Mini-Review | Palliative Medicine and Palliative Care for Incurable Cancer

Re-irradiation practice and ESTRO/EORTC consensus recommendations: 2023 ASTRO education panel

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Abstract: Indications for re-irradiation are increasing both for palliation and potentially curative attempts to achieve durable local control. This has been in part driven by the technological advances in the last decade including image-guided brachytherapy, volumetric-modulated arc therapy and stereotactic body radiotherapy. These enable high dose focal irradiation to be delivered to a limited target volume with minimal normal tissue re-irradiation. The European Society for Radiotherapy and Oncology (ESTRO) and the European Organisation for Research and Treatment of Cancer (EORTC) have collaboratively developed a comprehensive consensus on re-irradiation practices, aiming to standardise definitions, reporting, and clinical decision-making processes. The document introduces a universally applicable definition for re-irradiation, categorised into two primary types based on the presence of geometric overlap of irradiated volumes and concerns for cumulative dose toxicity. It also identifies "repeat organ irradiation" and "repeat irradiation" for cases without such overlap, emphasising the need to consider toxicity risks associated with cumulative doses. Additionally, the document presents detailed reporting guidelines for re-irradiation studies, specifying essential patient and tumour characteristics, treatment planning and delivery details, and follow-up protocols. These guidelines are designed to improve the quality and reproducibility of clinical research, thus fostering a more robust evidence base for future re-irradiation practices. The consensus underscores the necessity of interdisciplinary collaboration and shared decision-making, highlighting performance status, patient survival estimates, and response to initial radiotherapy as critical factors in determining eligibility for re-irradiation. It advocates for a patient-centric approach, with transparent communication about treatment intent and potential risks. Radiobiological considerations, including the application of the linear-quadratic model, are recommended for assessing cumulative doses and guiding re-irradiation strategies. By providing these comprehensive recommendations, the ESTRO-EORTC consensus aims to enhance the safety, efficacy, and quality of life for patients undergoing re-irradiation, while paving the way for future research and refinement of treatment protocols in the field of oncology.

Keywords: Palliation; re-irradiation; radiation therapy; radiobiology; consensus

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Re-irradiation in oncology, represents an increasingly common modality of cancer management for both radical salvage and palliative indications (1). The development of advanced precision radiotherapy techniques, including intensity-modulated radiotherapy, volumetric-modulated arc therapy, stereotactic body radiotherapy (2), and image-guided brachytherapy (3), along with the increased availability of advanced technologies like particle therapy (e.g., proton therapy) (4), has markedly improved the feasibility of re-irradiation. These technologies allow for higher precision in targeting tumours while minimising damage to the surrounding healthy tissues, thus making re-irradiation a more viable option than it was in the past. This review aims to summarise a presentation at the 2023 American Society for Radiation Oncology Annual Meeting that discussed the insights from the latest European Society for Radiotherapy and Oncology (ESTRO) and the European Organisation for Research and Treatment of Cancer (EORTC) consensus on re-irradiation, particularly in the palliative setting (5).

The first part of the published consensus statement describes a systematic review of the subject. The search of papers between 2000 and 2020 revealed 493 papers fulfilling the search criteria addressing re-irradiation. However, despite the quantity of data it was generally of poor quality with only 15% being prospective and no randomised trials. The variability in reporting was significant, particularly concerning the detailing of re-irradiation protocols, including cumulative dose-volume parameters for target volumes and organs at risk, quality-of-life outcomes, specific indications for re-irradiation, comprehensive treatment details, and patient demographics and characteristics. This inconsistency stemmed from the lack of established reporting standards, rendering it challenging to synthesise the findings or draw robust conclusions. The ESTRO-EORTC consensus panel therefore undertook a Delphi exercise to address three main issues around re-irradiation; definition, reporting guidelines and decision making in clinical practice.

In terms of re-irradiation two fundamentally different forms of re-irradiation were identified. When a new radiotherapy course is being planned following a previous one and there is geometrical overlap of irradiated volumes it is classified as "re-irradiation type 1", indicating that the new treatment field includes a previously irradiated volume.

If there is no such overlap, but there is concern over potential toxicity from cumulative doses this is classified as "re-irradiation type 2", where, despite the absence of direct overlap, the cumulative radiation doses necessitate careful consideration due to potential toxicities.

In the absence of both overlap and cumulative dose toxicity, a further distinction is made based on the location of target volumes. If the target volumes of the current and previous radiotherapy courses are within the same organ, it is categorised as "repeat organ irradiation". This implies a second treatment to the same organ but in a different region, avoiding the previously treated volume.

Conversely, if the target volumes are in different organs, the scenario is classified as "repeat irradiation". Here, a new radiotherapy course is planned for a different organ, ensuring that there are no shared volumes or cumulative dose concerns from the previous treatment.

The differentiation between type 1 and type 2 re-irradiation addresses the diverse scenarios clinicians encounter, ranging from overlapping radiation fields to concerns about cumulative toxicity. This is important when attempting to standardise the reporting of prospective and randomised studies. A reporting framework has been described which encompasses the entire pathway for re-irradiation including patient characteristics, tumour characteristics, previous and current oncological treatments, previous radiotherapy details, indications to perform retreatment, treatment planning, assessment of cumulative doses, treatment delivery and follow up.

The reporting guidelines aim to ensure high-quality data collection and reporting. Essential patient information, including demographics, performance status, and organ function, as well as detailed tumour characteristics like histology, location, and stage should be recorded. The treatment planning process, including dose prescription and fractionation, imaging methods for target and organs at risk delineation, and dose constraints, must be thoroughly described. An assessment of cumulative doses is also required, with a focus on the method used for dose summation and radiobiological considerations. The document advises on the specifics of treatment delivery, including image guidance and motion management, and sets standards for follow-up procedures, which should capture intervals, duration, and methods of clinical investigations. These serve to enhance the clarity and consistency of reporting in re-irradiation studies, contributing to the reliability and comparability of research findings in the field.

In clinical practice, selecting between palliative re-irradiation, other modalities, and best supportive care is challenging, particularly considering the debatable efficacy of interventions such as whole brain radiotherapy (6). The scarcity of evidence complicates re-irradiation decision-

making, underscoring the importance of tailored patient care. This involves a delicate balance between the potential benefits and risks of significant toxicities and impacts on quality of life after re-irradiation. The ESTRO-EORTC consensus on re-irradiation sets forth an interdisciplinary approach to shared decision-making. It recognises the importance of discussing all available treatment alternatives and emphasises that, particularly for patients with a limited life expectancy, re-irradiation should be considered if it can provide symptom relief without undue concern for irreversible toxicity. The intent of treatment—whether it is palliative, curative, or local ablative—must be clearly communicated with the patient to ensure informed decision-making. When it comes to patients and tumour-specific factors, a stable Eastern Cooperative Oncology Group performance status of ≤2 is recommended for those considering high-dose re-irradiation. High-dose re-irradiation with a curative intent is generally not recommended if the patient's estimated survival is less than six months. The document stresses the significance of radiobiological aspects, suggesting that the response to previous irradiation and the inherent radioresistance or radiosensitivity of the tumour should also guide the re-irradiation strategy. The use of the linear-quadratic equation using relevant α/β values for tumours and at-risk organs is recommended when assessing cumulative doses. Access to comprehensive information on previous treatments is considered valuable for dose reconstruction and estimation. In cases where this information is not available or incomplete, a conservative approach to dose approximation is advised. Specifically, if the previous dose distribution is not available in any reasonable format for reconstruction, it may be conservatively assumed that the prescription dose was uniformly delivered to the area or organ at risk. Moreover, if the previous dose distribution is not available in electronic format but can be reconstructed from simulation fields or portal images, employing conservative approximation is deemed reasonable for computer-calculated 3-dimensional dose summation. Calculations should include biologically equieffective doses (e.g., the equivalent total dose in 2 Gy fraction or biologically effective dose) when summating dose across treatment plans, especially when different fractionation schemes have been used (7). Dose constraints and target volumes should also take into account the patient's life expectancy and acceptance of risk. Regular follow-up after re-irradiation is recommended, including appropriate imaging and clinical examination, to monitor treatment outcomes and any potential toxicities.

In conclusion, the ESTRO-EORTC consensus is a step forward in standardising re-irradiation practices. A significant challenge in re-irradiation, as noted in the consensus, is the scarcity of prospective evidence for guidance (1) with most evidence based on retrospective studies and expert opinions, with their inherent bias and limitations in data quality. These corroborate with the insights gained from the recent international survey on re-irradiation practices (8). While re-irradiation is increasingly used as a viable treatment option, particularly for tumours in the brain, pelvis, thorax, and head & neck regions, widespread variability in treatment approaches were observed (8), underscoring the need for well-designed prospective clinical trials to better understand the efficacy, safety, and optimal usage of re-irradiation in various clinical contexts. The consensus has advocated for standardised reporting which allows for more meaningful comparisons and meta-analyses, essential for synthesising evidence and developing evidence-based guidelines. The inclusion of specific items in these guidelines ensures comprehensive coverage of all relevant aspects of re-irradiation studies. The integration of advanced radiotherapy techniques, along with a deeper understanding of radiobiology and personalised medicine, will provide increased opportunities for safe and effective re-irradiation, and adherence to these guidelines will be important in optimising re-irradiation strategies for cancer treatment in the future.

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References

1. Nieder C, Andratschke NH, Grosu AL. Increasing frequency of reirradiation studies in radiation oncology: systematic review of highly cited articles. Am J Cancer Res 2013;3:152-8.
2. John C, Dal Bello R, Andratschke N, et al. In-field stereotactic body radiotherapy (SBRT) reirradiation for pulmonary malignancies as a multicentre analysis of the German Society of Radiation Oncology (DEGRO). Sci Rep 2021;11:4590.
3. Mahantshetty U, Kalyani N, Engineer R, et al. Reirradiation using high-dose-rate brachytherapy in recurrent carcinoma of uterine cervix. Brachytherapy 2014;13:548-53.
4. Phan J, Sio TT, Nguyen TP, et al. Reirradiation of Head and Neck Cancers With Proton Therapy: Outcomes and Analyses. Int J Radiat Oncol Biol Phys 2016;96:30-41.
5. Andratschke N, Willmann J, Appelt AL, 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.
6. Mulvenna P, Nankivell M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. Lancet 2016;388:2004-14.
7. Bentzen SM, Dörr W, Gahbauer R, et al. Bioeffect modeling and equieffective dose concepts in radiation oncology--terminology, quantities and units. Radiother Oncol 2012;105:266-8.
8. Willmann J, Appelt AL, Balermpas P, et al. Re-irradiation in clinical practice: Results of an international patterns of care survey within the framework of the ESTRO-EORTC E2-RADIatE platform. Radiother Oncol 2023;189:109947.

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