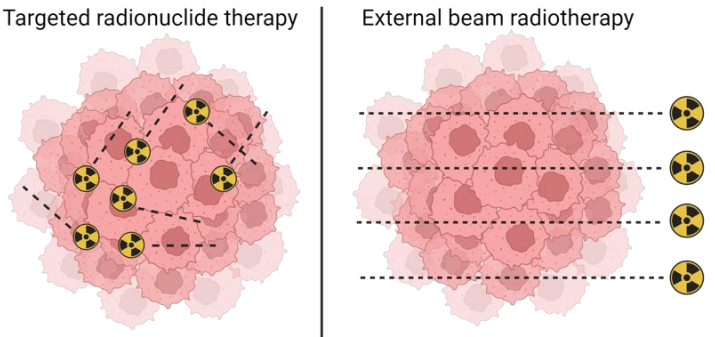
Radiobiology of radionuclide therapy

ESTRO was founded as the *European Society for Therapeutic Radiology and Oncology.* Instead of for X-ray imaging, electrons were used to irradiate and eradicate tumours using external beams, hence the term *therapeutic radiology*. A similar evolution has taken place in the world of nuclear imaging, in which tracers that were applied to image tumours have been adapted to irradiate cancer cells using alpha- or beta-emitting radionuclides. The radiobiology of external beam and radionuclide therapy, however, may differ from each other.

Targeted radionuclide therapy (TRT) involves the use of radiation treatment through the utilisation of radiolabelled vectors that can bind selectively to cancer cell-specific entities such as receptors. After systemic administration, these vectors localise in tumour lesions, where they induce DNA damage that leads to cancer-cell death upon radioactive decay. Notable TRTs that are approved by the European Medicines Agency (EMA) and/or the US Food and Drug Administration (FDA) include [^{177}Lu]Lu-[DOTA-Tyr^{3}]octreotate (DOTA is 1,4,7,10-tetraazacyclododecaneN,N′,N″,N‴-tetraacetic acid) for neuroendocrine tumours and [^{177}Lu]Lu-[DOTA]-prostate-specific membrane antigen (PSMA) for prostate cancer. Despite successful outcomes in a significant proportion of patients, which have been marked by improved progression-free survival and enhanced quality of life, a majority experience suboptimal responses or side effects. To enhance TRT efficacy, it is essential to gain a better understanding of the dose-effect relationship, and this necessitates the deciphering of underlying radiobiological effects.

Most studies on the (radio)biological effects of radiation treatments have focused predominantly on external beam radiotherapy (EBRT) with photons. Consequently, this knowledge has been extended to TRT, despite substantial differences between the two modalities. Variances in dose rate, radiation timing, linear energy transfer (LET), and dose distribution (illustrated in Figure 1) highlight the unlikelihood of accurate direct extrapolation from EBRT to TRT. Thus, there is a pressing need for additional studies to delve into the intricacies of the dose-effect relationship that is specific to TRT.



	Targeted radionuclide therapy	External beam radiotherapy
Dose rate	Low	High
LET	Depends on radionuclide	Low
Dose distribution	Heterogeneous	Homogeneous
Duration radiation	Days-weeks	Minutes

Figure 1. Schematic overview of different characteristics of TRT vs. EBRT. The differences in the treatments mean that the use of TRT induces cellular damage over a long time frame, while the use of EBRT results in the induction of high damage levels in a short time frame. Figure created using BioRender.

In recent years, there has been growing recognition of the clinical importance of TRT-specific radiobiology. Typically, TRT agents are administered in fixed ways, which limit the potential for adoption of personalised treatment strategies and result in examples of both over- and under-treatment. Various clinical studies on TRT have revealed a lack of correlation between the absorbed dose in the target tissue and the therapeutic response. These findings suggest that there may be other, yet undiscovered, radiobiological factors that influence therapy outcomes for both target and healthy tissues.

A notable contrast between TRT and EBRT lies in TRT's lower dose rate and dose distribution over a prolonged period of time, which results in a relatively low rate of induction of biological damage at specific time-points. This phenomenon leads to a simultaneous occurrence of damage induction and repair, so cells have more time to repair sub-lethal lesions. Consequently, the relative biological effectiveness of TRT is lower than that of EBRT when equivalent total doses in Gray are compared. Intriguingly, an observed inverse dose-rate effect suggests that lower dose rates of ionising radiation exhibit greater cytotoxicity per Gray than do higher dose rates. A hypothesis has been proposed that variation in the dose rate may cause distinct biological responses, including DNA damage repair in cancer cells. However, the precise biological mechanisms that underpin these seemingly contradictory effects and their relevance in the context of TRT remain to be fully understood.

The nature of biological effects after TRT is heavily influenced by the characteristics of the radionuclide used. Generally, α-particles have demonstrated more pronounced biological effects in target cells compared with β-particles due to their higher LET, resulting in increased cell killing. This is attributed to the high probability that α-particles induce DNA double-strand breaks, as has been shown extensively in preclinical studies. Additionally, the impact of dose distribution heterogeneity on TRT effects has not yet been thoroughly explored. Subcellular localisation of radionuclides may play a role; TRT agents may reside on the cellular membrane or become internalised and relocate to various cellular organelles, including the nucleus. The influence of subcellular localisation is expected to be most significant for α-particles due to their relatively short range and high LET. However, recent data suggests that subcellular localisation is also relevant for β-emitters such as lutetium-177. In vivo, dose distribution heterogeneity is complicated further at the tumour level by TRT target heterogeneity, an example of which is intra-lesion variations in receptor expression.

In conclusion, TRT holds promise for the treatment of various cancers through the application of radiolabelled vectors to induce DNA damage and subsequent cancer cell death. While EMA/FDA-approved TRTs such as [^{177}Lu]Lu-[DOTA-Tyr^{3}]octreotate and [^{177}Lu]Lu-[DOTA]-PSMA have been found to improve the survival rates and quality of life for a significant proportion of patients, challenges remain. Most patients do not respond optimally, and this emphasises the need to increase understanding of TRT-specific radiobiology. Distinct differences between TRT and EBRT, including dose rate, timing, LET, and dose distribution, highlight the limitations of extrapolating knowledge from one modality to the other. The lower dose rate that is used in TRT, an inverse dose-rate effect, and the influence of radionuclide characteristics on biological effects underscore the complexity of TRT's radiobiological landscape. The impact of dose distribution heterogeneity, especially in terms of subcellular localisation, remains an understudied aspect, and this adds intricacy to the understanding of TRT effects. Comprehensive research efforts are essential to unravel these complexities and to pave the way for personalised and more effective TRT strategies that can address the challenges of over-treatment and under-treatment, and improve therapeutic outcomes for a wider spectrum of patients.

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