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].

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 Röntgen [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 (Rüntgen unit) [9].

The successive period, from 1930 to 1950, was characterised by continuous scientific 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
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].

| 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)     | X-rays            | Rarely used. Skin cancer with deep penetration           |
| photons                          |                   |                                                          |
| Electron Beam Therapy            | Electrons         | Large or thick lesions                                   |
| (Linac)                          |                   |                                                          |
| Cobalt therapy                   | Gamma-rays        | Like Linac, by which they are often replaced             |
| Brachytherapy                    | Radioactive sources (e.g. Au, CO, Cesium, 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 2: Different modalities of radiotherapy available for the treatment of dermatological diseases

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 3: Different indications of RT

| NATURE OF RADIOTHERAPY | CLINICAL INDICATIONS                       |
|------------------------|-------------------------------------------|
| Lesions on the face    | Superficial lesions                       |
| Old patients           | Surgical indications with functional damage (e.g. eczema, parapsoriasis) of the facial area |
| Patients who cannot be treated surgically | Patients with nodal invasion |
| Positive/node margins | Patients with positive nodes;             |
| After surgical excision of tumour | Patients with perineural invasion; |
| The late stage of tumours, which could not be treated ||

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 4: Main dermatological indications for RT

| BCC                   | SCC                  | Bowen’s disease | Erythrasma | Angiosarcoma | Keratoacanthoma | Melanoma | Merkel cell carcinoma | Cutaneous lymphoma | Kaposis sarcoma | Fibrosarcoma |
|-----------------------|----------------------|-----------------|------------|--------------|-----------------|-----------|-----------------------|-------------------|----------------|-------------|

Table 5: Table 6
In this case, the gold standard - lesion. RT may be considered as therapeutic options for malignant skin disease, the case of solitary lesions, or as palliative therapy in lymphoma (FCCL) and the primary cutaneous T-cell lymphoma. In these cases, RT may be used as a valid option to their 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 fungoides, 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].

### References

1. Jonathan D. Tward JD, Christopher J. Anker CJ et Al. Radiation Therapy and Skin Cancer. In Natanasabapathi G. Modern Practices in Radiation Therapy. InTech ed. 2012: 207-246.

2. Rontgen WC. Uber eine neue Art von Strahlen. Vorl¨uaufige Mitteilung. In: Sitzungsberichte der physikalisch-medicinischen Gesellschaft zu W¨urzburg, Sitzung 1985. 30: 132–141.

3. Grubbe EH. Priority in the therapeutic use of X-rays. Radiology 1933. 21: 156–162. https://doi.org/10.1148/162859a0

4. Becquerel AH, Curie P. Action physiologique des rayons de radium. Compt. Rend. Acad. Sci. 1901. 132, 1289–1291.

5. Lawrence EO, Livingston MS. The production of high speed light ions without the use of high voltages. Phys. Rev. 1932. 40:19–35. https://doi.org/10.1103/PhysRev.40.19

6. Lederman M. The early history of radiotherapy: 1895–1939. Int. J. Radiat. Oncol. Biol. Phys. 1981. 7: 639–648. https://doi.org/10.1016/0360-3016(81)90379-5

7. Coutard H. Principles of X-ray therapy of malignant disease. Lancet 1934. 2:1–12. https://doi.org/10.1016/S0140-6736(00)90085-0

8. Taylor, L. S. History of the International Commission on Radiological Protection (ICRP). Health Phys. 1958:1:97–104. https://doi.org/10.1097/00004032-195804000-00001

9. Thoereus, R. A. A study of ionization method for measuring the intensity and absorption of roentgen rays and of the efficiency of different filters used in therapy. Acta Radiol. 1932: 15: 1–86.

10. Courant ED. Early Milestones in the Evolution of Accelerators. In Chao AW. Reviews of Accelerator. Science and Technology vol. 1. Ed. World Scientific, Singapore, 2008: 1–5. https://doi.org/10.1142/s1793626808000022

11. Boone MLM, Lawrence JH, Connor WG et al., Introduction to the use of protons and heavy ions in radiation therapy: historical perspective. Int. J. Radiat. Oncol. Biol. Phys. 1977:3:65–69. https://doi.org/10.1016/0360-3016(77)90229-2

12. Fry D W, Harvie RB, Mullett L et Al. A travelling-wave linear accelerator for 4-MeV electrons. Nature 1948:162:859–861. https://doi.org/10.1038/162859a0 PMid:18103121

13. Suit H, Goitein M, Munzenrider J et al., Evaluation of the clinical applicability of proton beams in definitive fractionated radiation therapy. Int. J. Radiat. Oncol. Biol. Phys. 1982:8:2199–2205. https://doi.org/10.1016/0360-3016(82)90570-3

14. Hall EJ. The Physics and Chemistry of Radiation Absorption. In: Radiobiology for the radiologists. 4th edition. Philadelphia: JB Lippincott, 1994:8-10.

15. Ying CH. Update of Radiotherapy for Skin Cancer. Hong Kong Dermatology & Venereology Bulletin.2001; 9(2): 52-59.

16. Mohan, R. Field shaping for three-dimensional conformal radiation therapy and multileaf collimation. Semin. Radiat. Oncol. 1995;5: 86–99. https://doi.org/10.1016/S1053-4296(95)80003-4
17. Milano MT, Katz AW, Zhang H et Al. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. Int. J. Radiat. Oncol. Biol. Phys. 2012; 83: 878–886. https://doi.org/10.1016/j.ijrobp.2011.08.036 PMid:22172903

18. Schwartz DL et al. Adaptive radiotherapy for head-and-neck cancer: initial clinical outcomes from a prospective trial. Int. J. Radiat. Oncol. Biol. Phys. 2012; 83: 986–993. https://doi.org/10.1016/j.ijrobp.2011.08.017 PMid:22138459 PMCid:PMC4271827

19. Veness M, Richards S. Radiotherapy. In: Bolognia J, Jorizzo J, and Schaffer J, eds. Dermatology, vol. 2. Philadelphia: WB Saunders; 2012: 2291–2301.

20. Ying CH. Update of Radiotherapy for Skin Cancer. Hong Kong Dermatology & Venereology Bulletin. 2001; 9(2): 52-58.

21. Cognetta A, Howard B, Heaton H, et. Al. Superficial X-ray in the treatment of basal and squamous cell carcinoma: a viable option in select patients. J Am Acad Dermatol. 2012;67:1237–1241. https://doi.org/10.1016/j.jaad.2012.06.001 PMid:22818756

22. Petit JY, Avril MF, Margulis A, et. al. Evaluation of cosmetic results of a randomized trial comparing surgery and radiotherapy in the treatment of basal cell carcinoma of the face. Plast Reconstr Surg. 2000;105:2544–2551. https://doi.org/10.1097/00006534-200006000-00039 PMid:10845311

23. Zagrodnik B, Kempf W, Seifert E, et. al. Superficial radiotherapy for patients with basal cell carcinoma. Cancer. 2003;98(12):2708–2714. https://doi.org/10.1002/cncr.11798 PMid:14689293

24. Wolstenholme V, Glees JP. The Role of Kilovoltage X-rays in the Treatment of Skin Cancers. European Oncological Disease, 2006;1(1):32-5. https://doi.org/10.17925/eho.2006.1.1.32

25. Barysch M, Eggman N, Beyeler M, et al. Long term recurrence rate of large and difficult to treat cutaneous squamous cell carcinomas after superficial radiotherapy. Dermatology. 2012;224:59–65. https://doi.org/10.1159/000337027 PMid:22433440

26. Gillenwater AM, et Al. Merkel cell carcinoma of the head and neck: effect of surgical excision and radiation on recurrence and survival. Arch Otolaryngol Head Neck Surg. 2001; 127(2):149-54. https://doi.org/10.1001/archotol.127.2.149 PMid:11177031

27. Jabbour J et Al. Merkel cell carcinoma: assessing the effect of wide local excision, lymph node dissection, and radiotherapy on recurrence and survival in early-stage disease--results from a review of 82 consecutive cases diagnosed between 1992 and 2004. Ann Surg Oncol, 2007;14(6): 1943-52. https://doi.org/10.1245/s10434-006-9327-y PMid:17356954

28. Micaly B, et Al. Radiotherapy for unilesional mycosis fungoides. Int J Radiat Oncol Biol Phys.1998;42(2): 361-4. https://doi.org/10.1016/S0360-3016(98)00218-1

29. Cooper JS. The influence of dose on the long-term control of classic (non-AIDS associated) Kaposi’s Sarcoma by radiotherapy. Int J Radiat Oncol Biol Phys. 1998;15:1141-6. https://doi.org/10.1016/S0360-3016(88)90196-4

30. Farshad, A., et al., A retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma and the efficacy of radiotherapy using Grenz or soft X-rays. Br J Dermatol. 2002;146(6):1042-6. https://doi.org/10.1046/j.1365-2133.2002.04750.x PMid:12072074

31. Chen, J.C., et al., Stereotactic radiosurgery in the treatment of metastatic disease to the brain. Neurosurgery. 2000; 47(2): 268-79. https://doi.org/10.1097/00006123-200008000-00003 PMid:10942000

32. Kamada, T. Clinical evidence of particle beam therapy (carbon). Int. J. Clin. Oncol. 2012;17: 85–88. https://doi.org/10.1007/s10147-012-0388-6 PMid:22426888