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THE INFLUENCE OF THE GUT MICROBIOTA ON THE EFFICACY AND TOXICITY OF RADIOTHERAPY IN CANCER TREATMENT: A LITERATURE REVIEW

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ABSTRACT

Radiotherapy is a cornerstone of cancer treatment, yet its effectiveness is limited by toxicity to healthy tissues, particularly the gastrointestinal mucosa. The gut microbiota interacts with radiotherapy in both directions, ionizing radiation alters its composition and function, and its state may influence tumour response and the severity of adverse effects. This narrative review, based on a search of the biomedical literature, aims to summarize current knowledge on the mechanisms by which radiotherapy affects tissues and the microbiota, the role of the microbiota in radiosensitivity and radioresistance, including the immune response, the tumour microenvironment, bacterial metabolites and its significance in the pathogenesis and prediction of radiation toxicity. Strategies for modifying the microbiota are also discussed: diet, prebiotics, probiotics, postbiotics, synbiotics, faecal microbiota transplantation, bacteriophages and genetically modified bacteria. The influence of the microbiota on radiotherapy toxicity is the best documented, and its composition before treatment may help to identify patients at risk of acute intestinal toxicity. Probiotics have been studied most extensively in clinical trials, but their efficacy remains inconsistent, particularly for severe complications. Evidence that the microbiota affects antitumour efficacy is mainly preclinical and correlative. Small samples, methodological heterogeneity, confounding factors and limited safety data in immunocompromised patients constrain interpretation. Well-designed prospective and interventional studies are needed.

KEYWORDS

Gut Microbiota, Radiotherapy, Radiation-Induced Toxicity, Radiosensitivity, Probiotics, Faecal Microbiota Transplantation

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1. Introduction

Radiotherapy is one of the main methods of treating malignant tumours; it is estimated to be used in more than half of oncology patients and remains one of the most effective forms of local treatment. Its effectiveness is, however, limited by the possibility of damage to normal tissues within the irradiated area, particularly the gastrointestinal mucosa, which is among the most radiosensitive structures (Li et al., 2025). This is especially important in abdominal and pelvic radiotherapy, in which parts of the intestine, the main habitat of the gut microbiota, are inevitably irradiated. For this reason, increasing attention is being paid to the interactions between the gut microbiota and radiotherapy. The relationship is bidirectional: ionizing radiation changes the composition and function of the microbiota, while the pre-existing or treatment-induced state of the microbiota may influence both the antitumour efficacy of radiotherapy and the severity of its adverse effects. The microbiota may therefore play a dual role: on the one hand, it may protect healthy tissues from radiation damage, and on the other, it may increase the sensitivity of cancer cells to radiation. Some microorganisms, however, may act in the opposite way and contribute to the development of tumour radioresistance (Kordahi & Chassaing, 2021; Li et al., 2023, 2025).

The aim of this narrative review is to summarize current knowledge on the mechanisms by which radiotherapy affects tissues and the microbiota, on the influence of the microbiota on the efficacy and toxicity of radiotherapy, and on strategies for modifying the microbiota, and to identify directions for further research.

2. Methodology

This article is a narrative review of the literature on the interactions between the gut microbiota and radiotherapy. The literature was search was conducted between 1 July and 25 October 2026 in PubMed, Web of Science, Google Scholar. The search combined the terms “gut microbiota”, “gut microbiome”, “radiotherapy”, “radiation-induced toxicity”, “radiosensitivity”, “probiotics”, “prebiotics”, “synbiotics”, “postbiotics” and “faecal microbiota transplantation”.

Preclinical studies, observational and interventional clinical studies, systematic reviews and meta-analyses published in English were considered. Titles and abstracts were screened for relevance to the aims of the review, and the reference lists of key articles were searched manually

Because this is a narrative review, no formal systematic review protocol was applied and the risk of bias in individual studies was not assessed quantitatively. The evidence was synthesized narratively and organized thematically.

3. Radiotherapy: Mechanism of Action and Effects on Tissues

The interactions between radiotherapy and the microbiota are based on changes occurring in cells and tissues under the influence of ionizing radiation. Radiation may damage cells directly, by causing DNA strand breaks, and indirectly, through the radiolysis of water and the formation of reactive oxygen species (ROS). In the intestinal epithelium this leads to apoptosis of crypt cells, flattening of villi and loss of barrier continuity, resulting in increased permeability and translocation of bacteria and their products. Moreover, ROS cause oxidation of lipids, proteins and nucleic acids and disturb mitochondrial function, which further increases oxidative stress. DNA damage activates cell-cycle control mechanisms and apoptotic pathways, including through the ATM/ATR–p53 axis (Crawford & Gordon, 2005; Li et al., 2025). Initially these processes affect individual cells, but as the damage increases they lead to disturbed function of whole tissues. Damage to the intestinal epithelium is particularly important, as it disrupts the intestinal barrier, produces erosions and increases intestinal permeability. Tissue damage also leads to the release of damage-associated molecular patterns (DAMPs), which activate Toll-like receptors (TLRs) and the NLRP3 inflammasome and intensify local and systemic inflammation (Kordahi & Chassaing, 2021; Li et al., 2025). Under these conditions the environment in which the microbiota functions is disturbed, which may lead to changes in its composition, diversity and metabolic activity.

4. Effects of Radiotherapy on the Gut Microbiota

Changes in the composition of the microbiota are closely related to damage to the intestinal barrier and the development of inflammation. Radiation damages epithelial cells and the mucus layer, which is one of the basic barriers protecting the body from contact with microorganisms. As a result, bacteria or their products may pass through the damaged epithelium, a process called bacterial translocation, which further stimulates the inflammatory response (Li et al., 2023). At the same time, dysbiosis resulting from radiotherapy may modify both the local and the systemic immune response. Activation of the transcription factor NF-κB is of particular importance; it may be enhanced by potentially pathogenic bacteria such as Enterobacteriaceae and *Bacteroides*. In turn, bacteria considered beneficial, including *Faecalibacterium prausnitzii* and *Bifidobacterium infantis*, may limit NF-κB activation and thereby reduce the severity of the inflammatory reaction (Li et al., 2025). The influence of bacteria on the mucus layer is also important. Some microorganisms, such as *Citrobacter rodentium*, may damage it, whereas *Akkermansia muciniphila* and bacteria of the genus *Lactobacillus* stimulate mucus production and help maintain intestinal barrier integrity (Li et al., 2025).

Radiotherapy is currently regarded as a significant stressor for the microbial ecosystem of the gastrointestinal tract (Li et al., 2023). Irradiation may reduce microbial diversity and change the relative abundance of individual groups of bacteria. In studies of patients with colorectal cancer, a reduced proportion of bacteria of the phylum Firmicutes and an increased abundance of *Proteus*, *Akkermansia*, *Fusobacteria* and *Bacteroides* have been observed (Al-Qadami et al., 2019; Wang et al., 2023). At the same time, in patients with advanced colorectal cancer after radiotherapy, a reduction in potentially pathogenic microorganisms and an increase in bacteria considered beneficial, such as *Lactobacillus* and *Streptococcus*, were reported. An increase in these microorganisms may be associated with a more favourable response to treatment. It has also been shown that the presence of certain bacterial taxa, including Thermi and Sphingomonadaceae, may be associated with an antitumour response in patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiotherapy (Fan et al., 2021; Wang et al., 2023). The oral microbiota may also influence the interaction between the microbiota and radiotherapy. Radiotherapy and the associated radiation-induced mucositis may alter its composition, and some microorganisms, in particular *Fusobacterium nucleatum*, may spread to more distal parts of the gastrointestinal tract and colonize colorectal tumours. The presence of *F. nucleatum* has been shown to promote radioresistance of colorectal cancer cells and to aggravate radiation injury, potentially limiting the efficacy of radiotherapy (Dong et al., 2021; Li et al., 2025; Wang et al., 2023). Migration of microorganisms between the oral cavity and the intestine may be facilitated by, among other factors, disruption of the mucosal barrier, changes in gastric acidity and faecal–oral transmission (Li et al., 2023). Consequently, the oral and intestinal microbiota remain closely interrelated, and their interactions may be relevant both to the efficacy of radiotherapy and to the development of its adverse effects (Dong et al., 2021; Li et al., 2023).

In studies of women with cervical cancer, a gradual decrease in microbiota diversity was observed during chemoradiotherapy, reaching its lowest level in the fifth week of treatment (Mitra et al., 2020). In patients who developed radiation enteritis, a reduction in microbiota diversity, an increase in the relative abundance of Proteobacteria and Gammaproteobacteria, and a decrease in the share of *Bacteroides* were also found (Wang et al., 2019). Similar relationships were observed in patients who developed diarrhoea after radiotherapy, and lower microbiota diversity in this group may indicate an association with treatment tolerance (Li et al., 2023; Manichanh et al., 2008). In turn, a study of patients with gynaecological cancers irradiated with a dose of 50.4 Gy showed a significant reduction in the number of detected taxa after the end of radiotherapy, accompanied by a decrease in the share of Firmicutes and an approximately six-fold increase in the relative abundance of Fusobacteria (Nam et al., 2013). It should be emphasized, however, that microbiota changes do not proceed identically in all patients. In a study of patients with rectal cancer treated with short-course radiotherapy combined with immunochemotherapy, an increase in the share of Firmicutes was noted, together with a decrease in the abundance of Bacteroidetes and Proteobacteria (Lu et al., 2026). These discrepancies suggest that the effect of radiotherapy on the gut microbiota may depend on the type of cancer, the treatment regimen used and concomitant therapeutic methods. The gut microbiota may therefore be an important factor related to the development of radiation toxicity, but defining its role in predicting treatment tolerance and efficacy requires further research.

5. Influence of the Gut Microbiota on the Efficacy of Radiotherapy

5.1. Radiosensitivity and Radioresistance of Cancer Cells

The influence of the microbiota on the efficacy of radiotherapy is related primarily to its ability to modify the response of cancer cells to radiation, to regulate the immune response and to affect the tumour microenvironment. The first evidence of the involvement of the microbiota in radiosensitivity came from experimental studies, which showed that the presence of intestinal microorganisms increased the radiosensitivity of some cells in irradiated mice (Crawford & Gordon, 2005; Li et al., 2023). Later studies also showed that changes in microbiota composition, including those related to the circadian rhythm, may affect the body's sensitivity to gamma radiation (Cui et al., 2016).

At the same time, not all bacteria increase the efficacy of radiotherapy. In colorectal cancer, an association has been described between activation of the FOXQ1–SIRT1–β-catenin axis, an increased abundance of potentially pathogenic bacteria and the development of radioresistance of cancer cells (Li et al., 2023). A similar effect is attributed to *F. nucleatum*, which, through activation of TLR4/MYD88-dependent autophagy, may modify the response of cancer cells to treatment and increase their resistance to radiation (Li et al., 2023, 2025). This indicates that the influence of the microbiota on radiotherapy is neither unequivocally beneficial nor unfavourable, but depends on the composition of the ecosystem and on the metabolic and immunological properties of the microorganisms within it.

Studies in mouse models showed that the presence of the microbiota may increase the radiosensitivity of endothelial cells and lymphocytes located in the core of intestinal villi, which was linked to inhibition of the secretion of Fiaf (Crawford & Gordon, 2005). In addition, the Wnt/β-catenin and PI3K/Akt/mTOR signalling pathways have been implicated in the regulation of intestinal epithelial regeneration, and the Nrf2 pathway in the response to oxidative stress, and these may participate in tissue responses to radiation injury (Li et al., 2025). On the other hand, the microbiota may promote the development of radioresistance of cancer cells. In studies of locally advanced rectal cancer, *Bacteroides vulgatus*, whose increased abundance was observed in patients not responding to chemoradiotherapy, was shown to enhance nucleotide biosynthesis, providing cancer cells with substrates necessary for DNA repair. In preclinical models, both colonization with this bacterium and administration of nucleosides increased the resistance of cancer cells to ionizing radiation and 5-fluorouracil (Teng et al., 2023). These results suggest that the microbiota may affect treatment efficacy by regulating metabolic processes and mechanisms of repair of cellular damage.

When interpreting these relationships, however, the limitations of the available studies must be taken into account, in particular differences between animal models and clinical conditions and between mouse and human microbiota. It is also important that the action of bacterial metabolites may depend on the site of their formation and the type of tissue. For example, butyrate may support protection of the intestinal epithelium, whereas in a study of the intratumoral microbiota of rectal cancer, signals related to its production were associated with a less favourable response to treatment (Huang et al., 2023). This indicates that the influence of the microbiota on the radiosensitivity of normal tissues and cancer cells is complex, and that the possibility of exploiting these relationships to improve the efficacy of radiotherapy requires further research.

5.2. Immune Response

An important mechanism of action of radiotherapy is activation of the immune response, the course of which may be modulated by the gut microbiota. Irradiation promotes the release of tumour antigens and their presentation to CD8+ T lymphocytes, and may also induce the abscopal effect, consisting in inhibition of the growth of tumour lesions outside the irradiated area (Li et al., 2023). The microbiota influences these processes by regulating the activity of dendritic cells, lymphocytes and receptors that recognize microbial structures. Preclinical studies showed that radiotherapy may promote the translocation of intestinal bacteria to the mesenteric lymph nodes, leading to activation of the TLR4 pathway and enhancement of the antitumour response (Paulos et al., 2007). The importance of the microbiota is also confirmed by observations concerning antibiotic therapy: administration of vancomycin may enhance the antitumour effect of irradiation by increasing dendritic cell–dependent cross-presentation of antigens, activation of cytotoxic CD8+ lymphocytes and production of interferon gamma (IFN-γ) (Uribe-Herranz et al., 2020). In turn, the use of broad-spectrum antibiotics may weaken the efficacy of radiotherapy, which indicates that not only the degree of microbiota disruption but also the type of microorganisms eliminated is important (Li et al., 2023). Moreover, laboratory studies showed that microbiota obtained from patients with radiation enteritis more strongly stimulated the

secretion of proinflammatory cytokines such as TNF-α and IL-1β and disturbed epithelial barrier function compared with microbiota from persons without this complication (Wang et al., 2019).

The importance of the microbiota for the response to chemoradiotherapy is also confirmed by clinical studies, particularly in rectal cancer. In patients achieving a favourable response to treatment, a higher share of butyrate-producing bacteria such as *Roseburia*, *Dorea* and *Anaerostipes* was observed, whereas Coriobacteriaceae and *Fusobacterium* were more frequent in non-responders (Yi et al., 2021). Relationships between the microbiota and therapeutic response were also observed in other cancers, including cervical cancer, in which greater microbiota diversity was associated with better survival and greater infiltration of the tumour by CD4+ lymphocytes, and oesophageal cancer, in which specific bacterial taxa were more frequent in patients responding to treatment (Sasaki et al., 2023; Shaikh et al., 2024; Sims et al., 2021). It should be emphasized, however, that the results are not unequivocal, and the relationships between microbiota diversity, immune system activity and the efficacy of radiotherapy may differ depending on the type of cancer and the treatment regimen. Current data therefore indicate that the gut microbiota may influence the efficacy of radiotherapy both by modulating the immune response and by affecting the metabolism of cancer cells, but its role as a predictive biomarker and a target of therapeutic interventions requires further clinical verification.

5.3. Bacterial Metabolites

Bacterial metabolites, which may act both locally within the intestine and systemically, are an important link between the gut microbiota and the efficacy of radiotherapy. Particular importance is attributed to short-chain fatty acids (SCFAs), including butyrate and propionate. Butyrate is the main energy source for colonocytes, strengthens tight junctions between epithelial cells and inhibits histone deacetylase activity. After entering the circulation, SCFAs may also regulate gene expression in distant organs and influence CD8+ lymphocyte function, potentially modifying the antitumour response (Li et al., 2023). The importance of these compounds is confirmed by experimental studies in which increased SCFA production was associated with a change in the radiosensitivity of cancer cells. For example, inulin supplementation increased the abundance of *Bacteroides acidifaciens* and SCFA production, which was accompanied by inhibition of the proliferation of bladder cancer cells and increased radiosensitivity during radiotherapy (Li et al., 2025).

Some metabolites also support epithelial regeneration after radiation injury, indole-3-aldehyde activates the AhR/IL-10/Wnt axis and accelerates epithelial renewal, while lactate stimulates the regeneration of Lgr5+ stem cells (Li et al., 2025; Xie et al., 2024). The radioprotective effects of propionate and tryptophan metabolites are discussed in Section 6.4. These results indicate that microbiota metabolites may influence tissue responses to radiation by strengthening the intestinal barrier and supporting repair processes.

Some metabolites may also act directly on cancer cells and their microenvironment. An example is urolithin A, which may inhibit proliferation and induce apoptosis of cancer cells by modulating the PI3K/Akt/mTOR pathway. At the same time, this compound may reduce the number of tumour-associated macrophages, potentially weakening the immunosuppressive tumour microenvironment (Li et al., 2025). Relationships between microbiota composition, vitamin D metabolism and radioresistance have also been described, suggesting that products of microbial activity may mediate the efficacy of radiotherapy (Huang et al., 2019; Li et al., 2023).

Despite promising preclinical results, the possibilities of translating them into clinical practice remain limited; clinical data from patients with leukaemia undergoing total body irradiation are discussed in Section 6.4. Therefore, although bacterial metabolites, especially SCFAs, are a promising link between the microbiota and the response to radiation, further clinical studies are needed to determine their importance in modifying the efficacy of radiotherapy and reducing its toxicity.

5.4. Bacteria as Potential Radiosensitizers

Another interesting line of research is the use of bacteria as potential radiosensitizers. An example is the genetically modified strain *Escherichia coli* Nissle 1917, targeted to the tumour microenvironment and capable of secreting catalase. This enzyme converts hydrogen peroxide produced by cancer cells into oxygen, which may reduce tumour hypoxia and increase the formation of reactive oxygen species during irradiation, leading to increased radiosensitivity of cancer cells (Li et al., 2025). In a lung cancer model, the use of *Bifidobacterium infantis* in combination with radiotherapy and a specific monoclonal antibody was also investigated. This approach reduced the expression of HIF-1α and TNF-α, increased apoptosis, and limited the proliferation of cancer cells and tumour hypoxia (Li et al., 2025). It should be emphasized, however, that direct evidence for the influence of the microbiota on the efficacy of radiotherapy alone is currently much scarcer than data on its influence on chemotherapy or immunotherapy. Most of the available observations are preclinical or correlative, so their clinical significance requires further verification (Li et al., 2023).

6. Influence of the Gut Microbiota on the Toxicity of Radiotherapy

The gut microbiota plays an important role in shaping tolerance of radiotherapy, influencing the development of complications both in the gastrointestinal tract and in other organ systems.

6.1. Pathogenesis of Radiation Enteritis

The involvement of the microbiota in the pathogenesis of radiation enteritis, which is among the most frequent and most serious adverse effects of irradiation of the abdomen, pelvis and retroperitoneal space, is particularly important (Li et al., 2023). One of the main mechanisms leading to this complication is damage to the intestinal barrier and the associated translocation of bacteria and their products into host tissues, together with disturbances in the composition and function of the microbiota, termed dysbiosis. Radiation damages intestinal epithelial cells and the mucus layer, increasing the permeability of the intestinal barrier. This facilitates contact of microorganisms and their components with the immune system, which may intensify the inflammatory response and deepen mucosal damage. At the same time, dysbiosis may disturb fatty acid and bile acid metabolism, further weakening the protective functions of the intestine (Li et al., 2023). In patients with radiation enteritis, changes in the abundance of, among others, *Dubosiella*, *Alistipes*, *Clostridium* IV, *Roseburia* and *Phascolarctobacterium* have been observed, as well as disturbances of glycerophospholipid metabolism and reduced concentrations of cytokines related to the maintenance of mucosal homeostasis (Li et al., 2023).

6.2. Radiation-Induced Diarrhoea and Prediction of Toxicity

One of the most common manifestations of acute intestinal toxicity is radiation-induced diarrhoea. Its occurrence is accompanied by changes in microbiota composition, including a reduction in the abundance of bacteria with potentially protective effects, such as *Bifidobacterium*, bacteria of the *Clostridium* cluster XIVa and *Faecalibacterium prausnitzii*, and an increase in Enterobacteriaceae and Bacteroidetes (Li et al., 2023; Nam et al., 2013). In patients with diarrhoea, lower microbiota diversity and an increased abundance of bacteria of the phylum Actinobacteria and the class Bacilli were also observed (Li et al., 2023). These changes may promote disturbances in intestinal barrier function and persistence of inflammation. Importantly, a growing body of data indicates that the microbiota may influence the risk of toxicity even before treatment begins. In studies analysing faecal samples collected before radiotherapy, baseline microbiota composition made it possible to distinguish some patients who subsequently developed diarrhoea from those who did not experience this complication (Wang et al., 2015, 2023). In patients who developed diarrhoea, differences in microbiota diversity and richness and in the Firmicutes-to-Bacteroidetes ratio were also observed (Wang et al., 2015). In cervical cancer, increased baseline abundance of the genus *Coprococcus* was associated with later radiation enteritis, whereas in patients with anal cancer, more severe toxicity was accompanied by a greater abundance of Clostridia, Actinobacteria and Clostridiales (Lin et al., 2022; Wang et al., 2019).

The predictive potential of the microbiota is also supported by studies involving larger groups of patients. In the MicroLearner study, conducted in a discovery cohort of 136 patients with prostate cancer and a validation cohort of 79 persons, a model was developed on the basis of the relative abundance of *Faecalibacterium*, *Bacteroides*, *Parabacteroides*, *Alistipes*, *Prevotella* and *Phascolarctobacterium* in samples collected before radiotherapy, allowing identification of patients at increased risk of persistent acute toxicity (Iacovacci et al., 2024). In turn, in a study of 50 women with cervical cancer treated with volumetric modulated arc therapy (VMAT), three enterotypes were identified, of which the *Faecalibacterium*-dominated enterotype was associated with a more than five-fold higher risk of severe acute radiation enteritis (OR = 5.400; p = 0.017) (Ma et al., 2024). At the same time, no single taxon had sufficient predictive value in receiver operating characteristic (ROC) analysis, which underscores the importance of assessing whole microbial communities rather than individual species alone (Ma et al., 2024). It should also be noted that microbiota diversity alone does not always predict later symptom severity. Although in one study greater diversity was associated with better bowel function at individual time points, its baseline value did not predict the final clinical outcome (Mitra et al., 2020). This suggests that specific microbiota composition may be more important in risk assessment than the number and diversity of taxa it contains.

6.3. Late Radiation Complications

Much less is known about the involvement of the microbiota in the development of late radiation complications. The available data come mainly from cross-sectional studies in which the microbiota was analysed after symptoms had appeared, which makes it impossible to establish whether dysbiosis contributes to the development of complications or is their consequence. In the MARS study, which included patients assessed at least two years after prostate radiotherapy, higher abundance of *Roseburia* was associated with more severe diarrhoea. Reduced concentrations of homeostasis-related cytokines were also found in the intestinal mucosa, and the abundance of mucosal *Roseburia* correlated inversely with IL-15 concentration (Reis Ferreira et al., 2019). In another study of women with chronic radiation proctitis, the presence of rectal bleeding was associated with increased abundance of bacteria of the family Peptostreptococcaceae and the genera *Eubacterium* and *Allisonella*, and with reduced abundance of Lachnospiraceae, *Megasphaera*, *Megamonas* and Ruminococcaceae (Liu et al., 2021). These observations indicate that microbiota changes may accompany both acute and chronic intestinal complications, but their causal significance requires confirmation in prospective studies.

6.4. Microorganisms and Metabolites with Radioprotective Effects

An important line of research is the identification of microorganisms and metabolites with radioprotective properties. In animal models, the families Lachnospiraceae and Enterococcaceae were associated with greater survival after irradiation and less intestinal damage. Administration of a consortium of bacteria belonging to Lachnospiraceae increased the survival of mice after a high dose of radiation, and higher faecal concentrations of acetate, butyrate and propionate were observed in protected animals. Importantly, propionate alone also had a protective effect, as did selected tryptophan metabolites (Guo et al., 2020). These results suggest that the microbiota may limit the toxicity of radiotherapy not only by regulating the immune response and maintaining the integrity of the intestinal barrier, but also by producing compounds that support tissue regeneration. In an analysis of 21 patients with leukaemia undergoing total body irradiation, changes in the microbiota were associated with better survival (Kordahi & Chassaing, 2021). In addition, preliminary observations indicate that in these patients a higher abundance of Lachnospiraceae and Enterococcaceae was found in persons with milder diarrhoea than in patients whose symptoms persisted longer (Guo et al., 2020; Kordahi & Chassaing, 2021). The interpretation of these results is limited, however, by the fact that the contribution of individual strains of the 23-strain mixture used to the protective effect has not been established, and that some beneficial microbiota changes appeared only after the end of treatment (Kordahi & Chassaing, 2021).

6.5. Complications Outside the Gastrointestinal Tract

The influence of the microbiota on radiotherapy toxicity may extend beyond the gastrointestinal tract. In patients with head and neck cancers, relationships between radiation-induced oral mucositis and changes in the oral and intestinal microbiota have been described (Li et al., 2025; Xia et al., 2021). In preclinical studies of thoracic irradiation, it was shown that bacterial L-histidine and its metabolite, imidazole propionate, may improve respiratory function and myocardial contractility in irradiated mice (Chen et al., 2021a). Potential protective effects have also been described for the haematopoietic system: indole-3-propionic acid increased thymus and spleen weight and supported the function of haematopoietic stem cells, while propionate limited DNA damage, stimulated proliferation of these cells and reduced the production of ROS (Guo et al., 2020; Li et al., 2025). Moreover, in patients with severe fatigue after chemoradiotherapy, a lower abundance of SCFA-producing bacteria and a higher abundance of taxa associated with inflammation were observed (Li et al., 2023; Xiao et al., 2021). Microbiota changes have also been described in persons after whole-brain irradiation, in whom they correlated with cognitive impairment, although the results of these studies remain inconclusive (Li et al., 2023; Luo et al., 2020). Disturbances of the gut and lung microbiota may also contribute to the development of radiation pneumonitis and pulmonary fibrosis and to bone loss (Li et al., 2020, 2023). For these extra-intestinal consequences of treatment, however, most data are preliminary and require further verification.

The gut microbiota may influence the toxicity of radiotherapy by regulating intestinal barrier integrity, the inflammatory response and repair processes, and by producing metabolites with potential protective effects. Particularly promising are results indicating that microbiota composition before treatment may help to identify patients at risk of acute toxicity. At the same time, relationships between individual taxa and the severity of complications are not always consistent, and data on late toxicity and protective effects outside the gastrointestinal tract remain limited. Further prospective and interventional studies are therefore needed to determine whether modification of the microbiota can effectively and safely reduce the adverse effects of radiotherapy.

7. Modifying the Gut Microbiota to Reduce the Toxicity of Radiotherapy

Because of the involvement of the gut microbiota in the development of radiation complications, strategies allowing its deliberate modification in order to improve tolerance of radiotherapy are of growing interest. These interventions include dietary modification, the use of prebiotics, probiotics, postbiotics and synbiotics, as well as faecal microbiota transplantation (FMT) and more advanced methods such as the use of bacteriophages and genetically modified bacteria. The potential effects of these methods are linked primarily to the possibility of regulating the inflammatory and immune response, strengthening the epithelial barrier, supporting tissue regeneration and modifying the production of bacterial metabolites with radioprotective properties (Cai et al., 2022; Li et al., 2020, 2025). In contrast to traditional methods, such as the use of glucocorticosteroids, antibiotics or free-radical scavengers, an approach targeting the microbiota may potentially act simultaneously on the immune response, epithelial barrier integrity, regenerative processes and stem cell function (Li et al., 2025). Key clinical studies of microbiota-directed interventions in patients undergoing radiotherapy are summarized in Table 1.

Table 1. Selected clinical studies of microbiota-directed interventions in patients undergoing radiotherapy

Intervention	Reference	Study design / population	Main finding
Prebiotic: inulin + FOS (6 g twice daily)	García-Peris et al., 2016	Randomized trial; 38 women undergoing radiotherapy	Restored *Lactobacillus* and *Bifidobacterium* after treatment; no significant reduction in days with watery stools (p = 0.08)
Prebiotic: partially hydrolysed guar gum	Rosli et al., 2021	Randomized controlled trial; pelvic radiotherapy	Increased *Bifidobacterium*; effect on diarrhoea differed by time of assessment
Prebiotic: resistant starch (30 g/day)	Sasidharan et al., 2019	Phase 2 randomized trial; 104 patients with cervical cancer	No reduction in acute radiation proctitis (12.2% vs 14.6%)
Probiotic mixture containing LGG	Xia et al., 2021	Phase II trial; 99 patients with nasopharyngeal cancer	Reduced severity of radiation-induced oral mucositis; improvement in selected immune parameters
Probiotic: VSL#3	Delia et al., 2007	490 patients after surgery for sigmoid, rectal or cervical cancer	Beneficial effect on frequency of radiation-induced diarrhoea
Probiotic: *Bacillus licheniformis*	Jo et al., 2024	Randomized, double-blind, placebo-controlled trial (PREP)	No reduction in grade 2 acute radiation enteropathy
Probiotic: *L. acidophilus* LAC-361 + *B. longum* BB-536	Demers et al., 2014	Randomized, double-blind, controlled trial	Benefit shown mainly in the subgroup of patients after surgery
Postbiotic: sodium butyrate enemas (80 mmol/l, 3 weeks)	Vernia et al., 2000	Randomized crossover trial; acute radiation proctitis	Clinical score 8.2 → 1.5 vs 7.9 → 8.1 with placebo; endoscopic and histological improvement
Postbiotic: SCFA enemas	Pinto et al., 1999	Randomized, double-blind, controlled trial; chronic radiation proctitis	Days with bleeding 4.4 → 1.4 (p = 0.001); effect not sustained at six months
Postbiotic: sodium butyrate enemas (prophylaxis)	Maggio et al., 2014	Randomized phase 2 trial; 166 prostate cancer patients	No reduction in days with proctitis of grade ≥1 or ≥2; no endoscopic improvement
Synbiotic: oat bran, *L. plantarum* HEAL19, bilberry husks	Stene et al., 2025	Controlled study; 30 patients with rectal cancer (short-course radiotherapy)	Smaller loss of microbiota diversity, less histological inflammation; no clinical toxicity endpoints
Faecal microbiota transplantation	Ding et al., 2020	Case series; 5 women with chronic radiation enteritis	Toxicity reduced by ≥1 grade at week 8 in 3 of 5 patients; one mild adverse event

FOS, fructo-oligosaccharides; LGG, *Lactobacillus rhamnosus* GG; SCFA, short-chain fatty acids.

7.1. Dietary Modification

One of the simplest strategies is dietary modification. In experimental studies, beneficial effects were observed, among others, after the use of vitamin D3, omega-3 fatty acids, epigallocatechin gallate and quercetin, which influenced microbiota composition, reduced inflammation and oxidative stress, and limited radiation injury (Cai et al., 2022; Li et al., 2020, 2025). At the present stage, however, this evidence does not allow unequivocal clinical recommendations to be formulated.

7.2. Prebiotics

Another method of modifying the microbiota is the use of prebiotics, that is, substances that support the growth or activity of selected groups of intestinal microorganisms. Clinical studies have evaluated, among others, inulin and fructo-oligosaccharides, partially hydrolysed guar gum and resistant starch. In a randomized study of 38 women undergoing radiotherapy, supplementation with a mixture of inulin and fructo-oligosaccharides at a dose of 6 g twice daily promoted restoration of *Lactobacillus* and *Bifidobacterium* populations after the end of treatment, but did not lead to a statistically significant reduction in the number of days with watery stools ($p = 0.08$) (García-Peris et al., 2016). Partially hydrolysed guar gum increased the abundance of *Bifidobacterium*, but its effect on the frequency of diarrhoea differed depending on the time of assessment (Rosli et al., 2021). In turn, in a study of 104 patients with cervical cancer, supplementation with resistant starch at a dose of 30 g daily did not reduce the incidence of acute radiation proctitis (12.2% vs 14.6%) (Sasidharan et al., 2019). In preclinical studies, beneficial effects were also observed after the use of konjac glucomannan and marine-derived oligosaccharides, which influenced microbiota composition, production of SCFAs and tryptophan metabolites, and the severity of oxidative stress and inflammation (Li et al., 2025). The available results therefore suggest that prebiotics may influence the microbiota during radiotherapy, but their effectiveness in preventing toxicity requires further confirmation.

7.3. Probiotics

Probiotics are among the best-studied microbiota-targeted interventions in the context of radiotherapy. Particular attention has been paid to *Lactobacillus rhamnosus* GG (LGG), which in experimental models limited apoptosis of intestinal epithelial cells and increased the survival of crypt cells. Its action has been linked, among other mechanisms, to modulation of TLR2 signalling, recruitment of stem cells to crypt niches, increased production of prostaglandin E_2 (PGE_2) and reduction of oxidative stress and inflammation. LGG may also influence the immune response by regulating the production of immunoglobulin A (IgA) (Ciorba et al., 2012; Li et al., 2025; Riehl et al., 2019). *Akkermansia muciniphila* also showed protective potential: its administration before irradiation increased the survival of mice, reduced intestinal inflammation, improved epithelial structure and increased the number of goblet cells (Li et al., 2025; Tian et al., 2019). In experimental models, a beneficial effect of *Lactobacillus plantarum* has also been described, which through activation of the FXR–FGF15 axis may support repair of DNA damage in intestinal stem cells (Jian et al., 2022).

Preliminary clinical data also indicate that some adverse effects of radiotherapy may be reduced with probiotics. In a phase II study of 99 patients with nasopharyngeal cancer, a probiotic mixture containing LGG reduced the severity of radiation-induced oral mucositis and was associated with improvement in selected immune parameters and with changes in gut microbiota composition (Xia et al., 2021). A beneficial effect on the frequency of radiation-induced diarrhoea was observed in studies of patients with cervical cancer (Chitapanarux et al., 2010; Linn et al., 2019) and in a larger study of 490 patients after surgery for sigmoid, rectal or cervical cancer, in which the VSL#3 mixture was used (Delia et al., 2007).

The efficacy of probiotics nevertheless remains inconsistent. In the largest and best-blinded studies, a protective effect was not always confirmed (Demers et al., 2014; Giralt et al., 2008; Jo et al., 2024; Muangwong et al., 2025): in the PREP study, *Bacillus licheniformis* did not reduce the incidence of grade 2 acute radiation enteropathy (Jo et al., 2024), and the benefit of a preparation containing *L. acidophilus* LAC-361 and *B. longum* BB-536 was shown mainly in the subgroup of patients after surgery (Demers et al., 2014).

These discrepancies are reflected in meta-analyses. Earlier analyses indicated a reduced risk of radiation-induced diarrhoea with probiotics (RR = 0.55; 95% CI: 0.34–0.88 and RR = 0.62; 95% CI: 0.46–0.83) (Devaraj et al., 2019; Liu et al., 2017). However, the Cochrane review rated the quality of the available evidence as low, and the reduction in the risk of diarrhoea of grade 2 or higher did not reach statistical significance (RR = 0.75; 95% CI: 0.55–1.03) (Wei et al., 2018). A meta-analysis limited to studies at low risk of bias showed a significant reduction in the risk of diarrhoea overall (RR = 0.64; 95% CI: 0.48–0.86; $p = 0.003$), but did not confirm an unequivocal reduction in severe diarrhoea (RR = 0.22; 95% CI: 0.05–1.08; $p = 0.06$) (Danis et al., 2022). These results indicate that the potential efficacy of probiotics may depend on the strain or mixture used, the dose, the duration of supplementation, the type of cancer and the treatment regimen. Not all probiotic preparations can therefore be regarded as equivalent in clinical efficacy.

7.4. Postbiotics

An alternative to live microorganisms is postbiotics, which include inactivated microorganisms, their components and metabolites with biological activity. They may potentially be characterized by greater stability and a more predictable safety profile than preparations containing live bacteria. In experimental studies, heat-inactivated *Lactobacillus acidophilus* supported intestinal epithelial regeneration and differentiation of mucus-producing cells. Exopolysaccharides produced by *L. rhamnosus* and other bacterial components affecting inflammatory processes, oxidative stress, and cell proliferation and apoptosis have also been investigated (Li et al., 2025).

Bacterial metabolites, especially SCFAs such as butyrate, which may support intestinal barrier integrity and epithelial regeneration, are of particular importance in this group. Their clinical potential has been evaluated, among other settings, in the treatment of radiation proctitis. In a randomized crossover study, the use of sodium butyrate enemas at a concentration of 80 mmol/l for three weeks was associated with marked clinical improvement in patients with acute radiation proctitis. The clinical score decreased from 8.2 to 1.5, whereas in the placebo group it changed from 7.9 to 8.1. The improvement was also confirmed in endoscopic and histological examinations (Vernia et al., 2000). In chronic radiation proctitis, enemas containing a mixture of SCFAs reduced the number of days with bleeding from 4.4 to 1.4 ($p = 0.001$) and improved the endoscopic picture, but the effect was not maintained after six months (Pinto et al., 1999).

The results of studies on butyrate depended, however, on whether it was used to treat existing complications or prophylactically. In a randomized phase 2 study of 166 patients undergoing prostate radiotherapy, prophylactic use of sodium butyrate enemas did not reduce the number of days with proctitis of grade 1 or higher or grade 2 or higher, nor did it improve the endoscopic picture (Maggio et al., 2014). A lack of significant improvement was also noted in an earlier study of chronic proctitis (Talley et al., 1997). In turn, in a single-arm study of microencapsulated butyrate involving 122 patients, an increase in abdominal pain relative to baseline values was found, which does not justify an unequivocal conclusion about the efficacy of the preparation (Bortolus et al., 2025). These data indicate that favourable results obtained in the treatment of already developed acute proctitis do not necessarily translate into prophylactic efficacy. The two uses therefore need to be assessed separately.

7.5. Synbiotics

Evidence on synbiotics, that is, preparations combining probiotics with substrates supporting their activity, is much more limited. In one controlled study of 30 patients with rectal cancer undergoing short-course radiotherapy, the use of oat bran, *Lactobacillus plantarum* HEAL19 and bilberry husks was associated with smaller loss of microbiota diversity and less severe inflammatory changes on histological examination. However, clinical endpoints related to radiotherapy toxicity were not assessed, which limits conclusions about the practical significance of this intervention (Stene et al., 2025).

7.6. Faecal Microbiota Transplantation

Another approach to modifying the microbiota is FMT, which involves transferring microbiota from a donor to a recipient. In animal studies, FMT increased survival and limited weight loss after total body irradiation, and also improved gastrointestinal function, epithelial integrity, mucus layer thickness and the number of goblet cells (Cui et al., 2017). The observed effects were linked to changes in the concentrations of metabolites and mediators involved in regulating inflammation and protecting tissues, including the intestine, lungs, heart and haematopoietic system (Chen et al., 2021a, 2021b; Li et al., 2025). Clinical data are, however, very limited. No randomized studies evaluating FMT in the treatment of radiation complications have been conducted to date. The available evidence includes a series of five women with chronic radiation enteritis, in which three patients showed a reduction in toxicity grade according to the RTOG/EORTC scale by at least one grade in the eighth week after the procedure. The improvement included symptoms such as diarrhoea, rectal bleeding, pain and faecal incontinence. During an observation period of 8–18 months, one mild adverse event was recorded, and no deaths or infectious complications were found during the study itself (Ding et al., 2020). These data are supplemented by a single case report (Wang et al., 2024). Because of the small number of patients, the lack of controlled studies and the unestablished principles of donor selection, material preparation, route of administration and number of FMT procedures, FMT should currently be regarded as an experimental method. The safety of this procedure in patients receiving concomitant chemotherapy or immunotherapy also requires special attention.

7.7. Bacteriophages, Viral Vectors and Genetically Modified Bacteria

Bacteriophages, viral vectors and genetically modified bacteria also remain at an early stage of development; in the future they may allow more precise influence on the microbiota or the tumour microenvironment. Bacteriophages, owing to their ability to selectively infect specific bacteria, may be used to control the abundance of selected microbial populations. In experimental studies, bacteriophage Qβ particles limited NF-κB pathway activation and DNA repair processes after irradiation and also slowed the growth of glioma cells (Li et al., 2025). Modified viral vectors targeted to the tumour microenvironment have also been investigated, and in combination with radiotherapy they showed synergistic antitumour activity in melanoma models (Li et al., 2025). Genetically modified bacteria, such as the *Escherichia coli* Nissle 1917 strain secreting catalase (Section 5.4), have in the studies described been used as tumour radiosensitizers rather than as a means of limiting radiotherapy toxicity; their potential use in protecting healthy tissues therefore requires separate investigation. These strategies require further preclinical and clinical studies before their efficacy and safety can be assessed in patients undergoing radiotherapy.

Modification of the gut microbiota is a promising direction for reducing the toxicity of radiotherapy. Most clinical data have been accumulated for probiotics, but their efficacy has not been unequivocally confirmed, especially for severe complications. Prebiotics and synbiotics show potential for modulating microbiota composition, whereas studies on postbiotics, particularly butyrate, indicate the possibility of alleviating selected symptoms of radiation proctitis. FMT and strategies using bacteriophages and genetically modified bacteria remain at the experimental stage. In the future, it will be important not only to confirm the efficacy of these methods in appropriately designed randomized trials, but also to determine which groups of patients may benefit most, which preparations and doses are optimal, and whether modification of the microbiota can reduce toxicity without weakening the antitumour effect of radiotherapy.

8. Discussion

8.1. Principal Findings in Context

The evidence reviewed here is markedly asymmetric. The association of the gut microbiota with radiotherapy toxicity is documented consistently across tumour types and study designs, from mechanistic work on barrier damage, bacterial translocation and inflammation (Li et al., 2023) to clinical studies in which baseline stool composition distinguished patients who later developed diarrhoea or radiation enteritis (Iacovacci et al., 2024; Ma et al., 2024; Wang et al., 2015). In contrast, evidence that the microbiota modifies the antitumour efficacy of radiotherapy comes mainly from preclinical models and correlative clinical observations, predominantly in rectal cancer (Teng et al., 2023; Yi et al., 2021). A plausible explanation is that toxicity arises in the very organ colonized by the microbiota, so that the relevant mechanisms are local and can be studied in the same samples, whereas an effect on tumour control would have to operate through immune and metabolic pathways acting at a distance and would require larger and longer studies with response and survival endpoints. This interpretation is, however, inferential and should not be read as evidence that the microbiota is irrelevant to efficacy.

A second theme is context dependence. The same microorganism or metabolite may be protective in one setting and detrimental in another. *Fusobacterium nucleatum* and *Bacteroides vulgatus* have been linked to radioresistance (Li et al., 2023, 2025; Teng et al., 2023); butyrate protects the intestinal epithelium, yet signals related to its production in the intratumoral microbiota were associated with a less favourable response (Huang et al., 2023); and in cervical cancer a *Faecalibacterium*-dominated enterotype carried a higher risk of severe radiation enteritis (Ma et al., 2024), although *F. prausnitzii*, a member of this genus, is generally regarded as beneficial (Li et al., 2025). The direction of change in Firmicutes after radiotherapy also differed between studies (Lu et al., 2026; Nam et al., 2013). Such findings argue against simple ‘good’ and ‘bad’ taxon labels and favour assessment of community structure and function, in line with the observation that no single taxon had adequate predictive value (Ma et al., 2024).

8.2. From Association to Intervention

Moving from association to intervention proves difficult. Altering microbiota composition does not necessarily improve clinical outcomes: inulin–fructo-oligosaccharide mixtures and partially hydrolysed guar gum influenced the abundance of *Lactobacillus* and *Bifidobacterium*, but their effect on diarrhoea was not significant or depended on the time of assessment (García-Peris et al., 2016; Rosli et al., 2021), and resistant starch did not reduce radiation proctitis (Sasidharan et al., 2019). For probiotics, meta-analyses diverge according to study quality: earlier analyses suggested a lower risk of radiation-induced diarrhoea (Devaraj et al., 2019; Liu et al., 2017), whereas the Cochrane review rated the evidence as low in quality (Wei et al., 2018) and the analysis restricted to trials at low risk of bias did not confirm a reduction in severe diarrhoea (Danis et al., 2022). The butyrate and short-chain fatty acid trials show that the purpose of an intervention matters: enemas were effective in established proctitis (Pinto et al., 1999; Vernia et al., 2000) but not as prophylaxis (Maggio et al., 2014). Taken together, these results suggest that efficacy is likely to be specific to the strain, dose, population and indication, and that demonstrating an effect on the microbiota is not a substitute for clinical endpoints.

An additional consideration is that interventions designed to protect normal tissue could, in principle, also influence the tumour or its response to treatment. The effects of antibiotics illustrate this duality: vancomycin enhanced radiotherapy-induced antitumour immunity in preclinical work (Uribe-Herranz et al., 2020), whereas broad-spectrum antibiotics may weaken the effect of radiotherapy (Li et al., 2023). The intervention studies summarized in Table 1 focused on toxicity endpoints, so whether modification of the microbiota can reduce toxicity without compromising antitumour efficacy remains largely unanswered.

From a practical standpoint, the current evidence does not support routine use of any microbiota-directed intervention to prevent radiotherapy toxicity. Profiling of the microbiota before treatment is a promising approach to risk stratification, but the available models derive from a small number of cohorts, rely on different taxa and have not been established in routine practice. Caution is also warranted with live microorganisms in immunocompromised patients, given the reported probiotic-associated bacteraemia and fungaemia (Redman et al., 2014), and professional guidance remains conservative (Bowen et al., 2019). FMT should for now be confined to research settings (Ding et al., 2020).

8.3. Limitations of the Evidence and Safety Considerations

The interpretation of the data presented is limited by a number of methodological factors. Many studies involved small groups of patients or were pilot in nature for example, the evidence for FMT consists of a series of only five patients, and the synbiotic study included 30 patients. Studies also differ in the methods used to analyse the microbiota: some used 16S rRNA gene sequencing (including older approaches based on pyrosequencing), others whole-genome (metagenomic) sequencing or multi-omic analyses, which provides different taxonomic resolution and makes direct comparison of results difficult. In addition, results depend on the timing of sample collection, the type of sample (faeces, mucosal biopsy, intratumoral material) and the method of toxicity assessment, which varies between studies.

Confounding factors are an additional important problem. The microbiota of cancer patients is shaped simultaneously by antibiotics, diet, chemotherapy and immunotherapy, as well as by the type of cancer, the irradiation schedule and the volume of irradiated bowel. Changes observed during treatment are therefore difficult to attribute to radiotherapy alone, and not all studies are able to account for these variables in their analyses. Moreover, many relationships were established in animal models, whose microbiota differs from that of humans, and the great majority of clinical studies are observational and correlative in nature, which does not allow determination of whether dysbiosis is a cause or a consequence of complications.

A separate issue is the safety of interventions using live microorganisms in immunocompromised patients. In a systematic review of the use of probiotics in people with cancer, whose safety analysis covered 17 studies (1,530 participants), five cases of bacteraemia, fungaemia or positive blood cultures related to probiotics were described, and the authors concluded that probiotics may be a rare cause of sepsis (Redman et al., 2014). This risk is particularly relevant in patients treated for cancer, in whom the intestinal barrier may additionally be damaged by irradiation. Similarly, the safety of FMT in patients receiving concomitant chemotherapy or immunotherapy requires further evaluation.

8.4. Directions for Future Research

Several priorities follow from the above. First, studies should collect samples before treatment and serially during and after radiotherapy, use harmonized sampling and sequencing methods, and record antibiotic use, diet and concomitant systemic therapy so that radiotherapy-specific effects can be separated from confounders. Second, predictive models should be validated in independent, preferably multicentre cohorts before clinical use is considered. Third, randomized, adequately blinded trials should test defined strains or preparations against clinically relevant endpoints in clearly specified populations, and should evaluate prevention and treatment separately. Fourth, such trials should include measures of tumour control to ensure that reduced toxicity is not achieved at the expense of efficacy. Finally, mechanistic studies are needed to clarify how specific metabolites, including short-chain fatty acids and tryptophan derivatives, act in normal and tumour tissue, and controlled trials with standardized protocols and safety monitoring are required before FMT, bacteriophages or genetically modified bacteria can be considered for clinical use.

9. Conclusions

Overall, the gut microbiota may be an important factor influencing the course and outcomes of radiotherapy, affecting both its antitumour efficacy and its toxicity. Ionizing radiation changes the composition and function of the microbiota, and the resulting dysbiosis may affect intestinal barrier integrity, inflammatory processes, the immune response and the tumour microenvironment. Consequently, the microbiota may both increase the radiosensitivity of cancer cells and, under certain conditions, contribute to their radioresistance. At the same time, one of the best-documented areas of its action is the influence on radiotherapy toxicity, especially radiation injury of the gastrointestinal tract and diarrhoea. The available studies indicate potential radioprotective properties of selected bacteria and their metabolites, and the possibility of reducing adverse effects with prebiotics, probiotics, postbiotics, bacterial metabolites and FMT. It should be emphasized, however, that evidence for the influence of the microbiota on the efficacy of radiotherapy itself is currently weaker and largely derives from experimental studies. The interpretation of the available data is also limited by small samples, methodological differences, numerous confounding factors and limited data on the safety of probiotics in immunocompromised patients. In the future, analysis of an individual microbiota profile before the start of treatment, followed by its deliberate modification, could be a subject of research on the personalization of radiotherapy, aimed at establishing whether toxicity can be reduced and, in the longer term, whether antitumour efficacy can also be improved.

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