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**Evolving role of salvage reirradiation: Is global harmonization required before treatment guidelines can be developed?**

Logie N *et al.* Evolving role of salvage reirradiation

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**Abstract**

Up to 90% of patients initially treated with curative-intent radiotherapy (RT) will experience locoregional failure. Historically, repeat irradiation (ReRT) was offered purely with palliative intent, if considered at all, due to concerns surrounding toxicity, tolerance of normal tissues, and choice of appropriate dose schedule. With technological advancements in RT delivery, coupled with longer survival in many malignancies secondary to improvements in systemic therapy, a small subset of patients presenting with localized recurrence is increasingly being offered salvage ReRT. However, this is largely on an ad hoc basis, guided mainly by small retrospective, single-institution reports. The patient population retreated, RT modality, dose received, degree of attrition and follow-up are extremely variable. The opportunity presently exists to apply lessons learned from the harmonization of the research efforts within the bone metastases community to the salvage ReRT situation: the adoption of common endpoints, minimum features to be incorporated into clinical trial design, and methods of data analysis and reporting. The ReRT data available must be harmonized so that valid, clinically applicable conclusions can be drawn. Collaboration in the form of an international registry of prospectively collected outcomes of patients reirradiated for cure for a variety of tumour sites would further support the evolution of Radiation Oncology towards personalized medicine, and away from the current “one-dose-fits-all” approach.

**Key words:** Reirradiation; Radiotherapy; Salvage; Treatment planning; Toxicity; Registry; Dose

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**Core tip:** Given the heterogeneity of the available reirradiation evidence, an international registry would provide a foundation on which to base consensus recommendations regarding many of the outstanding questions surrounding patient selection and treatment planning. Inter-centre collaboration will be required to build a critical mass of data sufficient for robust statistical analysis; however, in order to achieve this, global harmonization is needed. Standardized nomenclature would facilitate consistent coding of treated volumes, doses, toxicity rates, and quality of life outcomes. A registry would also assist in determining the feasibility of both phase II prospective studies and meta-analysis of currently available data.

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**INTRODUCTION**

Depending on the type and stage of cancer at first presentation, up to 90% of patients initially treated with curative-intent radiotherapy (RT) will experience locoregional failure[1]. For example, in breast cancer, despite local radiation, locoregional recurrences occur in up to 14% at 18 years[2], and after RT for non-melanoma skin cancer, in-field recurrence has been reported in up to 16%[3]. Pelvic recurrence occurs in 20%-40% of patients after radical radiation or surgery for gynecologic cancer[4]. In lung cancer, approximately one-third of those treated with radical chemoRT will develop a locoregional recurrence within five years[5,6]. Likewise, locoregional failure is the dominant pattern of failure after radical chemoRT for both head and neck cancer[7] and glioblastoma multiforme, with the latter recurring more than 90% of the time despite optimal up-front treatment[8].

At the time of local recurrence, treatment options may include resection, systemic therapy, laser or radiofrequency ablation, cryotherapy, hyperthermia, or photodynamic therapy. However, these options are not universally available; each has different and often stringent eligibility criteria; strength of supporting evidence varies; and in some, proof of long-term efficacy is lacking. Reirradiation (ReRT) with repeat conventional external beam radiotherapy (RT), highly conformal RT such as stereotactic body radiotherapy (SBRT) (Table 1), proton therapy, heavy ions or brachytherapy may also be considerations in those experiencing recurrence who have exhausted or are not eligible for other forms of therapy.

**REIRRADIATION: THE CASE FOR HARMONIZATION**

Historically, the use of ReRT has been limited by concerns surrounding toxicity, tumour radioresistance, and lack of robust evidence[1,9,10]. The complexity of delivering RT a second time to the same volume has been exacerbated by a dearth of individual radiation oncologist experience, a lack of confidence in the ability to reproduce the previous treatment’s dosimetric parameters, a scarcity of adequate data on recovery of normal organs after radiation injury, and the absence of guidelines supporting approaches to optimal RT planning. In a 2008 Canadian national survey, the majority of respondents reported a lack of departmental guidelines and “enthusiasm“ for instituting reirradiation[1]. Controversy surrounds the choice of appropriate prescription in the context of the initial dose and field arrangement, and the best combination of steps to limit further damage to normal structures which have already received maximum or near-tolerance doses. Consequently, repeat RT in past was primarily done with palliative intent[11]. This is echoed by results of the 2008 survey, in which only 32% of respondents would offer ReRT for salvage but 99% would institute ReRT if quality of life could be improved[1].

The situation where bothRT courses are delivered with palliative intent has been extensively studied in the setting of bone metastases. However, it required significant international effort over more than a decade to bring the Radiation Oncology community to the point of being able to answer even the most fundamental question of optimal ReRT dose. Prior to 2002, differences in endpoint definition and measurement, timing of follow-up, and interval to retreatment, for example, plagued cross-trial comparisons[12]. An update of the International Bone Metastasis Consensus Working Party recommendations in 2012 again encouraged investigators to adopt a common set of endpoints, described minimum features which should be incorporated into the design of future trials, and suggested methods of data analysis and reporting[13]. Together with the results of multiple meta-analyses[14-19], the steady evolution towards consensus has culminated in the recent publication of a phase III randomized controlled trial. This has finally provided level I evidence supporting a specific approach for treatment planning and dosing for external beam ReRT for bone metastases[20].

Given technological advancements in diagnostic imaging and RT delivery, coupled with longer survival in many malignancies secondary to improvements in systemic therapy, a small subset of patients presenting with localized recurrence is increasingly being offered ReRT for salvage (*i.e.*, with curative intent). At present, this is on an ad hoc basis, guided by data mainly from retrospective single-institution series which commonly span twenty years or more. Conclusions are limited by small patient numbers, attrition, heterogeneous baseline characteristics, and the presence of selection and referral bias. Descriptions of the patient population retreated, RT modality and dose received, endpoints reported and follow-up are extremely variable. Consequently, whether ReRT is offered, and how it is implemented, remains highly dependent on the specific radiation oncologist and may be limited by resource availability[9]. The opportunity presently exists to apply lessons learned from the harmonization of the research efforts within the bone metastases community to the salvage reirradiation situation.

In future publications, eligibility for retreatment should be defined prospectively; this may be symptom or radiologic progression or both. Baseline characteristics such as current symptom burden (and methodology of measurement), performance status, and previous treatment modalities should be documented. Controversy exists as to whether a favourable response to initial RT over a long disease-free interval should be required before considering ReRT. Information on toxicity experienced after first RT should be reviewed. Comprehensive restaging and pathologic confirmation is encouraged as outcomes after ReRT for a new primary will differ from those expected after treatment for in-field recurrence.

Initial and ReRT techniques, energies, field sizes, calculation algorithms, prescription points, doses, planning techniques, and volumes have varied significantly as can be expected from differing treatment indications, intents, geographic locations, and years[21]. Many past studies did not include all RT details, with the lack of information often due to treatment planning software changes and evolution of RT delivery techniques[21]. When reported, total dose over both courses was often the arithmetic cumulative dose, which does not take into account dose per fraction or overall treatment time. In comparison, biologically equivalent dose (BED) and equivalent dose in 2 Gy fractions (EQD2) provide the ability to compare different dose fractionation schedules. Data sufficient to calculate BED or EQD2 are not found in most studies, so conclusions which can be drawn at present regarding ReRT schedules are limited.

The rationale for ReRT dosing and cumulative allowed organ at risk tolerance doses should be stated, as should the radiobiological justification for minimum interval between RT courses. Prospective data on utilization of and outcomes after highly conformal techniques such as SBRT after conventional RT are urgently needed, including cost-effectiveness, as these approaches are steadily migrating into the clinical setting. While in theory, these technologies should allow optimal tumour localization and therefore normal tissue sparing, they also deposit extensive low dose wash resulting in higher integral doses. The methods of constructing a composite plan (*i.e.*, rigid versus deformable registration) and the resulting dosimetric parameters should be available and cumulative tumour and normal tissue BEDs reported.

Once such additional volumetric data are available (*e.g.*, median degree of overlap of 50% or 90% isodose lines), correlations can be explored with outcomes such as symptom response, progression and especially toxicity. Further understanding of organ tolerance to reirradiation is essential, as traditional recommendations based on the Emami[22] or QANTEC[23] guidelines may not be entirely generalizable to commonly used intensity-modulated and arc-based techniques. Construction of a prognostic score including demographic, disease and treatment-factors which render a patient likely to respond, and/or unlikely to complete a second course of RT, which can be easily applied in clinic is urgently needed.

Follow-up intervals as measured from a common starting point, endpoints assessed and investigations performed should be guided by standard practice for up-front curative-intent RT in the specific primary site, and patients should be monitored long-term by their radiation oncologist for outcomes and side effects[21]. Symptom improvement and progression rates and duration must be reported, notwithstanding that measurement of these can be confounded by progressive disease and comorbidities. The use of a validated patient-reported quality of life scale prior to ReRT and at regular follow-up intervals should be strongly considered. There is little data currently available on the important parameter of duration of symptom control in relation to overall survival which would be illustrative for patients during consent discussions.

Given the heterogeneity within the population of patients reirradiated for cure, an international registry would provide a foundation on which to base consensus recommendations regarding many of the outstanding questions regarding patient selection and treatment planning. Inter-centre collaboration will be required to build a critical mass of data sufficient for robust statistical analysis; however, in order to achieve this, global harmonization is needed. Standardized nomenclature would facilitate consistent coding of treated volumes, BEDs, toxicity measurement, systemic therapy use, quality of life outcomes, and duration of follow-up. Parameters such as the minimum recommended interval between courses for different indications and sites, along with guidelines around tolerance doses for critical organs at risk could be derived. Even the definition of reirradiation could be conclusively addressed, given the lack of clarity at present due to the increasing sequential use of different RT modalities. A registry would also assist in determining the feasibility of development of phase II prospective studies and meta-analysis of currently available data.

**CONCLUSION**

Given the evolving technological climate and number of patients who are being considered for salvage reirradiation, the data available must be harmonized so that valid conclusions can be available for translation to the clinic. In order to properly consent patients, physicians require information about the potential benefits as well as the potential risks in relation to other available treatment modalities. International collaboration in the form of a registry of prospectively collected data on patients reirradiated for cure for a variety of tumour sites would further support the evolution of Radiation Oncology towards personalized medicine, and away from the current “one-dose-fits-all” approach.

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**Table 1 Selected results of reirradiation: Both courses external beam radiotherapy unless otherwise specified**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Site of ReRT** | **Symptom overall response rate** | **Symptom response duration** | **Overall radiologic response rate** | **Radiologic response duration** | **Overall survival** | **Toxicity** | **% Not compl-eting ReRT** | **ReRT- related death** |
| **H and N**[24] | NR | NR | NR | NR | 44% @ 1 yr | 23% grade 3+ late @ 1 yr | 13% | 6.7% |
| **Thoracic** [21] | Average 69.2% | 0.5-5 mo | 55%-77%(0-11% CR; 7%-44% PR) | NR | 9%-59% @ 1 yr | Esophagitis 17.2%Pneumonitis 12.3%Skin 4.1%Fracture 0.5%Myelopathy 0.5% | 4.5% | 1.6% |
| **Breast**[25] | 100% (56% PR; 44% CR) | “For a long time of the patients’ lifetime in the majority” | NR | NR | 61% @ 1 yr | No grade 3-4 acute or late toxicity  | NR | NR |
| **Pancreasa**[26] | 57% at 1-2 mo | NR | “Tumour stabilization but… not…reduction in tumour size” | NR | Med surv after ReRT 8.8 mo (95%CI: 1.2-16.4 mo) | 28% acute grade 2 toxicity (fatigue, abdominal pain, anorexia, nausea, diarrhea)No acute grade 3+ toxicity6% grade 3 late toxicity | 0% | NR |
| **Cervixac**[27] | 71% achieved ≥ 50% drug reduction from baseline at 1-2 mo  | NR | 35% CR, 30% PR, 17% SD, 17% PD at 4 mo | NR | 43% @ 2 yr | 35% mild acute toxicity13% late grade 4 toxicity (all rectovaginal fistulae requiring colostomy) | NR | NR |
| **Abdomen / Pelvisa**[28] | 95% - pain75% - bleeding | NR | 100% | NR | 52% @ 1 yr | 0% grade 3-5 acute or late toxicityAcute22% grade 1-2 pain14% grade 1-2 skin reaction8% grade 1-2 diarrhea15% grade 1-2 nausea4% grade 2 vomiting4% grade 1 dysuria4% grade 1 dysphagiaLate4% grade 2 pain4% grade 2 skin reaction4% grade 1 diarrhea15% grade 1-2 dysuria19% grade 1-2 nerve complaints11% grade 1-2 limb dysfunction | NR | NR |
| **Bone metastases**[18,19] | 58%-68%(16%-28% CR; 28%-50% PR) | 1-9.7 mo | NR | NR | Median 3-6 mo | 30% (nausea, vomiting, fatigue, diarrhea) | NR | NR |
| **Bone metastases**[20] | 45%-51% of per protocol pts at 2 mob(11%-14% CR; 31%-40% PR) | NR | NR | NR | NR | AcutebSkin 14%-24%Anorexia 56%-66%Vomiting 13%-23%Diarrhea 23%-31%LatebFracture 5%-7%Spinal cord compression 1%-2%Myelopathy 0% | NR | 0% |

aEBRT followed by SBRT; bDepending on dose; c7/23 pts in this series did not have EBRT up front but results not reported separately. CR: Complete response; EBRT: External beam radiotherapy; med surv: Median survival; NR: Not reported; PD: Progressive disease; PR: Partial response; pts: Patients; ReRT: Reirradiation; SBRT: Stereotactic body radiotherapy; SD: Stable disease.