MATHEWS Open Access Journals

ISSN: 2474-6797

Mini Review | Mathews Journal of Cancer Science

Reirradiation of Skin Tumors

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Received Date: 18 Feb 2016
Accepted Date: 29 Feb 2016
Published Date: 09 Mar 2016

Citation: Virginia M. (2016). Reirradiation of Skin Tumors. M J Canc. 1(1): 003.

ABSTRACT

With the increase of life expectancy, there are more cases of local recurrence or in-field secondary cutaneous tumor in previously irradiated skin cancers. In most cases, due to the radiation-induced fibrosis and comorbidities associated with old age, patients have no indication for surgery or systemic treatments (e.g., chemotherapy, cetuximab). Therefore, reirradiation is the option available to try the local control of the cutaneous tumor, and consequently improve the survival. However, there are very few and heterogeneous pre-clinical studies described in literature, and the clinical reports that exist are small and retrospective revisions. This paper is a mini-review of these basic and clinical reports, and other analyses. Irradiation with curative intent is possible, but it must be aware of a decrease in tissue tolerance from previous radiation therapy, that may improve with the increased time between the two irradiations. It should also be take into account the risk-benefit, the comorbidities, the total dose, the fractionations, the irradiated volume, and the dose previously received by the organs at risk. This subject may justify a clinical trial.

KEYWORDS

Skin Cancer; Cutaneous Tumor; Reirradiation; Retreatment; Tolerance; Local Recurrence; Radiation Therapy.

ABBREVIATIONS

BED: Biologically Effective Dose;

BT: Brachytherapy;

EQD_2: Biological equivalent dose in 2 Gy fractions;

Gy_3: Biologically effective dose assuming an α/β of 3 Gy (dose for late reacting tissues);

IMRT: Intensity-modulated RT;

RT: Radiation Therapy;

SRT: Stereotactic RT.

INTRODUCTION

Studies of RT as definitive treatment in primary and recurrent skin cancers consistently report high rates of local control despite extremely variable total doses and fractionation schedules [1-6]. With the increase of life expectancy, many patients develop second primary tumors within or close to previous RT area or late in-field recurrences [7]. Moreover, surgical options are frequently compromised by local responses (e.g. fibrosis) to the first treatment [8]. Therefore, there are increasing request for reirradiation when other treatment options are discarded [7].

However, reirradiation remains clinically challenging, especially with curative intent, because such treatment is thought to induce severe iatrogenic complications (bleeding, ulceration, tissue necrosis), as demonstrated in mucosal tumor reirradiation [1,7,9-12]. On the other hand, preclinical data are relatively scarce, and there are no clinical data in

literature to support the safety and efficacy of skin cancer reirradiation with curative doses, only small retrospective studies, regardless of doses and fractional schedules, with limited statistical power. Moreover, the capacity for long-term recovery from RT injury varies considerably among tissues and species [1,7,9,13].

The Skin

Histologically, the skin is composed of three compartments: the epidermis, the dermis, and the hypodermis. The epidermis is a keratinized stratified squamous epithelium that is replaced continuously from the basal layer. The renewal cycle is about 3 weeks. The dermis is the most important layer of the skin. It provides strength, elasticity and self-renewal capacities to the skin, and contains blood and lymphatic vessels, nerve endings, hair follicles, and sweat and sebaceous glands. Most cutaneous sensory receptors are located in the hypodermis, or subcutaneous tissue. It also includes wider lymphatic and blood vessels, and fat tissue. The skin is a first defense against microbial agents and to physical and chemical compounds. It also allows regulate the temperature of the body via the sweat glands [14].

In terms of RT delineation, the skin coat corresponds to the whole body surface in a thickness of 3-5mm.

Radiobiological Aspects of Skin RT

The mechanisms involved in the genesis of radiation induced toxicity depend on the individual radiosensitivity, the tissue and cellular architecture, the total administered dose, the fractionation, and the volume irradiated [9].

Skin has no well-defined functional subunits, but responds in a way similar to tissues in parallel [15]. The loss of organ function after RT requires destruction of several subunits [9]. A fleeting erythema may appear within hours of irradiation and then disappears a few hours or days later [14,16]. The definitive destruction of adult stem cells by RT leads to a non-replacement of differentiated cells [9,17]. Therefore, the expression of side effects appears when cells enter again in mitosis [9]. The functional damage to the *stratum corneum* induced by RT starts within a mean period of 11 days and reaches maximal values after a mean of 27 days (range: 13-75) [16]. The grade 2 radiodermatitis , or epidermal necrosis, appears in 4-5 weeks after the beginning of conventional RT (1.8-2 Gy/fraction, one fraction/day, and five fractions/week) or after an EQD_2 to the skin of 40 Gy, and disappear 1-2 months after RT (skin renewal lasting 20-45 days) [14,18]. An EQD_2 to the skin of less than 45 Gy allows to limit the appearance of severe acute or late cutaneous toxicity [14, 19]. In addition to the stem cells, multiple cellular and molecular actors are involved in the genesis of the radiation induced toxicity after conventional RT, such as inflammatory and immune systems (via a chronic inflammatory response by the secretion of interleukins-1β, 4, 5, 6, 10, 13, and transforming growth factor β1), the endothelium compartment (via an imbalance of the thrombin/thrombomodulin equilibrium), and the mesenchymal compartment (by chronic activation of myofibroblasts and increased synthesis of extracellular matrix) [9,20-28]. However, no data have been described in the literature for the involvement of these actors in the genesis of toxicity induced by reirradiation [9].

The functionality of the sebaceous glands is altered as from EQD_2=12 Gy, that of sweat glands as from EQD_2=40 Gy (reversible, but the time to normalization is greater the greater had been the toxicity, and it can be more than a few weeks, even 6 months), and that of hair follicles as from EQD_2=10-20 Gy (hair loss within 1-2 weeks of RT, temporary, but reconstitution of hair may require up to one year) [14,19,29]. An EQD_2 of 43 Gy 4.5 mm under the skin can elicit 50% of permanent alopecia, and this rate increases with the dose [14,30]. Fibrosis of hair follicles is associated with a permanent alopecia [14,31].

Under an EQD_2 of 45 Gy, the risk of severe skin toxicity (grade 4-5) is low, and begins above an EQD_2 of 50 Gy, as late cutaneous toxicity [14,19]. Based on breast cancer studies, the appearance of telangiectasia takes place usually either when administering a dose complement (boost), either when there was an acute radiodermatitis of at least grade 3, although these are not predictive for other late skin toxicities [14,18,32,33].

Poikiloderma, atrophy, and subcutaneous fibrosis are more likely at doses of at least 54-58 Gy [34].

According to the linear-quadratic model, the α (intrinsic radiosensitivity)/β (repair capacity) ratio for acute skin toxicity is about 10 Gy (7.5 Gy for erythema and 11.2 Gy for desquamation), whereas it is about 3 Gy for late toxicity (1.9 Gy for fibrosis and 3.9 Gy for telangiectasia) [14,35-37]. Acute toxicity is greater when dose per fraction increases [14]. In hyperfractionation, where a higher number of fractions of less than 1.8 Gy is given, usually 2 fractions/day, not closer than 6 hours apart, because of incomplete damage repair, there is sparing of late-responding normal tissues (with low α/β values) relative to those which respond early, due to the differences in repair capability (therapeutic gain) [38-42]. Obviously, hyperfractionation was among the few strategies available in the past, before BT, SRT, IMRT, tomotherapy, and other tools became a part of our armamentarium [38]. By contrast, the high α/βvalues observed for acutely responding tissues indicate that the response is relatively linear over the

dose range of clinical interest. Consequently, less extra sparing effect is expected if lower doses/fraction are administered [38,39]. The hypofractionation favors the development and severity of late complications [43]. However, increasing the dose/fraction to 2.65 Gy does not seem to increase the acute and late dermal toxicity in breast cancer RT [14].

Above a surface of 40 x 40 mm, there is no increase in the severity of histological injury if the surface of irradiation increases [14,44]. Below this size, the higher the irradiated surface, the smaller the dose required to achieve the same toxicity [14].

Furthermore, toxicity is all the more severe the shorter the total RT time (impossibility for the skin to renew itself). Split-course schemes let improve skin tolerance to RT [14,45]. Moreover, the addition of concomitant chemotherapy (platinum salts) or cetuximab is associated with a more severe toxicity [14,46].

On the other hand, several factors linked to patients influence skin toxicity, such as performance status, undernutrition, old age, obesity, smoking, skin diseases, autoimmune diseases, failure of deoxyribonucleic acid reparation, human immunodeficiency virus infection, and skin infection [14,47,48].

Radiobiological Aspects of Skin Reirradiation

Rapidly proliferating tissues (e.g., tumor, epidermis) generally recover well from the initial RT and will tolerate reirradiation to almost full doses. Some slowly proliferating tissues (e.g., dermis, hypodermis) are also capable of partial proliferative and functional recovery, although this might take several months and some residual damage might remain [49].

Skin tolerance to reirradiation depends upon the number of surviving stem cells or units within the irradiated area, or stem cells migrating into the irradiated tissue from non-irradiated sites, and the dose of reirradiation [8,13]. In animal models, 10-45% of residual damage from previous RT has been reported [48,50-52]. In humans, Chen et al. [53] observed a reduction of 17-21% of reirradiation dose for endpoints of colony formation and healing ability [13]. Such reduction also was found to be dependent on fractionation schedule and the total dose of the first course of RT [13,54]. This "memory" of the tissues irradiated must be balanced with a "forgetting factor", according to the time interval between the two RT series [9].

Reirradiation is achievable with electrons (little penetrating rays), conventional RT in split-course, a very targeted or conformal RT (IMRT, BT, proton therapy, SRT), or conventional RT coupled to hyperthermia (which allows a reduction of RT dose) [12,14,45,55,56]. Reirradiation is complicated in 0-34% of cases with grade 3 acute radiodermatitis and 3-17% with chronic radiodermatitis of grade 3-4 [14,56]. Acute skin toxicity of grade 3-4 occurs in 2.9% of cases treated with IMRT, and in about 6.9% with hyperfractionated scheme in split-course with concomitant chemotherapy [12,14,45,55].

In breast cancer, an interval between the first RT (50 Gy in 25 fractions over 50 days) and reirradiation (mean dose of 45 Gy [range: 33-65] in 15 fractions over 33 days) exceeding 7 months decreases the occurrence of late complications [43], and a repeat course of RT (50 Gy in 25 fractions) to a new operative area (conservative surgery) of in-breast tumor recurrence no late sequelae presented other than skin pigmentation changes, fibrosis, and telangiectasia [57].

In epidermis of rodents, after RT with a single dose ranging between 15 and 37.5 Gy, a reirradiation was carried out in another single fraction (15-38 Gy) at different times after the initial irradiation. This shows that a delay is needed between the initial RT and reirradiation for optimum tissue recovery. With a delay of 2 months, it is observed a complete restoration of the cutaneous epidermis, and the skin can be reirradiated as if it had never been irradiated. On the other hand, the intensity of the acute toxicity (skin desquamation) following reirradiation appears to be more important after a high initial dose and also a high dose at the time of reirradiation. If the interval is one month, there is a "tissue memory" of RT of 11 Gy after a dose of 37.5 Gy [9,58].

In fractionated RT, the tolerance, in terms of acute inflammatory reactions and secondary deformation of the members, is limited to 80% of the initial dose after the initial RT of 50 Gy in 10 fractions of 5 Gy [9,50,59]. Therefore, it seems that the skin retains a "tissue memory" estimated from 10 to 20% of the total initial dose, with some residual damage even after 6 months [8,9,50]. The regain in the acute tolerance to reirradiation is likely a result of the ability of the epidermis to respond to RT damage by accelerated repopulation leading to restoration of the original cell number [7,60].

Subcutaneous fibrosis was evaluated in mice models that measured the stretchability of the leg irradiated [9,50,59]. Six months after reirradiation, there was a marked reduction in skin tolerance, with a significant retraction of the members. The severity of functional impairment is more marked after an initial intensive RT schedule (50 Gy in 10 fractions of 5 Gy vs. 40 Gy in 10 fractions of 4 Gy) [9,50]. For some late-responding tissues, like dermis and hypodermis, complete restoration of tolerance is observed after low and moderate initial doses (<60% of the initial tolerance), and, in general, a reduction to 50-70% of the EQD_2 of tolerance is found after reirradiation [8]. However, these late skin tolerance data are controversial because they were not confirmed by all teams

and depend on used models (lower limb vs. skin integument; mice vs. pig), representing different sensitivities between the anatomical structures and the species studied, and modalities of analysis. In pig, a single fraction of 18 Gy was considered to be the cutaneous maximum tolerated dose in both initial and reirradiation treatment to prevent dermal necrosis [9,60]. There was no or little (at most 2-7% of the initial dose) residual injury retained for late ischemic dermal necrosis. In addition, the latency for development of necrosis was not different. The exact mechanism underlying such recovery is not yet clearly understood [7,60]. In mouse studies, the reduced reirradiation tolerance for late toxicity may have been influenced by the severity of early epidermal reactions in the first RT, based on the development of consequential changes (when some manifestations of acute radiodermatitis extend in time even become chronic) [8,14,61].

The tolerance of human skin telangiectasia increases by roughly 3.9% of the total side effect per week. However, that long-term recovery appears to occur within a defined time period that depends on the size of the priming dose and differs among species and age [7,62]. In addition, late radiation toxicity rates are significantly higher (risk ratio of 1.4) for patients with hypertension or diabetes *mellitus,* indicating that comorbidities can confound risk assessment [7,48]. Unfavorable prognostic factors are a high tumor size of relapse, a short interval between the recurrence and the last RT, the presence of changes resulting from previous RT (skin fibrosis, atrophy, or telangiectasia), an organ dysfunction, a high Charlson comorbidity index, and a high dose of reirradiation [7,14,48,55,63].

In the context of reirradiation, while acute toxicity largely is comparable to that of first-line treatment, late toxicity resulting from high cumulative RT doses might often be observed [38,60,64]. Chronically progressive fibrosis has been described [38]. The median cumulative maximum dose to the tumor and its regions used by Abusaris et al. [49] in who received three courses of radiation therapy was 133 Gy_3 (range: 82-496) and after two radiations was 90 Gy_3 (range: 52-184). Grade 3 acute skin toxicity was only seen in the third radiation course.

May be, one should reirradiate with a BED that is substantially greater than the original therapy, which failed to control the tumor [1]. Rwigema et al. [65] found improved locoregional control with higher prescription doses of SRT. In Chao et al. [13], those patients with BED of previous treatment at 5 mm depth less than 55 Gy, and accumulated BED on skin surface of no more than 110 Gy had the best outcome (local control without subsequent complications). Higher accumulated BED did not seem to be beneficial and was associated with an increased chance of skin defects. Moreover, recurrent lesions receiving higher surface dose (BED>58 Gy) in initial RT seemed not to respond satisfactorily to subsequent reirradiation [13,62].

DISCUSSION AND CONCLUSIONS

Reirradiation not only palliates cancer-related symptoms but, under certain circumstances, it might contribute to improved survival, especially in diseases where local control determines survival [38,66]. The only chance for achieving locoregional control and cure is through the delivery of a full dose of RT, similar to the dose required for primary tumors. The delivery of a low RT dose, commonly practiced to avoid complications, is expected to achieve palliation only, but palliative reirradiation shows mediocre control rates, leading to symptomatic local recurrences [1,48]. However, the patient's life expectancy and the risk/benefit ratio assessment must be taken into account, considering both clinical and dosimetric aspects [7]. It is necessary to consider the total dose, fractionation, and total treatment time of previous irradiation, the irradiated volume, the time interval between the two irradiations, and the type of organs at risk in previously irradiated area. The evidence in favor of reirradiation is the limited size of recurrence, and consequently, a small volume of reirradiation, the initial tumor radiosensitivity (good response to initial RT), a long disease-free interval, and the exhaustion of other therapeutic modalities [8,9,48].

If curative reirradiation is to be administered, optimum treatment planning (conformation of dose) and proper choice of fractionation protocol are required [8]. In a recent Canadian survey on reirradiation, many respondents recommended BT or highly conformal external RT techniques [38,67]. SRT can be applied in the subset of patients with lesser disease burden [1].

Reirradiation is also feasible in total skin electron beam therapy, in mycosis fungoides and other cutaneous lymphomas [34,68,69]. Wilson et al. [34] recommend a repeat course of 30-36 Gy.

Although skin toxicity tends to be thought less than other risk organs' toxicities when patients are treated with curative intent, with increase in life expectancy and as a result of sun exposure and the reduction of the ozone layer, there are increasing cases of skin cancer, particularly in the elderly, and has increased the number of requests for reirradiation thereof. However, there is no sufficient clinical evidence to support the reirradiation of skin tumors with curative intent. Therefore, a trial of curative reirradiation of skin cancers should be considered.

Key Points

- There are no clinical trials on reirradiation of skin tumors;
- Skin seems to be an organ in parallel;
- The renewal cycle of epidermis is about 3 weeks;
- Late toxicities are significantly higher (risk ratio of 1.4) in patients with hypertension or diabetes *mellitus*;
- There is 10-45% of residual damage from previous RT;
- In rodents, with a delay of 2 months, there is a complete restoration of epidermis, after single fraction RT;
- For late-responding tissues (dermis, hypodermis), complete restoration of tolerance is observed after low-moderate initial doses (<60% of the initial tolerance);
- The severity of subcutaneous fibrosis and functional impairment is more marked after a more intensive (hypofractionated) schedule of initial RT;
- In pig, a single fraction of 18 Gy was the cutaneous maximum tolerated dose in both initial RT and reirradiation to prevent dermal necrosis;
- Recurrent lesions that receives high surface dose (BED>58 Gy) in initial RT does not respond satisfactorily to reirradiation;
- BED of previous RT at 5 mm depth <55 Gy, and an accumulated BED on skin surface of ≤110 Gy have the best outcomes (local control without subsequent complications);
- In late-responding tissues (dermis, hypodermis), after reirradiation, there is a reduction to 50-70% of the EQD_2 of tolerance.

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