



The 5Rs dilemma of radiotherapy for non-malignant diseases: 5Rs to darken OR 5Rs to shine

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ABSTRACT

Many benign diseases, so called because they are not a direct cause of death, nevertheless cause significant damage to the health of patients due to the associated pain, reduced functionality, increased disability and the negative impact they have on quality of life, which, together with the limited efficacy of many of the available treatments, make their management a challenge for every specialist. Radiotherapy, which has demonstrated its efficacy not only against cancer but also in many non-tumorous diseases, appears as a therapeutic option that deserves to be taken into account. However, there is still much resistance to considering the use of radiotherapy as a valid and acceptable alternative. The 5Rs to darken summarize the doubts and contradictions many specialists face to accept radiotherapy in non-neoplastic diseases. However, other 5Rs (to shine) can be argued to claim for the safety, reliability, and usefulness of radiation treatment for benign disease and as radiotherapy specialists we have to help the evidence shine and the darkness disappear.

Key words: radiation therapy; benign diseases; 5R

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It is harder to crack a prejudice than an atom.
Albert Einstein

Radiotherapy is, after surgery, the second most effective single strategy against cancer. Likewise, the use of radiotherapy for the treatment of non-malignant diseases has been common practice from the very beginning of ionizing radiation history. However, and despite the evidence accumulated over more than 120 years of radiotherapy, its use in diseases other than cancer continues to be questioned, even from radiotherapy specialists themselves. With the exception of some European countries, such as the United Kingdom (which has guidelines and recommendations from official agencies for the use of radio-

therapy in benign processes) or Germany (where radiotherapy of non-tumor pathology is standard in all centers and represents between 10% and 30% of daily activity), its routine use remains anecdotal [1, 2].

Knowing the behavior and response of tumors and healthy tissues after irradiation, has allowed to define the so called 5Rs of radiotherapy: **R**epair of sublethal damage, **R**edistribution within the cell cycle, **R**eoxygenation after irradiation, **R**epopulation and **R**adiosensitivity of the different cell types (some authors recently include a 6R referring to the **R**eactivation of anti-tumor immune response), which constitute the biological basis of cancer radiotherapy and justify the way in which radiotherapy is delivered providing a means of un-

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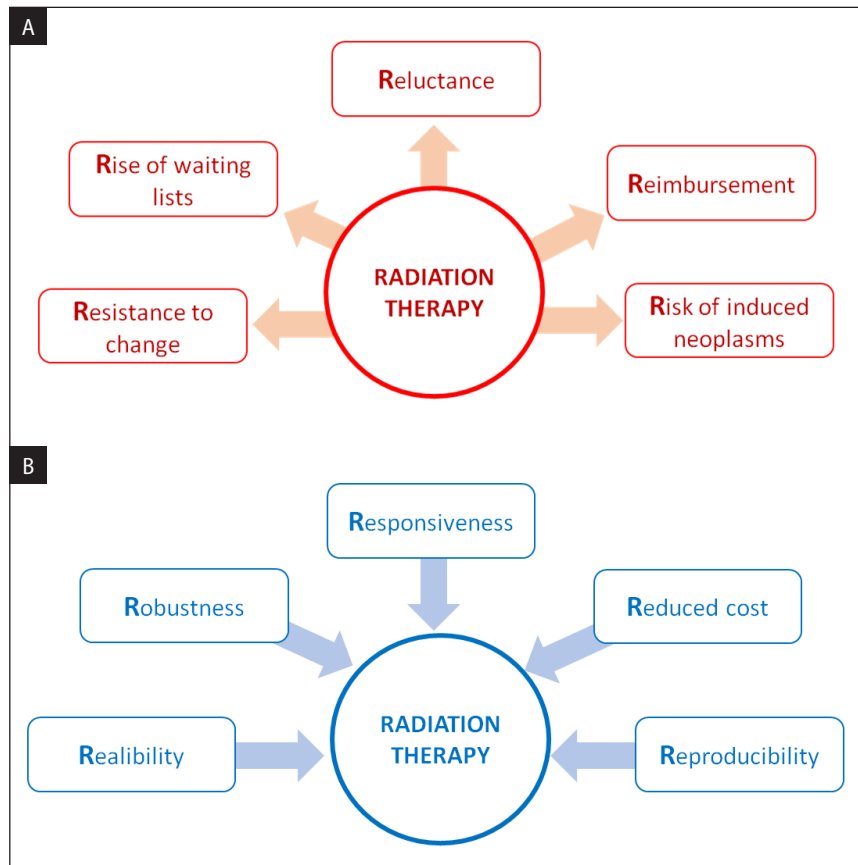


Figure 1. The 5Rs to darken (A) and the 5Rs to shine (B)

Understanding, to some extent, the success or failure of radiation therapy against cancer [3, 4].

In an attempt to find a plausible explanation for the rejection and lack of enthusiasm of many specialists to consider radiotherapy as an alternative in benign conditions, and imitating the 5Rs of radiobiology, one could hypothesize about the existence of other 5Rs that could suggest the reasons why radiotherapy is not used more widely in these type of diseases even though another 5Rs can be described to support and reinforce the usefulness of ionizing radiation for the treatment of benign disorders based on a long accumulated experience already (Fig. 1A, 1B).

The 5Rs to darken

Reluctance to treatment acceptance

A number of medical specialists still do not consider radiotherapy, traditionally reserved for cancer, as a useful, valid and even cost-effective option for non-cancerous diseases and are excessively wary of referring patients with these disorders, even being

refractory to previous treatments, to radiotherapy departments. Even more, a not negligible number of radiotherapy specialists in these departments are reluctant to consider it, thus depriving patients of a therapeutic possibility, which, without ensuring cure, can contribute to symptomatic relief effectively and safely.

Risk of secondary radio-induced tumors

A classic argument against the use of radiotherapy in benign pathology has been the potential risk of radio-induced carcinogenesis. However, numerous studies emphasize the safety of the use of ionizing radiation in these diseases, especially when low doses of irradiation are used, and the low associated risk, even more so considering the advanced age of many of the patients who would be candidates for these treatments and in whom the potential carcinogenic risk is even lower [5]. Thus, in the broad published experience in the treatment of degenerative and inflammatory osteoarticular pathology, no increase in the risk of secondary tumors appearance has been observed after treatment. On

the other hand, the absence of effective and safe therapeutic alternatives in life-threatening diseases, such as multidrug-resistant ventricular tachycardia or Alzheimer's disease, further relativizes the potential risks associated with its use.

Rise of waiting times

Ensuring an adequate treatment, in time and form, of cancerous processes should be a priority objective for all Radiotherapy Departments. The growing demand, due to the increase in the number of cancer diagnoses because of the increase in life expectancy of the general population and improvements in diagnostic techniques, has increased the pressure on Radiotherapy Departments.

The evidence demonstrating the negative impact that delayed initiation of planned radiotherapy has on the final results serves as a justification for many to not consider performing radiation treatments for benign pathologies that otherwise could increase waiting lists.

However, in recent years, the widespread use of shortened radiotherapy schedules is helping to optimize daily workloads and times. The ultra-hypofractionated 5-fraction schedules, already routinely used in many breast, prostate or rectal cancer treatments; the use of SABR modalities in 1, 3 or 5 fractions in the treatment of certain lung, renal, pancreatic tumors or in (oligo)metastatic disease, or brain radiosurgery (SRS) schemes, also in very few fractions, allows the reduction of the overall duration of treatments, optimize available resources and reduce the waiting lists for cancer radiotherapy in many departments, thus freeing up resources that could be used to treat other non-tumor diseases that could benefit from radiotherapy [1, 6–8].

Resistance to change

We've always done it that way (Grace Murray Hopper, 1976 [9]) is, undoubtedly, one of the most dangerous phrases that can be associated with the practice of medicine. The *ad antiquitatem* fallacy, which justifies the goodness of an act for the long it has been performed, and which rejects any alternative, often justifying it in the absence of experience in the field, is a burden for the advancement of science. The rejection generated among many radiotherapists by the use of ionizing radiation for the treatment of non-neoplastic diseases could be

explained, many times, by the lack of knowledge and experience, something that could currently be made up by studying and reviewing all the experience published. However, and as pointed out before by other authors, it is probably the inertia that determines resistance to any change and perpetuating denials towards other therapeutic possibilities of radiotherapy [10].

Reimbursement issues

Last but not least, the lack of recognition of the usefulness of radiotherapy in benign diseases, justified by the other previously mentioned Rs, has a direct impact on the acceptance of radiotherapy as a valid alternative by health care providers. Despite being one of the least expensive therapeutic options and bearing in mind the high cost associated with other treatments, paradoxically many of these providers and insurance companies are reluctant to include radiation treatment in their portfolio of services, although there is proven evidence of its efficacy, causing a disruption to patients who could benefit from it. Undoubtedly, greater knowledge of the bases, mechanisms of action and results to be expected with radiotherapy in certain benign diseases could help to reverse the resistance to its definitive acceptance and inclusion in the coverage of services, facilitating its access for potential patients.

These proposed 5 R's of radiotherapy in benign pathology summarize the barriers that a treatment that has been shown to be effective and safe faces when its possible use is considered. However, just as there are 5 R's that hinder the acceptance of radiotherapy as a valid treatment for certain non-neoplastic diseases, one can also think about the existence of other 5 R's that could help to justify the usefulness of irradiation in patients with those non-neoplastic diseases.

The 5Rs to shine

Robustness

Despite the lack of randomized studies, numerous prospective studies and observational series of treated patients support the efficacy of radiotherapy in benign pathology and the spectrum of non-malignant pathologies in which radiotherapy could be useful has been steadily increasing: from the early reported experiences of Nikolai Sokoloff

on the efficacy of radiotherapy for the symptomatic relief of juvenile arthritis or the success of Leopold Freund treating a hairy nevus or Hermann Gocht removing trigeminal neuralgia pain [3] to more recent pieces of evidence supporting its use in several inflammatory and degenerative musculoskeletal disorders such as osteoarthritis and tendinosis, hyperproliferative soft tissue disorders such as Dupuytren's or Lederhose disease, vascular and cardiac pathology such as arteriovenous malformations or intractable arrhythmias, chronic skin disorders such as psoriasis, functional CNS pathology such as essential tremor or various neuralgias and even a possible usefulness in neurodegenerative diseases such as Alzheimer's disease or in infectious pathologies without specific treatment [1, 2, 11–13].

Responsiveness

The response rates achieved with radiotherapy in certain non-tumor diseases are remarkable. The available evidence reinforces the good and sustained symptomatic response over time after irradiation in inflammatory or degenerative osteoarticular pathology, for hyperproliferative disorders, for cardiac arrhythmias or functional CNS diseases [1, 14, 15].

Reliability

Any radiotherapy procedure must not only be effective but also safe and reliable. 'First do no harm' as a principle should always be kept in mind in any medical practice. Although the balance between risk and benefit must always be taken into account, especially in the case of young patients, the probability of developing serious adverse effects after radiotherapy of benign processes is low. Total doses, fraction doses or treatment volumes are very different from those used in cancer radiotherapy, and contribute to this low risk, not forgetting that other alternative treatments also have side effects, especially considering the advanced age of many patients.

Reproducibility

Standardization of the radiotherapy processes for cancer has permitted the reproduction of the same in different institutions allowing comparable results to be obtained. Management of benign pathology with radiotherapy should always be done in the same way as the procedures car-

ried out for the treatment of tumors. Maintaining the same quality standards as in cancer treatment is an essential and non-negotiable requirement when considering it. Following specifically designed and detailed protocols for a rigorous control of all the stages of the irradiation procedure guarantees the viability of the treatment of these diseases and facilitates their adoption by any interested specialist.

Reasonable cost

So-called benign diseases are sometimes not only associated with an evident deterioration in the quality of life but can also contribute to a considerable increase in healthcare costs. Taking into account the progressive aging of the developed countries and the improvement in life expectancy, costs are likely to continue to increase in the coming years [16, 17]. Thus, the cost of treating degenerative osteoarticular pathology in Spain reaches, if not already exceeds, 0.5% of GDP, with a significant impact on overall healthcare expenditure [18, 19]. Implementation of radiotherapy for non-malignant pathologies, using the resources and facilities already existing for the treatment of cancer, and taking advantage of the progressive decrease in the treatment length due to the increasing use of hypofractionated and accelerated radiotherapy schedules, radiotherapy appears an attractive alternative for the symptomatic treatment of many and diverse non-cancer diseases that, in addition to its effectiveness, contributes to the reduction of health care costs, especially in elderly patients.

Conclusion

In conclusion, and taking into account all the points described above, the so-called benign diseases can be harmful, expensive and are managed with difficulty, and so, based on the "5Rs to shine", radiation therapy should be considered as an effective and safe therapeutic option, although many specialists are reluctant to accept it alluding to the "5Rs to darken". We, as radiotherapy specialists, have a duty to help the evidence shine and the darkness disappear.

Conflict of interest

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