for Research and Treatment of Cancer (EORTC) provides general guidance for safe re-irradiation, irrespective of tumor type, anatomical region, or radiotherapy technique [1].

We conducted a survey on the patterns of care of re-irradiation among physicians internationally, covering key steps in the re-irradiation workflow from patient selection to technical aspects. The survey was intended to uncover areas of controversy among participants. Thereby, we intended to guide future research efforts to address the most pertinent knowledge gaps affecting re-irradiation in clinical practice and foster the dissemination of new, and further the development of existing, guidelines on re-irradiation.

Materials and methods

Study design

We carried out a cross-sectional survey from March to September 2022 to investigate re-irradiation practices among radiation and clinical oncologists. This survey received endorsement from both the ESTRO and the EORTC, and their joint E^2-RADIatE platform that collects real-world data through prospective cohort studies to support radiotherapy research (NCT03818503). In the survey, re-irradiation was defined according to the ESTRO/EORTC consensus definition as a new course of radiation therapy either to a previously irradiated volume (irrespective of concerns of toxicity) or in which the cumulative dose raises concerns of toxicity [1].

Description of the questionnaire

The survey was structured into six sections, each corresponding to a specific anatomical region. Participants were instructed to complete the sections relevant to their clinical expertise. A total of 15 multiple-choice questions were included in each section, addressing various aspects of the re-irradiation process. These aspects encompassed indications for re-irradiation, planning and delivery techniques, as well as follow-up procedures. Additionally, a general section of the survey captured data on affiliation, location and experience of the participants. The questionnaire is provided in the Supplementary Material.

The survey was created in Google Forms and distributed online to assure good coverage of diverse settings and geographical regions. Radiation and clinical oncologists who are members of ESTRO and affiliated national professional societies were approached by email. Two reminders were sent about a month apart to ensure a higher response rate. To ensure further geographical outreach, the survey was distributed on social media platforms (Twitter, LinkedIn).

Statistical analysis

Percentages of responses for each question are calculated based on the total number of responses specific to that question, rather than using the total number of responses for the entire section. This method accounts for any missing response values that may be present. The impact of the participants' type of practice (academic hospital versus non-academic) and location (Europe versus other) on applying re-irradiation in the different anatomical regions was analyzed using the Chi-squared test. A two-sided P-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the R statistical software (version 4.2.3) and the tidyverse package.

Results of the survey are reported according to the Consensus-Based Checklist for Reporting of Survey Studies (CROSS) [13].

Results

Participants' demographic data

Our survey on re-irradiation patterns of care included 371 participants from 55 countries across 6 continents (Question I) (Fig. 1). Eightytwo percent (n = 304) of participants were working in European departments; the highest number of participants was from Italy (10%, n = 37), followed by Spain (7%, n = 27), Germany (6%, n = 23), the Netherlands (6%, n = 23), and the United Kingdom (6%, n = 22). The majority of participants were affiliated with academic hospitals (60%, n = 223) (Question III), and the median years of experience was 16 years (interquartile range: 10–25 years) (Question II).

Indications for re-irradiation and factors influencing decision making

The brain was treated with re-irradiation by most participants of the survey (77%, n = 287), followed by the pelvis (65%, n = 241), head and neck region (63%, n = 235), thorax (60%, n = 221), breast/chest wall (51%, n = 189), and abdomen (39%, n = 145) (Question 1). In the different anatomical regions, re-irradiation was applied for a variety of primary tumor types and stages - from local and locoregional recurrences to distant metastases - as outlined in Table 1 (Question 2).

The majority of participants of the survey selected persistent grade 3 or greater radiation-induced toxicity as a contraindication to re-irradiation in all regions (range across anatomical regions: 77%-80%) (Question 6). Table 2 outlines the contraindications to re-irradiation across various anatomical regions in detail. A minimum interval of 6–12 months since previous radiotherapy was most frequently used as the threshold for consideration of re-irradiation (range: 45–55%) (Question 5); a detailed overview is presented in Table 3.

The most commonly reported treatment goal for re-irradiation was prolonging local control across all regions (range: 90–96%) (Question 4). Other significant goals are shown in Table 4.

Indications for postoperative re-irradiation differed between respondents and anatomical sites and were variably influenced by factors such as resection status and extracapsular extension of lymph node metastases (Question 3), as highlighted in eTable 1 in the Supplementary Material.

Cumulative dose constraints

Participants reported variable cumulative dose constraints for organs at risk at re-irradiation (Question 11). For some organs, most participants assumed partial tissue recovery thereby allowing a higher cumulative dose across both treatment courses than simply applying the constraint used at initial radiotherapy across both the initial and re-irradiation courses. A minority of participants applied the constraint used at initial radiotherapy cumulatively (i.e. across both courses), without inclusion of recovery. A complete presentation of the results for all organs can be found in eTable 2 of the Supplementary Material.

Technical aspects of re-irradiation

Rigid image registration was the most commonly reported method for fusing different images to define target volumes (range: 68–77%), as indicated in the Supplementary Material eTable 3 (Question 8). Advanced imaging modalities such as PET (range: 30–88%) and MRI (range: 20–95%) of the recurrence are frequently co-registered for target volume definition, with varying frequency per anatomical region, as shown in the Supplementary Material eTable 4 (Question 7). A wide range of target volume concepts were applied for re-irradiation, as highlighted in Supplementary Material eTable 5 (Question 9).

Cumulative doses were reported to be most commonly evaluated as the dose to *specific points* with summation in equivalent dose in 2 Gy fractions (EQD2), ranging from 49% to 57% across the anatomical regions (Question 10). A more precise, yet technically challenging *3D dose summation* in EQD2 or biological effective dose (BED) was less frequently reported (range: 43–52% and 21–25%, respectively). The results for the assessment of cumulative doses are summarized in Supplementary Material eTable 6.

Modern conformal techniques like volumetric modulated arc therapy (VMAT) and hypofractionated stereotactic treatments are frequently used (Question 12) (Supplementary Material eTable 7), with cone beam CT (CBCT)-based image guidance for treatment delivery widely applied to reduce setup uncertainties and verify positioning (Question 13) (Supplementary Material eTable 11). Further details on delivery and treatment verification are outlined in Supplementary Material eTable 7 and eTable 8.

Guidelines and follow-up procedures

A scarcity of institutional guidelines and recommendations for re-irradiation was reported by participants for all anatomical regions (range: 16–19%) (Question 15). The availability of guidelines per anatomical region is summarized in Table 5, including an overview of guidelines on re-irradiation.

The vast majority of participants reported that follow-up after re-irradiation is primarily performed by radiation oncologists (range: 55–70%) (Question 14), as summarized in eTable 9 in the Supplementary Material.

Impact of demographic data on re-irradiation practice

The participant's continent of occupation had an impact on the anatomical regions treated with re-irradiation. Participants working in Europe were significantly more likely to apply re-irradiation in the thorax (Europe: 63% versus other: 48%, $p = 0.030$) and abdomen (Europe: 43% versus other: 27%, $p = 0.026$) (Supplementary Material eTable 10). We furthermore sought to investigate whether the type of institution (academic vs. non-academic) had an impact on the anatomical regions treated with re-irradiation, but found no statistically significant associations (Supplementary Material eTable 11).

Discussion

Despite scarce evidence on best practices, re-irradiation is an increasingly utilized treatment option. This study explores prevailing re-irradiation patterns, primarily reported for treatments in brain, pelvis, thorax, and head-neck region for diverse indications, from locoregional recurrences to distant metastases. Decision making on minimum interval post-radiotherapy, contraindications, and postoperative treatment vary widely, as do cumulative dose limits for organs at risk. Nevertheless, advanced techniques in imaging and treatment delivery are consistently applied in re-irradiation.

Randomized controlled trials on re-irradiation are scarce, with a few notable exceptions. Two trials have recently shaped the role of re-irradiation for recurrent nasopharyngeal cancer after radiotherapy. A randomized phase 2 trial compared intensity-modulated radiotherapy (IMRT) re-irradiation to salvage endoscopic nasopharyngectomy in resectable recurrent nasopharyngeal cancer [16]. Surgery significantly improved the 3-year overall survival, indicating the standard for

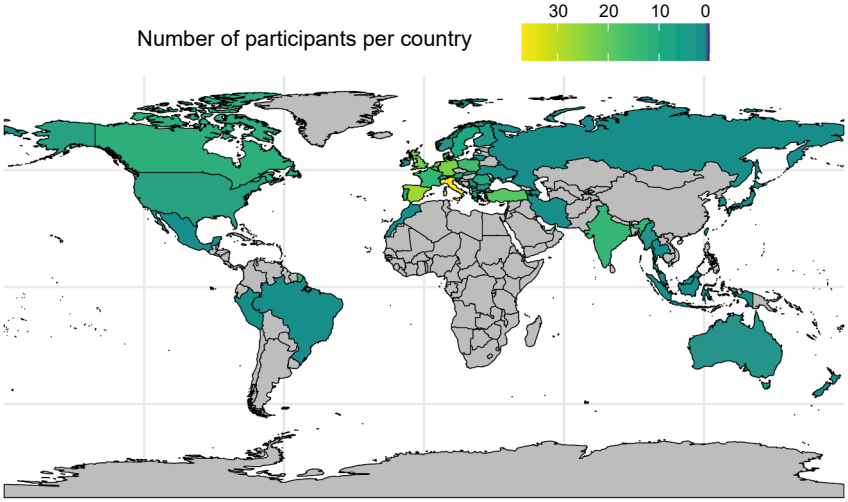

Fig. 1. Number of participants per country. (Question I).

Table 1
Indications for re-irradiation by anatomical region as reported by participants of the survey. (Question 2: Which tumors do you treat with re-irradiation? [multiple choice]).

Region	*Tumor type/stage*	*n (%)*
Brain *(n = 285)*	Brain metastases; newly developed	250 (87)
	Brain metastases; locally recurrent	218 (76)
	High grade brain tumors (WHO grade 3–4)	215 (75)
	Meningioma; any grade	112 (39)
	Low grade brain tumors (WHO Grad 1–2)	107 (37)
	Other	15 (5)
Head and neck *(n = 234)*	Lymph node recurrence	203 (87)
	Oropharyngeal cancer; locally recurrent	178 (76)
	Nasopharyngeal cancer; locally recurrent	176 (75)
	Oral cavity cancer; locally recurrent	157 (67)
	Laryngeal cancer; locally recurrent	136 (58)
	Other	15 (6)
Thorax *(n = 221)*	Lung cancer; locally recurrent	190 (86)
	Lymph node recurrence	175 (79)
	Lung/pleural metastases	157 (71)
	Esophageal cancer; locally recurrent	73 (33)
	Mesothelioma; locally recurrent	48 (22)
	Other	6 (3)
Breast/chest wall *(n = 187)*	Breast cancer; locally recurrent after mastectomy	176 (94)
	Lymph node recurrence	153 (82)
	Breast cancer; locally recurrent after breast conserving surgery	151 (81)
	Other	4 (2)
Abdomen *(n = 146)*	Lymph node recurrence	133 (91)
	Liver metastases	94 (64)
	Adrenal metastases	74 (51)
	Pancreas cancer; locally recurrent	63 (43)
	Liver or bile duct cancer; locally recurrent	51 (35)
	Gastric cancer; locally recurrent	27 (18)
	Other	7 (5)
Pelvis *(n = 238)*	Lymph node recurrence	201 (84)
	Prostate cancer; locally recurrent	163 (68)
	Rectal cancer; locally recurrent	161 (68)
	Cervical cancer; locally recurrent	152 (64)
	Endometrial cancer; locally recurrent	115 (48)
	Anal cancer; locally recurrent	107 (45)
	Other	4 (2)

resectable nasopharyngeal cancer. Notably, 5% of patients in the surgery arm and 20% in the re-irradiation arm died due to late toxic effects specific to radiotherapy. A subsequent randomized phase 3 trial investigated whether hyperfractionated IMRT could reduce severe late

Table 2
Conditions precluding re-irradiation by anatomical region. (Question 6: Which patient conditions preclude re-irradiation? [multiple choice]).

	Brain *(n = 282)* n (%)	**Head and neck** *(n = 233)* n (%)	**Thorax** *(n = 220)* n (%)	**Breast/chest wall** *(n = 188)* n (%)	**Abdomen** *(n = 145)* n (%)	**Pelvis** *(n = 237)* n (%)
Persistent grade 3 or greater radiation-induced toxicity	225 (80)	180 (77)	169 (77)	151 (80)	115 (79)	190 (80)
An ECOG performance status of > 2	185 (66)	157 (67)	144 (65)	112 (60)	88 (61)	146 (62)
Less than 6 months since previous radiotherapy	175 (62)	177 (76)	125 (57)	132 (70)	95 (66)	154 (65)
Progressive disease as best response to previous radiotherapy	171 (61)	138 (59)	124 (56)	102 (54)	76 (52)	127 (54)
Estimated survival < 6 months	120 (43)	124 (53)	103 (47)	100 (53)	84 (58)	122 (51)
Other	11 (4)	7 (3)	4 (2)	3 (2)	3 (2)	2 (1)
None	7 (2)	7 (3)	9 (4)	9 (5)	8 (6)	14 (6)

Table 3
Minimum interval since previous radiotherapy after which re-irradiation is considered. (Question 5: Which is the minimum interval after which you would consider re-irradiation? [single choice]).

	Brain *(n = 282)* n (%)	**Head and neck** *(n = 234)* n (%)	**Thorax** *(n = 221)* n (%)	**Breast/chest wall** *(n = 187)* n (%)	**Abdomen** *(n = 145)* n (%)	**Pelvis** *(n = 236)* n (%)
6–12 months	156 (55)	124 (53)	115 (52)	84 (45)	71 (49)	108 (46)
3–6 months	62 (22)	30 (13)	52 (24)	23 (12)	33 (23)	43 (18)
>12 months	46 (16)	64 (27)	26 (12)	63 (34)	26 (18)	59 (25)
No minimum interval	17 (6)	12 (5)	19 (9)	16 (9)	14 (10)	24 (10)
<3 months	1 (0)	4 (2)	9 (4)	1 (1)	1 (1)	2 (1)

complications and thus improve overall survival in inoperable recurrent nasopharyngeal cancer patients [17]. Hyperfractionated re-irradiation significantly reduced high-grade late toxicities and improved overall survival, supporting the radiobiological assumptions of the hyperfractionated regimen, i.e. equal tumoricidal effects but decreased late effects. A randomized controlled phase 2 trial compared bevacizumab alone to bevacizumab with re-irradiation for recurrent glioblastoma, finding a clinically meaningful improvement of progression-free survival, but no improvement in overall survival. No differences in severe toxicities were reported, but data on lower grade toxicities are lacking. However, for the majority of tumor types that are common indications for re-irradiation according to our survey - e.g., prostate, rectal, cervical or non-small cell lung cancer - no randomized clinical trials exist. These findings emphasize the necessity for collaborative, interdisciplinary efforts to conduct randomized controlled trials determining the role of re-

Table 4
Therapeutic goals for re-irradiation by anatomical region. (Question 4: What are therapeutic goals for re-irradiation? [multiple choice]).

	Brain *(n = 283)* n (%)	**Head and neck** *(n = 234)* n (%)	**Thorax** *(n = 221)* n (%)	**Breast/ chest wall** *(n = 188)* n (%)	**Abdomen** *(n = 145)* n (%)	**Pelvis** *(n = 238)* n (%)
Prolong local control	256 (90)	224 (96)	198 (90)	181 (96)	136 (93)	214 (90)
Alleviate symptoms	166 (59)	124 (53)	153 (69)	107 (57)	97 (66)	163 (68)
Prevent symptoms	158 (56)	123 (53)	132 (60)	104 (55)	89 (61)	157 (66)
Prolong survival	134 (47)	139 (59)	126 (57)	105 (56)	72 (49)	137 (58)
Avoiding or delaying time to other treatment	126 (45)	72 (31)	100 (45)	64 (34)	58 (40)	91 (38)
Achieve tumor shrinkage to facilitate surgery	30 (11)	27 (12)	26 (12)	42 (22)	31 (21)	56 (24)
Other	1 (0)	2 (1)	1 (0)	2 (1)	1 (1)	2 (1)

Table 5
Availability of institutional guidelines or recommendations on re-irradiation as reported by the participants of the survey according to anatomical region, and published guidelines. (Question 15: Do you have institutional guidelines and/or recommendations for re-irradiation? [single choice]).

Region	**Guidelines/ recommendations available n(%)**	**Guidelines published**	
		before the survey was conducted	***after the survey was conducted***
Brain (n=283)	48 (17)	[14]	
Head and neck (n=234)	43 (18)	[7]	
Thorax (n=218)	39 (18)	[8]	
Breast/chest wall (n=187)	36 (19)	[15]	
Abdomen (n=145)	23 (16)		
Pelvis (n=234)	37 (16)	[9–11]	[12]
General			[1]

irradiation for various tumor types, comparing it to state-of-the-art surgical treatments or novel systemic therapies, or in combination with radiosensitizing agents, and assessing different fractionation schemes. In the absence of randomized controlled trials and high level evidence, expert consensus documents and guidelines on re-irradiation (see Table 2) may be helpful to guide treatment decision making. While some participants in our survey reported use of the published guidelines, we cannot determine if others were not aware of them or disagreed with the expert opinions, which are mostly based on.

Defining safe dose constraints for previously irradiated organs is a central challenge of re-irradiation. Severe toxicities could outweigh survival benefits, but treatment failure may be disastrous if patients lack further treatment options. In some instances, less stringent dose constraints could be adopted for less critical organs to avoid salvage failure from insufficient dosage.

Evidence suggests tissue recovery in the central nervous system [18,19]. The guideline by Ng et al. for nasopharyngeal cancer re-irradiation with IMRT suggests cumulative dose constraints for the brainstem, spinal cord, temporal lobe and optic nerve, assuming partial recovery from the initial radiation therapy course, assuming partial recovery, but acknowledging moderate supporting evidence [7]. The recovery capacity of the central nervous system is fairly well recognized and utilized in clinical practice. However, the thoracic re-irradiation guideline by Rulach et al. revealed uncertainties about thoracic organ at risk recovery [8]. The authors compared their suggested cumulative dose constraints with other recently published (one only in abstract form) expert recommendations [20–22]. The pelvic re-irradiation guideline by Slevin et al. recommended cumulative dose constraints for bladder and cauda equina/spinal cord, with no consensus for colon, sigmoid, and rectum [9]. The prostate re-irradiation guidelines by Jereczek-Fossa et al. achieved significant agreement but no consensus for cumulative rectum and bladder dose constraints [10].

The radiobiological understanding of tissue recovery from radiation damage is derived to a large degree from animal experiments. For example, experiments in non-human primates, guinea pigs and rats indicated a substantial recovery of the spinal cord [23–26]. On the other hand, experiments in pigs and mice showed no long-term recovery of the kidneys [27,28]. A comprehensive review on normal tissue recovery and tolerance to re-irradiation, including studies in humans and animal models, has been published by Nieder and Langendijk [29]. Further studies are needed to determine the possible extent and influence factors on recovery from radiation damage - particularly for non-central nervous system tissues.

Practices incorporating radiobiological considerations in cumulative dose assessments are varied, with a minority reporting to use 3D radiobiologically corrected dose distributions. Despite published work on technical solutions and workflows for re-irradiation planning [21,30], a lack of clinical software solutions might contribute to the diverse practices observed in our survey. It is crucial to integrate re-irradiation tools into commercial planning systems to maintain standards [31]. Modern conformal techniques are commonly used in re-irradiation, aiding in balancing dose escalation and optimal organ protection. High-dose-per-fraction techniques, like SBRT, with their steep dose fall-off and favorable late-toxicity profile, warrant safety profile exploration.

Several limitations must be acknowledged when interpreting this study's results. Our survey was disseminated through various professional societies and shared on social media platforms to reach a broad spectrum of professionals in radiation and clinical oncology. Consequently, an accurate overall response rate cannot be determined. However, we have provided internal response rates for each specific anatomical region to offer insight into the received responses. Despite the absence of an overall response rate, we believe our study presents valuable insights, being the first to assess re-irradiation in clinical practice internationally. We did not ask participants to report annual patient figures or proportions of patients treated with re-irradiation. Based on the proportion of participants reporting re-irradiation in different anatomical regions, we may deduce the most common indications. It was, however, our deliberate choice not to ask for concrete patient figures, as these are notoriously hard to come by and thus potentially unreliable. Such data will be collected in the ReCare study - a prospective, observational cohort on high-dose re-irradiation in the E^2-RADIatE platform (NCT03818503). As our survey did not specifically focus on high-dose re-irradiation, respondents may have reported their practice for lower dose, palliative re-irradiation, which may differ from the former scenario. Notably, participation in the survey is biased towards Europe, with very few participants from Africa (and none from sub-Saharan Africa) and South America. The patterns of care in low-and-middle-income countries might likely differ significantly due to limitations of modern equipment and trained personnel [32].

Conclusion

Our survey reveals varied international re-irradiation practices, likely due to a lack of high-quality, prospective outcome data guiding clinical decisions. Addressing this requires interdisciplinary collaboration to evaluate re-irradiation across different tumor types, using various fractionation schemes and in comparison or combination with alternative therapies, ideally performed through randomized clinical trials. Studying tissue recovery from irradiation, particularly in organs outside the central nervous system, and developing re-irradiation specific dose constraints should be research priorities. These efforts, fundamental to optimizing re-irradiation and patient outcomes, will be tackled in the ReCare study.

CRediT authorship contribution statement

Jonas Willmann: Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **L. Appelt:** Conceptualization, Writing – review & editing. **Panagiotis Balermpas:** Conceptualization, Writing – review & editing. **G. Baumert:** Conceptualization, Writing – review & editing. **Dirk de Ruysscher:** Conceptualization, Writing – review & editing. **Morten Hoyer:** Conceptualization, Writing – review & editing. **Coen Hurkmans:** Conceptualization, Writing – review & editing. **Orit Kaidar-Person:** Conceptualization, Writing – review & editing. **Icro Meattini:** Conceptualization, Writing – review & editing. **Maximilian Niyazi:** Conceptualization, Writing – review & editing. **Philip Poortmans:** Conceptualization, Writing – review & editing. **Nick Reynaert:** Conceptualization, Writing – review & editing. **Stephanie Tandini-Lang:** Writing – review & editing. **Yvette van der Linden:** Conceptualization, Writing – review & editing. **Carsten Nieder:** Conceptualization, Writing – review & editing. **Nicolaus Andratschke:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [AA reports Institutional Research Collaboration Agreement between Leeds Teaching Hospitals NHS Trust and RaySearch Laboratories, which includes software development for re-irradiation as a specific area of collaboration. BGB is a member of the trial steering committee of the BRIOChe trial (Brain Re-Irradiation Or Chemotherapy: a phase II trial of re-irradiation or chemotherapy for recurrent glioblastoma). IM received honoraria for occasional attendance at advisory boards supported by Eli Lilly, Novartis, Pfizer, SeaGen, Gilead, Accuray. NA reports grants or contracts from ViewRay Inc., University of Zurich CRPP, Swiss National Fund, SAKK, EORTC, GHG, ESTRO, SRO, Swiss Cancer League, consulting fees from Brainlab AG, ViewRay Inc., AstraZeneca, honoraria from ViewRay Inc., AstraZeneca, participation on a Data Safety Monitoring Board or Advisory Board from AstraZeneca, leadership or fiduciary role in other boards, societies, committees in EORTC, GHG, SAKK, SRO. DR reports institutional financial interests (no personal financial interests) in the form of research grant/support/advisory board from AstraZeneca, BMS, Beigene, Philips, Olink, Eli-Lilly. All other authors report no conflicts of interest.].

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Appendix A. Supplementary material

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