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Re-irradiation in clinical practice: results of an international patterns of care survey within the framework of the ESTRO-EORTC E²-RADIatE platform

Short title: International patterns of care of re-irradiation

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Key words
Re-irradiation, patterns of care, survey

Highlights

- First international survey on the patterns of care of re-irradiation.
- Re-irradiation is predominantly employed in the brain, pelvis, and head and neck region.
- Variable decision-making regarding minimum interval, contraindications and dose constraints.
- Advanced radiation techniques and imaging are used, but dose accumulation methods diverge.
- Prospective studies are needed to support evidence-based re-irradiation.

Abstract

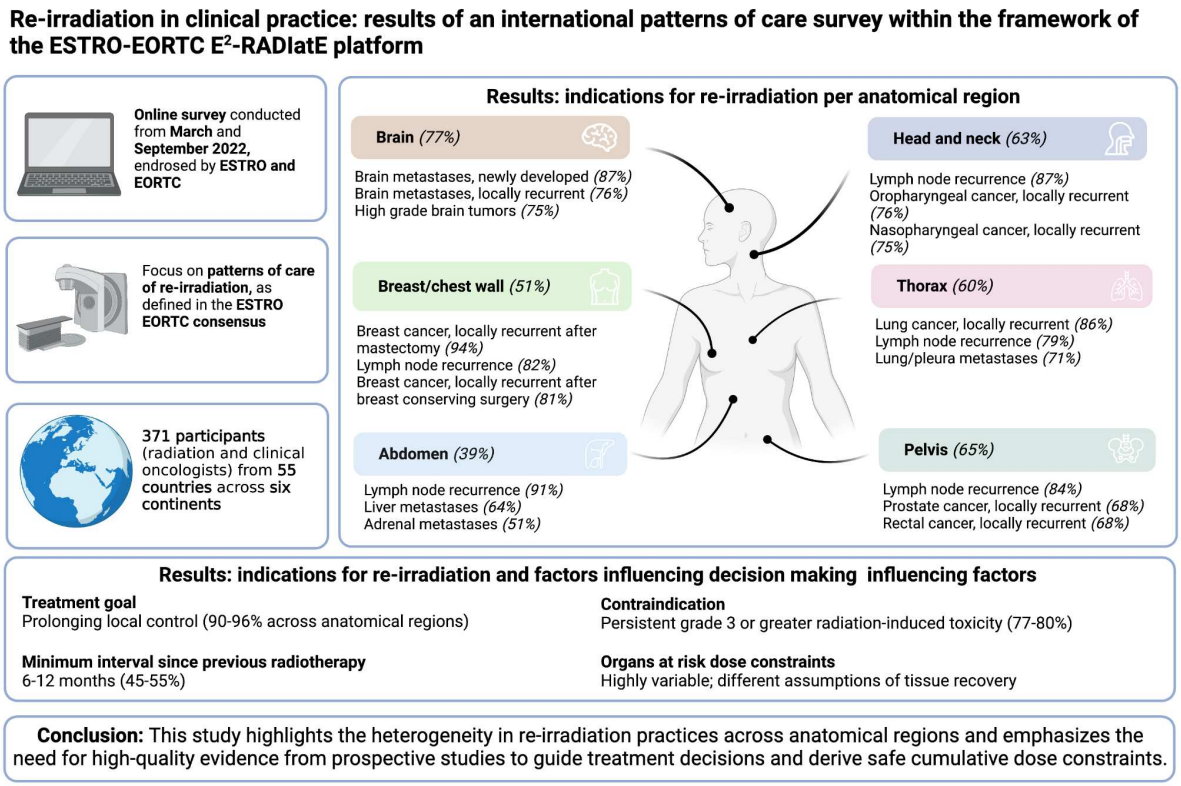
Background: Re-irradiation is an increasingly utilized treatment for recurrent, metastatic or new malignancies after previous radiotherapy. It is unclear how re-irradiation is applied in clinical practice. We aimed to investigate the patterns of care of re-irradiation internationally.

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 (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.

Graphical abstract



Introduction

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 E²-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) (Figure 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 4, 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 on nasopharyngeal cancer have recently shaped the role of re-irradiation for recurrent nasopharyngeal cancer (NPC) after radiotherapy. A randomized phase 2 trial compared intensity-modulated radiotherapy (IMRT) re-irradiation to salvage endoscopic nasopharyngectomy in resectable recurrent NPC [16]. Surgery significantly improved the 3-year overall survival, indicating the standard for resectable NPC. 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 complications and thus improve overall survival in inoperable recurrent NPC 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-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 NPC 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 upcoming ReCare study.

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Conflicts of interest

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.

References

[1] Andratschke N, Willmann J, Appelt AL, Alyamani N, Balermpas P, Baumert BG, et al. 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. Lancet Oncol 2022;23:e469–78.

[2] Jereczek-Fossa BA, Kowalczyk A, D'Onofrio A, Catalano G, Garibaldi C, Boboc G, et al. Three-Dimensional Conformal or Stereotactic Reirradiation of Recurrent, Metastatic or New Primary Tumors. Strahlenther Onkol 2008;184:36–40.

[3] Huisman M, van den Bosch MAAJ, Wijlemans JW, van Vulpen M, van der Linden YM, Verkooijen HM. Effectiveness of reirradiation for painful bone metastases: a systematic review and meta-analysis. Int J Radiat Oncol Biol Phys 2012;84:8–14.

[4] Griffioen GHMJ, Dahele M, de Haan PF, van de Ven PM, Slotman BJ, Senan S. High-dose, conventionally fractionated thoracic reirradiation for lung tumors. Lung Cancer 2014;83:356–62.

[5] Schröder C, Stiefel I, Tanadini-Lang S, Pytko I, Vu E, Guckenberger M, et al. Re-irradiation in the thorax - An analysis of efficacy and safety based on accumulated EQD2 doses. Radiother Oncol

2020;152:56–62.
[6] Stiefel I, Schröder C, Tanadini-Lang S, Pytko I, Vu E, Klement RJ, et al. High-dose re-irradiation of intracranial lesions – Efficacy and safety including dosimetric analysis based on accumulated EQD2Gy dose calculation. Clinical and Translational Radiation Oncology 2021;27:132–8. https://doi.org/10.1016/j.ctro.2021.01.011.
[7] Ng WT, Soong YL, Ahn YC, AlHussain H, Choi HCW, Corry J, et al. International recommendations on re-irradiation by intensity-modulated radiotherapy for locally recurrent nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2021.
[8] Rulach R, Ball D, Chua KLM, Dahele M, De Ruysscher D, Franks K, et al. An International Expert Survey on the Indications and Practice of Radical Thoracic Reirradiation for Non-Small Cell Lung Cancer. Adv Radiat Oncol 2021;6:100653.
[9] Slevin F, Aitken K, Alongi F, Arcangeli S, Chadwick E, Chang AR, et al. An international Delphi consensus for pelvic stereotactic ablative radiotherapy re-irradiation. Radiother Oncol 2021;164:104–14.
[10] Jereczek-Fossa BA, Marvaso G, Zaffaroni M, Gugliandolo SG, Zerini D, Corso F, et al. Salvage stereotactic body radiotherapy (SBRT) for intraprostatic relapse after prostate cancer radiotherapy: An ESTRO ACROP Delphi consensus. Cancer Treat Rev 2021;98:102206.
[11] Kaljouw E, Pieters BR, Kovács G, Hoskin PJ. A Delphi consensus study on salvage brachytherapy for prostate cancer relapse after radiotherapy, a Uro-GEC study. Radiother Oncol 2016;118:122–30.
[12] Corkum MT, Buyyounouski MK, Chang AJ, Chung HT, Chung P, Cox BW, et al. Salvage Prostate Brachytherapy in Radiorecurrent Prostate Cancer: An International Delphi Consensus Study. Radiother Oncol 2023:109672.
[13] Sharma A, Minh Duc NT, Luu Lam Thang T, Nam NH, Ng SJ, Abbas KS, et al. A Consensus-Based Checklist for Reporting of Survey Studies (CROSS). J Gen Intern Med 2021;36:3179–87.
[14] Ryu S, Buatti JM, Morris A, Kalkanis SN, Ryken TC, Olson JJ. The role of radiotherapy in the management of progressive glioblastoma. J Neurooncol 2014;118:489–99.
[15] Harms W, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, et al. DEGRO practical guidelines for radiotherapy of breast cancer VI: therapy of locoregional breast cancer recurrences. Strahlenther Onkol 2016;192:199–208.
[16] Liu Y-P, Wen Y-H, Tang J, Wei Y, You R, Zhu X-L, et al. Endoscopic surgery compared with intensity-modulated radiotherapy in resectable locally recurrent nasopharyngeal carcinoma: a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet Oncol 2021;22:381–90.
[17] You R, Liu Y-P, Xie Y-L, Lin C, Duan C-Y, Chen D-P, et al. Hyperfractionation compared with standard fractionation in intensity-modulated radiotherapy for patients with locally advanced recurrent nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. Lancet 2023.
[18] Sminia P, Mayer R. External beam radiotherapy of recurrent glioma: radiation tolerance of the human brain. Cancers 2012;4:379–99.
[19] Nieder C, Grosu AL, Andratschke NH, Molls M. Update of human spinal cord reirradiation tolerance based on additional data from 38 patients. Int J Radiat Oncol Biol Phys 2006;66:1446–9.
[20] Simone C, Amini A, Chetty I, Choi JI, Chun S, Donington J, et al. American Radium Society (ARS) and American College of Radiology (ACR) appropriate use criteria systematic review and guidelines on reirradiation for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 2020;108:E48–9.
[21] Paradis KC, Mayo C, Owen D, Spratt DE, Hearn J, Rosen B, et al. The Special Medical Physics Consult Process for Reirradiation Patients. Adv Radiat Oncol 2019;4:559–65.
[22] Troost EGC, Wink KCJ, Roelofs E, Simone CB 2nd, Makocki S, Löck S, et al. Photons or protons for reirradiation in (non-)small cell lung cancer: Results of the multicentric ROCOCO in silico study. Br J Radiol 2020;93:20190879.
[23] Ang KK, van der Kogel AJ, Van Dam J, van der Schueren E. The kinetics of repair of sublethal damage in the rat cervical spinal cord during fractionated irradiations. Radiother Oncol 1984;1:247–53.
[24] Mason KA, Withers HR, Chiang CS. Late effects of radiation on the lumbar spinal cord of guinea pigs: re-treatment tolerance. Int J Radiat Oncol Biol Phys 1993;26:643–8.
[25] Ang KK, Price RE, Stephens LC, Jiang GL, Feng Y, Schultheiss TE, et al. The tolerance of primate spinal cord to re-irradiation. Int J Radiat Oncol Biol Phys 1993;25:459–64.
[26] Ang KK, Jiang GL, Feng Y, Stephens LC, Tucker SL, Price RE. Extent and kinetics of recovery of occult spinal cord injury. Int J Radiat Oncol Biol Phys 2001;50:1013–20.

[27] Robbins ME, Bywaters T, Rezvani M, Golding SJ, Hopewell JW. Residual radiation-induced damage to the kidney of the pig as assayed by retreatment. Int J Radiat Biol 1991;60:917–28.
[28] Stewart FA, Lebesque JV, Hart AA. Progressive development of radiation damage in mouse kidneys and the consequences for reirradiation tolerance. Int J Radiat Biol Relat Stud Phys Chem Med 1988;53:405–15.
[29] Nieder C, Langendijk JA. Normal Tissue Tolerance to Reirradiation. Re-Irradiation: New Frontiers 2010:1–12.
[30] Murray L, Thompson C, Pagett C, Lilley J, Al-Qaisieh B, Svensson S, et al. Treatment plan optimisation for reirradiation. Radiother Oncol 2023;182:109545.
[31] Vasquez Osorio E, Mayo C, Jackson A, Appelt A. Challenges of re-irradiation: A call to arms for physicists - and radiotherapy vendors. Radiother Oncol 2023;182:109585.
[32] Christ SM, Willmann J. Measuring Global Inequity in Radiation Therapy: Resource Deficits in Low- and Middle-Income Countries Without Radiation Therapy Facilities. Adv Radiat Oncol 2023;8:101175.

Tables

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)

Table 2

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

	Brain *(n=282)*	**Head and neck** *(n=233)*	**Thorax** *(n=220)*	**Breast/chest wall** *(n=188)*	**Abdomen** *(n=145)*	**Pelvis** *(n=237)*
	n (%)	n (%)	n (%)	n (%)	n (%)	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)*	**Head and neck** *(n=234)*	**Thorax** *(n=221)*	**Breast/chest wall** *(n=187)*	**Abdomen** *(n=145)*	**Pelvis** *(n=236)*
	n (%)	n (%)	n (%)	n (%)	n (%)	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)

Table 4

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

	Brain *(n=283)*	**Head and neck** *(n=234)*	**Thorax** *(n=221)*	**Breast/chest wall** *(n=188)*	**Abdomen** *(n=145)*	**Pelvis** *(n=238)*
	n (%)	n (%)	n (%)	n (%)	n (%)	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**	**Guidelines published**	
	n (%)	***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]

Figures

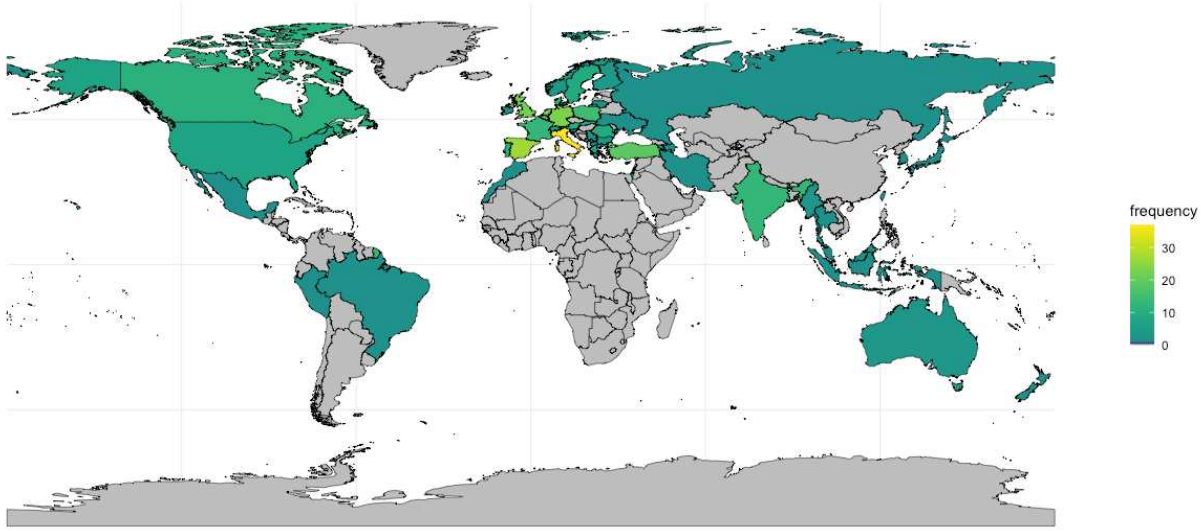

Figure 1

Number of participants per country.

Supplementary material

Questionnaire

Abbreviation: Q: question

General questions

- QI: Which country is your department in?
- QII: How many years of clinical experience in radiation oncology do you have?
- QIII: What kind of department are you employed at? (multiple choice)
    - Public hospital, University hospital*, Private center, Other

** all participants whose response included University hospital were categorized as "academic practice"*

Re-irradiation questions (divided in 6 sections: brain, head and neck, thorax, breast/chest wall, abdomen, pelvis)

- Q1: Do you treat patients with re-irradiation in the brain/head and neck region/thorax, breast or chest wall/abdomen/pelvis? (single choice)
    - All: Yes, no
- Q2: Which tumors do you treat with re-irradiation? (multiple choice)
    - Brain: Meningioma, any grade; Low grade brain tumors (WHO grade 1-2); High grade brain tumors (WHO grade 3-4); Brain metastases, locally recurrent; Brain metastases, newly developed; Other
    - Head and neck: Oral cavity cancer, locally recurrent; Nasopharyngeal cancer, locally recurrent; Oropharyngeal cancer, locally recurrent; Laryngeal cancer, locally recurrent; Lymph node recurrence; Other
    - Thorax: Lung cancer, locally recurrent; Esophageal cancer, locally recurrent; Mesothelioma, locally recurrent; Lymph node recurrence; Lung/pleural metastases; Other
    - Breast/chest wall: Breast cancer, locally recurrent after breast conserving surgery; Breast cancer, locally recurrent after mastectomy; Lymph node recurrence; Other
    - Abdomen: Gastric cancer, locally recurrent; Liver or bile duct cancer, locally recurrent; Pancreas cancer, locally recurrent; Liver metastases; Adrenal metastases; Lymph node recurrence; Other
    - Pelvis: Prostate cancer, locally recurrent; Rectal cancer, locally recurrent; Cervical cancer, locally recurrent; Anal cancer, locally recurrent; Endometrial cancer, locally recurrent; Lymph node recurrence; Other
- Q3: Do you treat tumors with re-irradiation in the postoperative setting? (single choice)
    - Brain: After incomplete resection; After complete resection; Never; Other
    - Head and neck: Extracapsular extension (ECE), irrespective of resection status; R1/2 resection status or extracapsular extension (ECE); Only R1 or R2 resection status,

irrespective of extracapsular extension (ECE); Only R2 resection status, irrespective of extracapsular extension (ECE; Never; Other
    - Thorax, Breast/chest wall, abdomen, pelvis: R1 and R2 resection status; Only R2 resection status; Only R2 resection status; Other
- Q4: What are therapeutic goals for re-irradiation? (multiple choice)
    - All: Prolong survival; Prolong local control; Prevent symptoms; Alleviate symptoms; Achieve tumor shrinkage to facilitate surgery; Avoiding or delaying time to other treatment; Other
- Q5: Which is the minimum interval after which you would consider re-irradiation? (single choice)
    - All: No minimum interval; < 3 months; 3 - 6 months; 6 - 12 months; >12 months
- Q6: Which patient conditions preclude re-irradiation? (multiple choice)
    - All: None; An ECOG performance status of >2; Estimated survival <6 months; Persistent grade 3 or greater radiation-induced toxicity; Less than 6 months since previous radiotherapy; Progressive disease as best response to previous radiotherapy; Other
- Q7: Which imaging modalities do you usually co-register? (multiple choice)
    - All: CT of the initial treatment; MRI of initial treatment; PET of initial treatment; CT of recurrence; MRI of recurrence; PET of recurrence; Other
- Q8: Which type of image co-registration do you usually apply? (multiple choice)
    - All: Rigid image registration; Non-rigid image registration
- Q9: What do you usually include in the target volume for re-irradiation? (multiple choice)
    - Brain: GTV including visible tumor, no CT; CTV based on isotropic expansion of GTV; CTV based on GTV expansion, adjusted to anatomical boundaries; Other
    - Head and neck. Thorax, Breast/Chest wall, Abdomen, Pelvis: GTV including visible tumor, no CTV; CTV based on isotropic expansion of GTV; CTV based on GTV expansion, adjusted to anatomical boundaries; CTV including affected lymph node levels; CTV including elective lymph node levels; Other
- Q10: Which type of dose summation do you usually calculate? (multiple choice)
    - All: None; Numerical sum of prescription doses without using treatment plans; Transfer of isodose lines; Overlay of physical dose distributions; Evaluation of dose to specific points, with EQD2 summation: Evaluation of dose to specific points, with BED summation; 3D dose summation in EQD2; 3D dose summation in BED; Other
- Q11: If organs at risk (OAR) dose constraints from primary irradiation are challenging to meet when planning re-irradiation, how do you proceed? (single choice)
    - Brain: optic chiasm; cochlea: spinal cord/brain stem; brain (Options: Keep cumulative equi-effective dose below accepted OAR constraints for a single course of irradiation; Allow higher cumulative equi-effective doses to OAR by assuming partial recovery of previously given dose; Use no dose constraints at all*; Other*)
    - Head and neck: salivary glands; mandible; cartilage; spinal cord/brain stem (Options: Keep cumulative equi-effective dose below accepted OAR constraints for a single

course of irradiation; Allow higher cumulative equi-effective doses to OAR by assuming partial recovery of previously given dose; Use no dose constraints at all*; Other*)

- Lung: lungs; esophagus; bronchial tree; chest wall, spinal cord; heart (Options: Keep cumulative equi-effective dose below accepted OAR constraints for a single course of irradiation**; Same dose constraints, compromise PTV coverage**; Allow higher cumulative equi-effective doses to OAR by assuming partial recovery of previously given dose; Other*)
- Breast/chest wall: lungs; heart (Options: Keep cumulative equi-effective dose below accepted OAR constraints for a single course of irradiation**; Same dose constraints, compromise PTV coverage**; Allow higher cumulative equi-effective doses to OAR by assuming partial recovery of previously given dose; Other*)
- Abdomen: bowel; liver; kidney; stomach (Options: Keep cumulative equi-effective dose below accepted OAR constraints for a single course of irradiation; Allow higher cumulative equi-effective doses to OAR by assuming partial recovery of previously given dose; Use no dose constraints at all*; Other*)
- Pelvis: bowel; sigmoid; rectum; bladder (Options: Keep cumulative equi-effective dose below accepted OAR constraints for a single course of irradiation; Allow higher cumulative equi-effective doses to OAR by assuming partial recovery of previously given dose; Use no dose constraints at all*; Other*)

** for analyses, combined to "other/no constraints"*

*** for analyses, combined to "same constraints/no recovery"*

- Q12: Which treatment techniques do you apply for re-irradiation? (multiple choice)
  - Brain: Three-dimensional conformal radiation therapy (3D-CRT); Intensity-modulated radiotherapy (IMRT); Volumetric-modulated arc therapy (VMAT); Stereotactic radiotherapy or radiosurgery (SRT/SRS); Particle therapy; Other
  - Head and neck: Three-dimensional conformal radiation therapy (3D-CRT); Intensity-modulated radiotherapy (IMRT); Volumetric-modulated arc therapy (VMAT); Stereotactic body radiotherapy (SBRT); Particle therapy; Brachytherapy; Other
  - Thorax; Breast/chest wall; Abdomen; Pelvis: Three-dimensional conformal radiation therapy (3D-CRT); Intensity-modulated radiotherapy (IMRT); Volumetric-modulated arc therapy (VMAT); Stereotactic body radiotherapy (SBRT); Particle therapy; Brachytherapy; Hyperthermia; Other
- Q13: Which type of patient setup and target verification do you apply? (multiple choice)
  - All: Portal imaging; Stereoscopic kV imaging; Conebeam computed tomography; Magnetic resonance imaging guidance; Surface guidance; Other
- Q14: After re-irradiation, how are patients followed up? (single choice)
  - All: Regular oncological follow-up as indicated, patient seen primarily by radiation oncologist; Regular oncological follow-up as indicated, patient seen primarily by other specialist; Re-irradiation specific follow-up; Other

- Q15: Do you have institutional guidelines and/or recommendations for re-irradiation? (single choice)
    - All: Yes, no
- Additionally, free text comments could be added to questions

eTable 1

Indications for postoperative re-irradiation. Blank rows indicate that the option was not available for the respective anatomical region. (Question 3)

	Brain *(n=281)*	**Head and neck** *(n=233)*	**Thorax** *(n=220)*	**Breast/chest wall** *(n=185)*	**Abdomen** *(n=143)*	**Pelvis** *(n=235)*
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
After incomplete resection	237 (84)					
After complete resection	82 (29)					
R1/2 resection status or extracapsular extension (ECE)		120 (51)				
Only R1 or R2 resection status; irrespective of extracapsular extension (ECE)		56 (24)				
Only R2 resection status; irrespective of extracapsular extension (ECE)		52 (22)				
Extracapsular extension (ECE); irrespective of resection status		45 (19)				
R1 and R2 resection status			78 (35)	107 (58)	54 (38)	103 (44)
Only R2 resection status			77 (35)	49 (26)	47 (33)	80 (34)

Never	32 (11)	28 (12)	74 (34)	19 (10)	46 (32)	63 (27)
Other	11 (4)	10 (4)	8 (4)	43 (23)	7 (5)	8 (3)

eTable 2

Re-irradiation organ at risk dose constraints and tissue recovery from previous irradiation. By assuming partial tissue recovery a higher cumulative dose across both treatment courses may be allowed compared to simply applying the same constraint used at initial radiotherapy across both the initial and re-irradiation courses. The constraint used at initial radiotherapy may be used cumulatively (i.e. across both courses) if no recovery is included. Other strategies may include not applying any dose constraints. (Question 11)

	Brain					**Head and neck**		
	Chiasm *(n=278)*	**Cochlea** *(n=272)*	**Brain** *(n=278)*	**Brainstem/spinal cord** *(n=282)*	**Salivary glands** *(n=228)*	**Mandible** *(n=228)*	**Cartilage** *(n=223)*	**Brainstem/spinal cord** *(n=231)*
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Same constraints/no recovery	147 (53)	123 (45)	53 (19)	122 (43)	31 (14)	67 (29)	51 (23)	106 (46)
Higher constraints/partial recovery	126 (45)	63 (23)	189 (68)	158 (56)	113 (50)	121 (53)	111 (50)	124 (54)
Other/no constraints	5 (2)	86 (32)	36 (13)	2 (1)	84 (37)	40 (18)	61 (27)	1 (0)

	Thorax					**Breast/chest wall**		
	Lungs *(n=220)*	**Esophagus** *(n=218)*	**Bronchial tree** *(n=219)*	**Spinal cord** *(n=220)*	**Heart** *(n=219)*	**Chest wall** *(n=217)*	**Lungs** *(n=184)*	**Heart** *(n=184)*

	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Same constraints/no recovery	105 (48)	126 (58)	117 (53)	113 (51)	134 (61)	81 (37)	97 (53)	120 (65)
Higher constraints/partial recovery	106 (48)	83 (38)	91 (42)	105 (48)	73 (33)	118 (54)	79 (43)	57 (31)
Other/no constraints	9 (4)	9 (4)	11 (5)	2 (1)	12 (5)	18 (8)	8 (4)	7 (4)

	Abdomen				**Pelvis**			
	Bowel *(n=144)*	**Liver** *(n=144)*	**Kidney** *(n=144)*	**Stomach** *(n=140)*	**Bowel** *(n=233)*	**Sigmoid** *(n=233)*	**Rectum** *(n=233)*	**Bladder** *(n=233)*
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Same constraints/no recovery	73 (51)	54 (38)	79 (55)	69 (49)	109 (47)	85 (36)	80 (34)	76 (33)
Higher constraints/partial recovery	66 (46)	81 (56)	58 (40)	66 (47)	112 (48)	129 (55)	137 (59)	138 (59)
Other/no constraints	5 (3)	9 (6)	7 (5)	5 (4)	12 (5)	19 (8)	16 (7)	19 (8)

eTable 3

Imaging modalities co-registered for re-irradiation treatment planning. (Question 8)

	Brain *(n=278)*	**Head and neck** *(n=226)*	**Thorax** (n=214)	**Breast/chest wall** (n=175)	**Abdomen** (n=138)	**Pelvis** (n=224)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Rigid image registration	215 (77)	161 (71)	151 (71)	123 (70)	94 (68)	157 (70)
Non-rigid image registration	93 (33)	96 (42)	92 (43)	71 (41)	64 (46)	101 (45)

eTable 4

Imaging modalities co-registered for re-irradiation treatment planning. (Question 7)

	Brain *(n=283)*	**Head and neck** *(n=235)*	**Thorax** *(n=219)*	**Breast/chest wall** *(n=184)*	**Abdomen** *(n=145)*	**Pelvis** *(n=236)*
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
MRI of recurrence	269 (95)	192 (82)	43 (20)	72 (39)	110 (76)	207 (88)
MRI of initial treatment	190 (67)	90 (38)	21 (10)	27 (15)	55 (38)	102 (43)
CT of recurrence	142 (50)	179 (76)	196 (89)	157 (85)	124 (86)	189 (80)
CT of initial treatment	122 (43)	138 (59)	153 (70)	123 (67)	89 (61)	136 (58)
PET of recurrence	86 (30)	179 (76)	191 (87)	93 (51)	127 (88)	194 (82)
PET of initial treatment	32 (11)	81 (34)	113 (52)	32 (17)	66 (46)	92 (39)
Other	2 (1)	4 (2)	2 (0)	6 (3)	0 (0)	3 (1)

eTable 5

Target volume definition for re-irradiation. Blank rows indicate that the option was not available for the respective anatomical region. (Question 9)

	Brain *(n=281)*	**Head and neck** *(n=232)*	**Thorax** (n=218)	**Breast/chest wall** (n=186)	**Abdomen** (n=145)	**Pelvis** (n=232)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
GTV including visible tumor; no CTV	171 (61)	76 (33)	89 (41)	44 (24)	72 (50)	95 (41)
CTV based on GTV expansion; adjusted to anatomical boundaries	128 (46)	148 (64)	118 (54)	118 (63)	68 (47)	139 (60)
CTV based on isotropic expansion of GTV	26 (9)	26 (11)	25 (11)	31 (17)	18 (12)	37 (16)
CTV including affected lymph node levels		88 (38)	61 (28)	84 (45)	28 (19)	66 (28)
CTV including elective lymph node levels		13 (6)	5 (2)	23 (12)	5 (3)	15 (6)
Other	4 (1)	5 (2)	1 (0)	5 (3)	2 (1)	0 (0)

eTable 6

Assessment of cumulative doses. (Question 10)

	Brain *(n=283)*	**Head and neck** *(n=234)*	**Thorax** (n=221)	**Breast/chest wall** (n=188)	**Abdomen** (n=145)	**Pelvis** (n=236)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Evaluation of dose to specific points; with EQD2 summation	147 (52)	125 (53)	117 (53)	92 (49)	83 (57)	126 (53)
3D dose summation in EQD2	126 (45)	101 (43)	100 (45)	87 (46)	74 (51)	122 (52)
Overlay of physical dose distributions	119 (42)	98 (42)	102 (46)	78 (41)	58 (40)	90 (38)
Transfer of isodose lines	98 (35)	72 (31)	77 (35)	55 (29)	52 (36)	72 (31)
Evaluation of dose to specific points; with BED summation	82 (29)	74 (32)	65 (29)	44 (23)	47 (32)	70 (30)
3D dose summation in BED	59 (21)	59 (25)	55 (25)	43 (23)	36 (25)	57 (24)
Numerical sum of prescription doses without using treatment plans	24 (8)	22 (9)	25 (11)	24 (13)	16 (11)	27 (11)

None	6 (2)	6 (3)	2 (1)	12 (6)	5 (3)	10 (4)
Other	4 (1)	4 (2)	0 (0)	2 (1)	0 (0)	1 (0)

eTable 7

Delivery of re-irradiation. Blank rows indicate that the option was not available for the respective anatomical region. (Question 12)

	Brain *(n=284)*	**Head and neck** *(n=235)*	**Thorax** *(n=221)*	**Breast/chest wall** *(n=189)*	**Abdomen** (n=147)	**Pelvis** (n=238)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Stereotactic radiotherapy or radiosurgery (SRT/SRS)	228 (80)					
Stereotactic body radiotherapy (SBRT)		122 (52)	176 (80)	63 (33)	116 (79)	153 (64)
Volumetric-modulated arc therapy (VMAT)	227 (80)	202 (86)	193 (87)	143 (76)	118 (80)	193 (81)
Intensity-modulated radiotherapy (IMRT)	102 (36)	104 (44)	103 (47)	106 (56)	57 (39)	101 (42)
Three-dimensional conformal radiotherapy (3D-CRT)	43 (15)	23 (10)	37 (17)	91 (48)	30 (20)	49 (21)
Particle therapy	24 (8)	22 (9)	12 (5)	7 (4)	8 (5)	14 (6)
Brachytherapy		36 (15)	19 (9)	39 (21)	9 (6)	69 (29)
Hyperthermia			6 (3)	15 (8)	6 (4)	10 (4)

Intraoperative radiotherapy (IORT)			5 (2)	15 (8)	9 (6)	14 (6)
Other	4 (1)	2 (1)	5 (2)	3 (2)	1 (1)	2 (1)

eTable 8

Setup and treatment verification. (Question 13)

	Brain *(n=282)*	**Head and neck** *(n=233)*	**Thorax** (n=218)	**Breast/chest wall** (n=187)	**Abdomen** (n=146)	**Pelvis** (n=234)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Conebeam computed tomography	250 (89)	214 (92)	201 (92)	155 (83)	132 (90)	211 (90)
Stereoscopic kV imaging	74 (26)	37 (16)	43 (20)	39 (21)	37 (25)	48 (21)
Surface guidance	57 (20)	34 (15)	43 (20)	53 (28)	31 (21)	37 (16)
Portal imaging	39 (14)	41 (18)	28 (13)	72 (39)	21 (14)	41 (18)
Magnetic resonance imaging guidance	10 (4)	8 (3)	12 (6)	3 (2)	16 (11)	26 (11)

Other	4 (1)	5 (2)	3 (1)	5 (3)	4 (3)	5 (2)

eTable 9

Follow-up procedures after re-irradiation. (Question 14)

	Brain *(n=283)*	**Head and neck** *(n=233)*	**Thorax** *(n=221)*	**Breast/chest wall** *(n=184)*	**Abdomen** *(n=145)*	**Pelvis** *(n=233)*
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Regular follow-up (primarily by radiation oncologist)	172 (61)	158 (68)	135 (61)	102 (55)	95 (66)	163 (70)
Regular follow-up (primarily by other specialist)	82 (29)	52 (22)	67 (30)	65 (35)	41 (28)	55 (24)
Re-irradiation-specific follow-up	23 (8)	19 (8)	14 (6)	11 (6)	9 (6)	13 (6)
Other	6 (2)	5 (2)	5 (2)	6 (3)	0 (0)	2 (1)

eTable 10

Pearson's Chi-squared test with Yates' continuity correction to test whether the location of practice (Europe versus other) had an impact on the anatomical regions treated with re-irradiation (Question 1). Significant p-values printed in bold.

	Chi-squared	Degrees of freedom	p-value
Brain	5,63E+05	1	0.453
Head and neck	1,04E-24	1	1
Thorax	4,70E+06	1	**0.030**
Breast/chest wall	7,88E+04	1	0.779
Abdomen	4,97E+06	1	**0.026**
Pelvis	2,01E+06	1	0.156

eTable 11

Pearson's Chi-squared test with Yates' continuity correction to test whether the type of institution (academic versus non-academic) had an impact on the anatomical regions treated with re-irradiation (Question 1).

	Chi-squared	Degrees of freedom	p-value
Brain	0.784	1	0.376
Head and neck	1.785	1	0.182
Thorax	0.261	1	0.609
Breast/chest wall	0.500	1	0.480
Abdomen	0	1	1
Pelvis	1.199	1	0.274

CROSS Checklist

Checklist for Reporting Of Survey Studies (CROSS) [13]

Section/topic	Item	Item description	
Title and abstract			
Title and abstract	1a	State the word “survey” along with a commonly used term in title or abstract to introduce the study’s design.	✓
	1b	Provide an informative summary in the abstract, covering background, objectives, methods, findings/results, interpretation/discussion, and conclusions.	✓
Introduction			
Background	2	Provide a background about the rationale of study, what has been previously done, and why this survey is needed.	✓
Purpose/aim	3	Identify specific purposes, aims, goals, or objectives of the study.	✓
Methods			

Study design	4	Specify the study design in the methods section with a commonly used term (e.g., cross-sectional or longitudinal).	✓
	5a	Describe the questionnaire (e.g., number of sections, number of questions, number and names of instruments used).	✓
Data collection methods	5b	Describe all questionnaire instruments that were used in the survey to measure particular concepts. Report target population, reported validity and reliability information, scoring/classification procedure, and reference links (if any).	✓
	5c	Provide information on pretesting of the questionnaire, if performed (in the article or in an online supplement). Report the method of pretesting, number of times questionnaire was pre-tested, number and demographics of participants used for pretesting, and the level of similarity of demographics between pre-testing participants and sample population.	NA
	5d	Questionnaire if possible, should be fully provided (in the article, or as appendices or as an online supplement).	✓
Sample characteristics	6a	Describe the study population (i.e., background, locations, eligibility criteria for participant inclusion in survey, exclusion criteria).	✓
	6b	Describe the sampling techniques used (e.g., single stage or multistage sampling, simple random sampling, stratified sampling, cluster sampling, convenience sampling). Specify the locations of sample participants whenever clustered sampling was applied.	NA

	6c	Provide information on sample size, along with details of sample size calculation.	✓
	6d	Describe how representative the sample is of the study population (or target population if possible), particularly for population-based surveys.	NA
Survey administration	7a	Provide information on modes of questionnaire administration, including the type and number of contacts, the location where the survey was conducted (e.g., outpatient room or by use of online tools, such as SurveyMonkey).	✓
	7b	Provide information of survey's time frame, such as periods of recruitment, exposure, and follow-up days.	✓
	7c	Provide information on the entry process: –>For non-web-based surveys, provide approaches to minimize human error in data entry. –>For web-based surveys, provide approaches to prevent "multiple participation" of participants.	NA
Study preparation	8	Describe any preparation process before conducting the survey (e.g., interviewers' training process, advertising the survey).	✓
Ethical considerations	9a	Provide information on ethical approval for the survey if obtained, including informed consent, institutional review board [IRB] approval, Helsinki declaration, and good clinical practice [GCP] declaration (as appropriate).	NA

	9b	Provide information about survey anonymity and confidentiality and describe what mechanisms were used to protect unauthorized access.	NA
Statistical analysis	10a	Describe statistical methods and analytical approach. Report the statistical software that was used for data analysis.	✓
	10b	Report any modification of variables used in the analysis, along with reference (if available).	✓
	10c	Report details about how missing data was handled. Include rate of missing items, missing data mechanism (i.e., missing completely at random [MCAR], missing at random [MAR] or missing not at random [MNAR]) and methods used to deal with missing data (e.g., multiple imputation).	NA
	10d	State how non-response error was addressed.	NA
	10e	For longitudinal surveys, state how loss to follow-up was addressed.	NA
	10f	Indicate whether any methods such as weighting of items or propensity scores have been used to adjust for non-representativeness of the sample.	NA
	10g	Describe any sensitivity analysis conducted.	NA

Results

Respondent characteristics	11a	Report numbers of individuals at each stage of the study. Consider using a flow diagram, if possible.	✓
	11b	Provide reasons for non-participation at each stage, if possible.	NA
	11c	Report response rate, present the definition of response rate or the formula used to calculate response rate.	✓
	11d	Provide information to define how unique visitors are determined. Report number of unique visitors along with relevant proportions (e.g., view proportion, participation proportion, completion proportion).	✓
Descriptive results	12	Provide characteristics of study participants, as well as information on potential confounders and assessed outcomes.	✓
Main findings	13a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates along with 95% confidence intervals and p-values.	✓
	13b	For multivariable analysis, provide information on the model building process, model fit statistics, and model assumptions (as appropriate).	NA

	13c	Provide details about any sensitivity analysis performed. If there are considerable amount of missing data, report sensitivity analyses comparing the results of complete cases with that of the imputed dataset (if possible).	NA
Discussion			
Limitations	14	Discuss the limitations of the study, considering sources of potential biases and imprecisions, such as non-representativeness of sample, study design, important uncontrolled confounders.	✓
Interpretations	15	Give a cautious overall interpretation of results, based on potential biases and imprecisions and suggest areas for future research.	✓
Generalizability	16	Discuss the external validity of the results.	✓
Other sections			
Role of funding source	17	State whether any funding organization has had any roles in the survey's design, implementation, and analysis.	NA
Conflict of interest	18	Declare any potential conflict of interest.	✓
Acknowledgements	19	Provide names of organizations/persons that are acknowledged along with their contribution to the research.	✓