Abstract

Skin toxicity induced by radiation therapy is a complex adverse event which can affect all the layers of the skin or its appendages. Depending on the time of occurrence, the radiation toxicities are classified in early side effects, that occur during the treatment and late side effects, that occur more than 6 months completing the irradiation. From the point of view of causal mechanisms, radiation effects are due to cellular depletion and to cellular and tissue dysfunction/reaction. The early effects concern the rapid proliferating tissue in the superficial layers of the skin (epidermis), while the later ones involve the slow proliferating tissues in dermal stroma and vascular network. The side effects are classified according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, (CTC-AC) and Radiation Therapy Oncology Group (RTOG) in 4 grades, each with specific treatment.

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Rezumat

Toxicitatea cutanată indusă de radioterapie este un fenomen complex ce poate afecta toate straturile pieii și anexelor sale. În funcție de momentul apariției, toxicitatea produsă de iradiere este clasificată în toxicitate acută, care apare în timpul tratamentului, și toxicitate tardivă, care apare după cel puțin 6 luni de la terminarea iradierii. Din perspectiva mecanismelor cauzale, efectele iradiierii se datorează depleției celulară și reacției și disfuncției celulare și tubulare. Efectele adverse acute privesc șețururile cu rata rapidă de proliferare din straturile superficiale ale pieii (epiderm), în timp ce toxicitatea tardivă șteșește șețurile cu proliferare lentă din stroma și retelele vasculare. Efectele adverse sunt clasificate conform recomandărilor National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, (CTC-AC) și Radiation Therapy Oncology Group (RTOG) în 4 grade, fiecare cu tratamentul său specific.
INTRODUCTION:
Skin toxicity induced by radiation therapy is a complex adverse event which can affect all the layers of skin or its appendages. Due to its ubiquitous position between the region of interest and the accelerator, it is a fact to be taken care in each case, at various degrees. Through this literature review, we describe this potentially limiting side-effect from the pathophysiology to treatment considering each skin layer or cellular type.

RADIOBIOLOGY:
Radiation causes a wide range of Deoxyribonucleic acid (DNA) lesions like double strand breaks, single strand breaks and base damages, a dose of 1-2 Gy (dose usually used in conventional fractionated external irradiation) producing approximately 1000 single strand breaks and base damages and 40 double strand breaks (1). The balance between the DNA lesions production and reparation decides the cell outcome:

a) DNA lesions remains unrepaired and cause permanent cell cycle arrest, induction of apoptosis or mitotic cell death;
b) DNA lesions are incorrectly repaired and induce chromosomal rearrangements which can lead to carcinogenesis (2);
c) DNA lesions are correctly repaired, so the cell survive with restitutio in integrum of their functions (3).

From radiobiology point of view, cell death is defined as the loss of reproductive capacity. Thus irradiated cells do not die immediately, but may produce only a modest and limited family of descendants.

The effect of radiation is evaluated in vitro by cell survival curve which represents the surviving fraction as a function of the radiation dose (4). The tool used to describe cell killing for tumor and normal tissue is the Linear-Quadratic model (LQ) which enables in clinical practice, the comparison of different radiotherapy regimens in term of biologic tolerance dose for late toxicity is established for conventional radiotherapy fractionation, meaning 1.8-2 Gy per fraction, 5 fractions per weeks. To assess the risk of toxicity for altered fractionation regimens (more than 2 Gy per fraction) physical dose must be converted into an equivalent biological dose (5).

\[
\frac{D_1}{D_2} = \frac{d_2 + \alpha/\beta}{d_1 + \alpha/\beta}
\]

D1, d1: Total Dose and dose per fraction for regimen 1 (Gy)
D2, d2: Total Dose and dose per fraction for regimen 2 (Gy)
\(\alpha/\beta\): Parameter which defines the tissue radiosensitivity (Gy) (6)

Depending on the time of occurrence, the normal tissue responses to radiation are divided into two categories: early effects that occur during the treatment and late effects that occur more than 6 months after irradiation. Acute effects occur in rapid renewal tissues due to the critical death of certain cell populations and are characterized by inflammation, oedema, denudation of epithelia and haemorrhage.

Chronic effects occur in slow renewal tissues and are characterized by fibrosis, atrophy, ulceration (7).

Cells’ radiosensitivity, according to law of Bergonie and Tribondeau is influenced by the stage of cellular differentiation and by cellular proliferating activity. Thus, less differentiated cells are more radiosensitive than highly differentiated cells and proliferating cells are more radiosensitive than non proliferating cells (8).

SKIN HISTOLOGY AND RADIosenSITIVITY:
Skin layers are the epidermis, a stratified squamous keratinized epithelium, the dermis, a subjacent conjunctive tissue that hosts vessels and nerves and the hypodermis, the deepest layer, which consists of pads of adipose tissue (9).

The epidermis is composed of the basal layer (germinative) that is mitotically active and with more superficial differentiated cell layers. Basal epidermal stem cells (basal keratinocytes) which have high proliferative potential, maintain the turnover responsible for continuous renewal of the epidermis. Only 15% of basal cells are mitotically active, the remaining ones being in a quiescent state (10).

Cell proliferation time in the basal cell monolayer is 2.6 days. About 4% of the new keratinocytes move toward the surface layers daily, maintaining constant population densities. The minimum transit time for a basal cell to reach the malpighian layer is 13 days which is nearly the same duration to pass through stratum corneum (12).

The dermis is a connective tissue which contains nerve and vascular networks. Dermal cells are fibroblasts, responsible for the synthesis and the degradation of fibrous and non fibrous connective tissue matrix proteins. Among acellular dermal fibres, the collagen represents 90% of dermal fibres (fibrilar type I and III) and is continuously synthesized by fibroblasts and degraded by collagenase. This provides skin tensile strength and creates a fine network around dermal blood vessels.

Elastic fibres, representing 10% of the fibres in the dermis, confer elasticity to the skin (13).

EARLY SKIN RADIATION SIDE EFFECTS:
From a pathophysiological perspective, acute skin radiation effects can be classified into effects due to cellular depletion and effects related to cellular and tissue dysfunction/reactive (14). From radiobiology point of view, this cellular compartment is characterized by a high \(\alpha/\beta\) ratio, 7.5 Gy for erythema and 11.2 Gy for skin desquamation (7).

The cellular depletion is a consequence of disrupting the normal process of cell division and regeneration in the early-responding cellular compartment. That effect concerns epidermal epithelial cells, hair follicles cells and the sebaceous and sweat glands (15).
Epidermal cells and hair follicles reaction:

Epidermal cells. The basal layer of the epidermis proliferates rapidly, leading to a high radiosensitivity. Epidermal cells undergo a growth arrest that interrupts the epidermal repopulation process and weakens (break) the integrity of the skin. The basal cell loss begins once the radiation dose has reached 20–25 Gy, and the maximum depletion of basal cells occurs when the patient has received a dose of 50 Gy. Proliferative impairment of epidermal basal cells results in insufficient cellular supply to the spinous cell layer causing different degrees of epithelial atrophy. When clonogenic cells in the basal layer are completely sterilised, the repopulation is stopped, the epidermis breaks inducing a moist desquamation occurs. Skin recovery after the end of radiation therapy depends on the importance of basal cell destruction, meaning the amount of surviving (stem) cells, which have a high migration potential. Small areas of moist desquamation tend to heal from the basal layer of the same zone, whereas large areas of broken epidermis require cells to migrate from the surrounding epidermis. Hair follicle cells. Due to its rapidly proliferating matrix of keratinocytes, the hair follicle is highly sensitive to ionizing irradiation. Follicular cells response to radiation is apoptosis. Hair loss is a dose-dependent effect that occurs in approximately 2–3 weeks after a fractionated radiation therapy (with standard 1.8–2 Gy per fraction) and is a reversible process for total skin dose up to 35 Gy. Temporary alopecia usually resolves within 2–3 months after the completion of radiotherapy. Doses greater than 35 Gy likely increase the risk of permanent alopecia, with a median risk rated at 5% for 36 Gy in 18 fractions and at 15% for 45 Gy in 25 fractions.

The skin glands damage:

Irradiation can reduce the activity of the sweat gland causing dryness of the skin which can be temporary for total dose up to 36 Gy with conventional fractionation, or permanent for higher doses. Cellular and tissue dysfunction represent a reactive early response of the stromal compartment, mainly characterized by increased vascular permeability and cytokine-mediated inflammation. This response can persist for several weeks or months until it fades.

Vascular permeability:

The main cells responsible for radiation vascular effects are mast cells and endothelial cells. The mast cell degranulation contributes to enhance vascular permeability following irradiation. This phenomenon is strongly correlated with the radiation dose. In an experimental study on mice, vascular permeability increased following irradiation, reaching a peak at 24 hours after irradiation and thereafter gradually decreased and returned to the baseline level from 3 to 10 days.

Vascular and peri-vascular inflammation:

The inflammation is initiated by cytokines and adhesion molecules, and then amplified by neutrophils. Interleukin 1 (IL-1) and tumour necrosis factor α (TNF-α) are the main cytokines involved in radio-dermatitis, and play an important role in the inflammatory skin injury. Neutrophils are initially recruited by changes on the surface of the endothelium (activated endothelial cells), then undergo transendothelial migration into the tissue and release myeloperoxidase, which produces reactive oxygen species (ROS), which are ultimately responsible for inflammation.

Clinical aspects of acute radiodermatitis:

Early radiation skin reactions occur within 1 to 4 weeks of treatment and may persist for 2 to 4 weeks following treatment. These reactions can be shown as a continuum of symptoms ranging from erythema, dry to moist desquamation and in more severe cases, ulceration. Erythema may begin within hours or days from radiation therapy initiation due to the dilatation of dermal blood capillaries. Dryness and epilation may occur within days to weeks due to damage of sebaceous glands and hair follicles in the dermal layer. Dry desquamation, eventually associated with dryness and pruritus, can occur after the third week or after a cumulative dose of 30 Gy related to the destruction of regenerative basal cells and therefore may induce an outer skin peeling. Moist desquamation occurs after four to five weeks of therapy (45 to 60 Gy cumulative dose) due to the loss of integrity of the epithelial barrier and a decrease in pressure exerted by plasma proteins on the capillary wall.

Assessment and classification of early radiation skin reactions:

The National Cancer Institute (NCI- Common Terminology Criteria for Adverse Events, version 4.0) and Radiation Therapy Oncology Group (RTOG) classify the skin acute reactions in 4 grades.

Grade 1: Faint erythema /epilation/or dry desquamation.
Grade 2: Moderate to brisk erythema or patchy moist desquamation, mostly confined to skin folds and creases; moderate oedema.
Grade 3: Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion.
Grade 4: Life-threatening consequences: Skin necrosis , ulceration of full-thickness dermis or haemorrhage (spontaneous bleeding from involved site).

Treatment of acute radiation dermatitis:

Two types of local skin interventions can be generally defined: preventive or management strategies.

Preventive strategies include hygiene measures, like minimising friction, avoiding sun exposure and use of soap and deodorants.

The use of oral or topical preventing therapies, as local treatment with Hyaluronic acid or trolamine or washing with soap were reported to be ineffective for preventing the development of acute radiodermatitis.

Only steroidal creams (topical preparation containing prednisolone with neomycin) are suggested to have some local benefit. Management
strategies include active treatment of skin lesions with oral drugs or steroidal and non-steroidal topical preparations.

**Oral systemic therapies:**

Wobe-Mugos, a combination of proteolytic enzymes containing papain (100 mg), trypsin (40 mg), and chymotrypsin (40 mg), proved to have a significant protection against radiation-induced skin reactions, reducing severity and duration of side effects \(^{37}\). Oral zinc supplementation (25 mg daily) was also effective for reducing the radiodermatitis severity at the end of treatment \(^{38}\).

**Steroidal topical treatment:**

A phase III randomised study including 176 patients with invasive breast carcinoma treated by external beam radiotherapy on breast or chest wall (minimum prescription dose, 50.0 Gy, 2 Gy per fraction) between September 21, 2007, and December 7, 2007, evaluated the efficacy of mometasone furoate (0.1 %) in combination with an emollient cream on radiation dermatitis. Placebo or steroidal cream were applied once daily on the area undergoing treatment, not less than 4 hours before or after radiotherapy until completion of the prescribed course of irradiation. Even if no reduction inradiation dermatitis (maximum grade of radiation dermatitis, assessed with CTCAE version 3.0) was observed, the mometasone furoate cream reduced skin symptoms compared with placebo (pruritus, burning, redness)\(^{39}\). In other small clinical trial, 0.1% betamethasone and 0.1% methylprednisolone are also proved to be beneficial for reducing the maximum level of acute skin reactions\(^{40,41}\).

**Non-steroidal topical treatment:**

Historically, the first most used cream in radio-dermatitis treatment was trolamine, a non-steroidal anti-inflammatory (early recruitment of macrophages and stimulation of granulation tissue), but studies on head and neck patients and breast cancer patients receiving radiotherapy did not confirm superiority of trolamine over usual care (institutional preference) in reducing the incidence of grade 2 or higher radiation dermatitis. Moreover Trolamine failed improving patient quality of life \(^{42,43}\). Hyaluronic acid, a natural polysaccharide representing the main component of the dermis extracellular matrix, plays an important role in skin healing process by stimulating fibroblast proliferation and fibrin development\(^{44}\). It is important to note that if moist desquamation is developing, topical creams should be discontinued and replaced by hydrocolloid or hydrogel-based treatments, with or without moistening cream in order to promote a moist environment for reepithelization \(^{45}\).

**LATE SKIN RADIATION SIDE EFFECTS:**

Late radiotherapy side effects typically concern slowly proliferating tissues. These effects occur more than 6 months after completing therapy and produce both permanent (irreversible) tissue damages and disorganisation\(^{46}\). From radiobiology point of view, the α/β ratio for late tissue toxicity is low, near to 3 Gy (1.9 Gy for fibrosis and 3.9 Gy for telangiectasias) \(^{7,46}\). The late skin toxicity results from a complex mechanism involving excessive fibroblast proliferation on one side and endothelial cells loss on the other side.

**Stromal radiation-induced fibrosis**

Fibrosis is the formation of excess fibrous connective tissue in an end-stage response to tissue injury by enhanced fibroblast proliferation and secretion, with excessive extracellular matrix deposition\(^{47,48}\). Fibroblasts are connective tissue secretory cells responsible for the generation, maintenance and degradation of the Extracellular Matrix (ECM), ensuring its balance between synthesis and degradation\(^{49}\). After injury, including radiation dermal damages, new connective tissue needs to be synthesized, involving “activation” of mesenchymal fibroblasts, their proliferation, and migration into the wound. These cells synthesize elevated levels of matrix proteins, including collagen and fibronectin\(^{50}\). Even several years after the end of the radiation therapy, abundant collagen I and III can be secreted and deposited in dermal ECM, leading to radiation fibrosis\(^{51}\). This chronic, long-term fibroblast activation can be explained by an abnormal production of stimulating factors such as cytokines (the main one is Transforming-Growth-Factor TGF-β1) and growth factors\(^{52}\). The studies of human fibrotic tissues distinguish two types of fibrosis, corresponding to two stages of development of the lesion:

a) The inflammatory fibrosis (active) contains a large amount of activated fibroblasts with high proliferation rate and a high secretion of TGF-β1\(^{53}\).

b) The non-inflammatory fibrosis (poorly cellularized) contains senescent-like phenotype fibroblasts with reduced proliferation and a low secretion of TGF-β. This type of fibrosis corresponds to late post radiation therapy fibrosis\(^{46}\).

**Vascular late effects:**

Late damage to the skin is primarily a function of radiation effects on the vasculature \(^{54}\). The vascular endothelium represents a slow renewal tissue, with only 0.1% of mitotically active cells and an endothelial turn-over of approximately 1 to several years \(^{55}\). Vascular late effects include on one side, reduction of capillary density, microvessels collapse and thickening of the basement membrane (capillary obliteration with dilation of the remaining vessels), and on the other side, persistence of an activated, pro-coagulant endothelial phenotype, that maintains a pro-inflammatory environment \(^{56,57}\).

**Clinical aspects of late radio-dermatitis:**

Chronic radio-dermatitis, occurs months or years after radiation therapy, and represents permanent changes of dermal layer, resulting in fibrosis, telangiectasias, epilation and atrophy. Fibrosis clinic, the the location and size of the treatment field, and...
involve a loss of softness of the skin and indurations (a feeling of firmness to the touch) associated with a significant increase of the roughness of the irradiated skin and cutaneous microrelief modifications (58). Fibrosis can be more precisely evaluated by ultrasonography and reported in terms of skin thickness (59). A study on 89 patients with early breast cancer treated with conservative surgery followed by adjuvant breast radiotherapy shows a mean increment in skin thickness by 0.52 ± 0.67 mm compared to the healthy breast (60). Telangiectasias, areas with visible dilated and thin-walled vessels, can develop from 6 months to multiple years following the completion of radiotherapy and can progress for at least 100 months. Telangiectasia is a dose-dependent effect both in incidence (at 5 years after irradiation the rate of skin telangiectasia being 10% for a dose of 50 Gy, 30% for 59 Gy and 65% for 70 Gy) and in progression (the higher the dose level is, the quicker the occurrence is) (61). Post-inflammatory hypopigmentation and hyperpigmentation depends on the concentration of melanin pigment produced by melanocytes that survived irradiation. Chronic hyperpigmentation is observed in 17% of breast cancer patients treated with conventional radiation therapy and in only 7% in patients treated with intensity-modulated radiotherapy (IMRT) (62). Dermal necrosis can occur after high doses of irradiation months to years following the end of the treatment and is related to dermal microvascular changes and ischemia (63).

**Assessment and classification of late radiation skin reactions**

Late radiation dermatitis. Radiation Therapy Oncology Group-European Organization for Research and Treatment of Cancer (RTOG-EORTC) classification:

- Grade 1: Slight atrophy. Increased density on palpation (discrete induration). Pigmentation change. Some hair loss.
- Grade 2: Patch atrophy. Marked increase in density (moderate fibrosis). Moderate telangiectasia; Total hair loss.
- Grade 3: Marked atrophy. Very marked density, retraction (more than 10%) or fixation. Gross telangiectasia.
- Grade 4: Ulceration or Necrosis (64).

**Treatment of late radiation dermatitis**

Radiation-induced telangiectasia can be effectively treated by the pulsed dye laser (PDL) with wavelengths of 585 and 595 nm with a very low incidence of adverse effects (65). Radiation dermal fibrosis need a long-standing treatment with Pentoxifylline (400 mg, three times each day) and Vitamin E (400 I.U. twice a day), treatment that seems to be effective. The fibrosis regression is exponential, with a two-thirds maximum response obtained after a mean of 2 years (66). Hyperbaric oxygen therapy (HBOT) uses 100% oxygen at higher pressure than atmospheric pressure in several sessions in order to promote angiogenesis and hyperoxygenation of the irradiated tissues, thereby initiating slow healing of radionecrotic wounds (67).

Surgical intervention must involve generous debridement with total excision of the ulcer and the surrounding irradiated tissue beyond the area of the telangiectasia followed by the coverage of the defect with well-vascularized non irradiated tissue (68). The reconstructive options usually include skin grafts, local flaps, regional flaps, or free flaps, the regional flaps or free flaps with uninvolved tissue derived from outside of the irradiated field. This management is considered as the best option (69).

**RISK FACTORS FOR RADIATION SKIN REACTIONS**

The incidence and severity of skin toxicity depends on the patient’s general health conditions, skin quality and technical details of irradiation.

**PATIENT’S PREDISPOSITIONS AND COMORBIDITIES**

**Genetic predisposition**

- The cellular DNA repair is the main mechanism involved, on which depends the tissues reaction to radiation therapy, a reduced recovery capacity being associated with hypersensitivity to radiation.
- DNA damage and its repair are more strongly associated with late rather than acute reactions (71). The main DNA repair disorders that cause radiation hypersensitivity are the autosomal recessive disorder Ataxia-telangiectasia, Nijmegen Breakage Syndrome and Fanconi anaemia (autosomal recessive DNA repair disorder) (72).

**Comorbidities**

- Non malignant systemic diseases, like collagen vascular diseases (Systemic lupus erythematosus, Scleroderma, Mixed connective tissue disease), uncontrolled arterial hypertension, diabetes mellitus and infections (particularly human immunodeficiency virus-HIV) represents risk factors for radiation toxicity. All these pathologies have in common tissue hypoxia and ischemia caused by microvascular occlusive changes and arteriolar obliteration or by marked medial hypertrophy with luminal narrowing (73). Although numerous case reports suggest an increased risk of acute and late radiation toxicities in patients with collagen vascular diseases. The results from large retrospective series remain controversial. In conclusion, treatment decisions should be made in conjunction with the patient, the radiation volume, total dose and daily dose must be reduced and all patients should be monitored with long-term follow-up to evaluate for late toxicity (74). Poor nutritional status and smoking may exacerbate radiodermatitis by impairing wound healing.

**Skin factors**

- Pre-existing skin disease (psoriasis), skin folds within the radiation field and application of skin creams on exposed areas immediately before treatment are factors that increase the risk for toxicity (75).

**RADIOTherapy RISK FACTORS**

Treatment-related risk factors include: radiotherapy technique and dose (total dose and fractionation)
the concurrent systemic therapy. Intensity Modulated Radiotherapy (IMRT) has significantly improved the dose distribution compared with standard radiation and significantly decreased acute radiodermatitis (moist desquamation 31.2% with IMRT versus 47.8% with standard treatment)\(^{76}\). Concurrent anticancer systemic therapies, like Vemurafenib (a BRAF inhibitor indicated for the treatment of metastatic melanoma) or Cetuximab (a monoclonal antibody against epidermal growth factor receptor used in Head and Neck, lung and colorectal cancers treatments) have significantly increased and prolongs radiodermatitis \(^{77, 78}\). The concomitant use of Tamoxifen (an antagonist of the estrogen receptor) is significantly associated with an increased incidence of grade 2 or greater subcutaneous fibrosis, especially in radiosensitive patients \(^{79}\).

**PREDICTION OF RADIATION TOXICITY**

The most appropriate test to predict intrinsic dermal radiosensitivity is the skin fibroblast clonogenic assays but this test is time-consuming (2-3 months) and therefore cannot be used as a diagnostic assay in routine practice\(^{(80)}\). Lymphocyte apoptosis is a representative type of programmed cellular response to ionizing radiation damage and was developed as a rapid tool for characterization of normal tissue radiosensitivity. Hence, individual radiation late toxicity can be predicted by radiation-induced apoptosis of CD4 (Helper) and CD8 (cytotoxic, killer) T-lymphocytes. No association was found between early toxicity and T-lymphocyte apoptosis, but the late radiation toxicity is inversely correlated with CD4 and CD8 apoptosis values. In clinical studies, no grade 3 side effects have been observed for patients with CD4 apoptosis >15% and CD8 apoptosis >24\%.\(^{(81)}\) The individual radiosensitivity is correlated with the Single Nucleotide Polymorphism (SNP), a DNA sequence variation in the genome, variation in which a single nucleotide —A (Adenine), T(Thymine), C(Cytosine) or G(Guanine) —differs\(^{(82)}\). Genes that were screened are involved in the protection against cell death like SOD2 (Superoxide dismutase 2), gene involved in DNA repair like ATM (Ataxia Telangiectasia Mutated), XRCC 1 and 3 (X-ray RepairCross-Complementing) and RAD21 (Double-Strand-Break Repair Rad21) and gene involved in the control of cell proliferation, and apoptosis like TGFB1 (Transforming Growth Factor Beta1)\(^{(83)}\). Clinical investigations on DNA isolated from blood samples obtained from patients have suggested that possession of multiple SNPs associated with radiosensitivity correlates with an increased probability for developing severe radiation side effects \(^{(84)}\).

**CONCLUSION**

Skin toxicity related to radiation therapy is a complex mechanism whose treatment is not well standardized. Multiple factors are implicated. Although, the severity of this side effect has decreased thanks to the improvement of radiotherapy techniques, further studies are still needed to screen the patients in function of their intrinsic radiosensitivity and enhance therapeutic options according to toxicity grade.

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![Figure 1.](image1)

**Figure 1.**

Dosimetric view of treatment by Tomotherapy in the same patient, in axial, sagittal and frontal views

![Figure 2.](image2)

**Figure 2.**

Examples of different skin toxicities in the same patient treated at Centre Hospitalier Lyon Sud, during cervical lymph nodes irradiation

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Photos from personal archives of Dr Tristan Brahmi

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