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Radiotherapy for Digestive Tract Tumors: An overview of the Different Approaches, Side Effects, and Recent Advances

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► ***Review article***

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ABSTRACT

Background: Digestive tract cancers, including esophageal, gastric, colorectal, liver, pancreatic, gastrointestinal stromal tumors (GISTs), and digestive blastomas, accounted for 26% of cancer cases and 38% of cancer-related deaths worldwide in 2020. Managing these malignancies is challenging due to frequent advanced-stage diagnosis, complicating treatment and resulting in poor prognoses. Radiotherapy has evolved from a palliative approach to a curative treatment for several digestive tract cancers, with advances in techniques like three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and stereotactic body radiotherapy (SBRT) improving precision and efficacy. ***Materials and Methods***: PubMed was searched from inception to September 2024 using various keywords with Boolean modifiers and operators. The abstracts were screened, and any relevant articles were imported into a reference manager. Additionally, the references of the selected articles were further screened for any further relevant articles. ***Results:*** This literature review examines the integration of radiotherapy into multimodal treatments, such as neoadjuvant chemoradiation for esophageal and gastric cancers, as demonstrated by the CROSS study. Challenges include resistance to therapy, often mediated by molecular mechanisms involving non-coding RNAs, and significant side effects like gastrointestinal toxicity and fatigue. The emerging role of the gut microbiome in influencing radiotherapy efficacy and side effects is also highlighted. ***Conclusion:*** Despite successes, overcoming resistance and reducing side effects remain significant challenges. Advances in radiotherapy techniques, combined with a deeper understanding of molecular biology and the gut microbiome offer promising avenues for enhancing efficacy and tolerability.

INTRODUCTION

Digestive tract cancers, such as esophageal, gastric, colorectal, liver, and pancreatic cancers, along with rarer types like gastrointestinal stromal tumors (GISTs) and digestive blastomas, are significant global health concerns. In 2020, these cancers constituted approximately 26% of all cancer cases and nearly 38% of cancer-related deaths worldwide [1]. A primary challenge in treating these cancers is their frequent diagnosis at advanced stages, limiting treatment options and worsening prognosis. Traditional treatments include surgical resection, chemotherapy, and radiotherapy, often in combination [2]. Radiotherapy has notably advanced over recent decades, evolving from a palliative approach to a core treatment for various digestive tract cancers [3].

Radiotherapy employs high-energy radiation, dosed in Gray (Gy) units, to target and destroy cancer cells. Initially used to alleviate symptoms in advanced cases, such as pain, bleeding, and obstruction, particularly for inoperable or metastatic tumors [4], advancements like three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT) [5], and stereotactic body radiotherapy (SBRT) [6] have made it crucial in neoadjuvant (pre-surgical) and adjuvant (post-surgical) settings for these cancers [7].

In esophageal and gastric cancers, often diagnosed late with poor prognosis, integrating radiotherapy into multimodal strategies has improved outcomes [3]. Neoadjuvant chemoradiation is now standard for locally advanced esophageal squamous cell carcinoma (ESCC), enhancing survival outcomes compared to surgery alone, as demonstrated by the CROSS trial [8, 9]. For gastric cancer, combining chemotherapy with radiotherapy is effective, especially in locally advanced cases, reducing tumor size and facilitating surgical resection [10,11]. In

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colorectal cancer, especially rectal cancer. Neoadjuvant chemoradiation followed by surgery is standard for locally advanced rectal cancer, enhancing local control and reducing recurrence risk [12]. MRI is vital in assessing tumor response to neoadjuvant therapy, aiding precise surgical planning and sometimes allowing patients to avoid radical surgery if a complete clinical response is achieved [13]. Consolidation chemotherapy post-chemoradiation increases the pathological complete response (pCR) rate, enhancing long-term survival [3, 14]. However, radiotherapy side effects, such as gastrointestinal toxicity, fatigue, and bowel dysfunction, present significant challenges [14].

Research highlights the gut microbiome's role in radiotherapy efficacy and side effects. The gut microbiota maintains intestinal homeostasis and modulates immune responses, affecting radiotherapy response. Dysbiosis can worsen radiation-induced side effects like diarrhea and mucosal damage. Probiotics have been explored to mitigate these side effects with limited success. These findings suggest microbiome modulation could become part of personalized radiotherapy [15].

For rare gastrointestinal tumors like gastroblastomas, radiotherapy is less prominent, typically used with surgery or chemotherapy for advanced or inoperable cases. Gastroblastomas, being extremely rare, lack established treatment protocols, and surgical resection is primary, with radiotherapy selectively used for recurrences [14].

Radiotherapy is indispensable in treating digestive tract cancers, yet challenges like therapy resistance and side effects persist. This review provides a broad overview of radiotherapy's role in various digestive tract tumors, covering technological advancements, treatment strategies, molecular mechanisms, and the gut microbiome's impact. Highlighting successes and challenges, it underscores the need for continued research and personalized, multifaceted strategies in managing digestive tract malignancies.

Search criteria

The search for relevant articles was performed in PubMed from inception to September 30th 2024. The following search terms were used ((esophag* [Title/ Abstract]) OR ((gastr* [Title/ Abstract]) OR ((colorec* [Title/ Abstract]) OR ((rect* [Title/ Abstract]) OR ((digest* [Title/ Abstract])) AND ((radiot* [Title/ Abstract]) OR (chemoradio* [Title/ Abstract])). The resulting articles were then screened by at least 2 authors based on their titles and abstracts. Relevant articles were added to a reference manager and duplicate entries were removed. Subsequently, any relevant references from the included articles were further assessed for inclusion. Wherever possible, we referenced the original article, irrespective of date.

Radiotherapy in esophagogastric tumors

Esophagogastric tumors, including esophageal and gastric cancers, are highly aggressive digestive tract malignancies often diagnosed late, resulting in poor prognoses. Treatment has evolved significantly, with radiotherapy becoming crucial in neoadjuvant and adjuvant settings, often combined with surgery and chemotherapy [1]. Esophageal cancer is categorized into two main histological subtypes: ESCC and esophageal adenocarcinoma (EAC) [2, 3]. ESCC is more common in Eastern countries, while EAC prevails in Western populations [4]. Both subtypes have poor prognoses, especially when diagnosed late. Radiotherapy is crucial in treating esophageal cancer, particularly as a neoadjuvant therapy [1].

Neoadjuvant chemoradiation, combining chemotherapy and radiotherapy before surgery, is the standard for locally advanced esophageal cancer, improving respectability and survival compared to surgery alone [3, 5-7]. This method aims to shrink tumors for easier surgical removal or better radiation response and targets micro-metastases, enhancing surgical success and potentially reducing the need for invasive procedures. Tumor response to neoadjuvant therapy offers insights into future treatment reactions. The CROSS trial confirmed that neoadjuvant chemoradiation improved survival for locally advanced esophageal cancer patients. Those receiving preoperative chemoradiation had better overall survival than surgery-only patients, with a 5-year survival rate of 47% versus 33%, and a higher complete tumor resection (R0) rate. Neoadjuvant treatment significantly shrank tumors, with 29% of patients achieving a pCR, indicating no residual cancer during surgery. This approach also reduced local and distant recurrence rates, down staged the disease, and improved surgical outcomes, establishing it as a standard treatment [8, 9].

In ESCC, radiotherapy is effective in shrinking tumors for easier surgical resection [10, 11]. Radiotherapy reduces the risk of local recurrence, which is crucial due to the tumor's proximity to critical structures like the lungs and heart [4]. Combining radiotherapy with chemotherapy enhances the cytotoxic effects, increasing the likelihood of achieving a pCR. Patients who achieve pCR following neoadjuvant therapy may qualify for less invasive surgery or a watch-and-wait approach [10–14]. Neoadjuvant chemoradiation is typically preferred for locally advanced esophageal cancer, but adjuvant radiotherapy may be considered for patients with positive surgical margins or those who did not receive neoadjuvant therapy. Adjuvant radiotherapy targets residual cancer cells post-surgery to reduce recurrence risk. Its use is less common due to the increasing adoption of neoadjuvant therapies [15, 16].

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Advances in imaging and delivery techniques have significantly improved radiotherapy for esophageal cancer. Methods like IMRT and 3D-CRT enhance radiation delivery precision, allowing for accurate tumor targeting while sparing healthy tissues. This precision is crucial in esophageal cancer, where radiation risks damaging vital organs like the lungs, heart, and spinal cord [17]. These techniques reduce radiation-induced side effects, such as pneumonitis and esophagitis, while maintaining therapeutic efficacy [18-21]. Moreover, image-guided radiation therapy (IGRT) has further refined delivery accuracy. IGRT uses CT and MRI to monitor tumor position during treatment, enabling real-time beam adjustments. This is particularly beneficial for esophageal cancer, where tumors can shift due to patient movement or changes in body position [22]. However, the added benefits of IGRT combined with chemoradiotherapy, compared to chemoradiotherapy alone, are debated and may be limited [23,24], and discussed later in this review.

Gastric cancer, similar to esophageal cancer, is a highly aggressive malignancy often diagnosed at advanced stages, ranking as the fifth most diagnosed cancer globally, particularly prevalent in East Asia [25]. Radiotherapy plays a complex role in managing gastric cancer, especially when combined with chemotherapy as adjuvant chemoradiotherapy. Historically, it has been used post-surgery to target residual cancer cells and improve survival, notably following inadequate lymph node dissection. The INT -0116 trial supported chemoradiotherapy for patients with less extensive lymphadenectomy, showing improved overall survival [26]. However, for patients undergoing D2 lymphadenectomy, trials like ARTIST [27] and ARTIST II [28] have not shown significant disease-free survival benefits from post-surgery radiotherapy. Radiotherapy for gastric cancer is often reserved for specific subgroups, such as lymph node-positive patients, where it may enhance disease-free survival. Its routine use after adequate D2 resection is not widely recommended due to a lack of clear benefit. Consequently, radiotherapy is typically considered for poor surgical outcomes or in palliative settings for symptomatic relief, rather than as standard post-surgical treatment [29].

In cases where surgery is not possible due to advanced disease or poor patient health, radiotherapy is often used palliatively to manage symptoms like pain, bleeding, and obstruction. Palliative radiotherapy significantly relieves symptoms in patients with inoperable gastric cancer, improving quality of life by reducing discomfort and addressing tumor-related complications. It can control local tumor growth, limit further disease progression, and sometimes prolong survival in patients with unresectable gastric cancer. The treatment is generally well-tolerated, with mild to moderate side effects like fatigue and localized irritation. Radiotherapy is valuable for patients unable to undergo aggressive surgery or chemotherapy, offering an effective option for symptom management and tumor control [30, 31].

A major challenge in using radiotherapy for gastric cancer is the risk of damage to surrounding organs, particularly the liver, kidneys, pancreas, and small bowel. These organs are highly sensitive to radiation, and damage can lead to significant complications, including radiation-induced hepatitis, nephritis, and enteritis. Advances in radiotherapy techniques, such as IMRT and proton beam therapy, have helped mitigate these risks by enabling more precise targeting of the tumor [32, 33].

Radiotherapy in rare gastrointestinal cancers

Rare gastrointestinal (GI) cancers, including GISTs and gastroblastomas, have low incidence rates, diverse pathology, and lack established treatment protocols due to limited clinical data [1,2]. Historically, radiotherapy has had a minimal role in treating these cancers, particularly radioresistant tumors like GISTs [3]. However, recent advances in radiotherapy techniques and molecular biology understanding have broadened its potential applications. This section examines the evolving role of radiotherapy in managing rare GI cancers, emphasizing its integration with other treatments and challenges related to radioresistance.

GISTs, the most common mesenchymal tumors of the digestive tract, arise from interstitial cells of Cajal [4]. Despite their rarity, with fewer than 6 cases per 100,000 individuals, they account for a significant proportion of submucosal tumors in the stomach and small intestine [5]. Traditionally deemed radioresistant, surgery remains the primary treatment for localized tumors. However, for unresectable or metastatic GISTs, radiotherapy is increasingly used palliatively or alongside tyrosine kinase inhibitors (TKIs) such as imatinib [1]. For patients with advanced or metastatic GISTs, radiotherapy can manage tumor growth and relieve symptoms like pain, bleeding, or obstruction. Despite GISTs' general resistance to radiation, palliative radiotherapy can offer symptomatic relief, especially when other treatments are limited. SBRT has shown potential in controlling localized disease in non-surgical candidates [6, 7].

TKIs like imatinib, sunitinib, and regorafenib have transformed GIST treatment by targeting KIT and PDGFRA mutations [8, 9]. However, resistance to TKIs can lead to disease progression. Recent studies suggest combining radiotherapy with targeted therapy to overcome TKI resistance. Radiotherapy can enhance TKI efficacy in controlling metastatic GISTs, especially in patients with oligometastatic disease, potentially improving tumor control and prolonging progression-free survival [10].

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Gastroblastomas, rare biphasic tumors in the stomach of young adults, lack standardized treatment protocols. Surgery is the primary treatment, with favorable outcomes following complete resection. Radiotherapy is considered for unresectable or recurrent tumors to control local growth. Limited data, mostly from case reports, suggest radiotherapy may be effective based on its success with similar soft tissue tumors [15–19]. Proton beam therapy and advanced radiotherapy techniques are important for treating these tumors, particularly near critical structures like the stomach and small intestine, where minimizing healthy tissue damage is crucial.

Radioresistance in rare GI tumors, especially GISTs, poses a significant treatment challenge. Although radiotherapy advancements have improved tumor control, radioresistance persists [1, 2, 20]. Molecular mechanisms, including ncRNAs, contribute to this resistance. In GISTs, lncRNAs and circRNAs potentially affect radiation sensitivity by regulating DNA repair, apoptosis, and cell cycle pathways, similar to other cancers [21]

Research into rare gastrointestinal cancers is exploring ways to enhance radiotherapy effectiveness. One promising approach is integrating radiotherapy with molecular-targeted therapies, such as TKIs for GISTs, to improve tumor control and overcome radiation resistance. Proton beam therapy and SBRT enable high-dose radiation delivery to tumors while minimizing damage to surrounding healthy tissues, making them ideal for tumors near critical structures.

Technical advances in radiotherapy

Recent technical advancements in radiotherapy have transformed cancer treatment by enhancing radiation precision and reducing harm to healthy tissues. For gastrointestinal cancers, these innovations have notably improved therapeutic outcomes due to their complex anatomy and proximity to vital organs. Techniques like 3D-CRT, IMRT, SBRT, and proton beam therapy enable more accurate tumor targeting while preserving nearby normal tissues. This section examines these advancements, the importance of MRI and CT imaging in planning, and emerging methods such as proton beam therapy and microbiome modulation in enhancing radiotherapy outcomes for gastrointestinal cancers.

3D-CRT, an early advancement in radiotherapy, enables clinicians to shape radiation beams to the tumor's three-dimensional form using imaging data from CT or MRI to precisely map the tumor's size, shape, and location. This technique is especially beneficial for cancers in complex anatomical regions like the digestive tract, as it conforms the radiation dose to the tumor's geometry, minimizing exposure to surrounding healthy tissues [22]. In gastrointestinal cancers, 3D-CRT has been effectively used to treat oesophageal, gastric, and rectal tumours, where precise radiation delivery is crucial due to their proximity to vital organs such as the heart, lungs, and intestines. Studies indicate that 3D-CRT enhances local control and reduces complications like radiation -induced esophagitis and pneumonitis in oesophageal cancer patients [23-25]. Although largely surpassed by newer techniques such as IMRT, 3D-CRT remains valuable, particularly in resource-limited settings where advanced technologies are less accessible.

IMRT significantly improves upon 3D-CRT by modulating radiation intensity within each beam. Using software, IMRT plans and delivers varying radiation doses across the tumor, effectively treating irregularly shaped tumors or those near sensitive structures. This is particularly advantageous in gastrointestinal cancers, where sparing critical structures like the liver, kidneys, and small bowel from excessive radiation is essential [23]. IMRT has shown considerable efficacy in treating esophageal cancer by reducing lung and heart damage, common in conventional radiotherapy. By adjusting radiation intensity within the treatment field, IMRT delivers high doses to the tumor while minimizing exposure to healthy tissues. This is crucial for treating cancers requiring high radiation doses, such as locally advanced esophageal and rectal cancers [25]. A key advantage of IMRT is its ability to reduce radiotherapy-associated toxicities, which is vital for gastrointestinal cancer patients prone to nausea, vomiting, diarrhoea, and fatigue. IMRT has been shown to decrease these side effects compared to 3D-CRT, thereby enhancing patient quality of life during treatment [23, 25].

SBRT is a sophisticated radiation therapy modality that delivers concentrated, high-dose radiation in a few sessions (typically 1-5). It is particularly effective for small, well-defined tumors or metastatic lesions and is increasingly used for pancreatic, hepatic, and colorectal metastases. Unlike conventional radiotherapy, which spans several weeks, SBRT achieves similar therapeutic outcomes in less time, making it suitable for patients with limited life expectancy or those ineligible for surgery [6, 53, 56, 69]. SBRT also excels in pain management, with a meta-analysis showing a significantly reduced risk of stationary pain during follow-up, although increases in partial pain relief and decreases in progressive pain were not significant [70]. In pancreatic cancer, SBRT is promising for managing locally advanced and unresectable tumors, offering high local control rates with minimal toxicity. Its precision minimizes radiation exposure to surrounding organs, such as the stomach, duodenum, and small bowel, reducing radiation-induced damage. SBRT ensures excellent tumor control with fewer side effects than traditional radiotherapy, making it valuable for palliative care in pancreatic cancer patients. A cohort study showed significant reductions in mean total gross tumor volume at 3 and 6 months post-SBRT, with progression-free survival rates of 88% and 65% at 6

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and 12 months, and overall survival rates of 89% and 56% at 6 and 12 months, with no grade 4/5 adverse events [26]. In colorectal cancer, SBRT is used for oligometastatic disease, especially when metastases are confined to the liver, bones, or lungs [27–30]. SBRT offers a non-invasive alternative to surgery, effectively treating metastatic lesions with minimal recovery time. It can be combined with systemic therapies like chemotherapy and immunotherapy to enhance efficacy, providing a multimodal approach to cancer treatment [31]. For instance, the ongoing RIFLE Phase II trial involves SBRT followed by fruquintinib and tislelizumab within 2 weeks for patients who failed first-line standard treatments [32].

Proton beam radiation therapy, an advanced form of radiation therapy, uses protons instead of X-rays to treat cancer. Protons' Bragg peak property allows energy deposition at a specific tissue depth, minimizing radiation beyond that point. This is particularly beneficial for tumors near critical structures, reducing damage to healthy tissues [33]. In gastrointestinal cancers, proton beam therapy is increasingly used for esophageal, liver, and pancreatic tumors, where traditional radiotherapy risks harming nearby organs. For instance, in esophageal cancer, it limits radiation exposure to the heart and lungs, lowering cardiopulmonary complication risks [34]. In liver cancer, it delivers higher doses to tumors while sparing surrounding liver tissue, reducing the risk of radiation-induced liver disease. A phase III trial showed proton beam therapy was safer than radiofrequency ablation for recurrent hepatocellular carcinoma, with fewer toxicities [35]. Proton beam therapy is also advantageous for pediatric gastrointestinal cancers [36], where minimizing radiation to developing organs is crucial. Its precision in targeting tumors while sparing surrounding tissues makes it ideal for young patients susceptible to long-term radiation side effects.

IGRT uses imaging techniques like CT, MRI, and ultrasound to monitor tumor positions during treatment, enabling real-time radiation beam adjustments. This is crucial for gastrointestinal cancers, where tumors may shift due to respiration, digestion, and patient movement [37, 38]. IGRT enhances radiotherapy accuracy for these cancers, reducing geographic misses and limiting radiation exposure to surrounding tissues. It adapts to changes in tumor size and shape during treatment, ensuring radiation doses target the tumor while sparing healthy tissues. This adaptation is vital during long-course radiotherapy, where tumor regression can occur over weeks of treatment [39-42].

MRI is essential in radiotherapy planning and delivery for gastrointestinal cancers, offering superior soft tissue contrast over CT for tumor delineation and identification of critical structures. In rectal cancer, MRI is the gold standard for staging and post-neoadjuvant chemoradiation therapy restaging [43]. MRI's key applications include assessing tumor regression, visualizing tumor shrinkage, and guiding surgery or additional treatments. It is also used for real-time tumor tracking during radiotherapy for precise targeting as the tumor moves with respiration [44] and digestion. Furthermore, MRI aids in adaptive radiotherapy, adjusting treatment plans based on tumor size and shape changes, potentially improving local control and reducing radiation-related side effects in gastrointestinal cancers [45-47].

Recent research emphasizes the gut microbiome's role in modulating radiotherapy efficacy and toxicity for gastrointestinal cancers [48]. The gut microbiome, comprising trillions of microorganisms in the digestive tract, is vital for maintaining gut homeostasis and regulating immune responses [49]. Dysbiosis, an imbalance in gut microbiota, is associated with increased gastrointestinal toxicity and reduced treatment efficacy during radiotherapy [50-53]. Studies indicate that probiotics and prebiotics can restore gut microbiota balance during radiotherapy, mitigating radiation-induced side effects like diarrhea and mucositis [54]. Emerging evidence also suggests the microbiome may enhance the immune response to radiotherapy, aiding in cancer cell recognition and destruction [51].

Advancements in radiotherapy technologies, such as proton arc therapy, which merges proton beam therapy with rotational radiation delivery, promise improved precision in treating gastrointestinal cancers. Additionally, integrating artificial intelligence (AI) into radiotherapy planning is expected to revolutionize the field by enabling personalized treatment plans tailored to individual tumor characteristics and anatomy. Machine learning has been used to enhance survival prediction [56] and preoperative lymphovascular and perineural invasion [57]. As computational power and methodologies advance, AI's role in improving prognosis and management of digestive tract tumors is likely to grow. Combining radiotherapy with immunotherapy, particularly immune checkpoint inhibitors, has shown synergistic effects in boosting the immune system’s cancer-fighting abilities. Early clinical trials for gastrointestinal cancers report improved survival outcomes [55-59].

Side effects of radiotherapy and treatments

Radiotherapy is essential for treating digestive tract cancers such as esophageal, gastric, and rectal cancers, along with rare gastrointestinal malignancies. Despite its efficacy, it can cause significant side effects that affect a patient’s quality of life. These side effects are categorized as acute (short-term) or chronic (long-term), based on their timing relative to the treatment period.

Acute side effects are immediate reactions

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occurring during or shortly after radiotherapy, significantly impacting patient well-being. Common across various digestive tract cancers due to similar tissue responses, some side effects are specific to cancer types based on anatomical and physiological differences. Patients treated for esophageal, stomach, rectal cancers, and rare gastrointestinal tumors frequently suffer from nausea and vomiting due to radiation-induced gastrointestinal inflammation. Lowering the treatment dose or halting therapy may provide relief but can compromise treatment effectiveness. Combining radiotherapy with chemotherapy increases the risk of these symptoms, as chemotherapeutic drugs heighten healthy tissue sensitivity to radiation.

Radiation-induced gastrointestinal mucosa inflammation can be managed pharmacologically. Loperamide, the first-line treatment for radiation-induced diarrhea, slows intestinal activity; if ineffective after 24 hours, fluoroquinolone antibiotics may be used, though rising resistance limits their efficacy. For loperamide-resistant cases, octreotide, especially in higher doses, may be used, though its efficacy varies. Amifostine, an FDA-approved radioprotector, mitigates mucositis by selectively protecting healthy cells without shielding tumors, beneficial for head and neck, lung, and pelvic cancer patients. Melatonin and metformin show promise due to their antioxidant and anti-inflammatory properties; melatonin enhances DNA repair and reduces inflammatory cytokines, while metformin stimulates DNA repair via the MAPK pathway and suppresses oxidative stress enzymes. Sucralfate, a topical cytoprotective agent, alleviates acute radiation proctitis symptoms like diarrhea and rectal bleeding in pelvic radiotherapy patients. Additionally, Glucagon-like Peptide 2 (GLP-2) analogs promote intestinal healing by stimulating crypt cell proliferation and reducing mucosal apoptosis [60].

Fatigue is another common acute side effect in digestive tract cancers treated with radiotherapy, including esophagogastric tumors, due to systemic inflammation, anemia, increased metabolic demands for tissue repair, and psychological stress [61].

Management of cancer-related fatigue (CRF) includes pharmacological and non-pharmacological treatments, often yielding moderate benefits. Pharmacologically, stimulants like methylphenidate show modest effects and can cause side effects such as sleep disturbances and appetite loss, possibly worsening fatigue. Methylphenidate is contraindicated for patients with uncontrolled hypertension or cardiac issues, suitable only for select survivors when benefits outweigh risks. Antidepressants like bupropion may help when CRF co-occurs with depression but require caution in anxious patients. Erythropoietin can alleviate anemia -related CRF by increasing hemoglobin but is recommended selectively due to risks like tumor progression and cardiovascular issues. Non-pharmacological treatments, especially exercise, show greater efficacy in reducing CRF. Aerobic exercise during treatment significantly reduces fatigue, with longer-duration programs post-treatment offering more benefits. Prehabilitation programs combining exercise, psychological support, and nutrition may improve postoperative outcomes, but their specific efficacy in CRF reduction needs more evidence [61, 62].

Radiation esophagitis, affecting under 1% of radiation therapy patients, usually appears within two months, presenting symptoms like dysphagia and odynophagia. Diagnosis is difficult due to nonspecific endoscopic findings and histological changes mimicking infections such as cytomegalovirus. Management is symptom-based, using topical analgesics like liquid morphine sulfate and combination solutions with viscous lidocaine, aluminum hydroxide–magnesium carbonate, and diphenhydramine [63]. Proton pump inhibitors and dietary modifications address reflux from decreased lower esophageal sphincter pressure, while sodium bicarbonate prevents *Candida albicans* superinfection. Endoscopic dilation treats esophageal strictures to improve swallowing [64]. Nutritional support, including tube feedings or parenteral nutrition, is necessary for severe weight loss or failure to thrive. In severe cases, radiation therapy may be temporarily halted to allow symptom improvement. Prokinetic agents like metoclopramide enhance esophageal motility, and nitrates, calcium channel blockers, and anticholinergic agents alleviate esophageal spasms. NSAIDs like indomethacin are proposed to reduce prostaglandin-mediated inflammation [65,66]. Management aims to relieve pain, manage complications, ensure nutrition, and maintain cancer therapy, requiring a multidisciplinary approach.

Radiation pneumonitis, a potential side effect for esophageal cancer patients due to esophagus-lung proximity, causes symptoms like cough, shortness of breath, and fever. Despite being less common with modern radiotherapy techniques like IMRT and proton beam therapy, it requires careful monitoring [67]. Accurate diagnosis distinguishes it from disease progression and infection. Treatment involves high-dose systemic corticosteroids for symptomatic patients or those with grade 2 or higher symptoms. Oral prednisone is prescribed at 1-2 mg/kg/day, tapered over 3-12 weeks, while severe cases (grades 3-4) require intravenous corticosteroids like methylprednisolone at 2-4 mg/kg/day, tapered over six weeks [68]. Glucocorticoids reduce inflammation by inhibiting TNF-induced nitric oxide-mediated endothelial cell and lymphocyte toxicity [69]. Prophylactic treatment for Pneumocystis jirovecii pneumonia is advised for patients on high-dose corticosteroids [70].

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Inhaled corticosteroids may treat grade 2 radiation pneumonitis by delivering high doses directly to the airway with reduced systemic side effects; however, their efficacy in cancer patients is less studied. Glucocorticoid therapy benefits are unlikely for chronic radiation fibrosis patients. Pentoxifylline, an immunomodulatory and anti-inflammatory agent, has shown promise in preventing fibrosis by suppressing TNF-α and IL-1 [71]. Administered at 400 mg orally three times daily for eight weeks, pentoxifylline has improved clinical signs and reduced lung fibrosis, especially with alpha-tocopherol (vitamin E) over six months [72, 73].

Amifostine, a radioprotective agent acting as a free radical scavenger, has been shown in meta-analyses to reduce radiation pneumonitis risk compared to placebo or no treatment, without affecting tumor response adversely [74-76]. Angiotensin-converting enzyme inhibitors exhibit antifibrotic activity against lung collagen accumulation, primarily observed in retrospective studies. Other agents like colchicine, penicillamine, statins, and interferon-gamma may also help modify fibrosis progression due to their effects on collagen synthesis [77, 78].

Recently, nintedanib has emerged as a promising therapeutic and prophylactic option for radiation-induced fibrosis, showing benefits in reducing the annual decline in forced vital capacity in idiopathic pulmonary fibrosis patients, a condition with similar pathophysiology to radiation-induced fibrosis [79]. A phase 3 clinical study revealed that in the general study population, the adjusted annual forced vital capacity decline was -80.8 ml for nintedanib recipients versus -187.8 ml for placebo. Among participants with a usual interstitial pneumonia-like fibrotic pattern, the adjusted forced vital capacity decline was -82.9 ml per year with nintedanib treatment, compared to -211.1 ml per year with placebo. The nintedanib group experienced higher incidences of diarrhea and liver function test abnormalities compared to the placebo group [80]. While corticosteroids remain the primary treatment for acute RP, these additional therapies offer potential for preventing or mitigating fibrosis development.

Diarrhea is a common acute side effect in patients treated for gastric and rectal cancers due to radiation-induced damage to the epithelial lining of the small intestine and colon, leading to increased stool frequency and urgency, dehydration, and electrolyte imbalances. Rectal cancer patients often experience radiation proctitis, characterized by inflammation of the rectal mucosa, causing diarrhea, rectal bleeding, painful defecation, and mucus discharge, which significantly impact quality of life. Pelvic irradiation can also cause urinary symptoms such as increased frequency and dysuria due to radiation cystitis [81]. Current management of radiation-induced intestinal injury focuses on symptom alleviation through supportive care, using medications like loperamide for diarrhea, anticonvulsants for abdominal pain, and antibiotics to prevent bacterial overgrowth [82].

Radiotherapy-induced skin irritation is another side effect in patients with esophageal cancer and rare gastrointestinal cancers, causing redness, dryness, or itching, depending on radiation dose and duration [83]. Topical corticosteroids, such as mometasone furoate (MMF), are highly effective in reducing inflammation and pro-inflammatory mediators in irradiated skin [84]. Emulsions with trolamine are used to treat radiation dermatitis, offering benefits like dead tissue removal, fibroblast growth enhancement, and reduced vascular alterations, without significant adverse effects [84–86].

The gut microbiome may modulate radiotherapy side effects, with dysbiosis linked to increased gastrointestinal toxicity, exacerbating diarrhea, nausea, and mucosal damage. Conversely, a healthy microbiome may enhance immune responses and treatment tolerability. Probiotic supplementation has shown promise in mitigating side effects by restoring microbial balance and enhancing mucosal healing, indicating potential for microbiome-targeted interventions to improve radiotherapy tolerability in digestive tract cancer patients.

Chronic side effects are long-term complications emerging months or years post-radiotherapy, significantly impacting patient quality of life and necessitating ongoing management. Common chronic side effects in digestive tract cancers include radiation-induced fibrosis and cardiotoxicity. Radiation-induced fibrosis can severely affect various organs. In esophageal cancer patients, it may cause esophageal scarring and narrowing, leading to chronic dysphagia. Pulmonary fibrosis, resulting from long-term lung tissue damage, can reduce pulmonary function, cause chronic cough, and shortness of breath [66, 87]. Treatments include dosimetry and reduced radiation doses, with therapies targeting broad pathways of radiation damage, such as anti-inflammatory drugs, antioxidants, and vascular interventions. Despite promising lab and animal studies, clinical trials show inconsistent results. This variability has shifted focus to combination therapies, like antioxidants with vascular treatments (e.g., pentoxifylline and Vitamin E), though constrained by small sample sizes and conflicting findings [87-89].

Chronic radiation proctitis (CRP) affects 5-20% of cancer patients, typically delayed by 3-6 months. Its likelihood is influenced by the irradiated rectum volume, total radiation dose, technique, and dose per fraction, alongside patient-specific factors like vascular disease, diabetes, connective tissue disorders, inflammatory bowel disease, smoking, and concurrent chemotherapy. CRP causes long-term bowel dysfunction, including persistent diarrhea, rectal bleeding, and bowel control loss. Radiation enteritis, from small intestine damage, can lead to malabsorption, chronic diarrhea, abdominal

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discomfort, and increased intestinal blockage risk. CRP treatments vary by patient factors and CRP subtype, with comprehensive reviews of therapeutic options available [90]. A meta-analysis showed that using alternative therapies, such as acupuncture and moxibustion (burning dried mugwort on certain points of the body) for radiation enteritis resulted in more favorable outcomes than traditional treatments [85].

Radiation-induced cardiotoxicity is a serious concern, especially in esophageal cancer patients due to heart proximity to the radiation field [88]. It includes pericarditis, cardiomyopathy, and accelerated coronary artery disease, significantly impacting morbidity, mortality, and manifesting years post-treatment [89, 90]. Cardiac events correlate with preexisting heart conditions and radiation therapy type (IMRT or proton beam), with fewer complications in patients receiving a mean heart dose below 15 Gy. These events also link to reduced overall survival rates [91].

A meta-analysis studied the risk factors of postoperative pulmonary infection in patients with colorectal cancer following radiotherapy. It was found that gender, body mass index (BMI), surgical method, and smoking history significantly influenced the risk. Specifically, male patients, those with a higher BMI, patients undergoing open surgery, and smokers were more likely to develop infections. Notably, age, TNM stage, operation time, and chronic obstructive pulmonary disease were not identified as risk factors [87].

Chronic side effects can include radiation nephritis, leading to hypertension and impaired kidney function when radiation involves the kidneys. There is also a rare risk of secondary malignancies in the irradiated area years after treatment. In pelvic radiotherapy, sexual dysfunction may occur, with potential long-term effects including erectile dysfunction in men and vaginal dryness or stenosis in women [92].

Advancements in radiotherapy techniques have reduced the incidence and severity of acute and chronic side effects. Precision methods like IMRT and proton beam therapy allow accurate targeting of tumors, sparing healthy tissues and reducing exposure to critical organs. This minimizes acute side effects such as esophagitis and radiation proctitis and decreases long-term complications like fibrosis and cardiotoxicity. Additionally, by more strictly controlling radial margin expansion when using radiotherapy for esophageal cancer with tomotherapy can help reduce the likelihood of radiation-related toxicity [92].

Supportive care is essential in managing side effects. Prophylactic treatments, such as antiemetics for nausea, analgesics for pain, and nutritional support, improve patient comfort during treatment. Early symptom management enhances treatment adherence and quality of life. Ongoing monitoring and management of chronic side effects are crucial for long-term outcomes and quality of life for cancer survivors. Table 1 summarizes potential side effects and treatment options. Understanding the acute and chronic side effects of radiotherapy in digestive tract cancers is essential for optimizing patient care. Acute side effects, including nausea, vomiting, fatigue, and organ-specific inflammations, impact patients during treatment, while chronic side effects like fibrosis, cardiotoxicity, and long-term organ dysfunction affect survivors' quality of life post-therapy. Advanced radiotherapy techniques, supportive care, and ongoing research into factors like the gut microbiome are crucial for minimizing these adverse effects and improving treatment outcomes.

Table 1. Summary of side effects and treatment options for radiotherapy-induced adverse events in digestive tract cancers.

Side Effect	Treatment Options
Nausea and vomiting	Lowering treatment dose (may compromise effectiveness)
	Stopping therapy (may compromise effectiveness)
Radiation-induced diarrhoea	Loperamide
	Fluoroquinolone antibiotics (for persistent symptoms)
	Octreotide (for severe cases)
	Amifostine (for mucositis)
	Sucralfate (for acute radiation proctitis)
	Glucagon-like Peptide 2 (GLP-2) analogues
Fatigue	Pharmacological: Methylphenidate, Antidepressants (e.g., Bupropion), Erythropoietin
	Non-Pharmacological: Exercise interventions, Prehabilitation programs
Radiation esophagitis	Pain relief: Topical analgesics (e.g., liquid morphine sulphate)
	Proton pump inhibitors (for reflux)
	Endoscopic dilation (for strictures)
	Prokinetic agents (e.g., metoclopramide)
	NSAIDs (e.g., indomethacin)
Radiation pneumonitis	Systemic corticosteroids (e.g., oral prednisone or intravenous corticosteroids for severe cases)
	Inhaled corticosteroids (less studied)
	Pentoxifylline (for fibrosis prevention)
	Amifostine (as a radioprotector)
diarrhoea (in gastric and rectal cancers)	Loperamide
	Compound phenoperidine
	Anticonvulsants (for abdominal pain)
	Antibiotics (to prevent bacterial overgrowth)
Skin irritation (radiotherapy-induced)	Topical corticosteroids (e.g., Mometasone furoate)
	Trolamine-containing emulsions
	Triethanolamine (for radiation dermatitis and skin damage)
Radiation-induced fibrosis	Combination therapies (e.g., Pentoxifylline and Vitamin E)
	Antioxidants
	Anti-inflammatory medications
	Vascular therapies
Chronic radiation proctitis	Individualized treatment plans depending on patient factors
	Symptomatic treatments (for bowel dysfunction, diarrhea, rectal bleeding)
Radiation-induced cardiotoxicity	Dosimetry adjustments to lower radiation dose
	Monitoring and management of existing heart conditions
	Use of modern techniques like IMRT or proton beam therapy (to minimize damage)
Radiotherapy-induced sexual dysfunction	Erectile dysfunction treatments (for men)
	Vaginal dryness/stenosis treatments (for women)

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DISCUSSION

Radiotherapy is crucial for treating digestive tract cancers, including esophageal, gastric, and rectal cancers, as well as rare gastrointestinal malignancies. Despite technological advancements, challenges like treatment precision, patient-specific factors, and radiotherapy resistance persist. Future strategies involve personalized treatment, novel therapeutic combinations, and optimizing current technologies.

Standardized radiotherapy protocols for rare gastrointestinal cancers, such as GISTs and pancreatoblastomas, are lacking. These tumors are often radioresistant, with surgery and tyrosine kinase inhibitors being standard treatments. Techniques like SBRT and proton beam therapy show promise, but clinical trials are needed to establish guidelines. Further research is required to evaluate radiotherapy's role in these rare tumors and develop clear protocols.

Personalizing radiotherapy based on genetics and tumor biology is a gap in current treatments. Most plans rely on tumor size and stage, while precision medicine in other oncology fields has not been fully integrated. Biomarkers like circulating tumor DNA could predict radiotherapy response, but more research is needed for validation and clinical incorporation.

Managing long-term side effects remains a major concern, with chronic complications like bowel dysfunction, urinary incontinence, and radiation fibrosis significantly impacting quality of life. Rectal cancer patients often face long-term bowel dysfunction, while esophageal cancer patients may develop strictures or pulmonary fibrosis. Techniques like IMRT and proton beam therapy have reduced these effects, but further strategies are needed to minimize long-term complications.

Future avenues to improve radiotherapy outcomes for gastrointestinal cancers include integrating AI to optimize treatment plans, predict tumor responses, and minimize damage to healthy tissues through large dataset analysis. Machine learning models are being developed to aid treatment planning and may enable real-time adaptive radiotherapy, adjusting radiation delivery based on tumor changes during treatment.

Proton beam therapy precisely targets tumors while minimizing exposure to adjacent healthy tissues, benefiting tumors near critical organs like the liver and pancreas, and reducing complications such as radiation-induced liver disease. Carbon ion therapy is being explored for treating radioresistant tumors, potentially offering advantages over conventional radiotherapy.

Combining radiotherapy with immunotherapy is an emerging research area. Radiotherapy can stimulate the immune system to attack tumors outside the radiation field by releasing tumor antigens during cell death, known as the abscopal effect. Clinical trials testing radiotherapy with immune checkpoint inhibitors have shown promising early results in cancers like esophageal and rectal cancer, potentially overcoming radioresistance and improving treatment outcomes.

Modulating the microbiome to enhance radiotherapy outcomes is also gaining interest. Dysbiosis, or gut microbiota imbalance, is linked to increased gastrointestinal toxicity during radiotherapy, while a healthy microbiome may boost immune responses and treatment efficacy. Strategies like probiotics, prebiotics, and fecal microbiota transplantation are being investigated to restore a healthy microbiome and mitigate radiotherapy side effects.

Combining radiotherapy with chemotherapy is becoming the standard approach for digestive tract tumors, with current approaches and indications summarized in table 2. The key clinical trials on approaches involving radiotherapy for gastrointestinal tumors are shown in table 3.

While radiotherapy has significantly advanced in treating gastrointestinal cancers, challenges such as radioresistance, long-term side effects, and the need for personalized treatments persist. Future developments, including artificial intelligence integration, advanced radiation techniques, and immunotherapy combination, hold promise for enhancing radiotherapy outcomes. Addressing these gaps will improve radiotherapy effectiveness and reduce side effects, ultimately improving patient quality of life.

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Table 2. Summary of radiotherapy approaches for digestive tract tumors.

Tumor type	Treatment approach	Chemotherapy regimen (if applicable)	Radiotherapy technique	Indications
Esophageal cancer	Neoadjuvant chemoradiotherapy	Carboplatin + Paclitaxel	IMRT or PBT	Locally advanced resectable tumors
	Palliative radiotherapy	N/A	SBRT, Brachytherapy	Symptomatic control in inoperable tumors
Gastric cancer	Neoadjuvant chemoradiotherapy	FLOT, ECF (Epirubicin, Cisplatin, 5-FU)	IMRT	High-risk, locally advanced tumors
	Adjuvant chemoradiotherapy	Fluorouracil-based regimens	IMRT	Post-surgery, high-risk patients
	Palliative radiotherapy	N/A	IMRT, SBRT	Symptom control in advanced disease
Pancreatic neuroendocrine Tumors	Palliative chemoradiotherapy	Fluorouracil-based or platinum-based regimens	SBRT, IMRT	Unresectable or borderline tumors
Hepatobiliary tumors	Palliative radiotherapy	N/A	SBRT	Localized control of unresectable tumors
Gastrointestinal stromal tumors (GIST)	Palliative radiotherapy	N/A	IFRT, SBRT	For TKI-resistant, unresectable disease
Lymphomas (MALT)	IFRT	N/A	IFRT	Localized gastric lymphomas

Table 3. summary of the major completed and ongoing clinical trials on radiotherapy for gastrointestinal cancers.

Trial Name	Cancer type	Treatment regimen	Outcomes	First author, year	Reference
CROSS	Esophageal adenocarcinoma & SCC	Neoadjuvant chemoradiotherapy (carboplatin + paclitaxel, 41.4 Gy in 23 fractions) followed by surgery	Improved 5-year overall survival (47% vs 34%) and R0 resection rate (92% vs 69%)	van Hagen *et al.*, 2012	(94)
ARTIST	Gastric cancer	Postoperative chemoradiotherapy (capecitabine + cisplatin, 45 Gy in 25 fractions) versus chemotherapy alone	No significant OS difference overall, but improved DFS in node-positive patients (HR 0.69)	Lee *et al.*, 2012	(95)
ARTIST II	Gastric cancer	S-1 (control), SOX (S-1 + oxaliplatin), or SOXRT (SOX + radiotherapy)	3-year DFS rates: S-1 (64.8%), SOX (74.3%), SOXRT (72.8%). HR for DFS: S-1 vs. SOX, 0.692 (P=0.042)	Park *et al.*, 2020	(96)
RTOG 8501	Esophageal cancer	Definitive chemoradiotherapy (cisplatin + 5-FU, 50 Gy radiotherapy)	Improved median survival (14.1 vs 9.3 months) compared to RT alone	Cooper *et al.*, 1999	(97)
CRITICS	Gastric cancer	Perioperative chemotherapy (epirubicin, cisplatin, capecitabine) ± postoperative chemoradiotherapy	No significant difference in 5-year OS or DFS (41.3% vs 40.9%)	Cats *et al.*, 2018	(98)
CRITICS-II	Gastric cancer	(1) 4 cycles of docetaxel + oxaliplatin + capecitabine (DOC), (2) 2 cycles of DOC followed by chemoradiotherapy (45Gy in combination with weekly paclitaxel and carboplatin) or (3) chemoradiotherapy.	Ongoing; evaluating survival and R0 resection rates	Slagter *et al.*, 2018	(99)
SWOG S1316	Gastric cancer	Comparison of palliative radiation therapy regimens (standard dose vs short-course high dose)	Ongoing; aims to evaluate symptom control and quality of life outcomes	Krouse *et al.*, 2023	(100)
CheckMate 577	Esophageal adenocarcinoma	Adjuvant nivolumab after chemoradiotherapy and resection	Improved DFS (22.4 vs 11.0 months, HR 0.69)	Kelly *et al.*, 2021	(101)
DURVA-EMERALD	Biliary tract cancer	Durvalumab + tremelimumab + gemcitabine/cisplatin ± resection	Ongoing; aims to assess conversion rates from unresectable to resectable and OS	-	-
KEYNOTE-585	Gastric and gastroesophageal cancer	Neoadjuvant pembrolizumab + chemotherapy followed by surgery	Ongoing; aims to assess pathologic complete response (pCR) and survival outcomes	Shitara *et al.*, 2024	(102)
NETTER-2	Gastroentero-pancreatic NETs	[177Lu]Lu-DOTA-TATE (Lutetium-based radiopharmaceutical)	Ongoing; evaluating progression-free survival and radiological response	ASCO GI Symposium	(103)

CONCLUSION

Radiotherapy is vital in treating several types of digestive tract tumours, offering improved survival and tumour control. Despite advancements, challenges like tumour radioresistance, long-term side effects, and lack of personalized protocols remain. Precision techniques, such as proton beam therapy, and innovations like AI-driven treatment planning show promise in enhancing outcomes and reducing complications. Emerging strategies, including combining radiotherapy with immunotherapy and microbiome modulation, aim to overcome resistance and improve efficacy.

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Addressing these gaps through research and clinical trials will optimize radiotherapy's effectiveness while prioritizing patient quality of life, paving the way for more targeted, adaptable, and successful treatments for digestive tract cancers.

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