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Review Article

An Overview on Radiotherapy: From Its History to Its Current Applications in Dermatology

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Abstract

For more than a century, radiotherapy has been an effective treatment for oncologic patients. The Authors report a brief history of the radiation therapy and its actual indication for the treatments of cutaneous malignant diseases.

Introduction

Radiotherapy (RT), also known as radiation therapy, is a treatment modality based on the use of high energy rays or radioactive substances, to damage tumoral cells and to halt their growth and division.

RT, used alone or in association with different treatments, has been an effective tool for treating cancer for more than 100 years [1].

Also today, it is an important therapeutic tool for the treatment of different kinds of cancer. It is estimated that about two-third of all cancer patients will receive RT as unique treatment or as a part of the more complex therapeutic protocol.

Radiotherapy in the history

Before the advent of ionising particle beams, medicine had few options for treating some diseases, both malignant and benign in nature. The scenario rapidly changed after the discovery of X-rays in 1895 by Wilhelm Conrad Rцntgen [2].

Also before understanding the physical properties of X-rays and their biological effects, one year later their discovery, X-rays were used by Emil Herman Grubbe to treat a patient with breast cancer [3].

In the same year, Antoine Henri Becquerel started to study the phenomenon of radioactivity and to research natural sources of radiation. In 1898, Maria Sklodowska-Curie and her husband Pierre Curie discovered the radium as a source of radiations.

Only three years later, Becquerel and Curie reported on the physiologic effects of radium rays [4].

By the first years of the new century, an increased number of studies reported the use of X-rays and radium in medicine. Skin cancers were the most frequent treated, even because of the low penetration in the tissue of radiations. In the 1910s, Coolidge developed a new device able to emit higher energy X-rays, to treat deeper cancers [5].

In real, due to the lack of knowledge on the properties and mechanism of actions of radiotherapy, the effective, beneficial results in the cancers treatment were poor in comparison to their side effects and physicians started new studies for a better understanding of the treatments [6].

New radioactive isotopes, type of rays and radiation techniques were discovered. Scientists began to understand the nature of radiations, their modalities of actions and the relationship between time and dose of radiations on cell survival. Nevertheless, it was only by 1920s, that physicians understood how the administration of the total radiation dose in fractionated ones was better than a singular treatment session, regarding cancers control and fewer side effects [7].

Another important scientific progress was achieved in 1928 when the International Commission on Radiological Protection (ICRP) was created to address the question of radioprotection [8].

Not less important was the introduction of an ionising chamber in 1932, which made physicians able to measure the radiation dose delivered to the first dose unit (Rцntgen unit) [9].

The successive period, from 1930 to 1950, was characterised by continuos scientifical progress to treat patients affected by deep cancers. This era (also known as Orthovoltage era) was mainly characterised by the use of the radium-based interstitial irradiation (brachytherapy) and by the development of supervoltage X-ray tubes able to deliver energy from 50 kV to 200 kV. The first one modality allowed to the operators to treat the tumour, without an external beam source, limiting the side effects on unaffected tissue. The second one conducted to the introduction of the electron beam therapy, a useful therapeutic option able to deliver higher and variable energies for treating deeper tumours [10].

The studies, which had been conducted in the successive three decades (Megavoltage era), were also focused on the development of more and more innovative radio-therapeutic devices able to treat cancers in the deep tissues. This period saw the introduction of the Cobalt teletherapy, producing high-energy γ-rays [11], and of more potent electron linear accelerators (also known as electron linacs) [12], able to deliver megavoltage X-rays. The new devices were able to deliver a higher dose of energies than the previous ones, making possible the treatment of deeper tumours with a greater skin sparing. Due to the difficulties of managing these sources and the risk to cause an excessive radiation in the tissue surrounding cancer, innovative multi-field plans of irradiations were designed [13].

Radiotherapy was becoming a recognised medical discipline, and the first radiologist associations were being founded. As well as new studies were confirming the efficacy of RT in improving survival of patients with different types of cancers, innovative devices with a computerised control were introduced in the medical practice.

However, a new era in the history of RT was starting. The 1970s and 1980s were characterised by the introduction of innovative devices delivering proton beam. Even if their first clinical use was dated in 1954 [14], was only by the late Seventies that computer-assisted accelerator for protons was successfully applied to treat a different kind of tumours [15].

The major advantage in the use of ion beams is its controllability, which allows providing a superior tool for cancer therapy and difficult-to-treat benign diseases.

Another important progress in radiotherapy was achieved by the end of the 1990s when the introduction of more sophisticated computer allowed the development of a 3D conformal radiotherapeutic device (Stereotactic radiation therapy), able to treat in a more efficacy and safer ways the patients [16].

The new millennium saw the affirmation of the Stereotactic radiation therapy, especially for the treatment of metastatic tumors [17], and the introduction of the adaptive RT (ART), a special form of image-guided radiotherapy (IGRT), that consent of replanning and sometimes optimizing the treatment technique, during the course of radiotherapy when clinically relevant [18].

Types of radiations useful in RT

Radiotherapy is based on the use of two main types of radiation: the electromagnetic and the particulate ones. The first is represented by the X-rays and by the Gamma-rays; the second one by electrons, neutrons and protons.

Radiations may be delivered externally or internally. In the first modality, the beam of radiations is delivered by a source of radiations, which is external to the body; in the second one, a radioactive source is placed inside the lesions that must be

treated.

In general, the choice of the treatment, which has to be used, depends on the localisation, size and type of cancer.

Mechanisms of action of radiotherapy

Even if the interaction radiations-tissue produces numerous effects (Table 1), radiotherapy mainly acts by killing the tumoral cells and halting their ability to reproduce [19]. Those events can be the result of the direct damage of DNA or other important cellular molecules (most commonly described in the case of particulate radiations, such as alpha particles, protons or electrons), or of an indirect cellular damage which occurs after the productions of free radicals (e.g. X-rays or Gamma-rays).

Unfortunately, during radiation therapy, normal cells, especially for those which divide frequently, may also be damaged and killed. This fact may be limited by the focusing the radiation beam on the tumour and by fractioning the total dose of irradiation so that normal tissue can recover and repair itself [20].

Table 1: Effects of radiations on the irradiated tissues

EFFECT	RESULTS
Physics	issue, transfer and absorption of energy
Biophysics	ionisation and excitation phenomenon
Physical-chemical	direct alterations of atoms and molecules or indirect damage through the productions of free radical
Chemical	the breaking of bonds, polymerization or depolymerization phenomenon
Biochemical	molecular alterations
Biochemical-biological	damage to DNA, RNA, cytoplasm, enzymes
Biological	aberrations of various cellular components, morpho-functional and metabolic lesions, damage to the genetic material

Radiotherapy in dermatology

Even if RT is often estimated to be an obsolete treatment available for a dermatologist, it has been used for nearly a century, and today it still represents a valid therapeutic tool even because innovative and more sophisticated techniques have been developed (Table 2) [20].

Radiation therapy may be used in dermatology as a curative treatment or as a palliative one (Table 3). In the first case, it is used to destroy the primary tumour or to reduce the risk of malignant recurrences after the surgical or chemotherapeutic treatment of cancer. In the second case, RT is mainly used to alleviate patient's pain by reducing the tumour's size.

Table 2: Different modalities of radiotherapy available for the treatment of dermatological diseases

TREATMENT	TYPE OF RADIATION	CLINICAL INDICATIONS
Low energy superficial kilovoltage	X-ray	Localised superficial skin cancers
Orthovoltage X-ray	X-rays	Localised superficial skin cancers
High energy megavoltage (MV) photons	X-rays	Rarely used. Skin cancer with deep penetration
Electron Beam Therapy (Linac)	Electrons	Large or thick lesions
Cobalt therapy	Gamma-rays	Like Linac, by which they are often replaced
Brachytherapy	Radioactive sources (e.g. Au, CO, Celsium, Iridium…) localised into tumour tissues (variable energy)	Tumours localised in critical sites

Although the clinical indications for RT are numerous (Table 4) [1], the treatment is more often performed in patients with known melanoma skin cancers (NMSC), such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and Merkel cell carcinoma.

Table 3: Different indications of RT

NATURE OF RADIOTHERAPY	CLINICAL INDICATIONS
THERAPY OF FIRST LINE	Lesions on the face;
	Superficial wide lesions;
	Old patients;
	Patients who cannot be treated surgically;
	Cases in which surgery may lead to important functional damage (e.g. ectropion, paralysis of the facial).
ADJUVANT THERAPY	Positive/close margins after surgical excision of tumour;
	Patients with positive nodes;
	Patients with perineural invasion.
PALLIATIVE TREATMENT	The Late stage of tumours, which could not be treated.

BCC is the most common type of skin cancer, and maybe one of the more common cancer in general. Even if malignant, BCC rarely metastasizes. Usually, it is treated with a simple excision or with Mohs micrographic surgery. Different therapeutic approaches include curettage, electrodesiccation, laser ablation, cryotherapy or medical therapies (e.g. imiquimod, 5-FU).

Table 4: Main dermatological indications for RT

BCC
SCC
Bowen's disease
Erythroplasia
Angiosarcoma
Keratoacanthoma
Melanoma
Merkel cell carcinoma
Cutaneous lymphoma
Kaposi's sarcoma
Fibrosarcoma

RT may be considered as a valid therapeutic options, especially in patients who cannot be surgically operated, in the case of large tumours or not well-defined ones, and finally in the case of cancers involving critical site (e.g. nose, ear). On the other hand, it has been estimated that the use of RT after the surgical excision of the primary tumours, is another valid therapeutic approach for patients with BCC, leading a reduction in the risk of recurrences [21-24] (Table 5, Table 6).

Table 5: Dose recommendation for BCC and SCC, accordingly to the National Comprehensive Cancer Network (NCCN) Guidelines version 2.2014

Tumour diameter (cm)	Dose (Gy)	Margins (cm)	Schedule of sessions
< 2	64	1.0-1.5	32 (6-6.4 weeks)
	55		20 (4 weeks)
	50		15 (3 weeks)
	35		5 (5 days)
≥ 2	66	1.5-2.0	33 (6-6.6 weeks)
	55		20 (4 weeks)
Postoperative adjuvant	50		20 (4 weeks)
	60		30 (6 weeks)

SCC is the second most common cutaneous cancer, and unlike BCC it is characterised by a significant metastatic potential.

Table 6: X-ray therapies most commonly used in dermatology

Modality of irradiation	Energy	Treatment depth
Grenz Rays	10-20 kv	< 1 mm
Contact therapy	40-50 kv	1-2 mm
Short source surface distance	40-50 kv	1-2 mm
Superfical therapy	50-150 kv	> 5 mm
Orthovoltage therapy	150-300 kv	> 5 mm and < 2 cm

Also, in this case, the surgical excision or the MOHS micrographic surgery represent the gold standard treatments. Different approaches include curettage, electrodesiccation and cryosurgery. RT may be considered as a valid therapeutic option, both as primary treatment and as adjuvant therapy for high-risk tumours [25]. In patients with positive nodes, the irradiation may be considered a valid option to their surgical dissection.

Another tumour which benefits of RT is the Merkel cell carcinoma (MCC), a neuroendocrine carcinoma of the skin, highly deadly. In this case, the surgical excision of the primary tumour is recommended such as the successive irradiation of the same site. In the case of positive nodes, they must be irradiated too [26, 27]

Among the other skin tumours, which may be treated with RT, there is the mycosis fungoids, a form of cutaneous T-cell lymphoma. In these cases, RT may be used as a curative treatment of localised form of lymphoma, or as a palliative treatment [28].

Also, the primary cutaneous follicle centre cell lymphoma (FCCL) and the primary cutaneous marginal zone lymphoma (MZL), two types of B cell lymphoma, if not surgically treated, may benefit from the radiation therapy [1].

Finally, there is the Kaposi's sarcoma. Also, in this case, RT may be used as the main treatment, in the case of solitary lesions, or as palliative therapy in the disseminated forms [20, 29].

Particular is the case of melanoma, the most malignant skin disease, characterised to have low radiosensitivity. In this case, the gold standard treatment is represented by surgical excision of the lesion. RT may be considered as therapeutic options only in few selective cases, such as unresectable primary tumours or lentigo malignant. In the other cases, RT is often used with the palliative purpose or as adjuvant therapy for the nodal and brain metastases [30, 31].

The latest introduction of carbon ions in RT seems to open new prospective in the melanoma treatment, even if new studies and researches need to be conducted [32].

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