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Re-irradiation: the "some like it hot – others not" dilemma

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Although re-irradiation as a therapeutic procedure has already been explored over a few decades, it still remains a field of various uncertainties, and the majority of retrospective clinical studies contain quite a lot of "blank points". The critical point of this therapy is the severity of the radiation response of the normal organs at risk, which limits the planned and delivered dose. Re-irradiation is often considered a palliative treatment, although the results of the stereotactic hypofractionation (SHRT) strongly suggest that it can easily be used with radical intent. While tolerance doses (TD) were more or less arbitrarily established (not estimated) many years ago, they have not been verified during the passing time, but at least accounted for the ⅔ or ⅓ volume of the organ at risk. Regarding the so-called "remembered dose", it becomes crucial when the primary and re-irradiated volume of normal organs overlap. Knowledge of that parameter contains many loopholes. Such "doses" have mainly been approximately deduced from experimental and some clinical studies, and for a few organs at risk only. Present review the selected studies including 8,427 recurrences reported in a small number of the retrospective studies providing complete factors and parameters of the primary and re-irradiation procedures. The review's results are presented and discussed. In 2022, the ESTRO/EORTC experts council defined re-irradiation procedures including three therapeutic scenarios, which are presently discussed. That consensus provides at least the detailed basics to optimize and improve quantitative knowledge on re-irradiation, which is the major aim of this paper.

Key words: re-irradiation, tolerance doses, remembered dose, ESTRO/EORTC therapeutic scenarios

Introduction

For many decades, the use of re-irradiation after radical radiotherapy has generally been considered taboo because of the strong belief and fear that re-irradiation may inevitably often induce severe late radiation sequelae (complications) in normal tissues/organs (organs at risk – OAR) surrounding recurrent tumors or metastasis. However, the progressive increase of experimental and clinical studies challenges this prevailing dogma, revealing at least partial capability of some normal tissues to repair radiation sublethal and potentially lethal damages (SLD, PLD).

Currently, conformal (CRT), dose modulated (IMRT) and arc (VMAT) techniques are widely used in radiotherapy and result in a higher rate of local tumor control and in prolonged overall survival. Particularly stereotactic hypofractionated radiotherapy (SHRT) is more often applied, since it tailors the dose focused on the tumor volume, with a large dose gradient beyond its margins. Despite substantial improvements in radiotherapeutic efficacy, the risks of local recurrences, distant metastases and secondary primary tumors still remain (e.g. a secondary primary tumor develops in more than 20% of irradiated patients with a primary cancer, among which 80% occurred in the H&N region). To a certain degree, these three types of failure may occur out of the initially irradiated volumes, and therefore "re-treatment" in such cases can be considered similar

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to the primary radiotherapy. On the other hand, recurrence may develop within the organ which is the site of the previous primary tumor, or even frequently, within or close to its original volume [1–12].

During recent years, re-irradiation has been more often explored in clinical practice. Two main scenarios are considered by radiation oncologists. Some of them advocate re-irradiation as a "Luke Warm Bath", by using palliative biological total doses (often with low fraction doses delivered twice-a-day – b.i.d.), because of a justified fear of severe late normal tissue toxicities. This scenario has usually been forced for a large recurrence (metastasis) developed close or within the previously irradiated volume. Sometimes it can be well grounded, since the risk of late complications (late radiation effects – LRE) can be more or less precisely predicted, but not eliminated. Moreover, various complications are individually scored in the different studies, and therefore they can be unreliable. This scenario does not seem reasonable in the case of a chance of long-term cure or durable palliation. Moderate total doses (e.g. 40–50 Gy) usually produce a partial regression of the recurrence only or a stable status of the disease. Such effects cannot be satisfied, since the survived tumor clonogens repopulate much faster than those of the untreated primary tumor. Furthermore, It should be remembered that possible morbidity from tumor progression is frequently greater and more severe than the re-irradiation toxicity. Thus, it encourages the consideration of higher doses, even if the price of such decisions might involve a higher risk of the LRE.

According to radiobiological principles, local recurrence (also metastasis) occurs when the primary dose is not radical enough, at least within a part of the tumor volume (e.g. a geographical miss), and results in the survival of some tumor clonogenic cells. Even one, well oxygenated tumor clonogen is definitely able to initiate a growth of the recurrent tumor, due to accelerated repopulation. It may likely suggest their higher radiosensitivity (more clonogens actively participate in the cell cycle), but also their aggressiveness and fast growth. On the other hand, some tumors recurring within or close to a previously irradiated volume may sometimes arise from radioresistant clonogens (e.g. the salivary gland) and make re-irradiation ineffective. The biology and kinetics of the recurrent malignant lesions suggest a radical scenario of the re-irradiation, called "Hot Bath-Therapy", with total doses higher than that previously. This may immediately raise a fear of much higher risk (~50%) of serious late complications (LRE), since the delivered dose comes closer or even above tolerance level of the $TD_{50/5}$ (50% risk within 5-year follow-up). But such potentially high incidence of severe late complications has not been reported yet.

The debate on the optimal re-irradiation dose fractionation continues. Different "Hot Bath" schedules have been explored to re-irradiate recurrent tumors (mainly in the head and neck region), among which hyperfractionated schedules have been recommended [2, 4, 6, 8, 10, 11, 29, 30, 34, 36], and its effectiveness has recently proven by the result of a Chinese trial [39]. The dose of at least 72 Gy in 60 fractions (1.2 Gy per fraction) given twice-a-day with a 6-hour interval is strongly advised by Benson et al. [2]. Hyperfractionation with two daily fractions below 1.8 Gy allows for the delivery of a high biological dose [18], since solid malignant tumors are usually much less sensitive to change in dose per fraction (high α/β ratio) than the majority of late responding normal tissues (very low α/β ratio, high rate of the β effects reflecting sublethal damages), and moreover it improves the sparing effect in normal tissues. For example, 72 Gy in 60 fractions delivered to normal tissue (organ) or to a part of it, is in fact, biologically equivalent to dose EQD_2 of 57 $izoGy_2$. It can lead to the escalation of a physical total dose to even 80–85 Gy. Moreover, low fraction doses lead to more effective repair of the sublethal and potentially lethal damage of the normal tissues, and also improve their functional recovery.

The next hypofractionation (single or a few large fractions) was widely used during the early years of the orthovoltage radiotherapy (geometrically regular fields). However, it resulted on an unacceptably high rate of serious and lethal late complications (severe deep necrosis), and therefore it was abandoned around 1920–1925. After about 80 years, hypofractionation came back to the market due to technologically innovative tools in the linacs (IMRT, VMAT) or stereotactic accelerators (CyberKnife), and became considered as a radical option offering a higher rate local control (>80–85%), including the recurrent tumors or multiple metastases [5, 14–16, 19, 20, 33, 35, 38]. Moreover, a major advantage of stereotactic hypofractionated radiotherapy (SHRT) of multiple metastases (e.g. in the liver, lung, brain or bone) is that a single high dose (~10–15 Gy) or a few large fractions can be delivered to each of a few lesions at the same time during the patient's set-up on therapeutic table and on each session of the irradiation. Another advantage of the SHRT is a specific dose distribution within the irradiated volume, characterized by a dose focused on the recurrent lesion, with a high dose gradient within a narrow tissue strip beyond the recurrence margins. It significantly improves the normal tissue sparing effect [11, 12, 17–21]. However, this advantage of the SHRT is that it is addressed to limited volumes of malignant lesions [14, 15, 16, 19–20], smaller than 4 cm in diameter.

An important and required basis for a proper and optimal selection of the re-irradiation scenario is detailed knowledge on the morphological and functional structure of the normal tissues (organs), and the radiobiological mechanisms of their response and tolerance to irradiation.

Late normal tissue's (organ's) radiation effects – tolerance doses

In contrast to acutely responding hierarchical epithelial tissues, late radiation effects (LRE) (injuries) develop in the mature tissues (organs) termed "flexible" (type F), and they can manifest

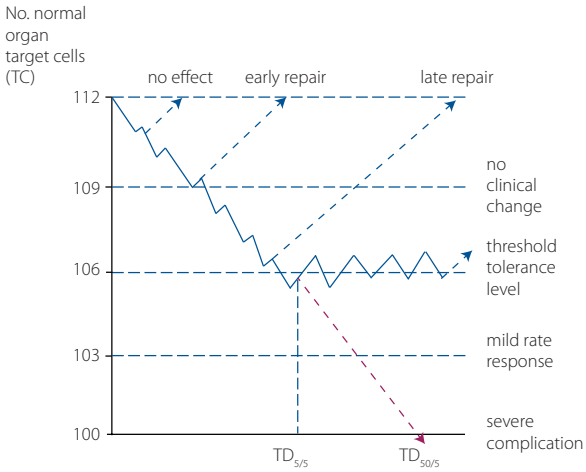

Figure 1. Radiation-induced target cell (TC) depletion in normal organ (tissue), and clinical manifestation of late radiation effect (LRE) – adopted from Rubin [24] If the TC depletion reaches the threshold tolerance level, it results in a 5% risk of late complications (LC) during 5-year follow-up ($TD_{5/5}$). After higher dose ($TD_{50/5}$) depletion, the TC continues and leads to a 50% risk of LC

months or even years after completing treatment [18, 22, 23, 29, 30]. Mature morphology does not however deny a component of the stem cells with retained proliferative potential. That said, the more affected the cells the deeper the cellular depletion. Some of them retain the potential to repair the SLD, PLD and to regenerate (fig. 1), and if such cellular and functional recovery reaches the threshold (tolerance) level, late effects may still not occur. But when the cellular damage progresses and continues, and the cellular reserve is completely depleted, then moderate or severe late complication occurs.

The severity and latency time of the LRE depend on the initial number of normal, so-called target cells (TC) with proliferative potential [14], which set-up the functional subunits (FSU). The higher the dose, the shorter the latency of the LRE. Moreover, residual, partly injured target cells may increasingly be recruited to the proliferative pool (when environmental conditions become favorable), to enter into a cascade (avalanche) of cell death, which speeds up morphological and functional tissue (organ) disorders. Surgery, chemotherapy, infection, or physical trauma usually accelerate the LRE severity.

Withers pointed out [23] that the tolerance dose (TD) for a given normal organ mainly depends on the number of their TCs per unit of the FSU rather than on the number of the FSUs. It may explain the relatively low TD for organs (e.g. hair follicles kidney, lung, liver) with a small number of the TCs within each FSU. Organs at risk (OARs) with acinar or alveolar structure (e.g. the salivary glands, pancreas, testis, mammary epithelium) respond to irradiation in a similar way to the kidney, in which the nephrons are well defined the structural FSUs with relatively small number of the TCs. It is well-known that among other factors, the risk of late effects depends on the irradiated volume of the OAR. The larger it is, the lower the delivered dose should be [23]. This condition can be fulfilled using the advanced 3D-radiotherapy techniques (IMRT, VMAT), brachytherapy and the SHRT as well, which offer significant dose gradient within a narrow strip of the normal tissues beyond the tumor margins.

An additional important factor, is the arrangement of the FSUs into serial or parallel networks within the OARs. The threshold tolerance-dose and volume of the re-irradiated OARs arranged in the parallel FSUs such as liver, kidney and lung can objectively be achieved, and the use of advanced RT techniques improves sparing effect in these organs [11, 14, 30]. Quite the reverse, if the FSUs are arranged in the series, like links in a chain (e.g. nerve tracts, spinal cord, cylindrical sheets of the peritoneum in the small intestine, named arteries), the loss of even one subunit may result in overt functional injury of the other subunits in the series. Post-irradiation small bowel obstruction or carotid blowout are examples of such volume effect. The key-point is that higher doses to previously irradiated volumes may not affect the function of the organs arranged in the parallel FSUs, but they can definitely be catastrophic for organs arranged in the serial FSUs. Tolerable re-irradiation of serial organs needs particular caution and should be focused on whether whole or a part of their volumes are involved within the irradiated volume.

It seems that the TCs and FSUs structure may by analogy also be referred to the primary malignant solid tumor and considered as a single, large FSU, within which even one surviving tumor clonogenic stem cell (TC) may lead to recurrence (on average 67% of irradiated tumors, since recurrence rate = 1 – TCP = 1 – e^{-1} = 0.67). However, the malignant TCs differ significantly from the normal ones, because they are highly heterogeneous regarding cellular radiosensitivity, oxygen consumption and proliferative potential. Nevertheless, both primary and recurrent tumors require a suitably high total dose to achieve a radical effect and complete local tumor control. The only limiting factor is the tolerance and volume of normal tissues (organs) surrounding the tumor and its impact on late complications, and on the quality of life after primary or re-irradiation.

Although many years passed off, the tolerance doses for normal tissues referred to the primary radiotherapy (fig. 2A) have not been precisely defined yet, but mainly interpreted only based on the results of various retrospective clinical studies [17, 23, 24, 25], and therefore their values are likely inaccurate. It is astounding that for over 50–60 years, TD values have not been as yet verified, and they remain as more or less approximate guidelines for clinical practice [24]. It means that after completing radiotherapy we have to wait for the occurrence of some failures (recurrence, metastases), or not, but we are unable to precisely *a priori* predict such events. There is a lack of clinical studies testing different dose fractionations to establish (not to deduce) an optimal TD, and therefore the tolerance doses for re-irradiation are still uncertain [10, 11, 14, 16, 17, 26, 28]. Some TD came from animal experiments

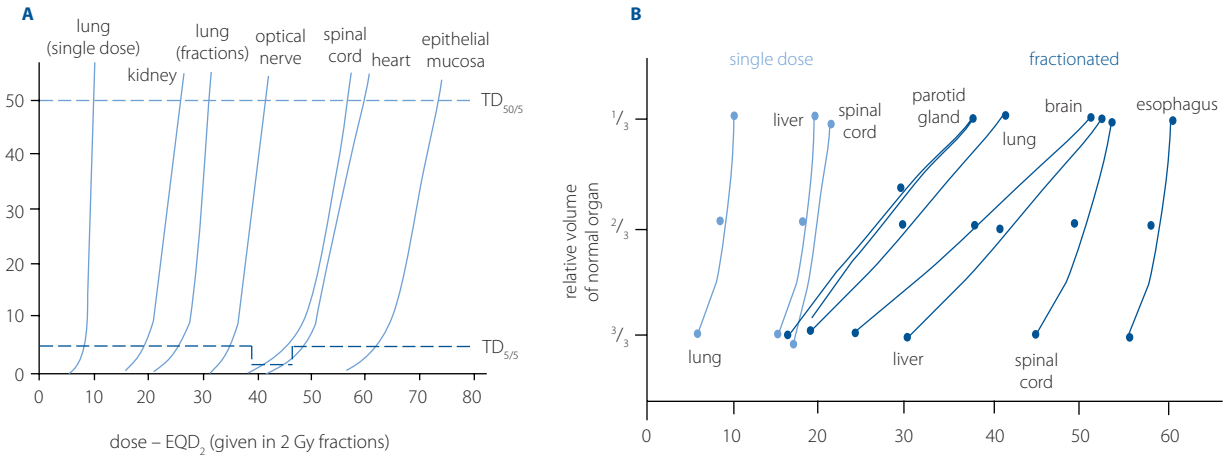

Figure 2. Tolerance dose ($TD_{5/5}$ and $TD_{50/5}$). **A** – whole volumes of the selected normal organs – according to Mc Bride, Withers [23] and Rubin [24]; **B** – the $TD_{5/5}$ in relation to the volume of the irradiated normal organs – according to Emami [17]

[22, 25–28], but they cannot be simply and directly transferred to clinical practice.

Despite some uncertainties, two levels of the Tolerance Dose have been proposed, i.e. the $TD_{5/5}$ referring to a low risk (5%), and $TD_{50/5}$ to a high risk (50%) of late complications, which may occur during the 5-year follow-up. Figure 2A shows a wide spectrum of the $TD_{5/5}$. We had to wait until 1990 when Emami et al. [17] defined $TD_{5/5}$ values depending on the volume of irradiated normal organs (fig. 2B). The smaller irradiated volume of the OARs, the higher $TD_{5/5}$ can be planned and delivered.

Apart from the volumetric factor, fraction size (d_{fx}) has also been found to have an important impact on the radiation response of the OARs, which are much more sensitive to change in the dose per fraction (d_{fx}) than malignant solid tumors. The lower the "d_{fx}", the more effective the sparing effect in the OARs. However, the physical doses expressed in the Gy do not necessarily correspond with bioequivalent doses [23, 25]. For example, 70 Gy in 35 fractions is not biologically equivalent to 70 Gy in 50 fractions, which is equal to 66.5 $izoGy_{2.0}$ for the tumor (α/β = 10.0 Gy) and 59.5 $izoGy_{2.0}$ for the normal organ (α/β = 2.0 Gy). Since the dose is not homogeneously distributed within the irradiated volume, it becomes practically important to convert physical Gy_s into bioequivalent $izoGy_{2.0}$, (if given in 2 Gy fractions) based on simple formulas:

$$EQD_{2.0} = TD_{phys}\,(d_{fx} + \alpha/\beta)\,/\,(2.0\ Gy + \alpha/\beta),$$

or in the case of the SHRT:

$$BED = TD_{phys}\,(1 + d_{fx}/\,\alpha/\beta)$$

(biological effective dose)

For example, if the planned total dose is e.g. 80 Gy, given in 40 fractions, and the DVH shows 56 Gy within a 5 cm length of the spinal cord (α/β = 2.0 Gy), the first thought would be to revise such a treatment plan, since 56 Gy is higher than a $TD_{5/5}$ of 50 Gy. However, the bioequivalent dose $EQR_{2.0}$ is equal to only 42 $izoGy_{2.0}$ [56 Gy x (80 Gy/40_{fx} + 2.0) / (2.0 Gy + 2.0)], that is below $TD_{5/5}$, and the original plan can be accepted with any doubts.

A belief in the sparing effect of a dose per fraction lower than 2.0 Gy has sometimes led in the past to a trap. Twenty years ago, Nguyen et al. [31] designed a super-hyperfractionated schedule of 40 fractions of 0.9 Gy delivered every 2 hours, 8 fractions per day, during 5 days, up to 36 Gy. After a 4-week break they repeated once again the same cycle, up to a total dose of 72 Gy. The authors used this schedule to treat 178 patients with advanced H&N cancer (mainly nasopharyngeal). Although a high rate of local tumor control was achieved, the price paid was tragic, mostly lethal late complications (wide and deep necrosis) which developed in about 80% of patients. Seven years later, Horiot et al. [32] also used small fractions of 1.15 Gy. given twice-a-day, but with 6–8 hour intervals, up to a total dose of 80.5 Gy. The 5-year local tumor control of the advanced H&N cancers was close to 50%, but in contrast to the Nguyen study, late complications were mild and their rate was low. It shows that the major and critical difference between these two quoted studies was too short a time interval between 8 daily fractions used by Nguyen et al.

Radiobiologically, mucosal "half-time" repair ($T_{1/2}$) of the epithelial cells is 1.5 hour. During short 2-hour intervals, a sublethal damage repair in the majority of cells is incomplete (~50%), which is increasingly accumulated through consecutive fractions, and finally leads to lethal necroses. Moreover, although at first glance it looks the 72 Gy given by Nguyen et al. is at the upper limit of the mucosal tolerance, about 50% of the incomplete repair should not be referred to the daily fraction of 0.9 Gy, but to about 3.6 Gy (0.5 x 7.2 Gy of the daily dose), which may raise the total $EQD_{2.0}$ to even 86.4 $izoGy_{2.0}$, in contrast to the Horiot study, in which the bioequivalent total dose $EQD_{2.0}$ reduces to 71.9 $izoGy_{2.0}$. These intentionally presented examples should be treated as a warning that even a single one risk factor missed or biased leads to much higher risk of the LRE than assumed. The situation remains even more risky when

a few OARs (with various α/β indices and $TD_{5/5}$) are within the irradiated volume. Current 3D-techniques nowadays allow for the complete exclusion of the cervical spinal cord from the irradiated area, but not other OARs. When re-irradiation is considered, fear and uncertainties arise, since one does not know, even intuitively, what may radiobiologically happen in the OARs during and after primary radiotherapy, and what proportion of the re-irradiated total dose can be delivered without pronounced increase in the risk of the LRE. It claims that re-irradiation still appears to be a really challenging approach.

Remembered dose mystery

There is still a common conviction that the OARs primarily irradiated to the upper limit of the $TD_{5/5}$ may not tolerate re-irradiation. Such a fear gets even stronger when the recurrence (metastasis) develops early and/or within or close to the previously irradiated volume, as often happens in the case of malignant brain tumors and their metastases. Recurrence or metastasis develops from surviving cancer cells, therefore they, like the original tumor, may likely not remember the primarily delivered dose. It logically suggests that the tumor (primary or recurrent) does not need any dose restriction, but the OARs absolutely do. Some functionally advanced normal tissues (organs) do retain residual proliferative potential due to redifferentiation of some of the mature cells into proliferative status (e.g. fibrocytes into fibroblasts), whereas some other organs can never do that (e.g. neurons). In fact, a proliferative activity plays a marginal role (by contrast with malignant tumors), with favor on capacity of the repair of the sublethal and potentially lethal (SLD, PLD) damages [11, 23, 25, 30]. The lower the dose and irradiated volume of the OAR, the higher the rate of the delivered dose which can be offset by the repair processes (fig. 3). The remaining part of the delivered but not repaired dose is termed the "remembered dose (RD)" [18, 23]. The lower the RD is the broader the "therapeutic window" becomes for re-irradiation. However, both kinetics of the OAR repair and the RD values are not precisely quantitated, but only approximately identified based on the results of animal experiments and fragmentary clinical studies on only a few OARs, and they practically remain unprecise.

Spinal cord tolerance to re-irradiation was intensively and experimentally tested on non-human primates [1, 22, 26, 28, 30]. The results suggest that the "remembered dose" by the spinal cord is close to 50% of the primary dose (fig. 4), if the interval between two types of irradiation is not shorter than 12 months. No myelopathy has occurred after a cumulative total-EQD_{2tot} <172%. Moreover, the pronounced sparing effect was noted [23, 27, 28, 30, 37] after twice-a-day hyperfractionation. Spinal cord re-irradiation using the SHRT [19, 33] can be safe if the cumulative $EQD_{2.0}$ does not exceed approximately 70–75 Gy. Generally, spinal cord re-irradiation practically limits to the recurrences in the spinal canal or spinal cord metastases. For re-irradiation of recurrences within the head and neck region, spinal cord tolerance is no longer a problem, since the cord can easily be left out of the irradiated volume. For example, for nasopharyngeal recurrences, a high dose re-irradiation is recommended [39], despite the treatment related morbidity. Re-irradiation to the cumulative dose EQD_2 of about 120 Gy (re-irradiation total dose of 60–65 Gy) generally resulted in retreatment complications lower than expected (e.g. risk of the carotid blowout of <3%), particularly when the intertreatment interval was longer than 2 years and the hyperfractionation schedule with 1.5 Gy per fraction (b.i.d.) was

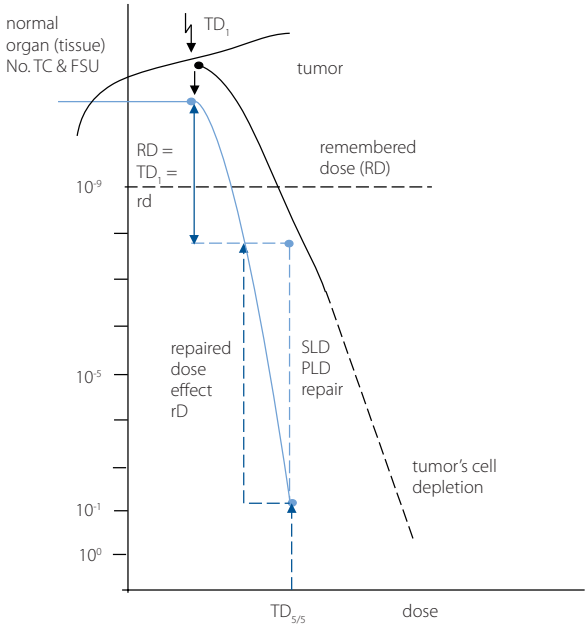

Figure 3. Theoretical scheme of critical organ (tissue) response to the primary total dose (TD_1) Part of the total dose (rD) absorbed by normal organ (tissue) is counterbalanced by the effective SLD and PLD repair, and therefore the remembered dose – rD = TD_1 – rD

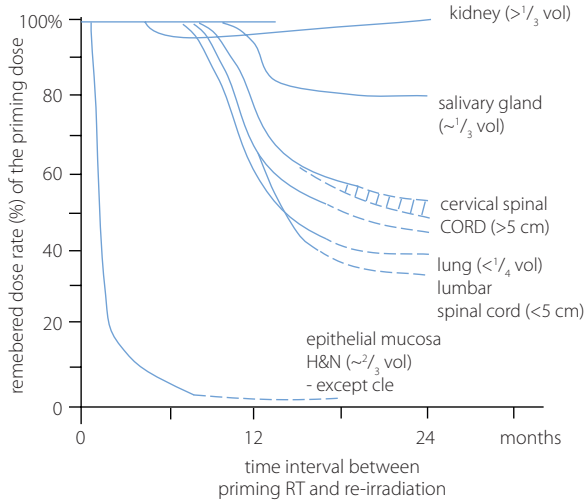

Figure 4. Remembered Dose for selected normal organs (tissues) depending on the time interval between primary and re-irradiation

used with a total dose higher than 60 Gy [1, 8, 11, 14, 25, 30], which can produce 35–50% of local tumor control. By contrast, lower total doses turned out to be definitely ineffective. Stereotactic hypofractionated re-irradiation (SHRT) has been recommended [15, 16, 19, 33, 35, 37, 38] for recurrent cancers, mainly localized beyond the previously irradiated area, with a relatively safe dose of BED < 130 Gy.

The "remembered dose" for the lung (fig. 4) was infrequently tested using the animal model [22]. Both the size of the priming dose and the time interval had a significant impact on the post-re-irradiation response [22, 25, 30, 34]. After a low primary single dose of 6 Gy, the lung tolerates re-irradiation as it was not previously irradiated. At least 1 month after the primary dose of 10 Gy, about half of that dose (25–75%) is remembered as a persistent residual damage. However, transferring quantitative experimental results to a clinic setting seems risky. Jackson and Ball's study on re-irradiation of recurrent non-small-cell lung cancer [34] has revealed a relatively large recovery potential of the occult injury. The re-irradiation dose $EQD_{2.0}$ of 20–30 Gy, delivered 18 months after the priming dose $EQD_{2.0}$ of 55 Gy did not cause any symptomatic radiation pneumonitis [22, 34]. However, re-irradiation of the lung can be a serious problem for patients who suffer(ed) from benign pulmonary diseases or heavy smokers.

Some experimental studies showed that kidney and salivary glands are the organs with a vestigial repair capacity [22], and the rate of remembered dose after priming irradiation can be high and close to 90% (fig. 4). Some functional recovery of the salivary glands may however occur 1 year after re-irradiation, if the cumulative $EQD_{2.0}$ did not exceed 40 Gy. Slight xerostomia has occurred after 10–15 Gy, if more than 30% of the gland was within the irradiated volume.

The kidney is classified as a highly radiosensitive organ (low number of the TC within a large number of the FSU), but the latent period before expression of the clinical late radiation injury can take years, particularly after low doses. Progressive renal damage may even develop many years after irradiation. For example, after an initial dose of 6 Gy (25% of the EQD_{2tot}), the tolerance to re-irradiation decreases during about 26 weeks, which may suggest continuous progression of the occult damage. Thus far, ⅓ of the kidney volume should not receive a cumulative dose higher than 30 Gy, and re-irradiation of the kidney, similar to the salivary gland, must be considered with extreme caution, or not at all.

Figure 4 shows the remembered doses, but for the selected tissues (organs) only, and they are rather deduced than quantitively estimated based on the available fragmentary clinical and experimental data, and therefore must be considered with a limited certainty. By contrast with the kidney and other mature tissues, the epithelium (head and neck aero-digestive mucosa) is a unique one with enormous repair and proliferative capacity, which effectively balances radiation cell kill and sublethal damage. The epithelial cells repopulate fast after the primary dose, and it is almost forgotten after a few weeks. This means that the remembered dose can drop close to zero (fig. 4), unless dose fractionation accelerates and is incessantly continued (including weekends). In such a case, the reserve of the epithelial cells completely depletes and radiation cellular effects gradually progress into a "consequential late effect" (CLE). Therefore, the CLE area (even if healed) should not be included in the re-irradiated volume.

Re-irradiation – know-how dilemma

Despite a few decades passed, clinical studies on re-irradiation still remain fragmentary. Although some animal experiments have been carried out, tolerance estimates and the remembered doses cannot be simply and directly transposed to clinical radiotherapy. Knowledge on the re-irradiation and underlying radiobiological mechanisms are incomplete, mostly limited to experimental and a few retrospective clinical studies. The majority of clinical guidelines are rather approximations based on expert opinions, but with uncertain reliability [3, 11, 22, 24, 29, 30]. Thus with a few exceptions, objective dose constraints (cumulative biological doses) for re-irradiation, prostate recurrence, radical thoracic re-irradiation of non-small-cell lung cancer, locally recurrent nasopharyngeal cancer, recurrent breast cancer, SHRT for spinal metastases and recurrent cervix cancer are generally sparse [4, 5, 15, 18, 19, 29, 30, 33, 34, 36, 37]. High-level evidence on re-irradiation is incidentally available, especially regarding optimal patient selection and the safety of high cumulative doses, since the entire spectrum of dose fractionations has been retrospectively explored and assigned to more or less precisely defined risk of the severe late complications. Although technological advances in radiotherapy offer the delivery of higher and radical biological doses to the tumor with improved sparing effects for normal tissues, radiation oncologists are understandably reluctant to re-irradiate tissues which primarily received high doses, especially if surgery can effectively be applied. There is still a scarcity of precise, quantitative data regarding the time interval between treatments, the dose fractionation pattern, the type of normal tissue at risk, incidence and severity of late complications after the priming irradiation [17] and the patient's life expectancy and quality.

Regarding retreatment, the following terms have been practically used in radiotherapy: re-irradiation, retreatment, salvage, recurrent, palliative, metastases' radiotherapy [3]. Andratschke et al. [21] pointed out that specific recommendations for re-irradiation did not exist until 2022, despite having been urgently needed to ensure common standards. The ESTRO and EORTC Delphi consensus of international experts (21) proposed the definition that: "re-irradiation is a new course of radiotherapy, either to a previously irradiated volume (irrespective of concerns of toxicity) or where the cumulative dose raises concerns of toxicity", which should fulfil the following four criteria:

- irradiated region defined,

- prescribed dose,
- time interval between treatments, and
- degree of the overlap of irradiated volumes.

Three scenarios of re-irradiation have been proposed (fig. 5):

- type 1 is a new course of RT that has geometrically overlapped with part or the whole of a previously irradiated volume,
- type 2 relates to a new course, with concerns of toxicity from the cumulative doses, but with no overlap of the irradiated volumes, and
- type 3 relates to the following two options:
  - repeat organ irradiation which is a new course of RT to a previously irradiated organ but with no overlap of the irradiated volumes, and
  - repeat irradiation means a new course of RT to a previously unirradiated organ, and without concerns for toxicity from the cumulative dose.

This decision-tree based on three binary questions (fig. 5) should help to classify the available treatment factors (at least 4 criteria previously mentioned), and to choose a proper scenario of a repeat course of RT.

Type 1 scenario relates to a complete or partial overlap of the irradiated volumes. It raises a challenging dilemma whether a radical (high) or palliative dose should be applied. The time interval between treatments is a crucial factor. It seems that at least a 12-month interval is reasonable. If it is shorter than 6 months, re-irradiation becomes riskier. However, if the recurrence (metastatic lesion) volume is small and the overlap is a small part of a previously irradiated volume, then precise 3D-IMRT, VMAT, SHRT offer the radiation beam(s) a direct focus on the tumor mass with sharp-down dose-gradient beyond. For larger re-irradiated volumes, radical hyperfractionation with a dose per fraction of 1.5 Gy (b.i.d.) or less is advocated as optimal.

The ESTRO and EORTC re-irradiation scenarios were established and published in 2022 [21]. In the previous years, although the number of clinical studies on re-irradiation has increased, the majority of them were retrospective and heterogeneous regarding the entire spectrum of dose fractionation schedules and treatment outcomes. Moreover, when recurrence developed in the organ with the primary tumor, the information as to whether primary and secondary volumes overlapped was not usually recorded, and the situation became even more difficult when the interval was short and allowed for little to no forgiveness of the prior RT, making the re-irradiation riskier and highly challenging. There are many reasons for such situations. A review of many retrospective studies [6–8, 10–13, 29, 30, 34] raises serious uncertainties since more than 9% of them were focused on a single anatomical site of recurrence, mainly the head and neck or brain. Only 14% of studies reported constraints for OARs and cumulative doses to the OARs were infrequently and inconsistently reported (17%); quality of life after re-irradiation was evaluated in only 8% of the reports. Such a deficit of information makes decision regarding re-irradiation quite challenging. When a type 1 scenario is chosen then the remembered dose of the OARs within the planned re-irradiation volume most be considered as an essential parameter. Thereby after 20 years or more, the RDs can only be anticipated and for a few OARs only (fig. 4). In case of the type 1 scenario, a deficiency of important information on the choice of the optimal total dose seems to be unattainable. If a high risk of complications is apprehended, a "Luke Warm Bath" with a dose of 50 Gy or less is chosen, instead of a "hot shower". One should keep in mind that such palliative doses (except the SHRT) are usually ineffective, but they can be an overload for late responding normal tissues. Such a dilemma might be solved by using 3D-IMRT, VMAT or SHRT, which offer the delivery of effective biological doses to maximize the chance of durable local control, and to achieve high and safe therapeutic gain.

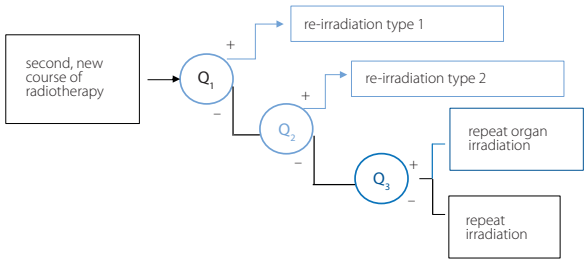

Figure 5. Decision tree for 4 scenarios of re-irradiation according to the ESTRO/EORTC consensus [21]

The type 2 and 3 scenarios of repeat- or re-irradiation are much less risky since the priming and recurrent volumes are not overlapped. Metastases in various normal organs are a "growing family of the customers" for these two types of repeat – or re-irradiation scenarios. For a few reasons (mentioned earlier), stereotactic hypofractionation (SHRT) has been recognized and documented as a highly effective option. Moreover, the SHRT significantly shortens overall treatment time from weeks to day(s), thereby providing an opportunity for out-patient therapy.

The sources of brain metastases are various primary tumors origins. The use of the SHRT reduces neurocognitive toxicities due to a significant reduction of the irradiated volume, and it can be used as a radical or salvage re-irradiation with high 1-year local control rates between 60% and 91% [3, 30], and with a low risk (8%) of radionecrosis. A few small metastatic lesions can easily be eradicated by a single dose or a few SHRT fractions, in contrast to a single metastasis but with a much larger volume (if in both situations the total volumes are equal), which would need a rather more conventionally fractionated dose than SHRT, and a local control of which is much lower.

Re-irradiation using the SHRT has also turned out to be effective for spinal cord with no risk of radiation myelopathy and liver metastases with the retained adequate function [19, 27, 30, 33, 35, 37]. For single or multiple bone metastases, the SHRT with

a single dose of 10–15 Gy or 3 fractions of 8–15 Gy has widely been accepted as an effective therapy with 58–65% complete pain relief, lasting 15–22 weeks [3, 20, 30].

Many studies, mainly retrospective, were not included since their results were incomplete or at least uncertain, and/or sample sizes were too small to accept the results as valid. Nevertheless, the selected number of respective studies [1, 3–8, 11, 17, 21, 30, 34, 37] fulfilled all established criteria for 8427 recurrent tumors, although they referred to a few normal organs only. They are presented in table I. The majority of parameters in that table are deduced rather than estimated. Among the various RT methods, the IMRT and the SHRT were the most often used. The relatively low incidence of the LRE may suggest that the re-irradiation doses were suboptimal and they can be higher. As a rule, the factors and parameters in table I should rather be interpreted as suggestions but not recommended standards, since there is a lack of information in the majority of studies regarding primary and re-irradiated lesions overlapping or not, is essential prerequisite for the type 1 re-irradiation scenario.

Table I. Review of the primary and re-irradiation parameters, cumulative doses, outcomes and risk of late complications for the selected normal organs (tissues) [1, 3, 7, 11, 13, 15, 21, 27, 29, 30, 34, 38, 39]

Organ at risk	First course RT, TD/no/fx	Time interval beetween first and second course of RT (months)	Re-irradiation second course TD/no/fx	Cumulative dose $EQD_2(\alpha/\beta)$ $BED(\alpha/\beta)$	Outcomes in years	Risk of LRE (%)	Technique
brain stem (230 GMB), atrocytm	50–60 Gy/ 25–30 fx 40.5 Gy/15 fx	>12 mo	<10–50 Gy/ 20–25 fx 12 Gy/1 fx 18–24 Gy/3 fx	$EQD_{2/3}$ = 100 Gy_3 135 Gy_3	1 yr PFS – 17% 1 yr OS – 36%	radionecrosis 2–5%	3D-IMRT SHRS
brain metastases (626 pts), various origins	various primary tumors, doses irrelevant	9–20 mo >100 mo	15–20 Gy/1 fx 21–30 Gy/3 fx 21–24 Gy 3 fx	BED_3 – 110–160 Gy BED_3 ~ 100 Gy	2 yr LC – 70–80% 2 yr OS – 30–52%	radionecrosis ~ 8.5% radionecrosis	SHRS
spinal cord (227 pts), rodents experiments – lumbar	40–45 Gy/2–22 fx (cervical) 10–12% higher	>6 mo >18 mo	20–35 Gy/ 12–14 fx 26–30 Gy/ 13–15 fx	BED_2 ~ 130–145 Gy_2 BED_2 ~ 140–150 Gy_2	2 yr LC ~ 85% 2 yr ~ 60%	~ 0.8% radiolopathy neuropathy <1%	SHRS IMRT SHRS
bone metastases (2672 pts), primary tumor: lung, prostate, breast, kidney	various primary tumors and doses irrelevant	unimportant	10 Gy/1 fx 10–10, 20 Gy/3 fx 30 Gy/10 fx	$BED_{2.5}$ ~ 30–70 $Gy_{2.5}$	complete pain relief ~ 30–50%	osteonecrosis bone fracture ~ <3%	IMRT SHRS
head and neck (2992 pts), • mandible • carotid arter • parotid	60–70 Gy/ 30–38 fx 50–60 Gy/ 25–30 fx 50–55 Gy/ 25–27 fx ~30 Gy/30 fx	>6 mo >1 year >1 year	60–72.4 Gy/ 50 fx (b.i.d.) 50–56 Gy/ 34–37 fx 50–56 Gy/ 34–37 fx 30 Gy (1/2 vol.) after >2 yrs salvage surgery 30–35%	BED_3 ~ 125–175 Gy_3 <120 BED_3 <100–125 BED_3 $BED_3 \leq 120$ Gy_3	3 yrs LRC – 35–69% 3 yrs OS – 25–39%	osteonecrosis 8–12% carotid blowout ~ 3% xerostomia <10%	IMRT (hyper fx) SHRT
lung – non--small-cell cancer (704 pts), organs: • lung • heart • great vessels • trachea • brachial plexus	50–65 Gy/ 25–37 fx 40 Gy/16 fx 48 Gy/3–5 fx ± chemotherapy	>6–12 mo	not well defined 48–56 Gy/ 30–35 fx (b.i.d.) 30–45 Gy/3–5 fx	IMRT SHRT	BED_4 < 14 $5Gy_4$ V_{20} < 20% V_{40} < 50% BED_{max} < 120 Gy BED_{max} < 110 Gy BED_{max} < 85 Gy	symptomatic response 60–75% 3 yr OS – 35% 1 yr LTC after SHRS > 70% mainly peripheral localisation	various LRE 7–21%
breast – local (482 pts)	45–50 Gy/ 25–28 fx + 16 Gy boost (IORT BRT) ± hormono--chemotherapy,	various usually >6 mo	optimal re-RT unclear >60 Gy 30 Gy + HPT ± chemotherapy	IMRT SHRT BRT	BED_5 < 150 Gy_5 <30 Gy for ⅓ vol. of lung <30 Gy for 15% vol. of heart	3 yr LC 63–75%	~ 10-25% teleangiectosis skin fabrosis & contracture cardiac disfunction

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Table I cont. Review of the primary and re-irradiation parameters, cumulative doses, outcomes and risk of late complications for the selected normal organs (tissues) [1, 3, 7, 11, 13, 15, 21, 27, 29, 30, 34, 38, 39]

Organ at risk	First course RT, TD / no.fx	Time interval beetween first and second course of RT (months)	Re-irradiation second course TD/no/fx	Cumulative dose $EQD_2(\alpha/\beta)$ $BED(\alpha/\beta)$	Outcomes in years	Risk of LRE (%)	Technique
	surgery, depending on stage of disease						lung local fibrosis
liver – hepatocellular cancer (575 pts), metastases	50 Gy/5 fx, 40–45 Gy/ 5 fx 30 Gy/5 fx (<½ vol.)	>8 mo	30 Gy/20 fx (b.i.d.) 25 Gy/ 156 fx Gy/3 fx 15 Gy/3 fx 20 Gy/6 fx 21 Gy/7 fx	SHRT IMRT (hiperfx) SHRT	EQD_2 98–105 Gy $D_{0.5max}$ < 10–15 Gy D_{800} < 9–13 Gy stomach	3 yr OS 28–56% 2 yr LC 80%	stomach perforation 7–10% radiat. induced liver disease 10–15%
pelvis (575 pts), mainly cervix ca OAR: bladder, rectum, kidney	54–76 Gy/ 27–38 fx BRT – 27–35 Gy	>18 mo	36 Gy/5 fx, 42 Gy/7 fx 40 Gy/4–6 fx 39 Gy/3 fx, 20 Gy/4 fx 40.8 Gy/34 fx (b.i.d.)	IMRT, BRT, SHRT chemotherapy hyperfx	kidney (½ vol.) < 15 Gy bladder BED_3 <120 Gy rectum D_{2cc} < 75 Gy sigmoid femoral head BED < 100 Gy	cervix ca: 3 yr LC ~ 75% OC ~ 33%	grade 3–4 toxicity 15–17% obturation perforation

TD – total dose in Gy; fx – number of fractions; $EQD_{2.0}$ – equivalent effective dose if given in 2.0 Gy fractions; BED_x – biologically effective dose for (x) – α/β value; LC – local control; OS – overall survival, LRE – late radiation effects; IMRT – intensity modulated radiotherapy; SHRT – stereotactic hypofractionated radiotherapy; BRT – brachytherapy; RT – fractionated radiotherapy

Conclusions

Knowledge on re-irradiation as one among various radiotherapy modalities has mainly been based on fragmentary results of retrospective clinical studies and some animal experiments until 2022; from that point ESTRO/EORTC experts defined what re-irradiation means and proposed a decision-tree for four clinical scenarios that fulfil the criteria for re-irradiation to be considered as obligatory, and parameters and clinical factors must be accounted for and reported (tab. II), before the choice one among four re-irradiation scenarios. If life expectancy is short, then symptoms referred to the re-irradiation might be considered without concerns for irreversible toxicity despite excessive cumulative doses. The ESTRO/EORTC guidelines and re-irradiation scenarios clarify some uncertainties and are important and useful for actual and prospective studies as a source of precise data and growing experience in the field of re-irradiation. However, nowadays we are still condemned to retrospective sources of re-irradiation using a spectrum of dose fractionations. Data on the remembered dose, so important for the type 1 scenario, dose tolerance constraints, cumulative biological dose for both treatments are fragmentary, often uncertain and sometimes are even "blank points". Therefore the palliative "bath" or a "hot" radical shower dilemma remains, since it is not easy to clarify immediately all uncertainties involved. However, the ESTRO/EORTC guidelines (tab. I and II) raise promising perspectives when all required factors

Table II. Factors and parameters required to select an optimal re-irradiation scenario and to report the results (according to the ESTRO/EORTC consensus [21])

Patient characteristics
age, sex, performance status
life style (drinking, smoking)
estimated life expectemcy
Tumor characteristics
primary tumor site location and histology
local recurrence, or metastases or new primary tumor
in field marginal or out-field lesion
retreatment target volume
Previous radiotherapy or other treatments
number of courses
dose, time, fractionation
standardised toxicity persisent or not
time interval since priming RT
previous surgical and/ on systemic therapies
RT technique
Indication to retreatment
treatment intent curative, palliative
goal local control symptom relief or prevention prolongation survival
type 1, 2 or 3 scenario (ESTRO, EORTC)

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Table II cont. Factors and parameters required to select an optimal re-irradiation scenario and to report the results (according to the ESTRO/EORTC consensus [21])

Re-irradiation planning
dose, fractionation targets of organs at risk and dose constraints
RT modality and technique
biological dose estimation
cumulative dose(s) of both treatments
organs at risk and its cumulative doses
Follow-up
standardised reports of toxicity
follow-up intervals and duration

and parameters of priming and re-irradiation treatments will be accurately recorded and collected. Crane [11] pointed out that the most practical way to solve the challenge in the field of the state-of the art practice of re-irradiation is to try to reach consensus among clinicians who see and treat such patients on a regular basis, and are confronted with optimal decisions.

Article information and declarations

Author contributions

Bogusław A. Maciejewski – concept of the work, determination of $TD_{5/5}$ and $TD_{50/5}$ doses and remembered doses, preliminary and final version of the manuscript.

Dorota Gabryś – development of the ESTRO/EORTC consensus and the radiobiological part of the response and health protection to radiotherapy, participation in proofreading the manuscript.

Aleksandra Napieralska – an addition to radiotherapy, IMRT and SHRT for palliative and radical recurrence and metastases.

Conflict of interest

None declared

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