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Overview

Re-irradiation and Hyperthermia in Breast Cancer

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Abstract

Half of locoregional recurrences after breast cancer treatment are isolated events. Restaging should be carried out to select patients for curative salvage treatment. The approach depends on the characteristics of the primary and recurrent cancer, previous locoregional and systemic treatments, site of recurrence, comorbidities and the patient's wishes. A multidisciplinary discussion should be associated with the shared decision-making process. In view of the potential long-term disease-free survival, meticulous target volume delineation and selection of the most appropriate techniques should be used to decrease the risk of toxicity. This overview aims to provide clinicians with tools to manage the different scenarios of breast cancer patients with locoregional recurrences in the context of re-irradiation.

Key words: Breast cancer; chest wall recurrence; hyperthermia; re-irradiation; second breast-conserving therapy

Statement of Search Strategies Used and Sources of Information

Traditional medical resources were used to find the contents for this review paper, including data related to one of the authors' own work (S.O.).

Introduction

Advances in breast cancer screening and treatments, including imaging to guide surgery and radiation therapy, have significantly decreased 5 and 10 year rates of locoregional recurrence (LRR), while overall survival is increasing [1]. Prolonged survival increases the chances for LRR and/or second ipsilateral breast cancer, enforcing the need for retreatment, including re-irradiation. For this, understanding the fundamental principles of re-irradiation is essential for the management of these patients, especially as about half of recurrent breast cancer patients present with isolated LRR and potentially long-term survival. This overview aims to provide clinicians with tools to manage the different scenarios of LRR with the limitation that much of the published data about re-irradiation come from animal studies, retrospective cohorts and small prospective studies, with only limited data from prospective multicentre trials.

General Principles and Challenges of Re-irradiation and Maximal Cumulative Dose in Breast Cancer

In the case of breast cancer (re-)irradiation, the main structures to be considered as organs at risk are the skin, subcutaneous and lymphatic basins, heart, lungs, rib cage and brachial plexus. Depending on the radiotherapy volumes and techniques, other organs, such as liver and thyroid gland, should be considered.

For rapidly proliferating tissues like the skin, the ability of the tissue to tolerate re-irradiation is assumed to be dependent on the response to radiation damage by repopulation and migration to recover the cell population and restore tissue integrity. In preclinical studies, re-irradiation

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in doses close to the initial full tolerance dose was found possible after a few months from the initial treatment if there was visible recovery of the skin before the second course [2]. Re-irradiation of the axillary lymph node areas has the potential for injury to the brachial plexus; both the lymphatic tissue and brachial plexus are slowly proliferative tissues with a higher risk for residual subclinical damage. Therefore, if possible, re-irradiation to these volumes should be avoided, as it may result in significant morbidity with lymphoedema, shoulder dysfunction and neurological damage. Irradiation of the rib cage can be associated with bone damage. Bone is estimated to have a α/β ratio of 1.8–2.8 Gy, indicating that the bone is behaving like a late responding tissue [3]. This complication can result in bone fragility (e.g. spontaneous/minimal trauma rib fracture) following osteoporosis/necrosis. Other factors that can contribute to bone-related complications in breast cancer patients include menopause, systemic treatments including aromatase inhibitors, osteoporosis and prolonged bisphosphonate treatments [4]. A recent study reported a 7% rate at 5 years of rib fractures in breast cancer patients who were treated with re-irradiation and hyperthermia [5]. Most of the fractures occurred at the photon/electron abutment area, suggesting high doses as a result of field overlap (area of up to 40% overdose). The maximum possible focal EQD2 (equivalent dose in 2 Gy fractions) with a 40 % overdose calculated for 8 × 4 Gy is 87 Gy, which is 74 % higher than the TD 5/5 (tolerance dose with 5% complications in 5 years). Other factors that were found to be significant predictors for rib fractures were high dose per fraction and large radiotherapy volumes, whereas increasing the number of hyperthermia sessions was not found to increase the rib fracture risk [5].

There are fewer data regarding the tolerance of the heart and/or lungs to re-irradiation, probably thanks to the care that is taken in avoiding excessive doses to these structures, as the risk of cardiac disease and pulmonary complications from radiotherapy is well recognised.

Tables 1 and 2 list the normal tissue constraints in two breast cancer re-irradiation prospective phase II trials. The differences illustrate the lack of consensus for normal tissue dose constraints in the case of breast/chest wall re-irradiation. Therefore, even more in cases of re-irradiation, efforts should be made to reduce the irradiated volumes and doses to normal tissues.

The re-irradiation dose/fractionation, radiotherapy cumulative dose and toxicity rates in the different re-irradiation studies are listed in Table 3. The radiotherapy cumulative dose in these studies ranged from less than 80 Gy to more than 130 Gy without significant reported toxicities. However, these values were retrieved from small series, using various radiotherapy schedules, volumes and techniques, and with scarce information about toxicity. Moreover, these studies do not provide a clear estimation of the optimal re-irradiation dose with regards to disease-specific outcomes. The extent of disease (e.g. gross versus microscopic; first/second recurrence or palliation for metastatic disease) and the interval between both radiation courses varied significantly within a single cohort and between studies [6,7]. These factors have a significant effect on local control rates, irrespective of the administration of concomitant treatment [6,8,9].

Therefore, we recommend that in the case of re-irradiation, the general principle of radiotherapy should be applied, with two main concerns: the possibility of radioresistance (especially for early recurrences) and potentially reduced normal tissue tolerance [10]:

- Full evaluation of the previous irradiation course, guiding subsequent treatment planning.
- The expected clinical benefit of re-irradiation should outweigh the potential toxicity.
- Careful evaluation of other potential contributors to poor tolerance for (re-)irradiation, such as patient-related factors (comorbidities, performance status) and treatment-related factors (systemic treatment).

Table 1
Normal tissue dose constraints used in RTOG 1014* for partial breast re-irradiation

Normal tissue	Constraint for the re-irradiation
Uninvolved ipsilateral breast	<60% of whole breast receive ≥ of prescribed dose <35% of whole breast receive prescribed dose
Contralateral breast	<3% receive prescribed dose
Ipsilateral lung	<15% receive 30% of the prescribed dose
Contralateral lung	<15% receive 5% of the prescribed dose
Heart	
Right side RT	<5% receive 5% of the prescribed dose
Left side RT	<5% receive 5% of the prescribed dose
Thyroid	Maximum point dose of 3% of the prescribed dose

* Radiation Therapy Oncology Group (RTOG) phase II trial of three-dimensional external beam partial breast re-irradiation, 1.5 Gy × 30 (twice a day), to a total dose of 45 Gy.

Table 2
Current normal tissue dose constraints adapted from NL31630.018.10* for chest wall/breast re-irradiation

Normal tissue	Constraint
Spinal cord	Dmax < 50 Gy in EQD2
Whole heart	Minimise mean
Mean lung dose (both lungs)	<16 Gy
V20 lung dose	<35%
V10 lung dose	<50%

* A phase II trial of three-dimensional external beam breast/chest wall re-irradiation with hyperthermia, with/without chemotherapy, 4 Gy × 8 (twice a week), to a total dose of 32 Gy. Currently, the total re-irradiation dose is 46 Gy given in 2 Gy fractions (five times a week), unless logistics or physical condition require otherwise. The prescription and dose constraints are adapted individually, based on estimated recovery of sublethal damage from previous treatments, size and site of target volumes and location of overlapping areas. The α/β value for the spinal cord was 2, for lung and heart it was 3.

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